

Heart Disease Diagnosis and Therapy

A Practical Approach

SECOND EDITION

M. Gabriel Khan

MD, FRCP(LONDON), FRCP(C), FACP, FACC



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HEART DISEASE DIAGNOSIS AND THERAPY

CONTEMPORARY CARDIOLOGY

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HEART DISEASE DIAGNOSIS AND THERAPY

A Practical Approach

Second Edition

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DEDICATION

Dedicated to my wife Brigid

FOREWORD

Dr. Khan has done it again. For the last several years he has produced books at a rate usually achieved only by writers of romantic novels. With seemingly little effort he has authored more than a book a year packed with eminently usable information, and he has now capped his series of authored volumes with another masterpiece. *Heart Disease Diagnosis and Therapy: A Practical Approach* is a unique assemblage of what a physician dealing with cardiac patients needs to have at his or her fingertips—or at least within easy reach—when confronted with a challenging cardiovascular problem.

Unique? Yes, because Dr. Khan has disregarded tradition and convention to produce a reader-friendly and practical, yet up-to-date and comprehensive, treatise. By omitting unnecessary anatomy and physiology, for instance, he has made room for more detailed coverage of pharmacology, which is important to the wielder of the deadly drugs in the field. By avoiding long discussions of matters of little interest to the physician in the front line, he has managed to keep his book to a reasonable, handy size; in so doing, he has, in some important sections, managed to exceed the coverage of even the monumental Hurst and Braunwald tomes. His thrust is essentially clinical; his aim is to aid the clinician in his hour of need.

The electrocardiogram, often considered somewhat passé, is still the most often ordered, the most often diagnostic, the most cost-effective and yet, by cardiologist and computer alike, the most often misinterpreted of all cardiologic tests. Well aware of this, Dr. Khan has included a large number of illustrative electrocardiograms.

Two vitally important aspects of cardiology are the diagnosis and management of myocardial infarction and the recognition and treatment of cardiac arrhythmias. Accordingly, the practical aspects of these two challenges are handled in lavish detail. I would like to have seen emphasis on the reciprocal changes in the early diagnosis of acute inferior myocardial infarction, and details of the morphologic clues in the diagnosis of ventricular tachycardia could have been usefully expanded.

But no one could thumb through these pages without being impressed with the infinite amount of work that must have gone into their preparations and the author's breadth of knowledge. Whenever I read Khan, I am affected as the rustics were by Oliver Goldsmith's parson:

And still they gaz'd, and still the wonder grew
That one small head could carry all he knew.

Khan's knowledge is truly encyclopedic and, for his fortunate readers, he translates it into easily read prose.

Henry J. L. Marriott, MD, FACP, FACC

PREFACE

In preparing this second edition of *Heart Disease Diagnosis and Therapy: A Practical Approach*, I was determined that this book must remain clinically focused because of the changing role of clinical cardiologists. The majority of cardiologists prefer to be invasive cardiologists; those who practice noninvasive cardiology spend much of their time performing and interpreting noninvasive cardiac tests. Across North America and worldwide a large number of interns go into internal medicine programs. More than half go on to become general internists, and these internists render care to more than 60% of patients with cardiac problems. Thus, these physicians must acquire a sound knowledge base in clinical cardiology in order to render competent care to this large pool of patients that is not serviced by cardiologists. In particular, these trainees must have at their fingertips the basis for the clinical diagnosis and pharmacologic therapy of cardiac disorders. They do not require much information on invasive and noninvasive cardiac testing, neither of which they are called on to perform.

I believe that most trainees have difficulty extracting essential information from available large volume textbooks that are aimed at nonseasoned cardiologists. These are good reference books, but they are not study books. What type of textbook must the internal medicine resident use as a study book to improve clinical acumen and cram prior to the board examination? I strongly believe that such a text should:

- Have greater depth of coverage in clinical cardiology than the available medium-sized textbooks that range from 700 to 1000 pages; none of these books are suitable study books.
- Be thorough in its coverage. Most available texts are compressed; the tightly run lines make it difficult to use them as study books.

The format and printing style, therefore, should display the material so that the information can rapidly reach the visual cortex and be relayed to the storage area for memory in the brain. It is still necessary for students and senior trainees to commit the essentials to memory, and to rework these facts through patient's problem formulation and plan of management. The assessment of the factual information from a computer may suffice but this cannot replace the human touch at the bedside, where a sound knowledge base and clinical judgment can outsmart the computer program.

Many advances have been made in cardiology since publication of the first edition in 1996. The colossal amount of new scientific information necessitated the expansion of virtually all chapters in the preparation of this new edition. Results of recent randomized clinical trials are put in a special section in each chapter. An extensive current and relevant bibliography has been provided. The chapter on hypertension criticizes the national guidelines for the management of hypertension. The first edition warned that the World Health Organization, the International Society of Hypertension, and the JNC

should reexamine their logic for the recommendation of alpha blockers as initial therapy. The American College of Cardiology issued a warning in 2000, and the ALLHAT study that showed the detrimental effects of these agents was published in 2002.

We believe that a niche exists for a succinct user-friendly text that gives in-depth coverage of common cardiologic problems with emphasis on practical aspects of diagnosis, cardiovascular pharmacology, and other therapeutic strategies.

Our book is aimed at internists; clinical cardiologists; physicians in emergency rooms, intensive care units, and coronary care units; residents in cardiology, internal medicine, and family medicine; generalists; family physicians; and critical care nurses.

We did not intend to produce a comprehensive textbook of cardiology and intentionally did not discuss the following:

- Anatomy and physiology. A 20-page overview of this topic is not relevant to clinical practice. Clinicians and trainees have been sufficiently afflicted in their preclinical years with anatomy and physiology. Although we agree that physicians must be conversant with normal structure and function, a short coverage of the topic is irrelevant to the reader.
- Radiology of the heart. This is now used mainly to detect congestive heart failure, which is covered in our chapter on heart failure. The echocardiogram is superior for most other conditions. Thus, a discussion of radiology of the heart was omitted.
- Echocardiography. A superficial overview of this important diagnostic tool does not assist the intended audience. There are many excellent books on this subject.
- Congenital heart disease is adequately covered in pediatric cardiology texts.

The space saved by the omission of the aforementioned topics has made room in our text for expansion of areas that we believe are requirements for physicians and trainees who render care to cardiac patients. Thus, our text gives considerably more coverage than the available competing texts in the following areas:

- Coronary artery disease. Because coronary artery disease is the most common form of heart disease and manifests as acute myocardial infarction, angina, arrhythmias, heart failure, and sudden cardiac death, chapters on these topics are extensive.
- ECG. The ECG is the most commonly requested cardiac diagnostic test. Although there are sophisticated and extensive investigations available to cardiologists, the ECG is the main diagnostic test for the early diagnosis of acute myocardial infarction. To reap the benefit of saving lives, percutaneous intervention or thrombolytic therapy must be instituted at the earliest moment after the onset of symptoms; therefore, a rapid diagnosis is imperative. Early diagnosis cannot be made by evaluation of serum creatine kinase (CK) or troponin. The ECG, however, is subject to many errors in interpretation; many conditions mimic the electrocardiographic diagnosis of infarction. Our text, therefore, has in-depth coverage of the electrocardiographic diagnosis of myocardial infarction.
- Valvular heart disease is a common problem. Diagnostic pearls are bulleted; management is covered succinctly and with appropriate depth.
- Drug therapy of heart diseases. Practical cardiovascular pharmacology is a strong point of this book because it is the final prescription given to a patient after a consultation that ameliorates symptoms and saves lives. The prescription may, however, cause adverse effects and inadvertently increase the risk of death. Inappropriate prescribing of cardiovascular drugs is not an uncommon occurrence. Our book aims to strengthen the physicians' expertise in this vast area of relevant cardiovascular therapeutics. The old query, "What harm have you done today, Doctor?" still holds.

In the preparation of the text, we insisted that the discussion of appropriate therapy should be based on sound pathophysiologic principles to further strengthen the physician's ability to formulate a reasonable plan of management. Appropriate management and decision-making strategies require integration and orchestration of the following:

- Accurate diagnosis
- Pathophysiological implications
- Prediction of outcome or risk stratification
- Knowledge of the action of pharmacological agents and their correct indications
- Advantages and disadvantages of interventional therapy

To cover this wealth of clinical information, we prepared a succinct and straightforward text, highlighted by bullets to allow rapid retrieval of information. Chapters are formatted as follows: diagnosis and then therapy.

This clinically focused text should find a place in the hands of all residents in internal medicine and all clinicians.

M. Gabriel Khan, MD, FRCP(LONDON), FRCP(C), FACP, FACC

CONTENTS

Foreword by Henry J. L. Marriott, MD	vii
Preface	ix
Value-Added eBook/PDA	xiv
1. Acute Myocardial Infarction	1
2. Complications of Myocardial Infarction and Postinfarction Care	69
3. Cardiogenic Shock	109
4. Angina	127
5. Heart Failure	175
6. Arrhythmias	213
7. Cardiac Arrest	289
8. Hypertension	299
9. Dyslipidemias	345
10. Aortic Dissection	369
11. Valvular Heart Diseases and Rheumatic Fever	375
12. Infective Endocarditis	415
13. Pericarditis and Myocarditis	427
14. Cardiomyopathy	443
15. Syncope	473
16. Preoperative Management of Cardiac Patients Undergoing Noncardiac Surgery	491
Index	507
About the Author	530

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1

Acute Myocardial Infarction

CONTENTS

SIZE OF THE PROBLEM
CLINICALLY RELEVANT PATHOPHYSIOLOGY
CLINICAL STUDIES THAT RELATE TO PLAQUE VULNERABILITY
DIAGNOSIS
THE ELECTROCARDIOGRAM
ECG MIMICS OF MYOCARDIAL INFARCTION
LBBB NEW DIAGNOSTIC CLUES
ECHOCARDIOGRAPHY
PUBLIC EDUCATION AND PHYSICIAN INTERACTION
RISK STRATIFICATION
THERAPY
NEW ACC/AHA GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ST ELEVATION MI
PRIMARY ANGIOPLASTY/STENT
CONTROL OF EARLY LIFE-THREATENING ARRHYTHMIAS
THROMBOLYTIC THERAPY
β -BLOCKER THERAPY
CLINICAL TRIALS
WHICH β -BLOCKER TO CHOOSE
NITROGLYCERIN
ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS
CALCIUM ANTAGONISTS
NON-ST ELEVATION MI (NON-Q-WAVE MI)
TIMI RISK SCORE
ANTIPLATELET AGENTS FOR ACUTE CORONARY SYNDROME
BIBLIOGRAPHY

SIZE OF THE PROBLEM

More than 1.1 million patients have an acute myocardial infarction (MI) in the United States (US) annually, and more than 50% of these patients die within the first hour, caused mainly by arrhythmias, particularly ventricular fibrillation (VF). Of those admitted to a hospital, approximately 15% die during hospitalization. In addition, more than 1 million patients with symptoms suggestive of acute MI are admitted annually to coronary care units (CCUs).

From: *Contemporary Cardiology: Heart Disease Diagnosis and Therapy:
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In the year 2000, more than 12 million people worldwide died because of cardiovascular disorders mainly caused by the disease atheroma and subsequent thrombosis (atherothrombosis). It is estimated that by the year 2020, more than 24 million people will die annually from this disease in a world population of approximately 7.4 billion.

Intensive research is required to prevent atherothrombosis rather than the management of its complications, which include fatal and nonfatal heart attack, angina, heart failure (HF), abdominal aortic aneurysm, stroke, kidney failure, peripheral vascular disease causing intermittent claudication, and gangrene of the lower limb. Most research done in major institutions in the US and in developed countries is directed at the management of complications of atherosclerotic coronary artery disease (CAD). The worldwide advent of CCUs in the early 1970s, thrombolytic agents in the late 1980s, coronary angioplasty in the 1980s and 1990s, and stents during the past decade have improved survival but this can be considered as modest. Most importantly, the development of left ventricular (LV) assist devices (that are clearly a bridge to transplantation and not artificial hearts) requires considerable financial support for their development. They will save less than 1000 lives annually worldwide because these devices are not artificial hearts and their success depends on the ability to obtain donor hearts, of which, there are presently less than 4000 worldwide.

Obstructive atherosclerotic CAD leads to the following:

- Stable or unstable angina.
- Fatal or nonfatal MI.
- Sudden death.
- HF.
- Arrhythmias, atrial fibrillation, and thromboembolism that may cause stroke.

Approximately 20 million Americans have coronary heart disease, close to 7 million of whom have angina and more than 10 million have had a heart attack. The approximate economic cost of CAD and stroke in North America is approximately \$350 billion, with roughly \$120 billion for CAD. Although there has been a mild decrease in the incidence of CAD in North America during the past decade, the disease process and its complications are expected to increase because of an aging population.

Unfortunately in developing countries, the prevalence of CAD and its complications have increased in the past decade, and it is estimated that by 2020 cardiovascular disease (CVD) will reach epidemic proportions worldwide. It is relevant that developing countries constitute more than 80% of the world's population and in these regions, particularly in India and other Asian countries, the incidence of CAD is on the increase.

The high incidence of communicable, maternal, perinatal and nutritional diseases in these countries will fall from roughly 41 to near 17% but CVDs will increase from about 20% to more than 33% over the next 20 years. Japan is unique among the developed countries in that although the stroke rates were the highest in the world during the 1960s, the incidence did not rise as sharply as in other developed countries and have remained lower. In Japan, CVD rates have fallen more than 60% since the 1960s, largely because of a decrease in stroke rates. Life expectancies for men and women are the highest in the world and reach 77 years for men and 83 years for women.

The CAD mortality per 100,000 men and women respectively in countries where data is available is as follows:

- Russian Federation: 767 and 288.
- Ukraine: 749 and 342, yet in the neighboring Slovenia the mortality rate is low.

- Scotland: 655 and 273.
- Finland: 631 and 587.
- Portugal: 207 and 73.
- Spain: 181 and 52.
- France: enjoys the lowest cardiovascular mortality of all the developed countries; also, the CAD mortality is low: 142 and 36.

CVD mortality rates in Canada, New Zealand, and Australia are similar to those in the US.

Prevention

Yusuf et al. reported on an extensive case-control study in 52 countries. Nine modifiable risk factors were all significantly related to acute myocardial infarction:

- abnormal lipids
- smoking
- hypertension
- diabetes
- abdominal obesity
- psychosocial factors
- lack of daily consumption of fruits and vegetables
- regular physical activity
- regular alcohol consumption

CLINICALLY RELEVANT PATHOPHYSIOLOGY

Acute MI is nearly always caused by occlusion of a coronary artery by thrombus overlying a fissured or ruptured atheromatous plaque. The ruptured plaque, by direct release of tissue factor (TF) and exposure of the subintima, is highly thrombogenic. Exposed collagen provokes platelet aggregation. The extrinsic coagulation cascade is activated through the interaction between vascular TF and the circulating blood, causing *in vivo* generation of thrombin, which converts fibrinogen to fibrin.

Fibrin interacts with activated platelets to form a mesh structure that stabilizes the mural thrombus. Thus, atherothrombosis completes the occlusion of the artery. Lipid-rich atheromatous plaques contain TF associated with macrophages within the lesion that may enhance the thrombogenicity of these plaques. In coronary angiography performed during the early hours of ST elevation, MI has confirmed the presence of total occlusion of the infarct-related artery in more than 90% of patients. It is not surprising that aspirin, through inhibition of platelet aggregation, reduces the incidence of coronary thrombosis and is especially useful in prevention of the progression of unstable angina to thrombosis and MI. Chewable aspirin (160 to 320 mg) is particularly useful when given at the onset of chest pain produced by infarction. Patients must be informed that the use of chewable aspirin can prevent fatal and nonfatal infarction but that nitroglycerin does not. This advice should serve to motivate individuals to carry chewable aspirins for emergency use.

However, aspirin does not block all pathways that relate to platelet aggregation and does not nullify the intensely thrombogenic constituents of atheromatous plaques. In addition, aspirin does not decrease the incidence of sudden death in patients with acute MI. Aspirin does however reduce the incidence of MI in patients postinfarction and in those with unstable and stable angina. Thus, chewable aspirin administration plays a key role in the prevention and management of acute MI.

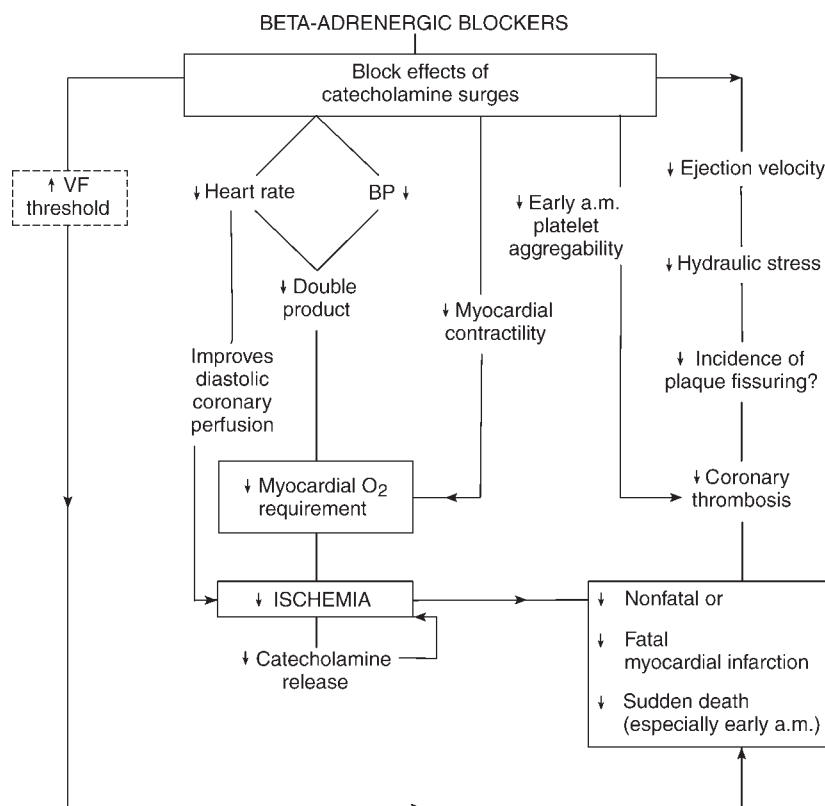


Fig. 1.1. Salutary effects of β -adrenergic blockade. \uparrow , increase; \downarrow , decrease. From Khan M. Gabriel, *Cardiac Drug Therapy*, Philadelphia, WB Saunders 2003, with permission from Elsevier.

The increased morning incidence of acute MI, documented in several studies of the diurnal variation of infarction, is related to the early-morning catecholamine surges, which induce platelet aggregation, and an increase in blood pressure and hydraulic stress, which may lead to plaque rupture (Fig. 1.1.). β -adrenergic blockers have been shown to decrease the early-morning peak incidence of acute infarction and sudden death. It is important for clinicians to recognize that calcium antagonists and nitrates do not have these lifesaving effects and that these agents are overprescribed and β -adrenergic blocking agents are underused.

Unfortunately, when an atheromatous plaque ruptures, the thrombogenic effect of plaque contents cannot be completely nullified by the inhibition of all aspects of platelet aggregation, and chemical agents that can arrest the effects of these thrombogenic substances deserve intensive study. Preliminary studies in patients suggest that direct thrombin inhibitors such as hirudin, administered with aspirin, are effective in the prevention of coronary thrombosis. These studies may pave the way for further research that may uncover newer types of antithrombotic agents that are superior to available agents in preventing coronary thrombosis.

Coronary artery spasm appears to play a lesser role in the pathogenesis of coronary occlusion leading to infarction. Evidence of coronary vasoconstriction was found when angiography was performed shortly after infarction, and intermittent occlusion, presum-

ably on a vasomotor basis, has been apparent in some cases. Vasoconstriction appears to be a secondary factor.

The first gene linked directly to acute MI has been isolated from an extended Iowa family that has been plagued for generations with CAD. The gene, *MEF2A*, appears to protect the artery walls from building up atheroma. Individuals who have this gene mutation are destined to have the disease.

Vulnerable (High-Risk) Atheromatous Plaques

Plaque disruption is associated with physical forces, and occurs more frequently with the fibrous cap that is weakest, that is, when it is thinnest and most heavily infiltrated by foam cells. For eccentric plaques, this is often the shoulder or between the plaque and adjacent vessel wall. The shoulder regions of plaques often have a thinner fibrous cap that is highly infiltrated with macrophages and is prone to rupture. In sudden coronary death, often only a superficial erosion of a markedly stenotic and fibrotic plaque is observed

Thrombosis occurs over plaques because of the following:

- Denudation and erosion of the endothelial surface.
- Disruption or tear in the cap of a lipid-rich plaque; blood from the lumen enters the lipid core of the plaque, where thrombus is formed. Plaque disruption appears to be three times more common than the more superficial process of endothelial denudation. Sudden death as a result of CAD in relatively young subjects, however, has put the ratio of thrombi owing to plaque rupture compared with endothelial erosion as 1.3:1.

In sudden death in younger patients, plaque rupture is more commonly caused by endothelial erosion. Acute MI with thrombosis caused by endothelial erosion is reportedly more common at a younger age and particularly in women.

Three major factors determine the vulnerability of the fibrous cap:

1. Circumferential wall stress or cap fatigue.
2. Location, size, and consistency of atheromatous core.
3. Blood flow characteristics, particularly the impact of flow on the configuration and angulation of the plaque.

Plaque Rupture

Uneven thinning and fracture or fissuring of the plaque's fibrous cap leads to rupture. The porridge-like substances exposed to the flowing blood is highly thrombogenic and trigger thrombosis that blocks the lumen of the artery. This is the main cause underlying an MI. Fracture of the fibrous cap occurs often at the shoulders of a lipid-rich plaque where macrophages enter. The fibrous cap is believed to become thin because of the depletion of matrix components through the activation of enzymes such as matrix-degrading proteinases and cysteine and aspartate proteases, and through the reduction in the number of smooth muscle cells. Endothelial-cell desquamation through activation of basement membrane degrading metalloproteinases appears to be involved, but the mechanisms are unclear.

Activated T cells may also inhibit matrix synthesis through the production of interferon- γ . Evidence of superficial erosion of the intimal lining has been observed in approximately 25% of patients who had sustained an MI and died within a few hours.

- The provision of durable collagenous tissue processed by smooth muscle cells is important in maintaining the existence of the plaque's fibrous cap. Collagen provides most of the biomechanical resistance to disruption of the fibrous cap. Substances found in

degranulating platelets appear to increase smooth-muscle cell collagen synthesis that may reinforce the strength and viability of the fibrous cap. In addition, in some lesions there is a marked decrease in the presence of smooth muscle cells or increased smooth-muscle cell death within the plaque occurs and reduces collagen production.

- It is possible that the new capillaries and vessels within the plaque may be important for the survival of smooth muscle cells.

Platelets play an important role in initiating clotting in arteries and arterioles. Platelets form an initial plug of clot and are followed by the deposit of a fibrin mesh that forms a firm clot. Platelets are trapped by the material exposed by the fractured plaque, and the first phase of thrombosis is initiated. Aspirin or platelet glycoprotein (GP) IIa/IIIb receptor blockers are used to prevent this deleterious platelet aggregation.

Hemorrhage Into the Plaque

New capillaries and small vessels grow into the plaque and provide a useful function in that they may provide nutrient material for smooth muscle cells that form collagen necessary to strengthen the fibrous cap. However, these new vessels are fragile and may burst, causing a minute hemorrhage within the plaque. The pressure within the plaque may cause disruption of the fibrous cap, and thrombosis completes the occlusion of the artery. In approximately 5% of patients with acute MI, the initiating cause is hemorrhage into a plaque of atheroma rather than erosion–rupture followed by thrombosis. Angiogenesis and gene therapy may promote hemorrhage into plaques, and caution is required.

Myocardial Necrosis

In about 20 minutes, occlusion of a coronary artery leads to death of cells in areas of severely ischemic tissue, which will usually become necrotic over 4 to 6 hours. Because early and late mortality are directly related to the size of the infarct, limitation of infarct size (or even prevention of necrosis) initiated at the earliest possible moment is of the utmost importance. The ischemic zone surrounding the necrotic tissue provides electrophysiologic inhomogeneity that predisposes the occurrence of lethal arrhythmias. These arrhythmias are most common during the early hours after onset and contribute to one of the major mechanisms of sudden death.

Extensive myocardial necrosis is the major determinant of HF; papillary, septal, and freewall rupture; and cardiogenic shock in which more than 35% of the myocardium is usually infarcted. The most effective means of reducing the extent of myocardial necrosis is the administration of chewable aspirin and a β -blocking agent (metoprolol or carvedilol) and establishment of patency of the infarct-related artery by thrombolytic therapy or percutaneous coronary intervention (PCI) within 1 hour of the onset of symptoms of coronary thrombosis.

CLINICAL STUDIES THAT RELATE TO PLAQUE VULNERABILITY

Maehara et al.

Study question: What are the clinical and angiographic correlates of plaque rupture detected by intravascular ultrasound?

Methods: Three-hundred plaque ruptures in 254 patients were assessed by angiographic and intravascular ultrasound.

Results: The plaque rupture occurred in 46% of patients with unstable angina and 33% of patients with MI but was also observed in 11% of patients with stable angina. The tear

in the fibrous cap (63%) occurred at the shoulder and 37% in the center of the plaque. Thrombi were common in patients with unstable angina. The plaque rupture site contained the minimum lumen area site in only 28% of patients; rupture sites had larger arterial and lumen areas and more positive remodeling than minimum lumen area sites.

AM Varnava et al.

Study question: Is there a relationship between the morphologic characteristics of coronary plaque vulnerability, lipid core size and macrophage count and coronary artery positive remodeling (no lumen narrowing), or increased constrictive adventitial fibrosis and thickening with negative remodeling (lumen narrowing)?

Methods: The hearts of 88 male patients with sudden cardiac death were assessed.

Results: One-hundred-eight plaques were studied, 59% had positive remodeling and 40% had negative remodeling. Plaques with positive remodeling had a larger lipid core (39% vs 22%, $p < 0.001$) and a higher macrophage count. Plaques with negative remodeling were associated with greater thinning of the medial and adventitial wall opposite the plaque.

Conclusions: Plaques with positive remodeling have a high-lipid content and macrophage count. This may explain why plaque rupture often occurs at sites with only modest lumen stenosis.

The processes and mechanisms that underlie thinning, erosions, fracture, and rupture of plaques are unclear and are presently a subject of extensive research. Also, investigative strategies to define high-risk plaques must be sought.

Hydrodynamic Stress and Catecholamine Surge

Use of a β -blocking agent may inhibit plaque rupture perhaps by its ability to decrease cardiac ejection velocity. This action reduces hydraulic stress on the arterial wall that might be critical at the arterial site where the atheromatous plaque is predisposed to rupture or erosion (Fig. 1.1.).

- Catecholamine-dependent activity could explain not only the increase in the incidence of sudden death and acute coronary syndromes (ACS) after emotional and physical stress, but also the circadian distribution of these events.
- Only some β -blockers, however, have been proven to prevent fatal or nonfatal coronary events as well as HF; carvedilol and metoprolol are the preferred agents to be administered. **Atenolol a commonly used agent is not advisable (see later discussion of which β -blocking agent to choose).**

DIAGNOSIS

Chest Pain

- Usually lasts more than 20 minutes and often persists for several hours. The pain of infarction, however, can last for only 15 minutes, and, occasionally, fatal infarction is ushered in by only a few minutes of severe pain or even unheralded cardiac arrest. Infarction may be relatively silent, particularly in diabetic patients and in the elderly.
- Typically retrosternal and across the chest.
- Variations of a crushing, vice-like, heavy weight on the chest and pressure, tightness, strangling, aching.
- At times, only a discomfort with an oppression and burning or indigestion-like feeling.

- May radiate to the throat, jaws, neck, shoulders, arms, scapulae, or the epigastrium. At times, pain is centered at any one of these areas (e.g., the epigastrium, left wrist, or shoulder, without radiation).
- Upper epigastric and lower chest pain believed to be gastroesophageal in origin without feelings of indigestion is not uncommonly caused by a heart attack.
- Usually builds up over minutes or hours, as opposed to aortic dissection, in which pain has an abrupt onset like a gunshot.

Associated symptoms and factors include the following:

- Diaphoresis, cold clammy skin, and apprehension (however, all of these symptoms may be absent).
- Shortness of breath, nausea, vomiting, dizziness.
- Women with acute MI often reveal atypical symptoms with low levels of chest pain or absence of pain. In one study, acute chest pain was absent in 43%; acute symptoms were shortness of breath (57.9%), weakness (54.8%), and fatigue (42.9%).
- Presyncope and, rarely, syncope may occur owing to bradyarrhythmias, especially in inferior MI.
- Occasionally there is no pain. A marked decrease in blood pressure with associated symptoms, along with electrocardiogram (ECG) findings, should suffice in making the diagnosis.
- Painless infarcts (in about 10% of patients), especially in diabetics or the elderly. In these patients, associated symptoms are often prominent and serve as clues to diagnosis.
- More than 30% of patients have a history of angina or prior infarction.
- Approximately 33% of patients with acute infarction have no major risk factors, which include death of a parent or sibling younger than age 55, cigarette smoking, hypertension, or diabetes; and more than 25% have cholesterol levels less than 5.2 mmol/L (200 mg/dL). Importantly, absence of these factors should not influence the diagnosis.

Physical Signs

- Patient appears apprehensive, anxious, cold, clammy.
- Area of chest pain may be indicated with a clenched fist.
- Tachycardia 100–120 per minute. An increase in blood pressure owing to increased sympathetic tone is observed in approximately 50% of patients with anterior infarction.
- Bradycardia less than 60 beats per minute (BPM) and a decrease in blood pressure in about two-thirds of inferior infarcts; many of these patients become hypotensive, sometimes profoundly.
- S₄ gallop is common; S₃ and S₄ if in HF or cardiogenic shock.
- Murmur of mitral regurgitation as a result of papillary muscle dysfunction.
- Crepitations, more prominent over the lower third of the lung fields, may be present.
- Elevated jugular venous pressure owing to left and right HF or a very high venous pressure in the presence of right ventricular infarction or cardiac tamponade.
- Frequently, there are no abnormal physical signs, and this finding in a patient with suggestive symptoms should not decrease the level of suspicion that the patient may have an MI.

Although sophisticated tests have evolved to improve diagnostic accuracy, they are of limited value in the era of thrombolysis and aggressive PCI. Thus, a relevant history and correct interpretation of the ECG are of paramount importance in the implementation of early thrombolytic therapy, or PCI, which will be of greatest benefit if instituted within 2 hours of symptom onset.

THE ELECTROCARDIOGRAM

Despite varied criticisms and the advent of new and expensive diagnostic technologies, the ECG has retained its prominent and vital role as an irreplaceable noninvasive and inexpensive test for diagnosis of acute MI.

DIAGNOSTIC ECG FEATURES OF ST SEGMENT ELEVATION

Acute MI:

- ST segment elevation of at least 1 mm in two or more contiguous limb leads ([Fig. 1.2.](#)).
- or
- At least 1 mm ST elevation in two or more contiguous precordial leads ([Fig. 1.3.](#)).

The above criteria, which have been used in most clinical trials of thrombolytic therapy, have become internationally standard and are considered diagnostic in patients with symptoms suggestive of acute MI. Where symptoms are not typical, the response to nitroglycerin is ascertained. Also, minimal ST segment elevation in black patients must be reassessed to exclude the occasional normal variant. There is clear recognition that Q-waves may evolve early or late and cannot be relied on for early diagnosis. Thus, the terms “transmural” and “nontransmural” have been abandoned and Q-wave or non-Q-wave infarction cannot be categorized in the early phase. The best differentiating feature is ST segment elevation, which is present in more than 90% of patients with acute coronary thrombotic occlusion.

In addition, later ECG signs of infarction include:

- Diminution of R waves (poor R wave progression).
- Evolving Q-waves.
- The simultaneous presence of reciprocal ST segment depression is not diagnostic of but provides major support to confirm the electrocardiographic diagnosis ([Fig. 1.2.](#)).
- Patients who are developing non-ST elevation (non-Q-wave infarction) often manifest ST depression, or T-wave change (see later discussion of non-Q-wave infarction and ACS).

In patients with ischemic-type chest discomfort, ST segment elevation greater than 1 mm in two contiguous leads reportedly has a specificity of 91% and sensitivity of approximately 50% for diagnosing acute MI. The sensitivity increases to more than 85% with serial ECG done every 30 minutes for 6 hours or more in those in whom the initial ECG reveals no ST segment elevation. *See* later discussion of ST depression and non-Q-wave infarction.

Because the ECG is a vital yet nonspecific tool, it is necessary to correlate the ECG findings with the clinical presentation. In this regard, it is wise to recall Marriott’s “warnings”:

- An “abnormal” ECG does not necessarily mean an abnormal heart.
- Exclude normal variants (*see* later discussion of mimics).
- Consider causes of heart disease other than coronary.

If the first ECG is not diagnostic of acute injury or infarction but the patient is strongly suspected of having an ACS, the ECG is repeated every 30 minutes until diagnostic changes are observed and until troponin or creatine kinase MB (CK-MB) results are reported. If the ECG is equivocal and there is a strong clinical impression that acute MI is present, valuable clues may be obtained from an echocardiogram; a magnetic resonance imaging (MRI), if available, can assist in this clinical setting with the diagnosis of

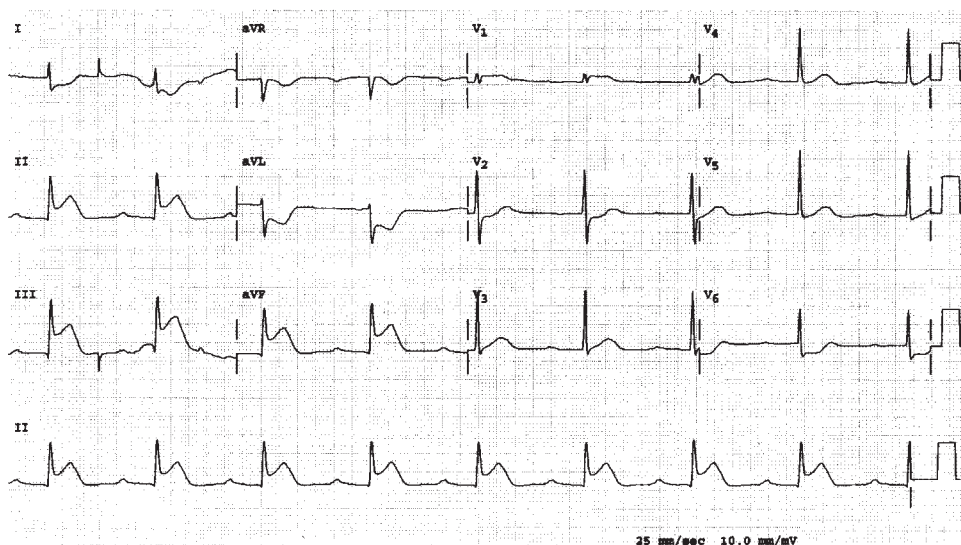


Fig. 1.2. ST segment elevation leads II, III, and aVF indicate acute injury, acute inferior infarction; note reciprocal ST segment depression.

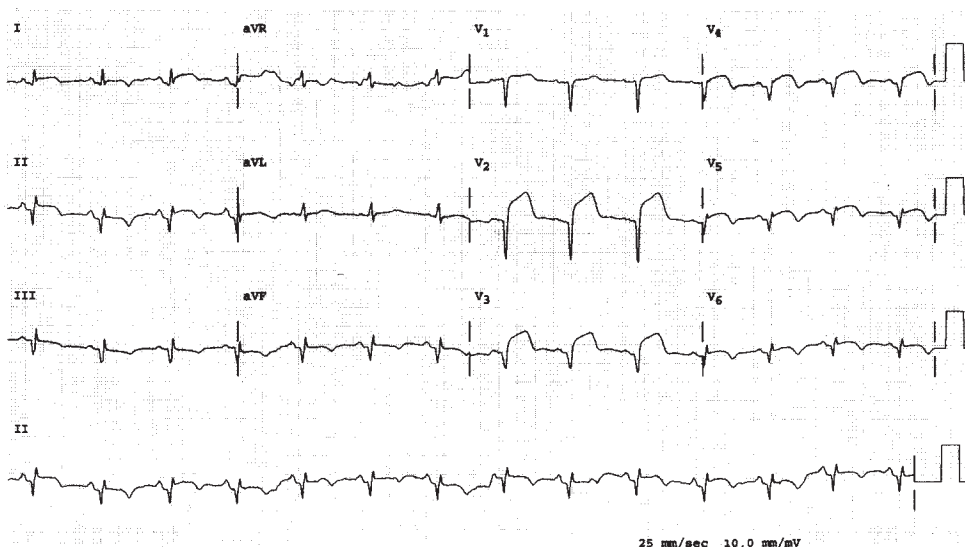


Fig. 1.3. ST segment elevation and Q waves V₂–V₆; acute anterior infarction. Q waves leads II, III, and aVF: inferior infarct, age indeterminate.

acute MI. In patients presenting with ACS, an expensive MRI is not justifiable when the inexpensive and time-honored ECG reveals diagnostic ST segment elevation with reciprocal depression.

Because the initial ECG abnormality may not be fully diagnostic in up to 40% of cases, it is imperative to correlate the findings with accurate historical details. In patients with

chest pain, new or presumably new Q waves in two contiguous leads with ST elevation are diagnostic in more than 90% of cases:

- Q-waves are fully developed in 4 to 12 hours and may manifest as early as 2 to 4 hours from onset of chest discomfort or associated symptoms.
- Evolutionary ST-T changes occur during 12 to 24 hours but may be delayed up to 30 hours.
- Inferior MI: ST elevation in leads 2 and 3 and aVF with evolving Q-waves and reciprocal depression in, leads 1, aVL, V₁–V₃. The latter depression may be the result of reciprocal changes, but there is evidence to suggest that in some patients it is owing to left anterior descending (LAD) artery disease. The evolutionary changes in repolarization that occur with inferior infarction evolve more rapidly than with anterior infarcts.
- Tachycardia may increase ischemic injury, causing elevation of the ST segment that must be differentiated from extension of infarction or pericarditis.

In pericarditis however, reciprocal ST depression occurs in aVR minimally in V₁, and does not occur in other leads. Also PR depression is a common feature of acute pericarditis (*see* Chapter 13).

VALUE OF LEAD aVR IN DIAGNOSIS OF ACUTE MI

- aVR is a lead that is often ignored, but recently has gained importance in the diagnosis of left main coronary artery (LMCA) occlusion.
- [Figures 1.4](#) and [1.5](#) show ST elevation in aVR that is greater than the elevation in lead V₁, marker of LMCA obstruction. This criterion is nonspecific: specificity is 80% and sensitivity is 81%. Circumflex branch occlusion also may cause ST elevation in aVR, both with no elevation in lead V₁. In addition, right ventricular overload may reveal ST elevation in aVR, but the clinical scenario is easily differentiated. Subendocardial infarction with marked ST segment depression in V₄ through V₆ that is not caused by LMCA occlusion may reveal ST segment and elevation in aVR, but the elevation is less than that observed in lead V₁.
- Because LMCA occlusion is a highly serious condition, any noninvasive diagnostic clue represents a valuable addition for the clinical assessment of acute MI.

NONDIAGNOSTIC ECG

Acute MI may be present with ECG changes that are nonspecific in 10–20% of cases and may result from the following:

- Slow evolution of ECG changes. The tracing may remain normal for several hours.
- Old infarction masking the ECG effect of a new infarct.
- Inferior MI associated with left anterior hemiblock in which R waves are expected to be small or minute in lead 3 and aVF.
- Left bundle branch block (LBBB).
- Apical infarction.
- Posterior infarction not associated with ST elevation or Q waves.

ECG and Location of Infarction Sites

- Anteroseptal: ST elevation V₁, V₂, V₃, may involve V₄ ([Fig. 1.6](#)). [Figure 1.7](#) shows the evolutionary changes in the same patient 10 hours later.
- Anterior: ST segment elevation V₃–V₄, may involve V₂ and V₅ ([Fig. 1.3](#)).
- Extensive anterior: V₁–V₆, 1 aVL ([Fig. 1.8](#)).
- Anterolateral: V₅–V₆, 1 aVL, may involve V₄ ([Fig. 1.9](#)).
- Inferior: II, III, aVF ([Fig. 1.2](#), [1.10](#), [1.11](#)); inferolateral II, III, aVF, V₆, may involve V₅, aVL.

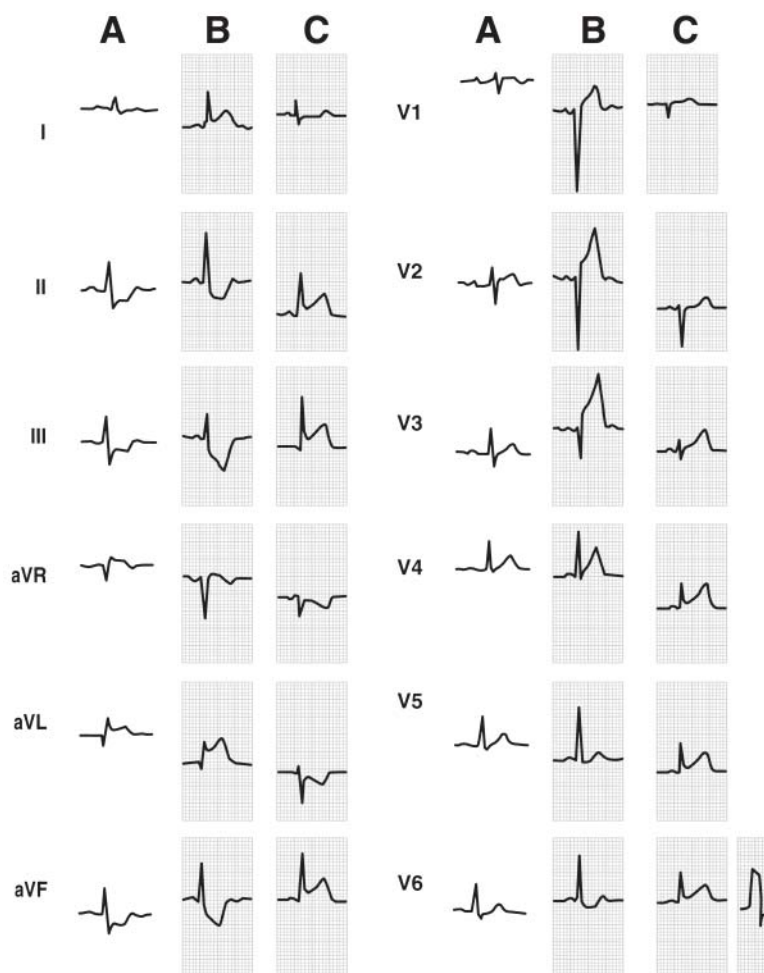


Fig. 1.4. Representative 12 lead ECG tracings at admission in a patient in the left main coronary artery (LMCA) group (A), the left anterior descending (LAD) coronary artery group (B), and the right coronary artery (RCA) group (C). In the patient in the LMCA group, ST segment elevation is apparent in lead aVR. In the patient in the LAD group, significant ST segment elevation in the precordial leads is seen, whereas ST segment shift in lead aVR is negligible. In the patient in the RCA group, ST segment elevation in the inferior leads is marked. From Yamaji H et al: J Am Coll Cardiol 58:1351, 2001, with permission from American College of Cardiology Foundation.

- Posterior infarction: Tall R waves and upright T waves in V_1 , V_2 (Fig. 1.12.); occasionally ST depression V_1 – V_2 , and often inferior or inferolateral infarct signs.
 - Right ventricular infarction: ST segment elevation V_3R , V_4R , associated with inferior infarction (Fig. 1.13.).
- Localization of infarction from the ECG is, however, not precise.
- LMCA occlusion: ST segment elevation in lead aVR is greater than elevation in lead V_1 associated with ST depression in lead V_1 V_4 to V_6 (Figs. 1.4., 1.5.).

ECG and Size of Infarction

The extent of ST segment elevation gives clues to infarct size, but the correlation is not close. The site of infarction influences mortality but is not as paramount as the size of

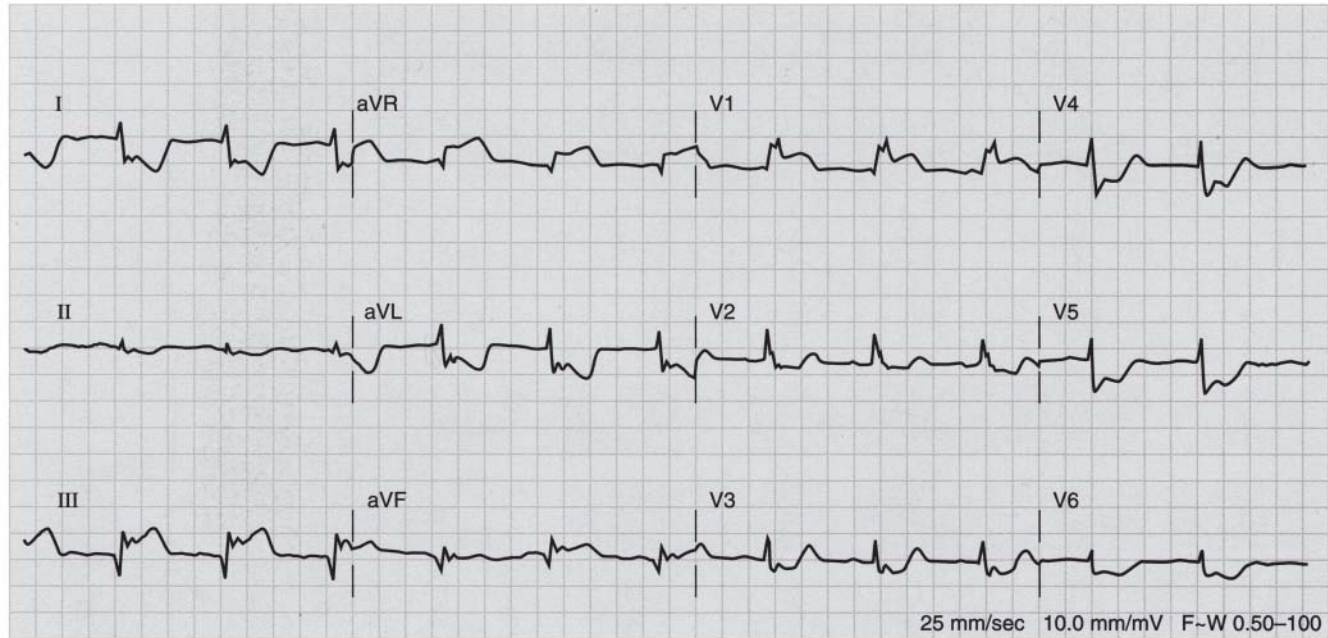


Fig. 1.5. Patient with chest pain for 3 hours. Inferior myocardial infarction and ST elevation in aVR and aV₁ indicates left main occlusion. From Khan M Gabriel. Rapid ECG interpretation, Second edition, Philadelphia 2003. WB Saunders, with permission from Elsevier.

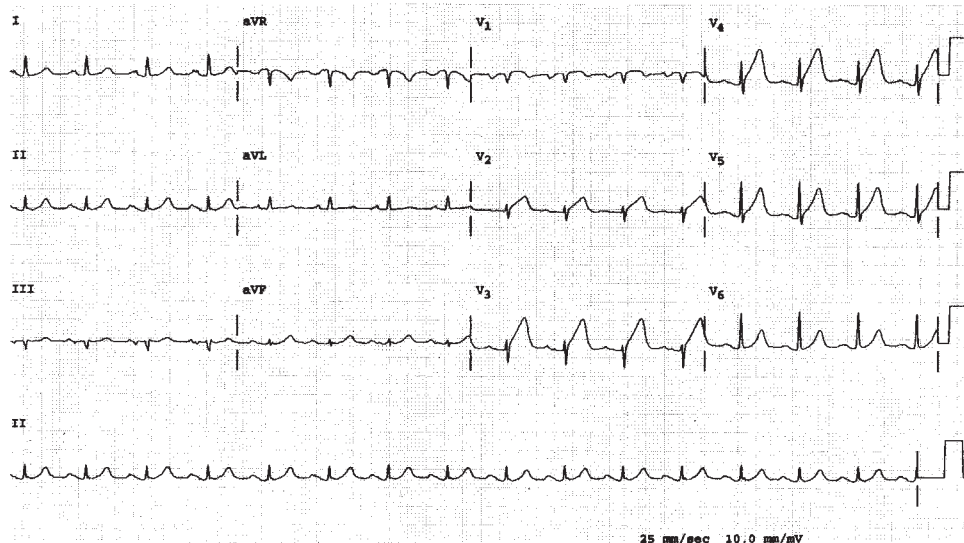


Fig. 1.6. ST segment elevation V_1 – V_4 : acute anteroseptal infarction; note loss of normal ST concavity.

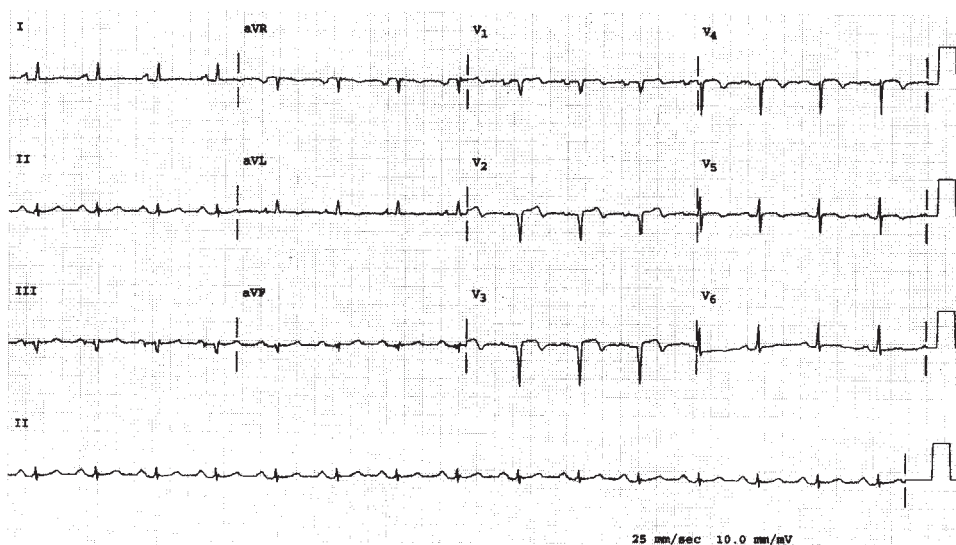


Fig. 1.7. The same patient as shown in Fig. 1.4., 10 hours later indicates evolutionary changes: Q waves, V_1 – V_4 , convex ST segment elevation has decreased and T wave inversion has emerged.

infarction, which can be reasonably ascertained from the number of leads showing ST elevation, as follows:

- Small MI: two or three leads.
- Moderate: four or five leads.
- Large: six or seven leads.
- Extensive: eight or nine leads (Fig. 1.8.).

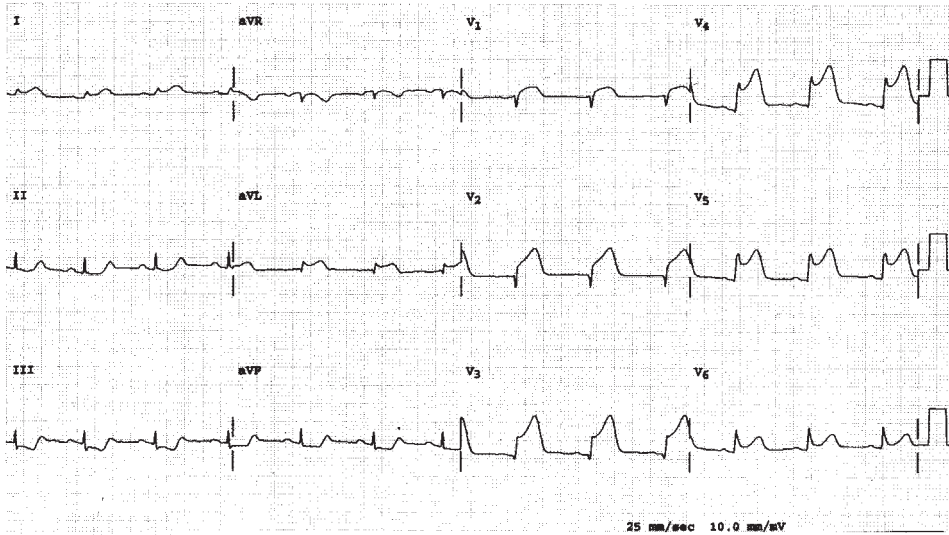


Fig. 1.8. Marked ST segment elevation in eight leads: I, aVL, V₁–V₆: extensive anterior infarction; note reciprocal depression in inferior leads.

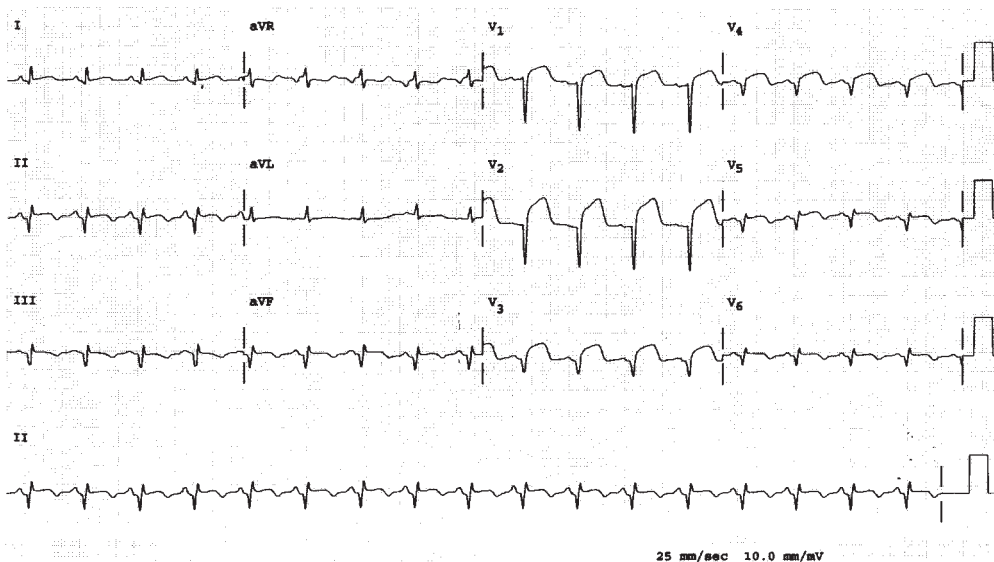


Fig. 1.9. Acute anterolateral infarction; inferior infarct age indeterminate.

ECG MIMICS OF MYOCARDIAL INFARCTION

- So-called early repolarization pattern: If early repolarization pattern involves limb leads, the ST segment is more elevated in lead II than in lead III. Early repolarization of atrial tissue is also present, resulting in PR-segment depression, but the PR-segment depression is not as marked as that in patients with acute pericarditis in which there is reciprocal ST segment depression in lead aVR but not in aVL, whereas in most patients with inferior

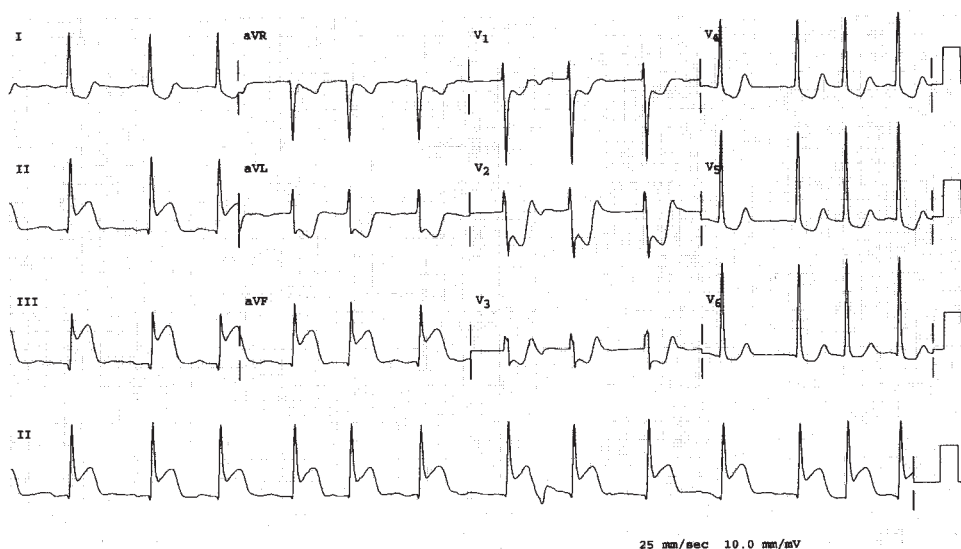


Fig. 1.10. ST elevation leads II, III, and aVF and marked reciprocal depression anterior and lateral leads: acute inferior infarction; also, acute atrial fibrillation.

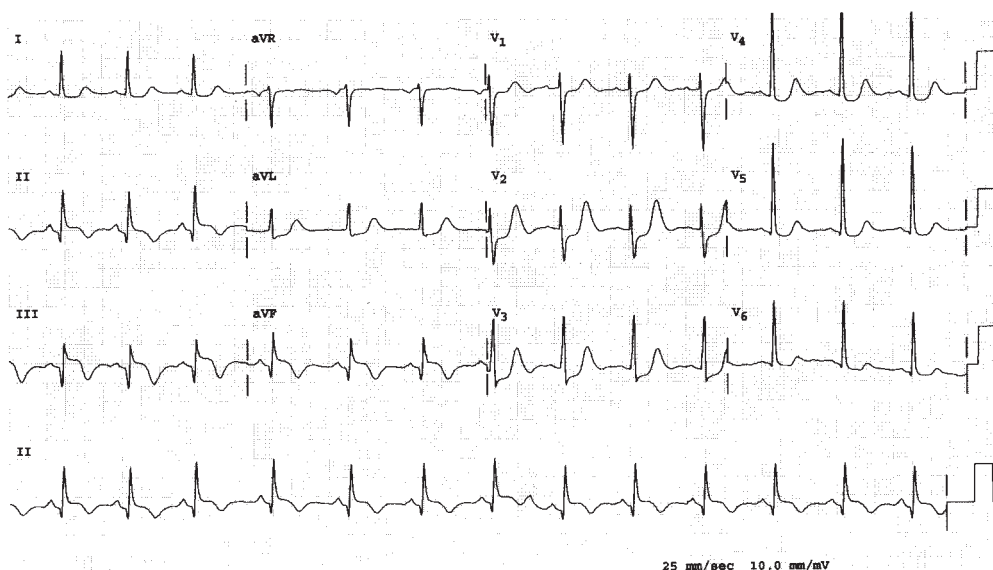


Fig. 1.11. ECG from the same patient as in Fig. 1.8., 24 hours later, indicates evolutionary changes.

infarctions, the ST segment is often more elevated in lead 3 than in lead 2 and there is reciprocal ST-segment depression in lead aVL (Fig. 1.10.).

- In some young individuals, especially African-Americans, the ST segment is elevated in V₃ to V₅ associated with minor T-wave inversion as a normal variant; the ST segment tends to be slightly coved and may mimic acute MI, and caution is required to assess the clinical findings (see pp. 20 and 21).

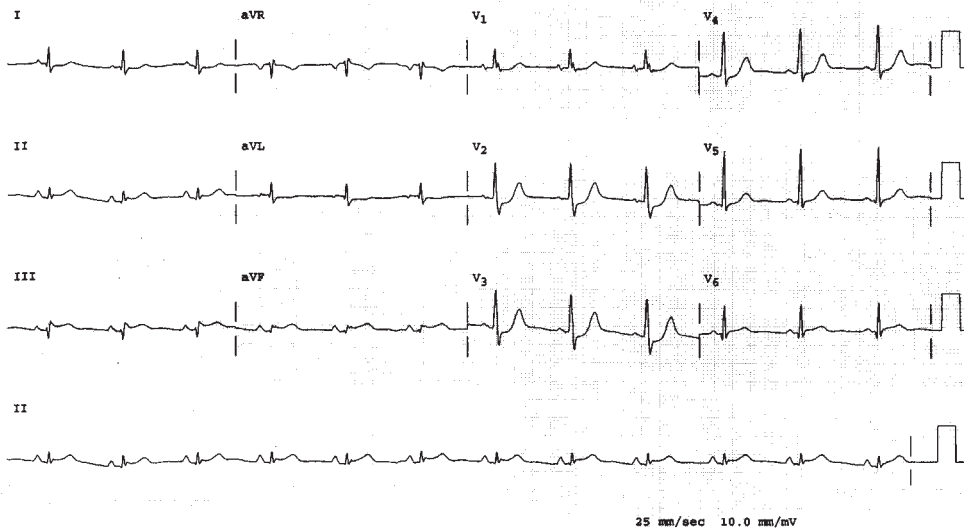


Fig. 1.12. Acute inferior infarct. Note tall R waves V_1 – V_2 in the absence of right ventricular hypertrophy, WPW or RBBB and thus in keeping with posterior infarction; note upright T wave V_1 , V_2 .

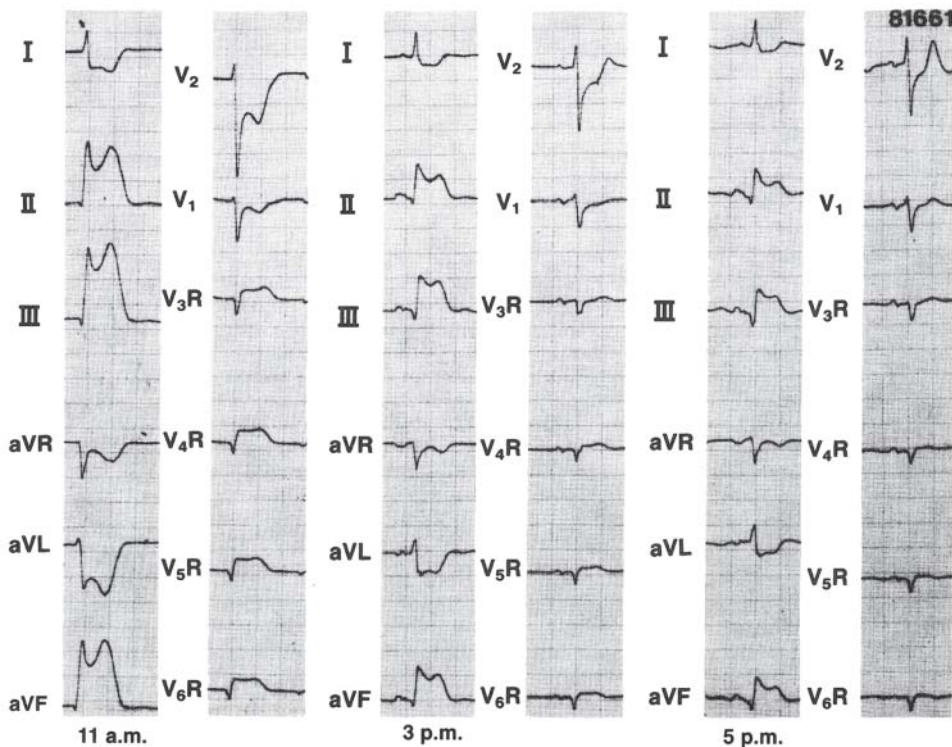


Fig. 1.13. Serial tracings from a patient with acute inferoposterior and right ventricular infarction. Note that the diagnostic changes for right ventricular infarction seen in lead V_4R have disappeared 7.5 hours after the onset of pain. From Wellens Hein JJ, Conover MB. The ECG in emergency decision making. Philadelphia: WB Saunders, 1992:92. Reprinted with permission from Elsevier.

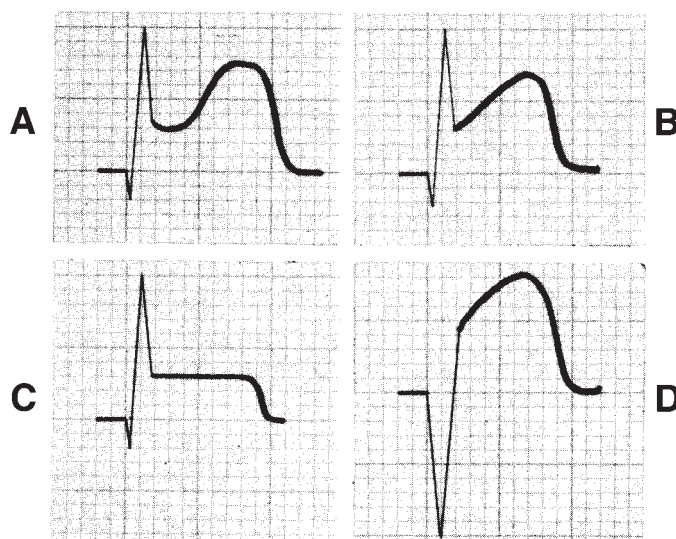


Fig. 1.14. Types of ST elevation seen with acute myocardial infarction (current of injury pattern). (A) Upwardly concave. The ST segment appears to have been lifted evenly off the baseline. A similar pattern occurs with benign early repolarization variant and acute pericarditis. (B) Obliquely straightened. (C) Plateau shaped. (D) Convex (similar elevations to this are sometimes seen in the right precordial leads with left bundle branch and left ventricular hypertrophy in the absence of infarction). From Goldberger AL. Myocardial infarction, electrocardiographic differential diagnosis. 4th ed. St. Louis: Mosby Year Book, 1991. Reprinted with permission from Elsevier.

These ST segment elevations meet the criterion for acute MI, according to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA): “ST elevation greater than 0.1 mV in two or more contiguous leads.” Because of this misleading criteria, The Clinical Policies Subcommittee of the American College of Emergency Physicians have added the qualifier “ST-segment elevations that are not characteristic of early repolarization or pericarditis, nor of a repolarization abnormality from LVH or bundle-branch block.”

Types of ST segment elevation caused by acute MI are illustrated in [Fig. 1.14](#).

Most important, ST elevation of infarction must be distinguished from the following:

Acute Pericarditis

- The ST segment is elevated diffusely in the limb leads as well as in the precordial leads and are not confined to leads referable to an anatomic segmental blood supply as occurs with acute MI.
- Elevation in lead I is accompanied by elevation in leads II, III, and aVF; the ST elevation is concave ([Fig. 1.15](#)), as opposed to convex upward with an injury current of infarction ([Fig 1.14](#)).
- Reciprocal ST depression and PR segment elevation in aVR is a typical finding with pericarditis ([Fig. 1.15](#)).
- The PR segment is diffusely depressed in pericarditis whereas, in acute infarction, the PR segment is not depressed except with the rare occurrence of atrial infarction.

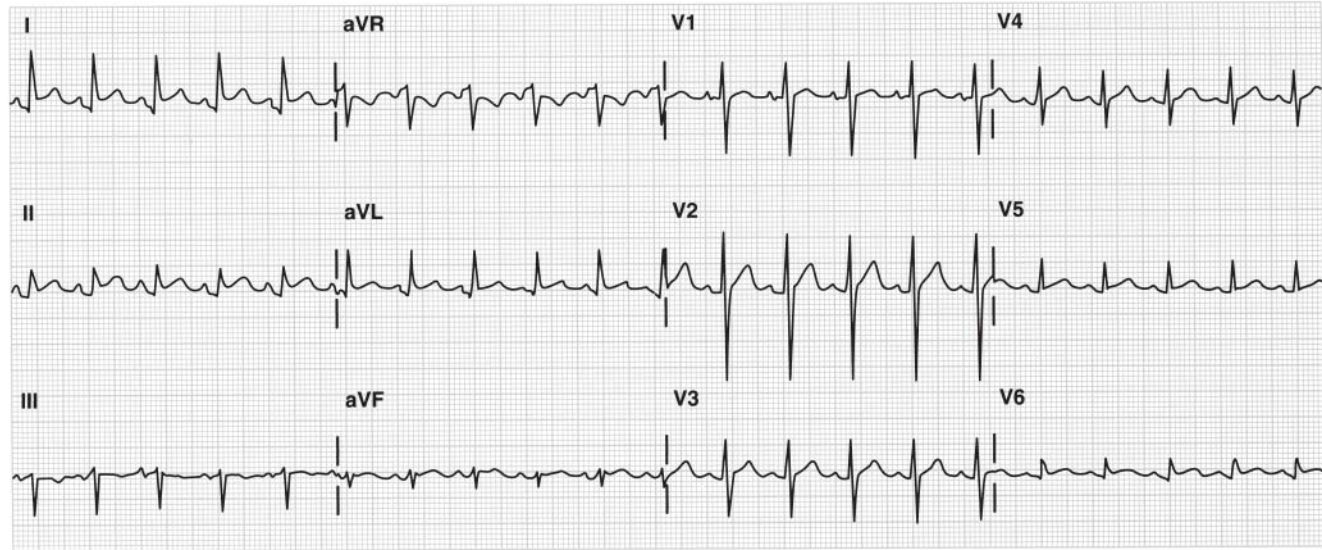


Fig. 1.15. Characteristic features of acute pericarditis: ST segment elevation in most leads; I, II, aVL, aVF, V₅ and V₆, with reciprocal ST depression and PR segment elevation in aVR. In addition note sinus tachycardia and prominent PR segment depression commonly seen with acute pericarditis. From Khan M Gabriel. *Rapid ECG Interpretation*, Second edition, Philadelphia 2003. WB Saunders, with permission from Elsevier.

- Depression of the PR segment is the atrial counterpart of ST-segment elevation. Diffuse pericarditis involves not only the subepicardial layer of the ventricular wall, which is responsible for the ST-segment elevation, but also the subepicardial layer of the atrial wall, which causes an atrial injury pattern.
- Depression of the PR segment is not specific for acute pericarditis; early repolarization can also cause PR depression, but marked and widespread PR depressions in several leads are not observed in early repolarization or normal variant ST elevation; in addition, atrial infarction may cause PR depression.
- ST-segment elevation in patients with acute pericarditis or early repolarization and normal variants do not result in ST-segment depression in aVL (Fig. 1.15.).
- With pericarditis, there is reciprocal ST-segment depression in aVR. But when pericarditis is localized, this rule does not apply.
- In acute inferior MI caused by circumflex occlusion, the ST segment is elevated to a similar degree in leads 2 and 3, is equally depressed in leads aVR and aVL, and is not depressed in lead 1. ST elevation in patients with acute pericarditis seldom exceeds 5 mm, whereas it commonly does in patients with acute MI.

Normal ST Elevations

- At the age (>40) at which acute MI commonly occurs, approximately 33% of men have ST elevation of 1 to 3 mm in one to three precordial leads often most prominent in lead V₂. This is a normal finding, not a normal variant, or early repolarization change and should be termed male pattern normal ST elevation. The ECGs of less than 15% of women at all ages may reveal minor 1-mm ST elevations in precordial leads. ST elevation, including so-called repolarization changes, that is occasionally seen in healthy individuals may mimic infarction; these changes are usually observed in leads V₂–V₃, V₄, or V₅, often most marked in V₄ with notching at J point producing a subtle “fishhook” configuration commonly seen in V₃, V₄, or V₅. (see Figs. 1.16. A–B and 1.17. A–C.) The ST elevation reveals the normal concave shape and is most often observed in individuals of African origin and occasionally in Hispanics. The precordial T waves are often tall. When the limb leads show ST elevation, reciprocal depression may be observed in aVR but not in aVL as occurs in MI.
- Early repolarization of atrial tissue may also be present, resulting in PR-segment depression, but the PR-segment depression is minimal compared with marked depression in patients with acute pericarditis as outlined earlier.
- Less commonly, in some healthy young individuals, particularly those of African origin, the ST segment is elevated by 1 to 4 mm in the midprecordial leads (V₃–V₅) as a normal variant. Most importantly the ST segment may be somewhat coved and may be associated with a juvenile-like T wave inversion (see Fig. 1.16. A). This ECG pattern may be mistaken for IHD and MI. If the limb leads show normal-type ST elevations, there is more elevation in lead 2 than in lead 3 and there may be reciprocal ST segment depression in lead aVR but not in aVL; the tracing may mimic acute pericarditis. The QT interval tends to be short and with a high QRS voltage.
- Figure 1.18. shows variations in normal ST elevations to be compared with the abnormal shapes of acute MI depicted in Fig. 1.14.

Other Mimics

- Brugada syndrome reveals an ECG pattern of atypical incomplete right bundle branch block (RBBB) or RBBB with mild ST elevation with a characteristic coved or saddle back shape in V₁ and or V₂ (see Fig. 1.19.); often the downsloping ST elevation begins from the top of the R1 wave ending in an inverted T wave. The ST elevation appears to

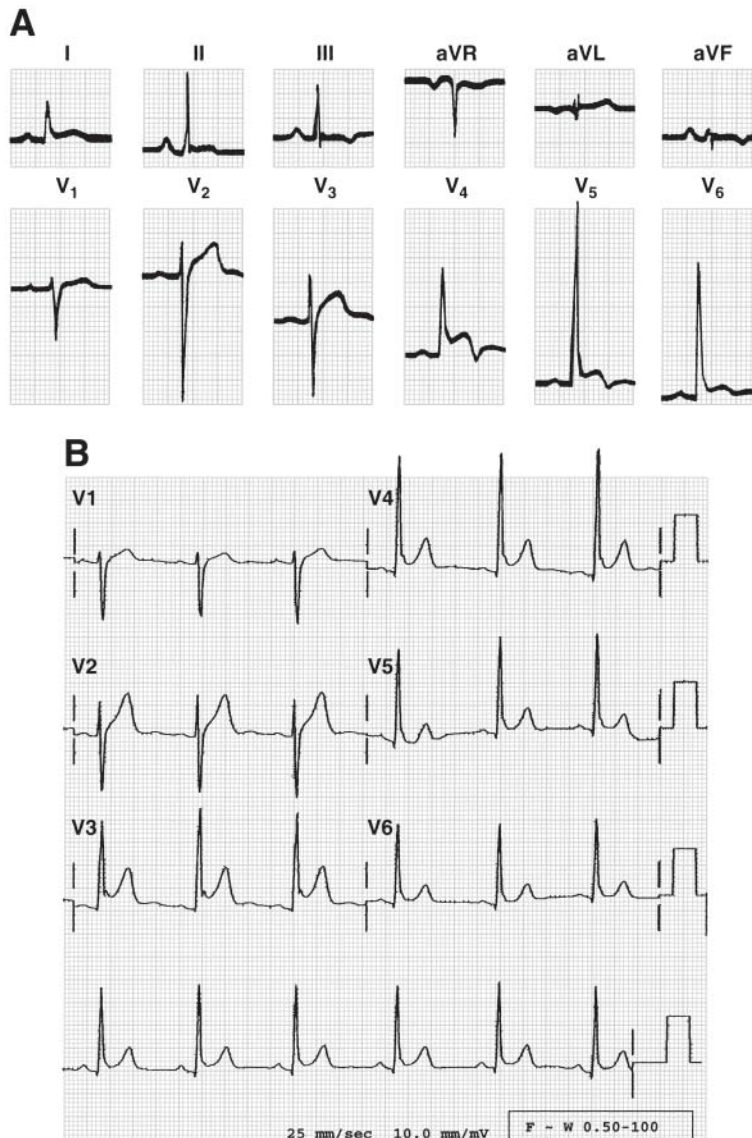


Fig. 1.16. (A) Benign ST and T-wave changes in a healthy 24-year-old professional athlete. The changes, especially in the V₄ and V₅, mimic myocardial injury and ischemia and remained the same 15 months later. From Chou TC: electrocardiography in clinical practice 4e. Philadelphia 1996, WB Saunders. (B). ST segment elevation in the normal 25-year-old: normal variant; note the notched J point “fish hook” appearance in lead V₃. Khan M. Gabriel: On Call Cardiology, Second edition, Philadelphia 2001 WB Saunders, with permission from Elsevier.

be caused by an early, high take-off (J wave) and mimics RBBB. An rSR1 pattern occurs in V₁, V₂ but there is no widened S wave in V₅, V₆ (Fig. 1.19.) as occurs in true RBBB; in which the S wave in V₆ or lead I is longer in duration than the preceding R wave.

- MI age, indeterminate with mild ST elevation, in the absence of true aneurysm, is not uncommon (Fig. 1.20.).
- LV aneurysm, in which there may be permanent ST elevation (Fig. 1.21.).

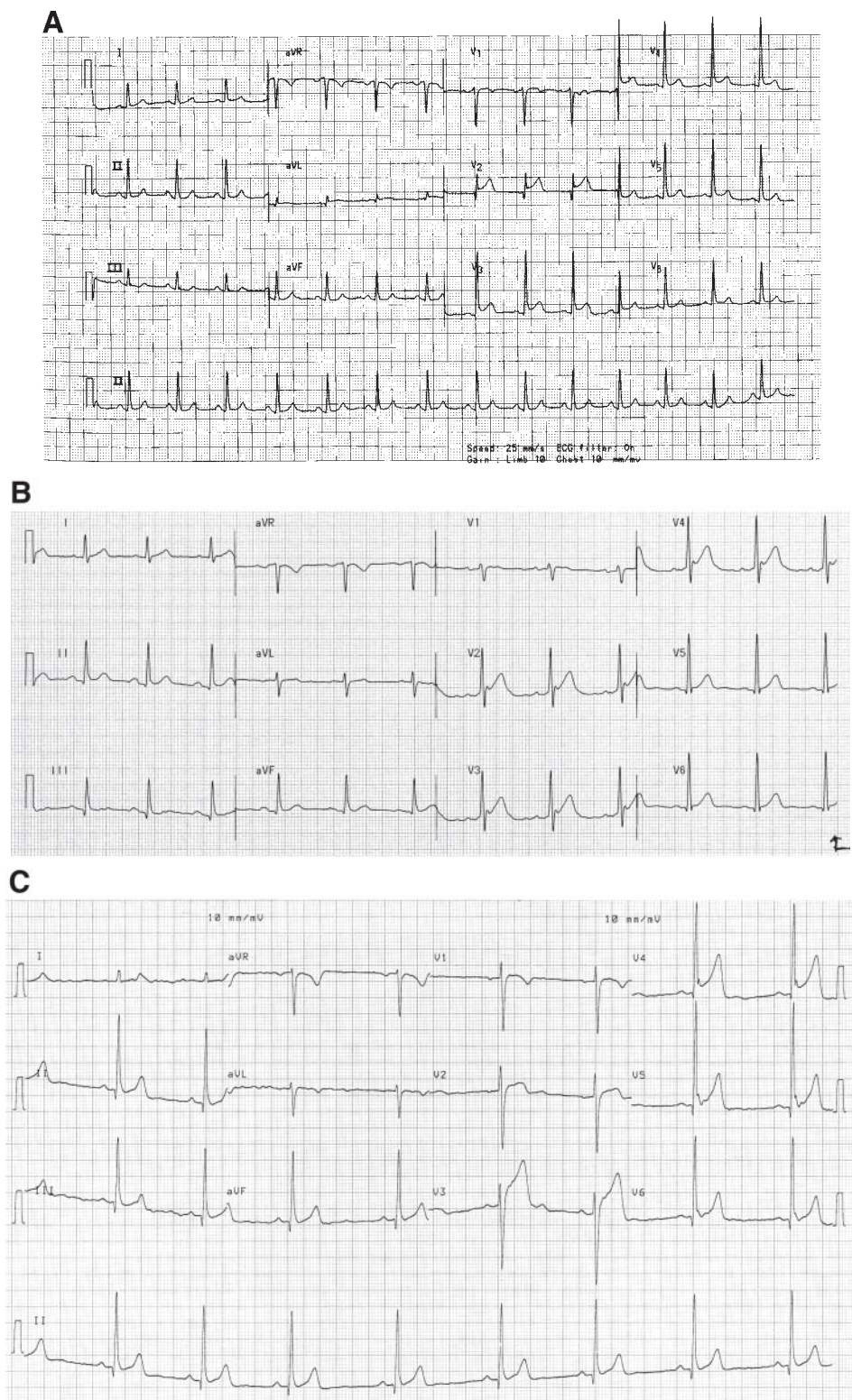


Fig. . 1.17. **(A)** A normal 43-year-old white male. Lead V_2 indicates a common feature of the normal variant: the J point may be notched, giving the complex a qRs' or “fishhook” appearance. **(B)** ST segment elevation leads V_2 – V_4 : normal variant. **(C)** ST elevation leads V_2 – V_6 in a healthy individual: normal variant.

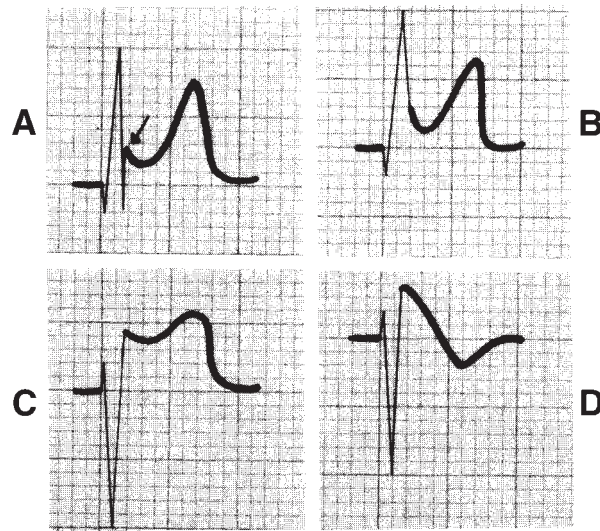


Fig. 1.18. Left and right precordial early repolarization patterns. **(A and B)** Left precordial variants. With this benign type of early repolarization, there are ST elevations in the middle to lateral precordial leads and in limb leads that have a positive QRS. The ST segment always retains its normal concave form and often is followed by a prominent T wave, simulating the hyperacute phase of infarction. The J point may be notched (arrow in **A**), giving the complex a qRs' appearance. In other cases (**B**), the ST segment may be smooth or slurred. **(C and D)** Right precordial variants. With this pattern there are ST elevations in the right-sided chest leads. The ST may show a saddle-back or humpback morphology (**C**) or have a coved appearance with terminal T wave inversion (**D**). The QRS usually has an rSr' configuration. From Goldberger AL. Myocardial infarction, electrocardiographic differential diagnosis. 4th ed. St.Louis: Mosby Year Book, 1991. Reprinted with permission from Elsevier.

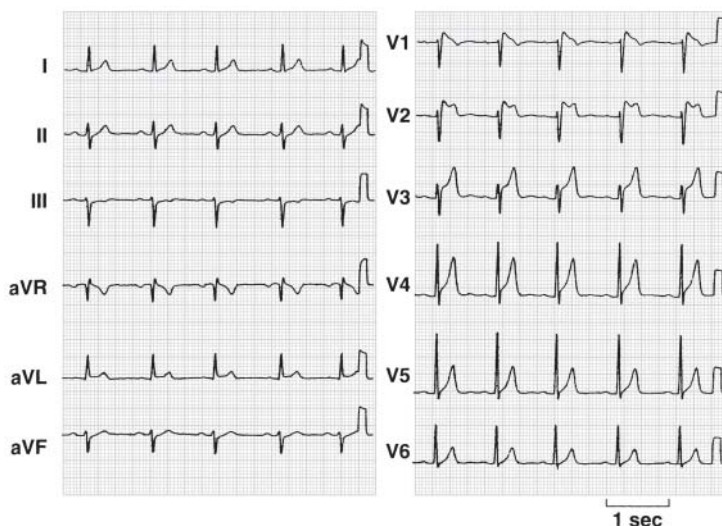


Fig. 1.19. Brugada syndrome may mimic MI. Electrocardiograms from patient during sinus rhythm. ST segment elevation of the coved (lead V₁) and saddle backed types (lead V₂) can be seen. From Muyazski T et al: J Am Coll Cardiol 27:1063, 1996, with permission from American College of Cardiology Foundation.

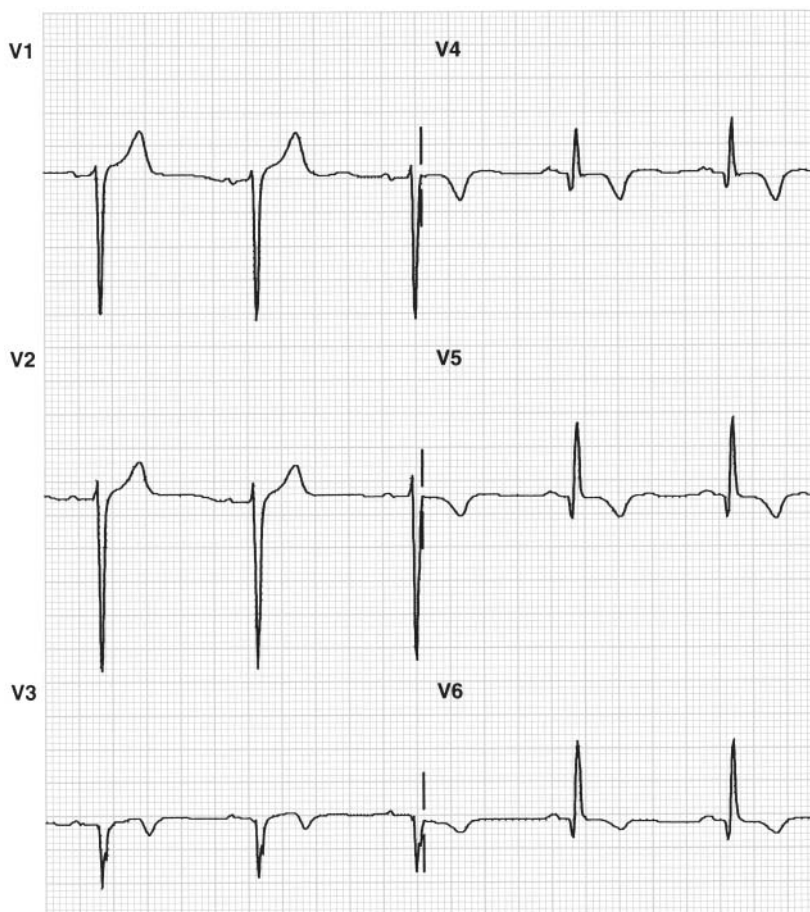


Fig. 1.20. Loss of R wave in V₃–V₆ indicates anterolateral infarction; note the iso-electric ST segment. However, the ST segment has an abnormal shape with deep T-wave inversion, localized to leads 1, aVL, and V₃ through V₆, which indicates anterolateral infarction age indeterminate. Comparison with old ECGs and clinical correlation are required to date the time of infarction. From Khan M. Gabriel. *Rapid ECG Interpretation*, Second edition, Philadelphia, 2003 WB Saunders, with permission from Elsevier.

- LBBB: the V leads commonly show small r waves in V₁, V₂, or QS complexes with ST elevation that can be misinterpreted as an anteroseptal infarct if the physician fails to note the QRS duration greater than 0.11 seconds (Fig. 1.22.).
- Left ventricular hypertrophy (LVH) is a common cause of poor R wave progression in V₁–V₃ and occasionally ST segment elevation occurs (Fig. 1.23.).
- Prinzmetal's (variant) angina caused by coronary artery spasm. In this uncommon condition, transient ST elevation occurs during pain and resolves with relief of pain or with the administration of nitroglycerin (Fig. 1.24.).
- Hyperkalemia can cause ST elevation and, rarely, transient Q waves (Fig. 1.25.).
- Hypothermia with rectal temperatures below 93°F (34°C) may cause distortion of the earliest stage of repolarization; the ST segment becomes elevated in a curious "hitched-up" pattern.
- Primary or secondary tumors may cause ST elevation and Q-waves.

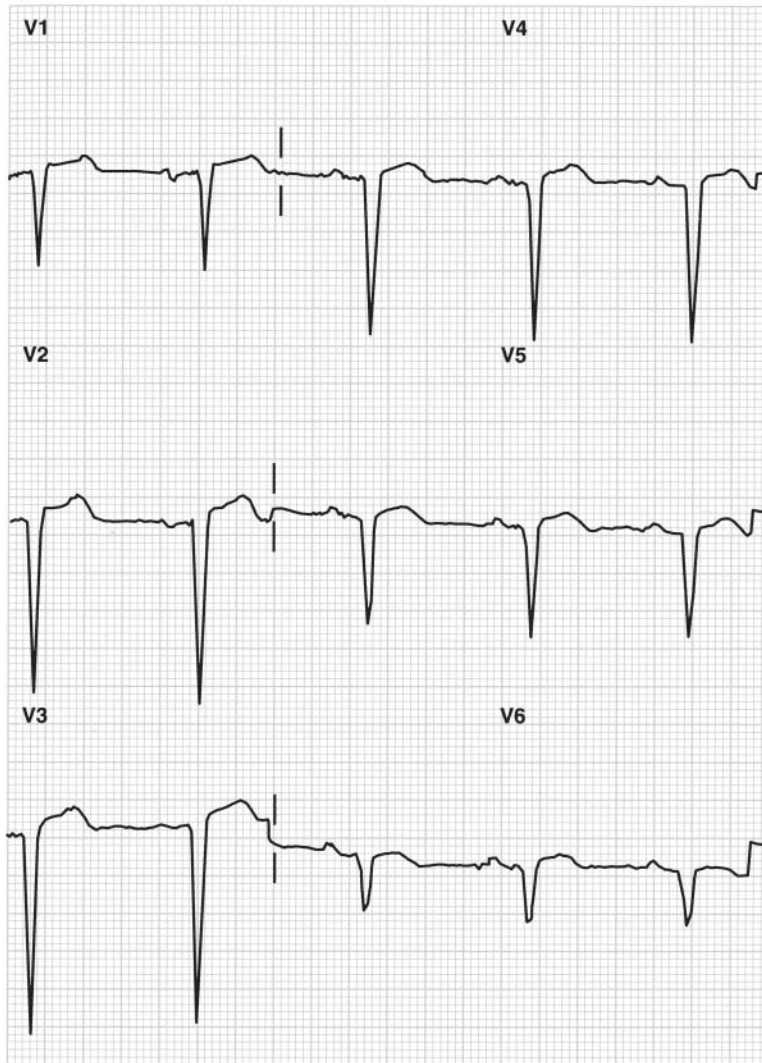


Fig. 1.21. V leads of a patient who sustained an anterior infarction 6 months earlier. Pathologic Q-waves are present from V₁–V₆. The ST segment is elevated in V₁–V₅. The tracing is in keeping with an old anterior myocardial infarction with left ventricular aneurysm. From Khan M. Gabriel. *Rapid ECG Interpretation*, Second edition, Philadelphia, 2003 WB Saunders, with permission from Elsevier.

- Acute myocarditis may present with ST elevation with or without Q-waves (Fig. 1.26.; see Chapter 13).
- Chagasic myocarditis can cause ST and Q-wave changes.
- Subarachnoid hemorrhage or intracranial hemorrhage may cause ST segment shifts or alteration of the QT interval. Torsades de pointes and transient LV dysfunction have been associated.
- Hypertrophic cardiomyopathy (HCM) usually causes Q waves, but can present with Q waves and ST elevation (Fig. 1.27.).
- Acute cor pulmonale, especially caused by pulmonary embolism, may cause ST elevation and Q waves, simulating acute MI (Fig. 1.28.).

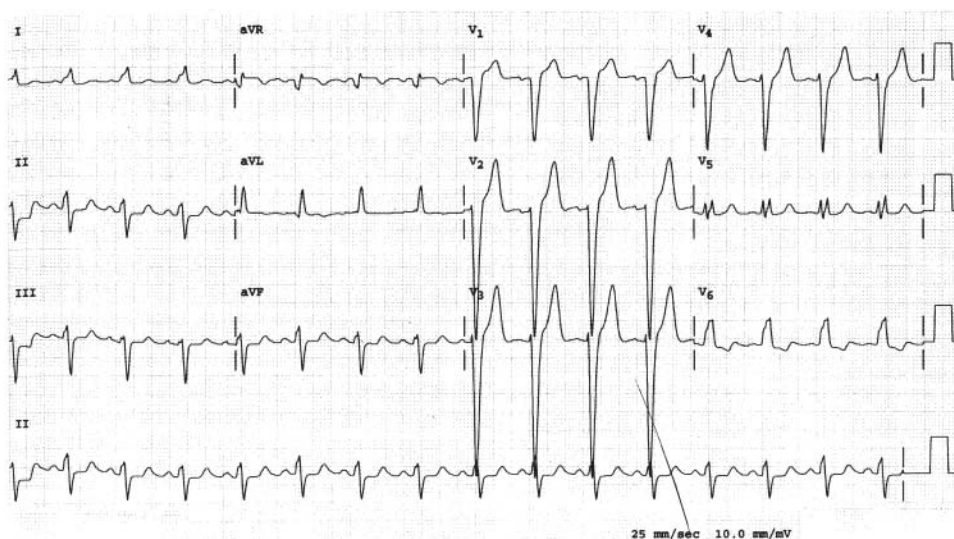


Fig. 1.22. Poor R-wave progression and ST elevation in V_1 – V_3 , but QRS > 0.12 seconds: left bundle branch block.

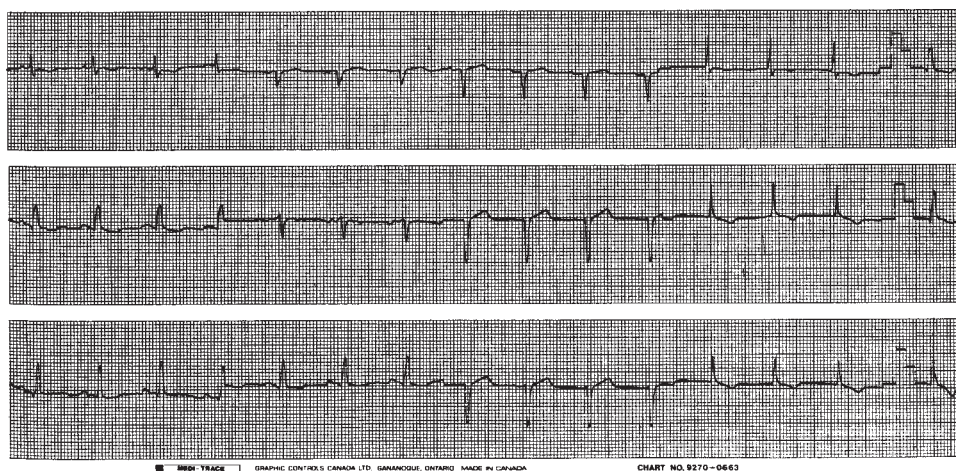


Fig. 1.23. Poor R-wave progression. The ST segment may be elevated in V_1 , V_2 , or V_3 significantly more than indicated in this tracing. Note one-half standardization and ST-T changes V_5 – V_6 typical of LVH.

- Severe trauma may cause myocardial injury and thus ST segment elevation, with or without Q waves.
- Electrocution may cause ST-segment elevation and occasionally Q waves and recurrent VF.
- Scorpion sting may cause ST-segment elevation, with or without Q waves, RBBB and other conduction defects.
- It is necessary to make the ECG diagnosis of old MI because patients with acute MI and previous infarction are at high risk for complications, including decreased long-term survival (Fig. 1.29).

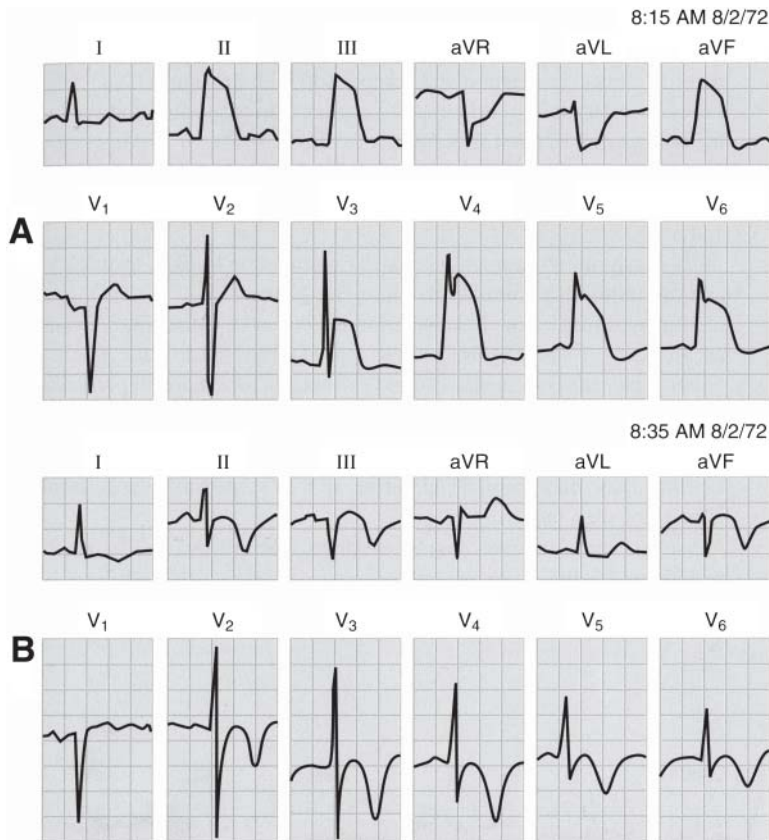


Fig. 1.24. Variant angina. The patient had severe coronary artery disease involving all three major vessels, especially the anterior descending branch, as demonstrated by coronary arteriogram. (A) Tracing recorded during angina at rest. (B) Tracing recorded 20 minutes after the pain had subsided. The latter tracing is representative of the patient's baseline ECG. During angina (A), marked ST segment elevation is present in leads II, III, aVF and V₃–V₆, with reciprocal ST segment depression in leads aVR and aVL. There is also an increase of the amplitude of the R wave in leads II, III, and aVF, with the disappearance of the S waves in leads showing significant ST segment elevation. The resulting complexes resemble the monophasic transmembrane potential. Many similar episodes were observed in this patient. From Chou TC: *Electrocardiography in clinical practice*, Fourth edition, Philadelphia, 1996 WB Saunders, with permission from Elsevier.

Mimics of old MI include the following:

- Reversal of electrodes may cause pseudoinfarction. [Figure 1.30](#) shows Q waves in leads 2, 3, and aVF. The two arm leads are on the legs; lead I with virtually no deflection is the tipoff. Incorrect chest lead placement may simulate old infarction. A QS pattern in V₁ and V₂ or small R in V₂ may be observed in some women, even with correct lead placement.
- LVH commonly causes poor R wave progression V₁–V₃ and can thus mimic anteroseptal infarction ([Figs. 1.21.](#) and [1.31.](#)).
- Other mimics include incomplete LBBB, cardiomyopathy, and myocardial replacement. In an autopsied series of 63 patients, a QS in V₁–V₂, V₁–V₃, and V₁–V₄ indicated anteroseptal infarction in 20%, 66%, and 100%, respectively.
- Severe right ventricular hypertrophy (RVH) may produce small Q-waves in V₁–V₃, simulating anteroseptal infarction.

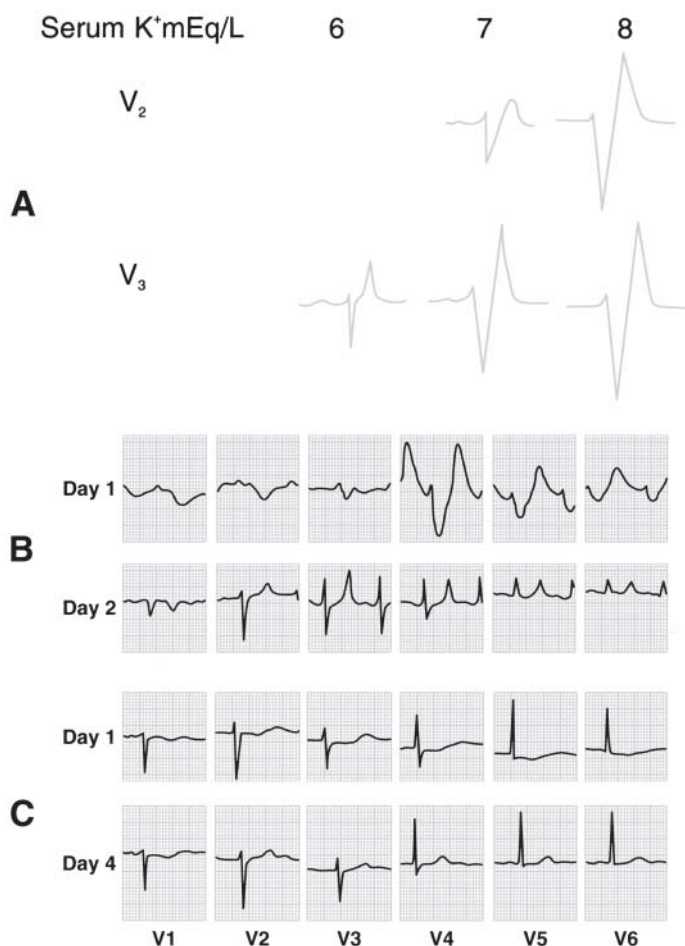


Fig. 1.25. ECG signs of hyperkalemia.

(A) • K⁺ >5.7 mEq/L: Earliest signs are T wave peaked and narrow base ("tented"); PR interval may be prolonged.
 • K⁺ >7 mEq/L: P wave flat or absent; QRS widens; prominent S wave.
 • K⁺ >8 mEq/L: S wave becomes wider and deeper and moves steeply into the T wave; there is virtually no isoelectric ST segment; occasionally ST segment elevation. (B) ECG changes in hyperkalemia. On day 1, at a K⁺ level of 8.6 mEq/L, the P wave is no longer recognizable and the QRS complex is diffusely prolonged. Initial and terminal QRS delay is characteristic of K⁺-induced intraventricular conduction and is best illustrated in leads V₂ and V₆. On day 2, at a K⁺ level of 5.8 mEq/L, the P wave is recognizable with a PR interval of 0.24 second, the duration of the QRS complex is approximately 0.10 second, and the T waves are characteristically tented. (C) ECG changes in hypokalemia. On day 1, at a K⁺ level of 1.5 mEq/L, the T and U waves are merged. The U wave is prominent and the QU interval is prolonged. On day 4, at a K⁺ level of 3.7 mEq/L, the tracing is normal. (A) is from Khan M. Gabriel, *Medical Diagnosis and Therapy*, Philadelphia 1994 Lea and Febiger, and (B,C) are from Braunwald E. *Heart Disease: a textbook of cardiovascular medicine*, Fifth edition. Philadelphia 1997 WB Saunders, with permission from Elsevier.

- Cor pulmonale caused by chronic bronchitis and emphysema is a common cause of poor R wave progression or QS patterns in the precordial leads. The finding of right atrial enlargement and an S wave in V₄ or V₅ equal to, or greater than, the R wave in V₄ or V₅ favors the diagnosis of cor pulmonale.

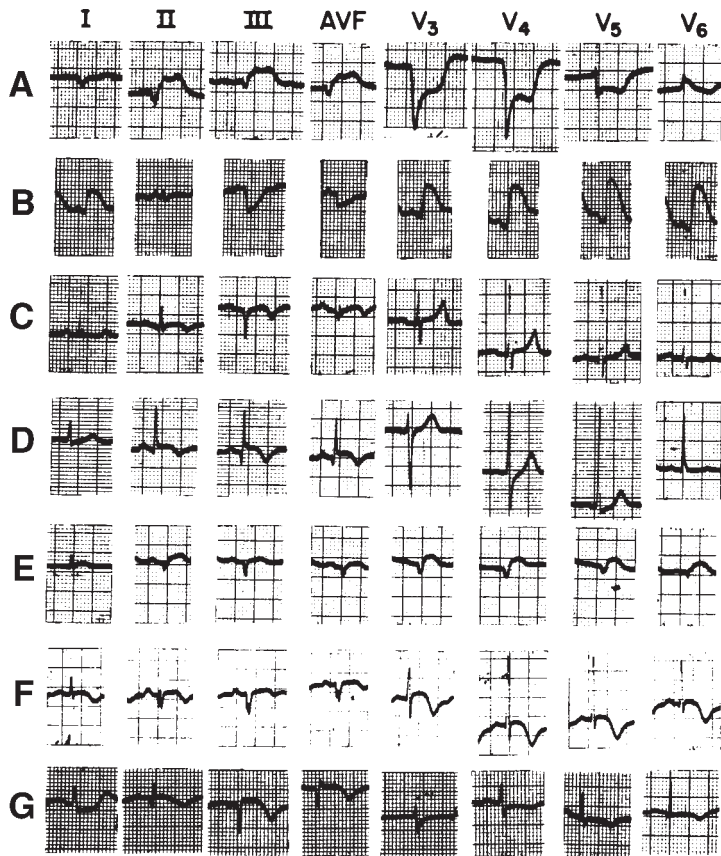


Fig. 1.26. ECG changes simulating acute myocardial infarction but due to other causes. The following causes (proved at autopsy) produced the changes seen in tracings A–G are as follows. **(A)** Acute diffuse myocarditis in a 76-year-old man. **(B)** Viral myocarditis in an 11-month-old girl. **(C)** A 2-cm gastric ulcer in the supradiaphragmatic area enroding into the inferior myocardial surface, penetrating the posterior descending branch of the right coronary artery with active bleeding from this artery in a 63-year-old woman. **(D)** Bacterial endocarditis with a septic embolism to the right coronary artery in a 9-year-old girl. **(E)** Periarteritis nodosa with rupture of the myocardium in a 61-year-old woman. **(F)** Cerebellar pontine angle tumor (neurilemmoma of the acoustic nerve) in a 56-year-old woman. **(G)** Angioendothelial sarcoma (of Kaposi) of right A-V origin, with formation of a right coronary artery to right atrial fistula and with occlusion of the midportion of the right coronary artery by this tumor in a 52-year-old woman. The ECGs in cases **A**, **C**, **D**, and **G** simulate an inferior myocardial infarction and that of **B** an anterior infarction. Cases **E** and **F** simulated an apical infarction (anterior and inferior). Autopsies in these cases showed no evidence of significant coronary atherosclerosis. From Gazes PC. Clinical cardiology, Third edition. Philadelphia: Lea & Febiger, 1990:45. Reprinted with permission.

- Wolff-Parkinson-White (WPW) syndrome may simulate inferior or anterior infarction (Fig. 1.32.). Pseudo-Q-waves are commonly seen in leads 3 and aVF but can occur in leads 2, 3, and aVF; the diagnosis of inferior MI is a common error (Fig. 1.32.). The P wave is usually stuck into the commencement of the Q-wave. If the ECG suggests inferior MI but looks somewhat atypical, the presence of WPW should be considered. The delta wave and short PR become obvious to the eye at this point. WPW may also mask the ECG findings of acute MI. Note that if normal conduction occurs in these patients (intermittent WPW), the MI mimic is not observed.

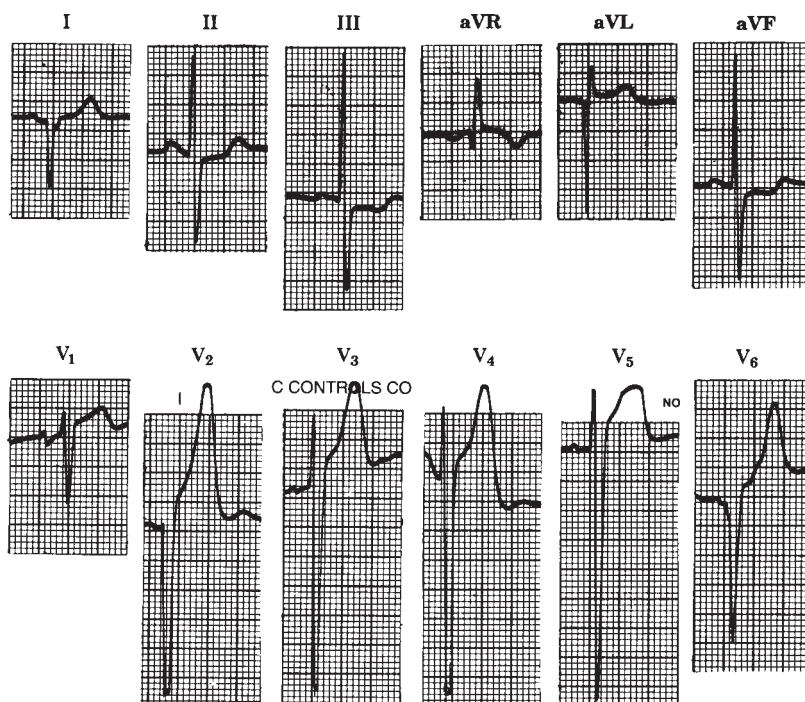


Fig. 1.27. Hypertrophic cardiomyopathy simulating anterolateral infarction in a 19-year-old man. Prominent Q waves are present in leads I, aVL, and V₆. The voltage is markedly increased, and right axis deviation is present. In addition, the precordial leads show vaulting T waves with a high ST takeoff, mimicking the hyperacute phase of infarction. Borderline wide P waves in II and V₁ suggest left atrial abnormality. Nonspecific ST-T changes are seen in leads II, III, and aVF. (From Goldberger AL. Myocardial infarction, electrocardiographic differential diagnosis, Fourth edition. St. Louis: Mosby Year Book, 1991:87. Reprinted with permission from Elsevier.)

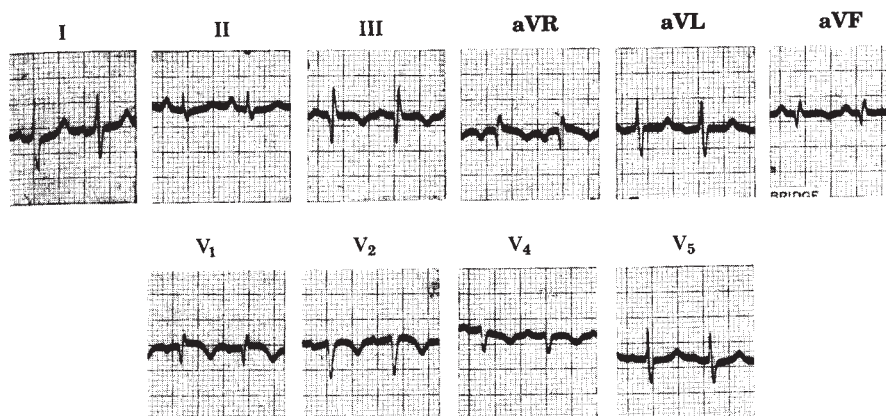


Fig. 1.28. Acute cor pulmonale secondary to embolism simulating inferior and anterior infarction. This tracing exemplifies the classic pseudoinfarct patterns sometimes seen: an S₁Q_{III}T_{III}, a QR in V₁ with poor R wave progression in the right precordial leads (clockwise rotation), and right ventricular strain T wave inversions (in V₁–V₄). Sinus tachycardia is also present. The S₁Q_{III} pattern is usually associated with a QR or QS complex but not an rS in aVR. Furthermore, acute cor pulmonale per se does not cause abnormal Q waves in II (only in III and aVF). (From Goldberger AL. Myocardial infarction, electrocardiographic differential diagnosis, Fourth edition. St. Louis: Mosby Year Book, 1991:68. Reprinted with permission from Elsevier.)

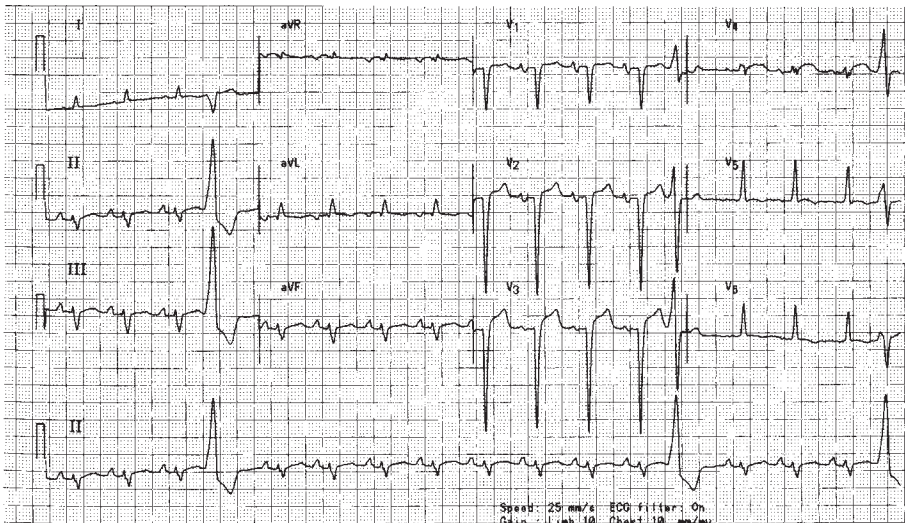


Fig. 1.29. Old anterior infarction; residual ST elevation probably caused by left ventricular aneurysm; left atrial abnormality is common in this setting.

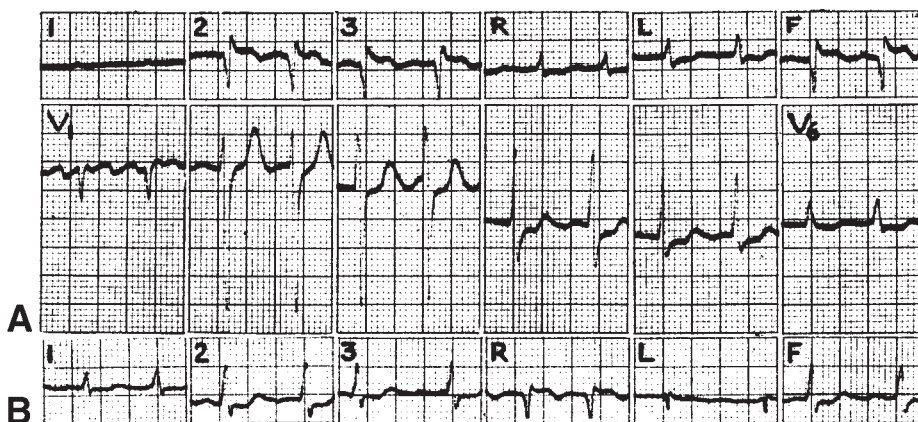


Fig. 1.30. (A) Atrial fibrillation and pseudoinferior infarction due to electrode misplacement. With Q waves and ST elevation in leads 2, 3, and aVF and with reciprocal depression of the ST segment in aVL and chest leads, this tracing suggests acute inferior infarction, but lead 1 with virtually no deflections is the tipoff. The two-arm electrodes are on the two legs (and the leg electrodes are on the arms). (B) Limb leads with the electrodes attached correctly. From Marriott HJL. Practical electrocardiography, Eighth edition. Baltimore: Williams & Wilkins, 1988:469. Reprinted with permission.

- The ECG hallmarks of HCM include narrow Q-waves in leads 2, 3, aVF, or 1, aVL, V₅, V₆ or V₁, V₂ (Fig. 1.27.).
- Dilated cardiomyopathy, involvement by neoplasms or amyloids are well-known causes of Q-waves in the absence of CAD.
- Chagas' disease: The presence of Q-waves, T-wave inversion, and conduction defects in an individual who has previously lived in an endemic area should suggest Chagasic heart muscle disease.

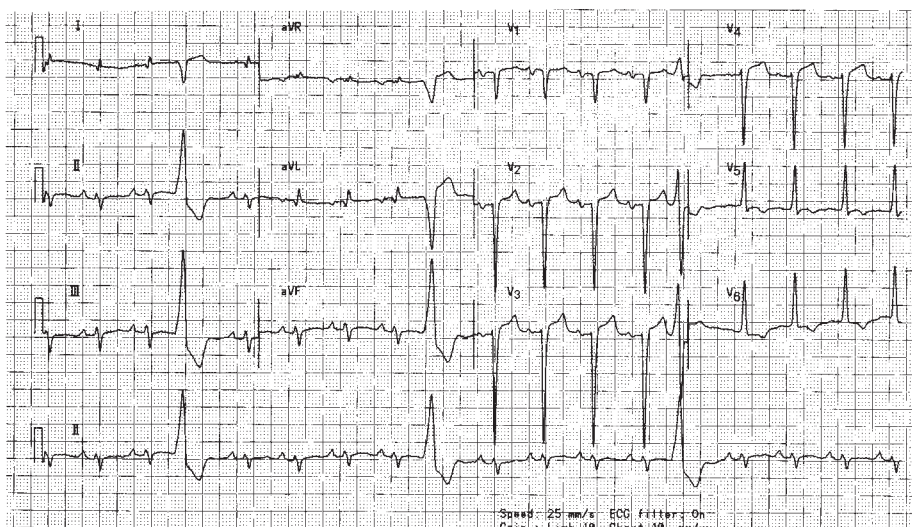


Fig. 1.31. Poor R-wave progression V_1 – V_3 . A common error is to interpret this as an old anteroseptal infarct. Note left atrial enlargement, a common feature of LVH. One-half standardization, high voltage, and typical ST-T strain pattern in V_5 , V_6 caused by left ventricular hypertrophy.

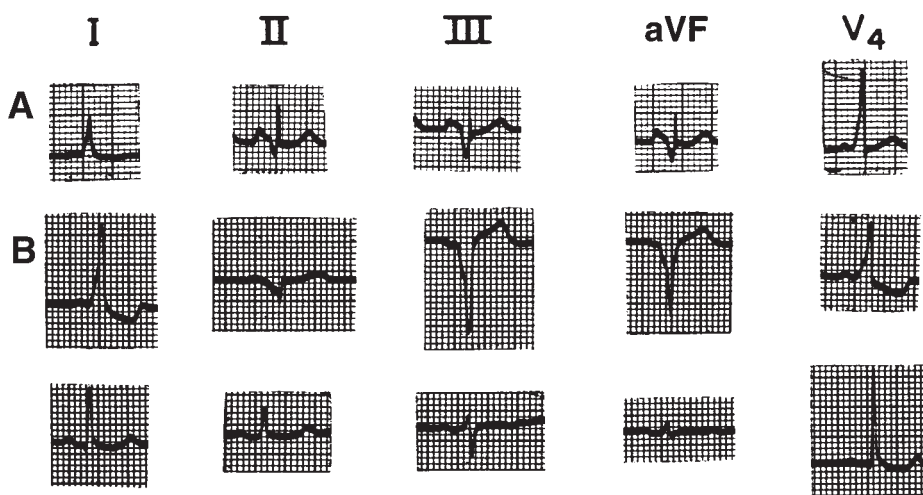


Fig. 1.32. (A) Wolff-Parkinson-White syndrome simulating an inferior infarction. (B) A second patient with Wolff-Parkinson-White syndrome simulating an inferior infarction. With normal conduction (bottom tracing), these findings have cleared. From Gazes PC. Clinical cardiology, Third edition. Lea & Febiger, 1990:46. Reprinted with permission.

- Myotonic dystrophy and other neuromuscular disorders commonly cause Q-waves and conduction defects.
- Rare causes include hemochromatosis, scleroderma, sarcoidosis, and echinococcal cyst. These diseases and other conditions that cause myocardial fibrosis and thinning of the LV wall can produce Q-waves, and some may produce bulging with aneurysm-like formation, thus resulting in some degree of ST elevation.

ECG and LBBB

Patients with acute MI presenting with new, or presumably new, LBBB derive considerable benefits from thrombolytic therapy.

- Because LBBB causes a derangement of vector forces, the usual criteria for the diagnosis of MI cannot be made. ST elevation and poor R wave progression or QS, V₁, and V₂ are usual findings of LBBB (Fig. 1.22.).
- Q-waves are not observed in leads 1, aVL, V₅, and V₆ in patients with pure LBBB. Because the ECG findings of acute MI in patients with LBBB are nonspecific, careful analysis of the presenting symptoms is of paramount importance.

Most books on cardiology and the report of the Multicenter Investigation of the Limitation of Infarct Size (MILIS) state that the finding of Q-waves in at least two of leads 1, aVL, V₅, or V₆ indicates anteroseptal infarction. The authors of the MILIS study indicate that in the presence of lateral Q-waves, it is presumed the necrosis must involve the septum to alter the initial leftward vector. This assumption is, however, incorrect. A review of the literature, and particularly a study by Norris and Scott, does not support the diagnosis of anteroseptal infarction in patients with LBBB and Q1 aVL or V₅–V₆; these authors studied 85 autopsy-controlled cases. At autopsy, 50 patients with Q1 aVL or V₅–V₆ exhibited no infarction. The most common associated findings were LVH and patchy fibrosis. The LV freewall showed infarction in 14 patients. The intraventricular septum alone or the septum and left ventricular freewall showed infarction in 21 cases.

Figure 1.33. shows LBBB with Q-waves 1, aVL, and V₅–V₆. Autopsy revealed occlusion of the left circumflex artery and extensive recent lateral infarction. The MILIS study was not an autopsy-controlled study; in 985 patients with acute MI, LBBB with enzyme confirmation of infarction was observed in 20 patients. Fewer than four patients had Q-waves in 1 aVL or V₅–V₆ observed. In addition, R wave regression and other ECG findings are not sensitive or sufficiently specific to document the diagnosis of acute infarction in the presence of LBBB.

LBBB NEW DIAGNOSTIC CLUES

- In patients with LBBB, abnormal ST-segment deviations are caused by myocardial necrosis and these changes have been documented during PCI.
- Discordant ST segment deviations occur as an exaggeration of normal ST-segment elevation usually observed in leads V₁ to V₄ that possess a dominant S wave. Figures 1.34. and 1.35. show extensive ST-segment elevation in leads V₂ to V₃ and V₄ indicating acute injury pattern manifested by discordant ST-segment elevation that is equal to or exceeds the QRS amplitude in leads V₂ through V₄.
- In patients with LBBB, an acute onset of chest pain and features of inferior infarction are indicated by ST-segment elevation in inferior leads with concordant reciprocal ST-segment depression in leads V₁ through V₄. The concordant reciprocal ST-segment depression is in the opposite direction to the usual secondary ST-segment elevation observed in V₁ through V₄ in patients with LBBB; discordant and concordant patterns reportedly have a specificity of 92% to 96% but the sensitivity is low.
- Figure 1.36. shows complete LBBB with acute inferior MI. The prominent ST-segment elevation in leads 11, 111 and aVF is associated with reciprocal ST-segment depression in leads 1 and aVL superimposed on the usual secondary ST-T changes.

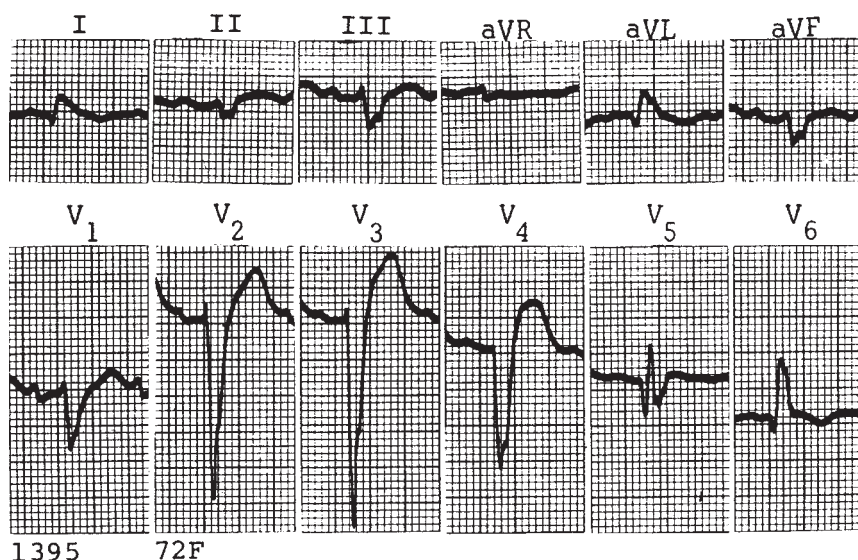


Fig. 1.33. Complete left bundle branch block with myocardial infarction proved by autopsy. The ECG diagnosis of myocardial infarction is based on the Q waves in leads I, aVL, V₅, and V₆. An autopsy was performed 10 days later and showed severe generalized coronary atherosclerosis with total occlusion of the left circumflex artery. There was an extensive recent lateral wall myocardial infarction in addition to a previous one. Left ventricular hypertrophy also was present. From Chou T.-C. *Electrocardiography in clinical practice*. 3rd ed. Philadelphia: WB Saunders, 1991:164. Reprinted with permission from Elsevier.

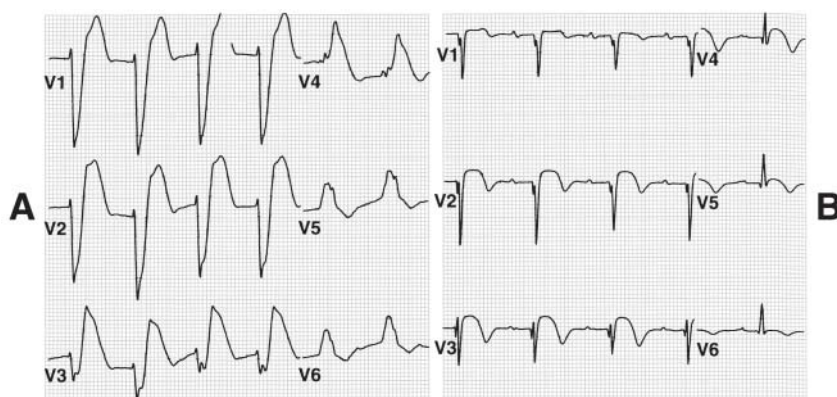


Fig. 1.34. Precordial leads of an 84-year-old man with acute myocardial infarction of the anterior wall. (A) LBBB with acute injury pattern causes discordant ST segment elevation, which in leads V₂ and V₃ exceeds 1 mV. (B) One day later there is evolution of the infarction without LBBB. Cardiac catheterization revealed severe three-vessel coronary artery disease with apical akinesis and a left ventricular ejection fraction of 30%. From Chou TC: *Electrocardiography in clinical practice*, Fifth edition. Philadelphia, 2001 WB Saunders, with permission from Elsevier.

ECG and RBBB

RBBB may be associated with non-diagnostic Q waves that simulate inferior or anteroseptal infarction. Horan et al. reported 10 of 40 cases of RBBB with Q waves and no autopsy evidence of infarction.

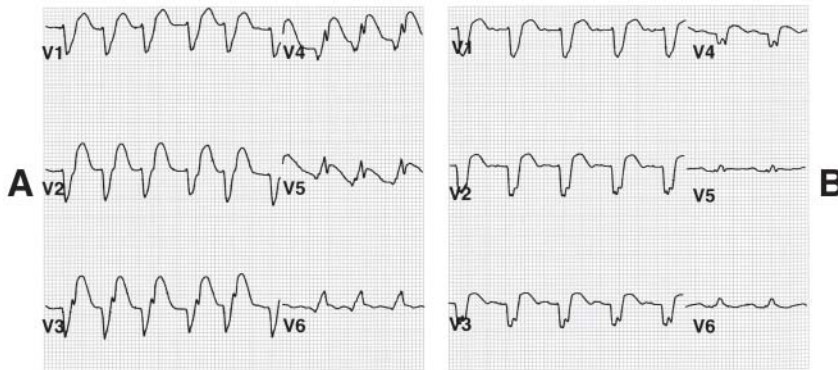


Fig. 1.35. Precordial leads of a 45-year-old man with LBBB and acute myocardial infarction of the anterior wall. (A) Acute injury pattern manifested by discordant ST segment elevation, which is equal to or exceeds the QRS amplitude in leads V_2 – V_4 . (B) One day later there is evolution of the infarction pattern with decreasing ST segment elevation and beginning terminal T-wave inversion in leads V_2 – V_4 . Note the Cabrera sign (notch on the S ascent in leads V_2 – V_4). Coronary angiography revealed a high-grade complex stenotic lesion in the proximal left anterior descending coronary artery. There was anterior apical akinesis with an estimated left ventricular ejection fraction of 40%. From Chou TC electrocardiography in clinical practice, Fifth edition. Philadelphia, 2001 WB Saunders, with permission from Elsevier.

- The non-diagnostic Q-waves of RBBB rarely extend beyond V_2 ; thus, Q in V_3 – V_6 indicates infarction. Non-diagnostic Q-waves may occur in leads 3 and aVF, usually sparing lead 2.; thus, Q-waves in 2, 3, and aVF in the presence of RBBB suggests inferior MI (Fig. 1.37.). With uncomplicated RBBB, there may be both ST depression and T-wave inversion in leads with an RSR1 complex.
- A non-diagnostic Q-wave may be present in leads V_1 and V_2 in patients with right atrial hypertrophy and RBBB.

Left anterior hemiblock may mask Q-waves of inferior infarction with resultant rS complexes in leads 3 and aVF.

ECHOCARDIOGRAPHY

Echocardiography is not required routinely in an uncomplicated MI, especially where the history and ECG are typical or with non-Q-wave infarction.

Indications include:

- Patients with cardiogenic shock often require assessment to determine the presence of mechanical complications: septal rupture, severe mitral regurgitation, myocardial rupture, and tamponade. Color doppler can provide quick results and, with the unconscious patient, a transesophageal echocardiogram is helpful and accurate.
- To distinguish acute severe mitral regurgitation from papillary muscle rupture;
- Echocardiography can assist with the diagnosis in patients with new LBBB with typical chest pain and history suggestive of acute infarction.
- Patients with an atypical ECG pattern and clinical features of MI.
- Suspected right ventricular infarction with high jugular venous pressure to assess right ventricular involvement and differentiate pericardial tamponade causing a high venous pressure.

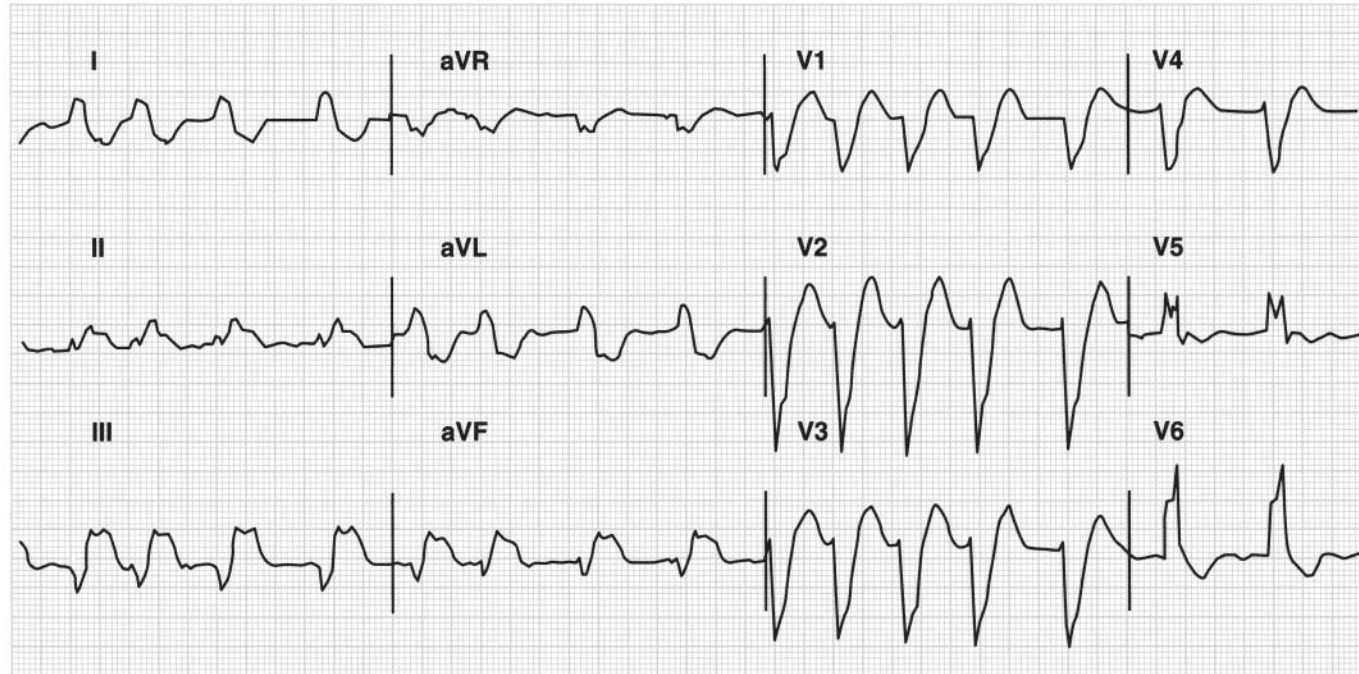


Fig. 1.36. Complete left bundle branch block with acute inferior myocardial infarction. Note the prominent ST segment elevation in leads II, III, and aVF, with reciprocal ST segment depression in I and aVL superimposed on second-degree ST-T changes. The underlying rhythm is atrial fibrillation. From Braunwald E, *Heart Disease: a textbook of cardiovascular medicine*, Sixth edition. Philadelphia, 2001 WB Saunders, with permission from Elsevier.

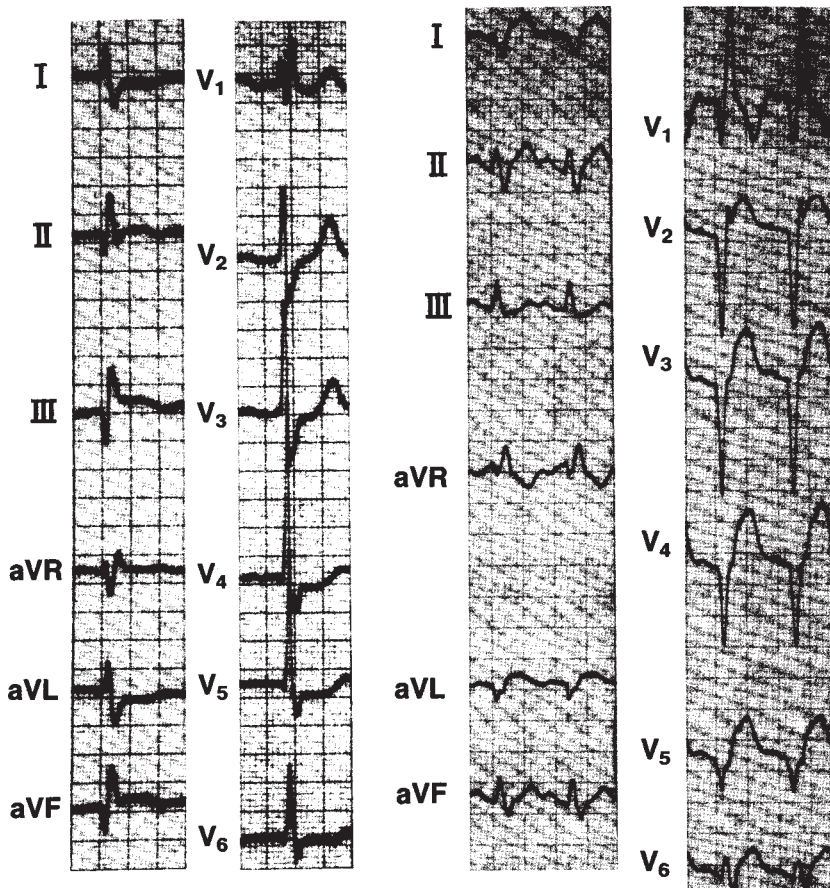


Fig. 1.37. Left. Right bundle branch block not caused by myocardial infarction. Note the classic rSR' pattern in lead V₁ and the qRS pattern in lead V₆. The patient has an inferior wall infarction. Right. Right bundle branch block caused by anteroseptal myocardial infarction. Note qR pattern in lead V₁. From Wellens Hein JJ, Conover MB. The ECG in emergency decision making. Philadelphia: WB Saunders, 1992:92. Reprinted with permission from Elsevier.

- To identify high-risk patients with multivessel disease. The contralateral remote zone should be hyperkinetic; if not, this usually indicates significant noninfarct vessel atherosclerotic disease.
- In patients with moderate heart failure not clearing after two or more doses of furosemide, echocardiographic assessment of left ventricular systolic function is useful. Although radionuclide ventriculography gives a more accurate assessment of the ejection fraction (EF), the estimate obtained from echocardiography is usually adequate to assist with the evaluation of outcomes and therapy and is cost-effective.

PUBLIC EDUCATION AND PHYSICIAN INTERACTION

It is estimated that in areas where thrombolytic therapy is available, less than 60% of patients with acute MI in North America and in the United Kingdom (UK) receive such treatment:

- Both thrombolytic therapy and PCI reduce mortality and morbidity, but timing of treatment is of great importance.

Table 1.1.
Thrombolytic Therapy, Timing of Admission, and Survival

<i>Hours From Onset of Symptoms</i>	<i>Lives Saved/1000 Treated</i>
Within 1 hour	65
2–3 hours	27
4–6 hours	25
7–12 hours	8

- The first hour of symptoms represents a huge opportunity for benefit for thrombolytic therapy or PCI. In the myocardial infarction triage and intervention trial, patients treated in the first 60 minutes had mortality reduced from 10% to 2%, and 40% of these patients had no infarct on thallium scintigraphy. In the Gruppo Italiano per lo Studio della Streptochinasi Nell Infarcto Miocardico (GISSI-1) and Second International Study of Infarct Survival (ISIS-2) trials, decrease in mortality was more than 50% compared with controls treated in the first hour. Unfortunately, fewer than 5% of patients actually received therapy in this time frame. The average delay in administration of thrombolytic therapy in emergency rooms (ERs) of more than 40 minutes largely accounts for the problem; this delay is inexcusable and should be reduced to less than 15 minutes. Table 1.1. gives the timing of thrombolytic therapy and number of lives saved per thousand treated.
- Major benefit is observed up to 4 hours, and reasonable benefit at 6 hours; between 6 and 12 hours, benefit is modest. In the late assessment of thrombolytic efficacy (LATE) double-blind placebo-controlled trial of 5700 patients treated between 6 and 24 hours of symptoms, patients receiving tissue plasminogen activator (tPA) within 12 hours had a 27% decrease of mortality compared with placebo. These data extend the time window of 0–6 hours, established by the GISSI-1 and the ISSI-2, to 12 hours.
- A major undertaking is the education of patients and the community at large about the importance of minimizing delays between the onset of symptoms of suspected heart attack and attention in the ER of the nearest hospital.
- It is not easy to motivate healthy individuals, and efforts to educate the public in this area of their care have not been sufficiently fruitful. Leaflets and health booklets appear to have little impact. A concerted effort must be made by physicians' groups in individual communities in conjunction with audiovisual programs for the public. In addition, hospitals must adopt policies to enforce rapid triage in the ER; physicians must be encouraged to institute thrombolytic therapy within 15 minutes of the patient's arrival.

Delays To Be Avoided

- Reaching the ER more than 4 hours after onset of symptoms: patient and public education should address this issue.
- Slow ER triage: patients with chest pain should be allowed quick passage, not exceeding a 1-minute delay at the so-called "triage area," to an area of the ER delineated for the rapid assessment of MI.
- Waiting for attending physician.
- ER physician delay: the ER physician must be well-trained to deal with patients who have chest pain. This physician must be allowed to give intravenous (IV) thrombolytic therapy to all those who qualify according to an approved well-outlined hospital ER protocol for IV use of thrombolytic agents. The protocol should clearly show the indications and contraindications to IV thrombolysis but should be simplified. The only well-documented contraindications are active bleeding, stroke, major trauma or surgery in the past 2 months, and uncontrolled hypertension.

Table 1.2.
Acute Myocardial Infarction In-Hospital Mortality Risk Stratification

<i>Parameters</i>	<i>*Approximate Mortality (%)</i>
Average	13
Age (years)	
75–85	24
65–74	15
50–65	9
< 50	<7
Cardiogenic shock	80
Large anterior infarcts associated with	
Severe heart failure, pulmonary edema	>30
Previous infarct and heart failure ejection fraction <30%	>25
Anterior infarct heart rate >100/min; blood pressure <110 mmHg	>20
New left bundle branch block proven infarction	>20
Anterior infarct uncomplicated	12
Inferior MI	3
Non-ST elevation MI (non-Q wave MI)	<5
ST elevation MI and age <55 uncomplicated	7
Non-ST elevation MI (non-Q wave MI) age <55	2

*Recent pooled trial results. MI, myocardial infarction.

- Waiting for CCU beds: transfer is advisable after commencement of thrombolysis and initial hemodynamic stability is achieved. Thus, ERs must be equipped to administer all functions that are available in the CCU.
- Waiting 1–2 hours for troponin or CK, CK-MB enzyme results: in most cases, cardiac enzymes are not sufficiently elevated within the first 3 hours to establish the diagnosis of infarction and can be used only after the fact. The object is to decrease or, in some cases, prevent enzyme release by rapid reperfusion of ischemic myocardium; shortest possible “door-to-needle” time.

RISK STRATIFICATION

On admission, risk stratification (Table 1.2.) assists in decision making, especially when relative contraindications to thrombolytic therapy are present. Characteristics of patients with acute MI who, on admission, have a high risk of death or complications include:

- Large infarcts usually associated with moderate to severe heart failure, pulmonary edema, with crackles observed over more than one-third of the lower lung field.
- An EF less than 35%.
- Cardiogenic shock indicating a large infarct or mechanical complication and high mortality.
- Over age 75: the 1-year mortality rate is more than 30% versus less than 10% in patients less than age 70.
- New LBBB.
- New RBBB with left ventricular failure.
- Previous MI and recent infarction with HF.

Table 1.3.
ISIS-2: Effects of Aspirin and Streptokinase (SK) Given Within 4 Hours
and Within 24 Hours of Onset of Myocardial Infarction

	<i>Placebo (I) Aspirin</i>	<i>SK</i>	<i>SK + Aspirin</i>	<i>Placebo (I) + Tablets</i>	<i>Neither</i>
35-day vascular mortality; therapy within 4 hours	12.3%	8.2%	6.4%	13.1%	8.9%
Within 24 hours	12% 9.4%	9.2%	8%	11.8%	13.3%
	1029/8595 568/4300	791/8592	804/8587	343/4292	1016/8600

I, infusion.

Modified from Lancet 1988; 2:350.

THERAPY

Emergency Management: Immediate Action

All patients should take or be given 160–320 mg of chewable noncoated aspirin, (two to four 80 mg chewable aspirin tablets immediately). The 160-mg dosage proved very effective in ISIS-2 (Table 1.3.) and ISIS-3; a 325-mg dose was used successfully in GISSI-2.

- An initial large dose of 320 mg chewable aspirin is strongly recommended because a lower dose may still leave substantial thromboxane activity at this crucial period and may take a few days before achieving more than 95% inhibition of platelet activity.

β -Blockers are administered without delay if there are no contraindications. Atorvastatin 60 to 80 mg, or other statin, is advisable in high-risk ACS patients (see Chapter 9). Primary angioplasty or thrombolytic therapy is commenced in properly selected patients. These treatment modalities are discussed in this chapter. The reader is advised to consult Chapter 2 for the management of complications of acute MI.

Pain Relief

- Immediate relief of pain is of paramount importance because pain enhances autonomic disturbances that may precipitate sudden death.
- Morphine: 4 mg IV over 1 minute, repeated if necessary at a dose of 2–5 mg every 5–30 minutes as needed at the rate of 1 mg/minute.
- β -Blocker: preferably given IV for two doses and then orally (Table 1.4.), if there is no contraindication. β -Blockade has been shown to abolish and may prevent recurrence of chest pain and decreases the need for morphine or nitroglycerin.
- Nitroglycerin: usually given sublingually for two doses. Recurrence of chest discomfort after adequate administration of morphine and a β -blocker should prompt the use of IV nitroglycerin (see Pump Infusion, Table 4.9.).

NEW ACC/AHA GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ST ELEVATION MI

Determine whether fibrinolysis of an invasive strategy is preferred:

- *If presentation is less than 3 hours and there is no delay to an invasive strategy, there is no preference for either strategy.*

Table 1.4.
Dosage of β -Blockers in Acute Myocardial Infarction*

IV	Oral Dosage First 7 Days	1 Week to 2 Years
Carvedilol	6.25 mg twice daily increasing to 12.5 mg up to 25 mg twice daily	12.5–25 mg twice daily
Esmolol	3–6 mg over 1 minute, Then 1–5 mg/minute	
Metoprolol (IV 5 mg at a rate of 1 mg/minute, 5 minutes later second 5-mg bolus, 5 minutes later third 5-mg bolus)	8 hours after IV 25–50 mg twice daily	50–100 mg twice daily
Propranolol (IV not approved for myocardial infarction in USA)	20 mg three times daily	80 mg long-acting, increasing to 160 mg once daily; maximum 240 mg daily

*Contraindications: bronchial asthma, severe heart failure, systolic blood pressure <100 mmHg, second- or third-degree AV block.

Halt IV if the following events develop: heart rate <50/minute, second- or third-degree AV block, PR >0.24, systolic blood pressure <95 mmHg, marked shortness of breath, wheezes, or crackles more than one-third of the lung fields, or pulmonary capillary wedge pressure (PCWP) > 22 mmHg, if this parameter is being monitored.

Fibrinolysis is generally preferred if: presentation is less than or equal to 3 hours from symptom onset and there is delay to invasive strategy.

Invasive strategy is not an option if:

- Catheterization laboratory occupied/not available; vascular access difficulties; lack of access to a skilled PCI laboratory; delay to invasive strategy; prolonged transport; door-to-balloon–door-to-needle time is more than 1 hour.

Invasive strategy is an option if:

- Skilled PCI laboratory available with surgical backup: door-to-balloon–door-to-needle is less than 1 hour.
- High risk from STEMI: cardiogenic shock; Killip class is greater than or equal to 3; contraindications to fibrinolysis, including increased risk of bleeding and intracranial hemorrhage; late presentation; symptom onset was more than 3 hours ago.

PRIMARY ANGIOPLASTY/STENT

If facilities are available the strategy of choice is PCI that involves stenting with or without angioplasty. Angioplasty alone is used in patients when stenting is not feasible or advisable; not all lesions are amenable to stenting. This strategy is of outmost importance in high-risk patients. Thus, risk stratification is needed to assist until such time that sufficiently skilled cardiologist and facilities are available to offer the best strategy for reperfusion to the majority of patients.

Most importantly, the early use of abciximab prior to angiography and during PCI has been shown to be the goal standard of therapy and is strongly recommended. Abciximab is used prior to angiography and is administered regardless of whether the culprit lesion is amenable for stenting or angioplasty.

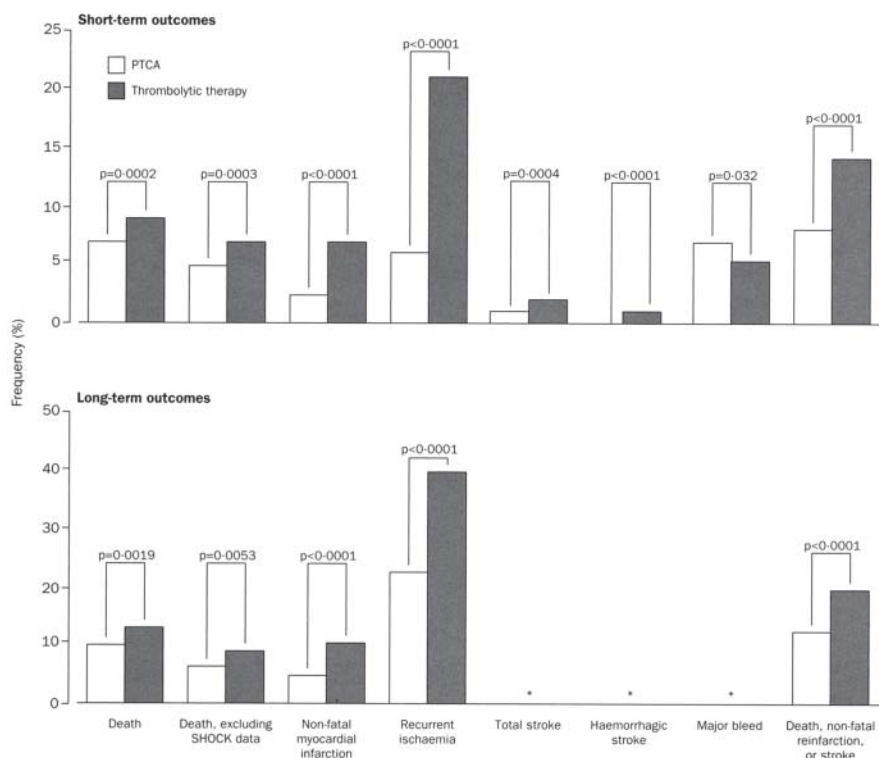


Fig. 1.38. Meta-analysis of 23 randomized trials of primary PCI vs thrombolysis. CVA indicates cerebrovascular accident. Reprinted with permission from Elsevier. The Lancet 2003; 361:13–20.

If a highly skilled team is available and the time between arrival at the center and balloon inflation is less than 90 minutes, PCI is preferred therapy.

- Patients presenting between 3 and 12 hours after symptoms have shown mortality benefits for PCI over thrombolysis.
- PCI is logical therapy for high-risk patients who reach a hospital with PCI facilities, or if transfer time from a referral hospital to the PCI center is less than 90 minutes and door to balloon time is less than 1 hour.
- Patients treated with thrombolysis within 3 hours appear to have the same survival compared with PCI; and low-risk patients seen within 3 hours of onset of symptoms are selected for thrombolysis in many countries. This strategy will continue until special PCI centers and results of RCTs are available.

Clinical Studies of PCI

In a randomized study by Saia et al., sirolimus-eluting stent implantation for patients with ST-elevation acute MI proved safe and without documented angiographic restenosis at 6 months.

- An overview of 23 trials and 7739 patients indicated the superiority of PCI over thrombolytic therapy in reducing the individual endpoints of reinfarction, and hemorrhagic stroke. (See Fig. 1.38.) In a meta-analysis of these studies Keeley et al. indicated that “primary PCI was associated with improved 30-day outcomes, including death (7% versus 9%, $p=0.0002$), nonfatal reinfarction (2.5% versus 6.8%, $p<0.0001$), and stroke

(1% versus 2%, $p = 0.0004$), with absolute differences so great that 60 patients would benefit for every 1000 patients treated.”

- The saving of 20 lives for every 1000 patients treated appears to be caused by higher patency and reduced reinfarction and stroke. In 1996, Grines advocated that mortality rates following acute MI appear to be inversely related to the ability to achieve Thrombolysis in Myocardial Infarction (TIMI)-3 flow. The greatest benefit of primary PCI is its ability to achieve TIMI-3 flow in more than 90% of patients, even when the patient is treated in the late stages of infarction.

DANAMI-2

In the multicenter Danish trial, 1572 patients with acute MI were randomized to fibrinolysis with accelerated IV alteplase or primary angioplasty. The primary study endpoint was a composite of death, clinical evidence of reinfarction, or disabling stroke at 30 days. Patients were treated at specialized referral centers or transferred quickly from 24 area hospitals that lacked PCI facilities within 70 minutes to a facility with skilled operators and personnel to perform coronary intervention within 100 minutes of arrival at the PCI center. Ninety-six percent of patients were transferred from referral hospitals to an invasive-treatment center within 2 hours. PCI patients showed significantly improved survival, decrease in reinfarction, and disabling stroke (13.75 versus 8.0%); for patients seen initially at referral centers, rates were 14.2% versus 8.5% and for patients seen initially at invasive centers, rates were 12.3% versus 6.7%. In the fibrinolysis group, 26 patients required repeat thrombolytics, 15 had rescue angioplasty, and 148 (19%) required revascularization within 30 days.

Importantly, no significant differences were observed in the rate of death (6.6% versus 7.8%; $p = 0.35$) or the rate of stroke (1.1% versus 2.0%, $p = 0.15$). Among all patients, the better outcome after angioplasty was driven primarily by a reduction in the rate of reinfarction (1.6% in the angioplasty group versus 6.3% in the fibrinolysis group; $p < 0.001$; a 75% reduction).

Criticisms of the trial include the following:

- The study patients represented only 37% of those screened; those deemed to be at “high risk” during ambulance transport were excluded.
- The investigators make the statement. “We chose to count clinical reinfarction and to omit recurrent ischemic episodes and reinfarction related to invasive procedures. If the reinfarctions associated with invasive procedures had been included, the difference would have been narrowed.
- Whereas patients with standard contraindications to fibrinolysis were excluded, those with a previous stroke were included; thus, the stroke data is inaccurate .
- PCI in both the DANAMI-2 and PRAGUE-2 studies failed to reduce 30-day mortality compared with thrombolytics given within 3 hours of symptoms.

PRAGUE Study

A trend was identified in 30-day mortality rate favoring primary angioplasty (6.8%) over thrombolysis (10%, $p = 0.12$). When analyzed by subgroup analysis, the patients who benefited most from primary angioplasty were enrolled 3 to 12 hours from symptoms onset (6% vs 15.3%, $p < 0.02$); more acute presentation (0 to 3 hours from symptoms onset) revealed similar mortality between primary angioplasty (7.3%) and thrombolysis (7.4%). As several patients crossed over between groups, re-analysis of overall 30-day mortality by treatment received revealed a significant reduction with primary angioplasty versus thrombolysis (6% versus 10.4%, $p < 0.05$).

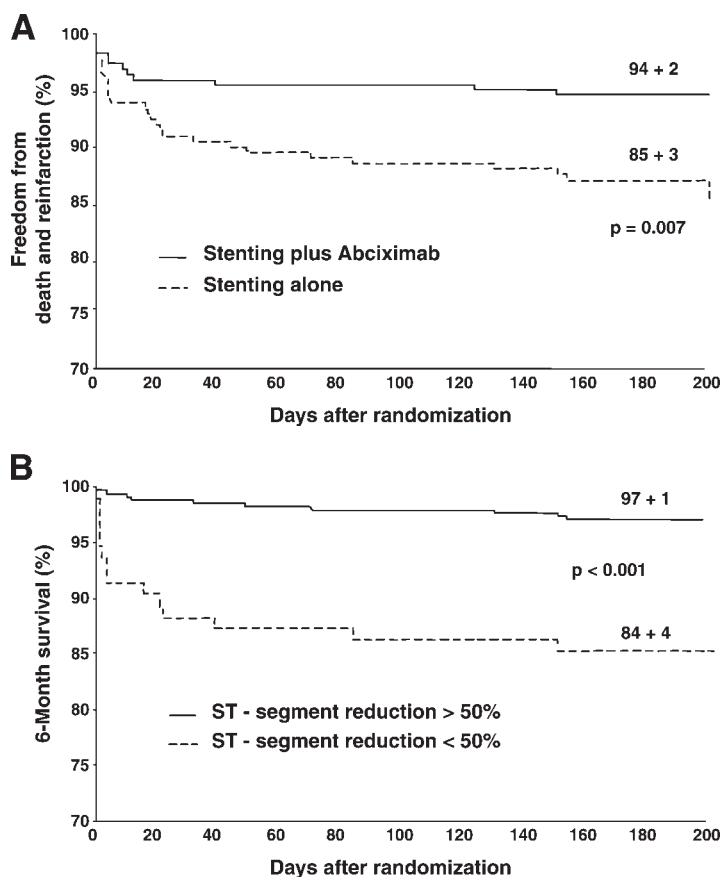


Fig. 1.39. (A) Kaplan-Meier curves for the composite of death and reinfarction at 6 months in the abciximab group and stenting only group (B) curves for 6 months mortality in patients with and without ST segment reduction. From Antoniucci et al. J Am Coll Cardiol 42:1884, 2003, with permission from the American College of Cardiology Foundation.

BRAVE

Investigators conducted a randomized evaluation of Early Administration of Reteplase Plus Abciximab or Abciximab Alone Prior to Percutaneous Coronary Intervention in Patients With Acute MI. The study assessed whether reteplase plus abciximab is more effective than abciximab alone when given (pre-cath lab) to patients with acute MI intended to undergo PCI.

Patients (253) were randomized to receive either half-doses of reteplase (2 boluses of 5 U) plus abciximab (bolus and 12-hour infusion), group reteplase plus abciximab (R+A), or abciximab alone, group A. The combined 30-day incidence of death, recurrent MI, and stroke was 3.2% in group R+A and 1.6% in group A ($p = 0.66$). The study showed that pretreatment with R+A is not superior to abciximab alone in patients with acute MI who will undergo a PCI and increases the risk of bleeding.

Grines et al. make the statement that the available data demonstrate that primary PCI is superior to thrombolysis in reducing death, reinfarction, intracranial bleeding, recurrent ischemia, and infarct vessel reocclusion. Primary PCI without thrombolysis to facilitate reperfusion is the treatment of choice if it can be performed within 3 hours by a competent operator.

In urban and suburban centers with primary PCI capability, policies should evolve to allow transfer of all patients with ST-elevation MI to a specialized PCI tertiary center within a 2-hour travel radius.

ACE Trial

Antoniucci et al. completed a study called the Abciximab and Carbostent Evaluation trial (ACE trial). The ACE trial was a randomized trial comparing primary infarct artery stenting with or without abciximab in acute MI. Four-hundred patients with acute MI were randomized to undergo infarct-related artery stenting alone or stenting plus abciximab.

The incidence of the primary endpoint: composite of death, reinfarction, target vessel revascularization, and stroke at 1 month was lower in the abciximab group than in the stent-only group (4.5% and 10.5%, respectively; $p = 0.023$); see Fig. 1.39. Early ST-segment resolution was more frequent in the abciximab group (85% versus 68%, $p < 0.001$). Infarct size, as assessed by 1-month technetium-99m sestamibi scintigraphy, revealed smaller infarcts in the abciximab group.

Importantly, at 6 months, the cumulative difference in mortality between the groups increased (4.5% versus 8%), and the incidence of the composite of 6-month death and reinfarction was lower in the abciximab group than in the stent only group (5.5% and 13.5%, respectively; $p = 0.006$).

Topol et al. point out in an editorial that the results of the ACE trial, amalgamated with the other catheter-based reperfusion trials, provide robust evidence for the use of abciximab as a standard adjunctive therapy with catheter based reperfusion. Considering stent plus abciximab as the gold standard therapy for ST elevation MI.

CONTROL OF EARLY LIFE-THREATENING ARRHYTHMIAS

Lives can be saved by:

- Prompt defibrillation or conversion of ventricular tachycardia (VT) by medical teams or paramedics.
- Lidocaine (lignocaine) IV: Effective for the control of ventricular tachycardia, but its prophylactic use is not recommended.
- In the first 24–48 hours, ventricular premature beats (VPBs) and short runs of VT bear little relation to the occurrence of VF; suppression of VPBs did not result in a lower mortality rate following acute MI. R-on-T are an exception but usually appear less than 2 minutes before VF. Lidocaine is far from completely effective in preventing VF that occurs in approximately 5% of patients with acute MI and many patients must be treated to prevent some episodes of VF. A meta-analysis of 14 RCTs indicated that lidocaine reduced the incidence of VF 33%, without a decrease in mortality
- The effect on mortality rates is uncertain because of the increase in bradyarrhythmic deaths. Trials and meta-analyses suggest that prophylactic lidocaine increases mortality because of its ability to cause asystole. Inexperienced staff were often tempted quite unnecessarily to push the dose to toxic levels to “control” VPBs.

Indications include:

- Sustained VT (see Fig. 6.4).
- Lidocaine is given for 48 hours after VT occurring in the first 24 hours of infarction.
- Post-VF or repetitive VF.

Contraindications include: sinus bradycardia, sinoatrial dysfunction, which may precipitate sinus arrest; atrioventricular (AV) block, all grades, which can cause asystole; patients recovering from asystole; idioventricular rhythm; severe HF; and porphyria.

Dosage: a bolus IV 1.0–1.5 mg/kg, 75–100 mg over 5 minutes, during which time a continuous infusion of 2 mg/min for a 70- to 80-kg patient less than age 70 is commenced (Table 1.7.). An additional bolus of 50% of the original amount given 10 minutes after the first bolus prevents a dip in plasma level below the therapeutic range, which commonly occurs 20–60 minutes after starting the infusion. In the elderly, a bolus of 0.75 mg/kg is given, and then, if needed, a 25–30 mg IV bolus. Do not allow a time lapse of minutes between the bolus and commencement of the infusion, as inadequate blood levels may ensue. Halve the dose in patients with HF, shock, hepatic dysfunction, or concomitant use of a hepatic-metabolized β -blocker or cimetidine (*see* Table 1.8.).

Adverse effects include increased incidence of asystole with increased lidocaine use. Also, confusion, seizures, drowsiness, dizziness, lip or tongue numbness, slurred speech, muscle twitching, double vision, tremor, altered consciousness, respiratory depression or arrest, complete heart block in patients with impaired AV conduction, and hypotension owing to peripheral vasodilation are seen.

- β -Blockers: May be required as therapy independent of pain control to abolish ventricular arrhythmias or to prevent their occurrence, especially if these arrhythmias are catecholamine induced. These agents decrease the incidence of VF and myocardial rupture; they should not be given with hypotension, bradycardia, or signs of HF (Table 1.4.).
- Monitoring of the cardiac rhythm is routine practice. Computer algorithms for detection of arrhythmias have proven superior to that of nursing and physician personnel.
- Autonomic disturbances are triggered by ischemic tissue as well as pain and may result in sinus tachycardia and tachyarrhythmias that are associated with inappropriate catecholamine release, thereby intensifying ischemia, which further increases release of catecholamines. Alternatively, bradycardia may occur and the associated hypotension may enlarge the infarct. This vicious cycle results in an increase in infarct size, which can culminate in progressive HF and shock.
- Autonomic disturbances may be abolished by morphine and β -blockade.
- Symptomatic bradycardias with pulse rates of less than 40 per minute are controlled with the judicious use of atropine (0.4–0.6 mg) IV given slowly every 5–10 minutes as needed, to a maximum of 2 mg. Caution: Do not increase the heart rate beyond 60 per minute. Administering atropine too rapidly may result in sinus tachycardia in some patients, and, rarely, VF may be precipitated.

Ancillary Therapy

- Oxygen 2–4 L/minute via nasal prongs is given during the first 3 hours until assessment is completed; then O₂ is continued if the patient is short of breath, tachypneic, or if there is proven hypoxemia. Pulmonary edema causes hypoxemia, but ventilation perfusion mismatch plays a role. Cessation of O₂ administration indicates to the patient that some improvement is occurring and helps to allay anxiety.
- Diet: Fluids only for 8–12 hours until it is established that the infarction is uncomplicated, and then light diet as tolerated with no added salt until the patient is discharged from the CCU.
- A stool softener is routinely prescribed, for example, docusate (100–200 mg) twice daily.
- Bedrest and bedside commode for 24 hours, and then washroom privileges and ambulation (Table 1.5.).

Table 1.5.
Activity Levels

Stage I (Day 2)
Use a bedside/commode. Feed self-prepared tray with arm and back support. Need assistance with bathing. Passive range of motion to all extremities 5 to 10 times. Active-ankle motion. Emphasize relaxation and deep breathing. Bed to chair transfers for 1–2 hours per day
Stage II (Days 3–4)
If hemodynamically stable, uncomplicated, myocardial infarction, ambulate in room and corridor in preparation for discharge day 4 or 5. Stop activity if shortness of breath, chest pain or presyncope or heart rate > 110 per minute.

- Mild sedation: oxazepam (15 mg) or a similar agent at bedtime; some patients may require twice daily dosing.
- Psychological management is discussed in Chapter 2.
- Computer algorithms for detection of arrhythmias have proven superior to detection by nursing and physician personnel.

RECOMMENDATIONS FOR BALLOON FLOTATION RIGHT

Heart Catheter. Hemodynamic monitoring is required when information is not clinically available and is needed to assess the degree of cardiac decompensation or to guide the administration of pharmacological agents. Pulmonary artery catheters should not be used routinely; the major and minor complications from their use reportedly occur in 4% and 22% of patients. Indications include:

- Cardiogenic shock or signs of systemic hypoperfusion.
- HF.
- Suspected mechanical complications: ventricular septal or papillary muscle rupture, suspected severe mitral regurgitation, pericardial tamponade.
- Diagnosis of right ventricular infarction when there is also a degree of left ventricular failure.
- Progressive or unexplained hypotension failing to respond to fluid administration in patients without pulmonary congestion.

THROMBOLYTIC THERAPY

Reduction in major events and mortality is achieved by thrombolytic therapy instituted within 6 hours of onset of symptoms. Pooled mortality results of trials in more than 58,000 patients randomized to thrombolytic therapy or placebo demonstrate a near 30% reduction of 30-day mortality. The important determinants of outcome are age and administration within 2 hours of onset of symptoms not exceeding a door-to-needle time of 20 minutes. Although the relative survival benefit is greatest for patients aged 65–75 years, the most absolute benefit is in the elderly aged more than 70 years with anterior infarction. Uncomplicated acute inferior MI carries a low risk in the younger and elderly individual.

Tables 1.3. and 1.6. give relevant results of ISIS-2, GISSI-2, and ISIS-3, respectively. No evidence of any real difference in 5-week mortality between Streptokinase (SK) and tPA or APSAC was observed despite randomization of more than 60,000 patients in ISIS-3 and GISSI-2.

Table 1.6.
Dosage of Thrombolytic Agents

Drug	Dosage
Streptokinase	1.5 million U in 100 mL 0.9% saline IV infusion over 30–60 minutes
Anistreplase (Eminase)	30 U in 5 mL sterile water or saline by slow IV bolus over 2–5 minutes
tPA alteplase (front-loaded)	15-mg bolus; 0.75 mg/kg over 30 minutes (not >50 mg) 0.50 mg/kg over 30 minutes (not >35 mg) Total dose < 100 mg
Tenecteplase (TNKase)	0.5 mg/kg bolus

tPA, tissue plasminogen activator

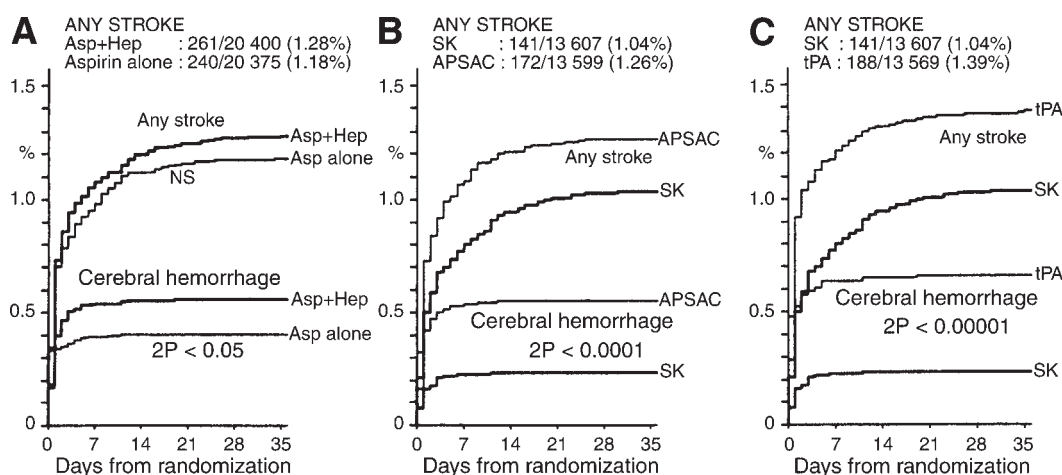


Fig. 1.40. Cumulative percentage with any stroke (*upper lines*) and with (definite or probable) cerebral hemorrhage in hospital up to day 35 or before discharge. (A) All patients allocated aspirin plus heparin (*thicker line*) vs all allocated aspirin alone. (B) All patients allocated tPA. From ISIS-3. A randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. Reprinted with permission from Elsevier, *The Lancet* 1992;339:757.

t-PA plus heparin caused a significantly greater number of hemorrhagic strokes than SK without heparin use (Fig. 1-40.) Heparin is not required when streptokinase is used; thus, SK is used in many countries outside the US particularly in patients at low risk and in the elderly over age 75 and particularly in patients seen within 3 hours of onset.

Assessment of global and regional left ventricular function 3 weeks after a first infarction indicated similar effects for SK and tPA. It is important to note that tPA must be used in conjunction with IV heparin to achieve excellent late patency rates and to avoid reocclusion. The results of The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study provided new definitive data to help resolve the controversies and define the role of IV heparin. To consider the net clinical benefit of the aggressive thrombolytic regimens of front-loaded tPA,

Table 1.7
Lidocaine (Lignocaine) Dosage

	Normal dosage (e.g., 60–90 kg/patient)	Half Dose: Elderly, Congestive heart failure, shock, hepatic dysfunction, Cimetidine, some β -blockers, *halothane
First IV bolus (mg/kg)	1.5	0.75
Usually (mg)	100	50
Second bolus (mg/kg)	0.75	0.5
Usually (mg)	50	25–30
Concomitant infusion (mg/minute)	2–3 mg/minute (50 μ g/kg/minute)	1–2 mg/minute (20 μ g/kg/minute)

Therapeutic level, 1.5–5 μ g/mL, 1.5–5 mg/L, 6–26 μ mol/L. Seizures, levels > 6 mg/L. *Hepatic, metabolized β -blockers: propranolol, metoprolol.

Table 1.8.
Warnings to Avoid Lidocaine (Lignocaine) Toxicity

Reduce bolus dose and infusion rate in the elderly (over age 70).
Determine the dose utilizing lean body weight.
Decrease the dose in heart failure, hypotension, cardiogenic shock.
Decrease dosage with hepatic dysfunction or concomitant use of cimetidine, propranolol, or drugs that decrease hepatic blood flow or metabolism.
Check for previous seizure activity or central nervous system disease.
Determine blood levels if infusion rates are high (≥ 4 mg/minute) or neurological adverse effects.
Reevaluate the clinical situation, including serum K, magnesium, presence of bradycardia or sinus tachycardia and contraindications, and factors that increase lidocaine toxicity before increasing the rate to a maximum of 4 mg/minute for a patient less than 200 lbs (90 kg).

which opens the infarct vessel faster than previous strategies used along with carefully titrated IV heparin in GUSTO, a 41,021-patient trial in 15 countries and 1100 hospitals demonstrated a modest 14% mortality reduction compared with SK or combined tPA and SK.

- The authors of the study postulate that a small increase in hemorrhagic stroke for these aggressive regimens is acceptable for the tradeoff of a modest 14% “net” mortality decrease.
- ASSENT-2 compared single bolus tenecteplase (TNKase) with front loaded tPA in 16,949 patients. At 30 days, mortality rates were almost identical in patients treated after 4 hours; mortality was 7% for TNKase and 9.2% with tPA ($p = 0.018$).
- Speed of reperfusion is particularly important in patients presenting within 3 hours of onset of symptoms and tenecteplase, administration is preferred, particularly in patients at high risk: anterior MI, diabetes, LBBB, and HF.
- Patients over age 79 are at high risk for intracranial hemorrhage, and the choice of tenecteplase or SK should be individualized. In patients presenting between 4 and 12 hours after symptom onset, speed of reperfusion is of less importance and the choice of SK and tenecteplase are equivalent choices.

- SK is the logical choice in the young or older patient with an uncomplicated inferior MI but the thrombolytic choice for this subset of patients remains varied in the US.
- The choice of tenecteplase, tPA, or SK is of little consequence to public health worldwide, particularly when the real problem is the ER door-to-needle time which, is still inexcusably high, in excess of 40 minutes in more than 50% of patients admitted in the US.

Absolute contraindications include:

- Active internal bleeding within the prior weeks.
- Suspected aortic dissection.
- Recent head injury or cerebral neoplasm.
- Recent trauma, major surgery within 8 weeks.
- Recent prolonged or clearly traumatic cardiopulmonary resuscitation.
- History of cerebrovascular accident known to be hemorrhagic.
- Cerebrovascular accident within 6 months.
- Severe hypertension, uncontrolled blood pressure more than 200/110 mmHg.

Relative contraindications include:

- Known bleeding diathesis or current use of anticoagulants.
- Active peptic ulcer without bleeding; patient on medications.
- History of severe hypertension under drug treatment; systolic more than 180 mmHg, diastolic more than 110 mmHg.
- Significant liver dysfunction or esophageal varices.
- Underlying malignancy.
- Elderly patients who are confused, lethargic, or agitated.

Complications of thrombolytic therapy include:

- Bleeding, especially in patients requiring invasive procedures. Intracranial bleeding reportedly occurs in 0.3–1.4% and is more common in patients older than 70.
- Rarely myocardial and splenic rupture, cholesterol embolization.
- Hypotension and allergic reaction occur in approximately 5–10% with SK or anistreplase.

STREPTOKINASE (STREPTASE, KABIKINASE)

The SK combines with plasminogen to form plasminogen activator complex. The complex converts free plasminogen to plasmin, which causes fibrinogenolysis and independent lysis of fibrin. SK also causes activation of fibrin-bound plasminogen; thus, two independent actions occur. The activator complex has a half-life of about 85 minutes. The extensive coagulation defect begins rapidly after administration, remains intense for about 4–8 hours, and dwindles over the following 36–48 hours. Heparin is not required when SK is administered.

About 65% coronary patency rate is observed when 1.5 million U of the drug are given within 3 hours of onset of symptoms of infarction. Concomitant heparin is not advisable. Allergic reactions are seen in about 2% of patients. Edema, bronchospasm, angioneurotic edema, and anaphylaxis are reported in 0.1–0.5% with apparently no fatalities. Hypotension occurs in 6–8% of patients but usually is responsive to fluid administration.

tPA is the physiological activator of plasminogen but has a higher affinity for fibrin-bound plasminogen. tPA's specificity for fibrin-bound plasminogen is, however, relative and dose-dependent. Activation of free plasminogen occurs with increasing dosage and blood levels of tPA. Thus, bleeding complications are similar to SK. Because tPA therapy results in a significantly faster achieved higher vessel patency rate (85% at 90 minutes) than SK, and tPA was used in ISIS-3 without front loading and without the necessary combination with IV heparin for 24–48 hours; further randomized studies using different

heparin regimens were conducted to resolve the issue. The net clinical outcome (total death plus stroke) in ISIS-3 was similar (11.1%) in the SK- versus the tPA-treated group. As outlined earlier, the GUSTO trial showed accelerated tPA led to a significant 14% mortality reduction compared with SK. The preferred dose of tPA is a 15-mg bolus, 50 mg over 30 minutes, and the remaining 35 mg over the next 30 minutes. Plasma clearance is decreased with hepatic dysfunction, and the drug is not advisable in patients who have hepatic disease (dosage, [Table 1.6.](#)).

Retepase, a recombinant plasminogen activator, is as effective as SK when administered as two IV boluses of 10 million U, 30 minutes apart.

TENECTEPLASE (TNKase)

TNKase is a genetically engineered triple-combination mutant of native tPA. In ASSENT 11 the drug caused a similar mortality reduction as did tPA in patients administered the drug's less than 4 hours from onset, but it was superior in patients treated more than 4 hours. The major advantage is the ease of single bolus injection; TNKase has replaced tPA in many institutions.

The ASSENT-3 trial randomized patients with ST elevation MI to receive one of three treatment strategies: full-dose tenecteplase with unfractionated heparin, full-dose TNKase with enoxaparin, or half dose TNKase with abciximab and unfractionated heparin. Results of the trial indicated that the use of enoxaparin with standard dose fibrinolysis provides a similar reduction in mortality and cardiac events as combination of reduced dose of thrombolytic agent plus abciximab without an increased risk of major hemorrhage.

Dosage for TNKase:

- < 60kg 30 mg in 6 mL over 5 seconds.
- 60–70 kg 35 mg in 7 mL fluid.
- 70–80 kg 40 mg in 8 mL.
- 80–90 kg 45 mg in 9 mL.
- > 90 kg 50 mg in 10 mL.

Heparin

Heparin use is necessary with tPA, or TNKase:

- Dosage: 60 U/kg bolus IV heparin, 4000 U/bolus maximum, then infusion 12 U/kg/hour, maximum 1000 U/hour, with assessment of the partial thromboplastin (PTT) at 3 hours and careful adjustment of the PTT time between 50 and 70 seconds (or 1.5 to 2 times control).
- Use a heparin normogram to adjust dose.
- PTT < 35 seconds, give 2000 U and increase infusion 2 U/kg/hour.
- 36–45 seconds, increase infusion 2 U/kg.
- 46–70 seconds, no change.
- 71–81 seconds, decrease infusion 1U /kg/hour.
- 81–90 seconds, decrease 2U /kg/hour.
- Low-molecular-weight heparin (LMWH), Enoxaparin, has replaced IV heparin in many institutions and is used if the serum creatinine is not elevated > 1.5 mg/dL (133 μ mol/L).

β -BLOCKER THERAPY

Acute coronary occlusion producing anteroseptal or anterior MI is often associated with sinus tachycardia. Necrotic tissue is surrounded for a time by a zone of severe

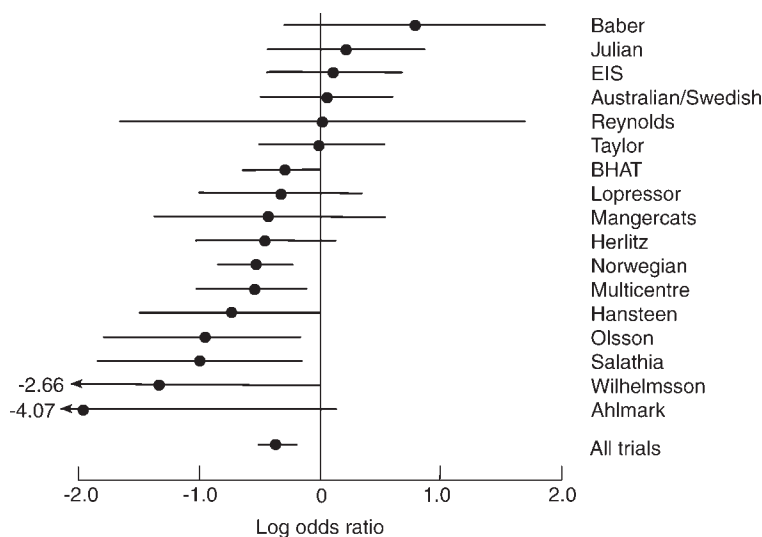


Fig. 1.41. Change in incidence of sudden cardiac death as a result of beta blockade. Odds ratios. From Julian D, Braunwald E. Management of acute myocardial infarction. London: WB Saunders, 1994:203. Reprinted with permission, from Elsevier.

myocardial ischemia and injury that causes pain. Both ischemia and pain initiate catecholamine release and the vicious circle is perpetuated (Fig. 1.1.). During the early phase of infarction, the amount of myocardial damage is not fixed and a dynamic process is usually in evolution. β -blockers decrease the incidence of sudden cardiac death. Timolol has been shown to cause a 67% reduction in the risk of sudden death. Change in the incidence of sudden cardiac death as a result of β -blockade is shown in Fig. 1.41. It is relevant that:

- Baber studied only 49 patients.
- Julian used sotalol, an agent that is not lipophilic, and thus achieves low brain concentration and also predisposes to torsades de pointes.
- The European Infarction Study used oxprenolol, which has moderate intrinsic sympathomimetic activity (ISA) and negates cardioprotective effects.
- Taylor's group was administered oxprenolol.

Thus, all of the negative studies shown in Fig. 1.41. used an ISA agent or sotalol. Significant survival benefit was documented for metoprolol and timolol.

β -blockers have a proven beneficial effect when relieving pain, ischemia, and injury current during the early phase of acute MI. Decreased mortality, modest decrease in infarct size, and decrease in the reinfarction rates have been documented in patients given IV β -blockers, followed by oral therapy from day 1 and for 30–90 days, as well as up to 2 years postinfarction. The early decrease in mortality and infarction rates have been sufficiently significant to warrant early β -blocker therapy for all patients with MI, especially anterior MI with sinus tachycardia, provided that the systolic blood pressure (SBP) is more than 100 mmHg and there is no contraindication to β -blockade. If adverse effects are feared, esmolol IV is advisable because its action dissipates in about 10 minutes. In the US, esmolol and metoprolol are approved for IV use during acute MI. Oral or IV atenolol has not been shown to reduce mortality or reinfarction and is not advisable (see

discussion on which β -blocker to choose) (*see* Table 1.4. for dosage). The merits of β -adrenergic blockade in ACS are given in Fig. 1.1.

- Decrease in heart rate prolongs the diastolic interval during which coronary perfusion normally occurs. Thus, an increase in blood flow may ensue to ischemic areas of myocardium. Necrotic tissue is not capable of salvage, but the area subject to infarction may remain ischemic for several hours, and increased perfusion to ischemic areas may limit the ultimate size of infarction.
- Sinus tachycardia causes increased O_2 demand and can shift the balance in ischemic tissue toward necrosis; sinus tachycardia decreases VF threshold. β -Blockers relieve sinus tachycardia and associated hypertension, and increase VF threshold; some trials showed decrease in the incidence of VF.
- β -Blockers decrease phase 4 depolarization and thus suppress arrhythmias that may arise in ischemic tissue, especially when initiated by catecholamines.
- Decrease in myocardial contractility decreases O_2 requirement.
- Decrease in stress on infarcting tissue by the remaining myocardium appears to be responsible for the modest but important decrease in the incidence of early myocardial rupture owing to acute MI.
- In patients given thrombolytics, there is currently no confirmation of experimental findings that viability of ischemic myocardium is prolonged. β -Blockers have been shown to decrease the incidence of postthrombolytic ischemic events in patients.
- Where there is some residual patency of the infarcted-related artery, β -blockers do exert a strong antiischemic effect and will decrease infarct size; in this group of patients, perhaps equivalent to non-Q-wave infarction, β -blockers have been demonstrated to have a major impact on pain and serious events.

The ACC/AHA Task Force recommends β -blocker IV therapy given at the same time as aspirin, as soon as the diagnosis of acute MI is entertained. This is especially important in patients with anteroseptal and anterior MI with a heart rate of more than 100 and/or SBP more than 110 mmHg in whom no contraindication to β -blockade exists. In this subset, β -blockers should be given in the ER at the same time as aspirin and sublingual nitroglycerin. No harm can occur if the patient is not selected later for thrombolytic therapy. The concomitant use with a thrombolytic agent has been documented in TIMI 2-B, and other trials as safe and worthwhile. β -Blocker therapy from day 3 for 2 years is expected to save 4 lives annually per 100 treated (*see* Chapter 4).

Early IV followed by oral β -blocker therapy should be strongly considered for all patients presenting with definite or probable acute infarction in whom contraindications do not exist. These agents are particularly strongly indicated in the following situations:

- Sinus tachycardia unassociated with hypotension or clinically apparent heart failure;
- Rapid ventricular response to atrial fibrillation (AF) or atrial flutter;
- Administration of thrombolytic agents: to prevent arrhythmias and/or ischemia and improve survival;
- Recurrent ischemic pain;
- Moderate impairment of left ventricular function with frequent or complex ventricular ectopy after the first week postinfarction.

CLINICAL TRIALS

Clinical trials have not adequately tested the use of β -blockers during the first 3 hours of onset of symptoms.

MIAMI Trial

The Metoprolol in Acute Myocardial Infarction (MIAMI) trial is often quoted as showing a lack of effectiveness of early β -blocker (atenolol) use in reducing mortality, but the mean treatment time was 11 hours. In ISIS-1, 80% of patients were treated up to 8 hours and less than 30% within 4 hours of onset, resulting in a 15% decrease in cardiovascular mortality with significant prevention of early myocardial rupture. In addition, atenolol is a poorly effective β -blocker.

TIMI 2-B

β -Blockers were given to 720 patients at about 3–4 hours after onset of symptoms in the TIMI 2-B and resulted in a 47% decrease in the incidence of reinfarction in 6 days; also, the incidence of recurrent chest pain was significantly decreased. A decrease in mortality and myocardial rupture was not observed in TIMI-2, probably owing to the small number of patients studied, resulting in a type II error. Pooled trial results with the use of β -blockade covering mainly 4–6 hours from onset of symptoms indicate a 23% decrease in mortality occurring on day 1 and then no significant decrease during the next few weeks.

Norwegian Postinfarction Timolol Trial

This hallmark clinical trial was the first to document the lifesaving effects of β -blockers in patients following a heart attack followed for up to 2 years. In this superbly conducted Norwegian study, 1884 patients were randomized to two groups. The first group of 942 patients were started on a β -blocker, timolol, 7 days after their heart attack. The other group received a placebo. At the end of 2 years, the treated group had a 35% reduction in heart death, 28% reduction in new heart attack, and 67% reduction in sudden death ($p < 0.001$). The impressive results were observed in smokers and nonsmokers and was published in 1981; see Fig. 1.1.

Clinical trials have documented that β -blockers significantly prevent death in patients who are given the drug from the first week of the heart attack and for an additional 2 years.

The American β -Blocker Heart Attack Trial (BHAT)

This trial gave similar, if not just as impressive results. In 16,400 randomized patients, propranolol, 120–240 mg administered to patients from 14 days after MI and followed for 2 years showed a significant 26% reduction in mortality rate. Propranolol was not effective in smokers, however, because of the interactions in the liver; cigarette smoking lowers the blood levels of propranolol and decreases cardioprotective effects.

The CAPRICORN Study

In this recent large multicenter study, patients from 1 to 21 days after acute MI and EF $< 40\%$ were randomized. The control group received optimal medical therapy, including the use of ACE inhibitors. The treated group received carvedilol 6.25 mg, increased progressively to 25 g twice daily. Carvedilol caused a significant 23% reduction in all-cause mortality in patients observed for 2.5 years; the mortality was 116 (12%) in the treated versus 151 (15%) in the placebo group. The absolute reduction in risk was 2.3%. Forty-three patients need to be treated for 1 year to save one life. Importantly, the reduction observed with carvedilol is in addition to those of ACE inhibitors alone; this reduction is virtually the same as that observed in a meta-analysis of three ACE inhibitor trials, Save, AIRE, and TRACE.

Carvedilol in COPERNICUS showed significant survival benefits and decrease in hospitalization rates in patients with moderate and severe HF indicating the safety and salutary benefits of specific β -blockers in patients with sick hearts (*see* Chapter on heart failure).

The UK Prospective Diabetes Study (UKPDS) Results

The UKPDS results confirm that in type II diabetes, β -blockers significantly reduced mortality, risk for heart attack, stroke, and, importantly, peripheral vascular disease as well as microvascular disease. Over a 9-year follow-up, the change in albuminuria and serum creatinine was the same in the ACE inhibitor, captopril group, and the β -blocker group.

- Implications. β -Blockers and aspirin are proven to prevent death from heart attack. About 450,000 heart attack patients survive to leave hospitals in the US and Canada annually, and about 100,000 of these patients will have another heart attack in the following year. β -Blockers can prevent a heart attack in approximately 20% (30,000) of these patients and prevent death in about 25%. Yet these cardioprotective drugs that can prolong life are not advocated and prescribed by many internists and family physicians because of the fear of impotence and fatigue that may occur, albeit rarely. Many practitioners continue to use newer agents, particularly, calcium antagonists, nitrates, and other agents that have not been shown to prolong life in randomized clinical trials (RCTs).

WHICH β -BLOCKER TO CHOOSE

- Sufficient attention has not been paid by the medical profession and researchers regarding the subtle differences that exist amongst the available β -blocking drugs.
- Cardioselective agents are safer than nonselective β -blockers in diabetic patients and in those with mild-to-moderate chronic obstructive pulmonary disease (COPD); this information appears to be well-known worldwide, but a recent study indicates that carvedilol is superior to metoprolol in diabetics.
- Agents with β -agonist activity (intrinsic sympathomimetic activity [ISA]) are not cardioprotective (eg., pindolol) and should become obsolete
- Of the cardioselective agents only metoprolol has been shown to significantly reduce coronary heart disease mortality and events in RCTs. Bisoprolol has not been tried in trials of patients with MI, but was beneficial in HF trial. A most popular cardioselective agent, atenolol, is used worldwide, but has never been tested in an RCT in the post-MI patients or in patients with left ventricular dysfunction, or HF. It should not be assumed that this agent has similar cardioprotective properties as shown for metoprolol, carvedilol, propranolol, bisoprolol, and timolol (*see* earlier discussion of clinical trials).
- Brain concentration: Lipophilicity allows high concentration of drug in the brain; appears to block sympathetic discharge in the hypothalamus and elevates central vagal tone to a greater extent than water soluble, hydrophilic agents, such as atenolol, and this may relate to the prevention of sudden cardiac death. Abal et al., in a rabbit model, showed that although both metoprolol (lipophilic) and atenolol (hydrophilic) caused equal β -blockade, only metoprolol caused a reduction in sudden cardiac death. It appears that this information has not reached clinicians or researchers.
- Of the cardioselective agents, only bisoprolol and metoprolol, both with lipophilic properties, have been shown to decrease cardiac mortality. Only carvedilol, timolol, and propranolol, of all lipophilic agents, have been shown to reduce mortality and morbidity in postinfarction patients. Atenolol, a most widely used β -blocker is non-lipophilic and probably provides less cardioprotection than proven agents and has not been adequately

tested in RCTs; sotalol and nonlipophilic oxprenolol have been tested in RCTs and have not been shown to significantly reduce mortality or morbidity. Oxprenolol has some β -agonist activity that negates cardioprotection.

- Both nonselectivity and lipophilicity may provide enhanced cardioprotection. It is possible that cardioselective agents are not as cardioprotective as β_1 β_2 blocking agents. Large, RCTs in the post-MI patients with long-term follow-up have only been carried out with the nonselective agents timolol and propranolol, and recently with carvedilol; each agent proved beneficial in reducing cardiac mortality and morbidity. The cardioselective agent, metoprolol, reduced mortality and morbidity in a postinfarction trial but follow-up was 3 months. The drug was also successful in an HF trial (MERIT). The cardioselective agent Bisoprolol reduced mortality and morbidity in a heart failure trial (CIBIS 11), and is partially lipophilic. Atenolol was used in an early acute MI trial, and the result was only modestly significant. The methodology was unsound; patients were admitted 4, 6, and 12 hours following infarction, so this was not a genuine trial of a β -blocker during the first few hours of infarction. Unfortunately, atenolol is the β -blocking drug most often used in antihypertensive trials comparing β -blocker with the diuretics, calcium antagonists, and ACE inhibitors. A nonselective, lipophilic drug that is proven effective in postinfarction patients and in patients with severe HF such as carvedilol should be tested in hypertensive patients. The cardioselective agent bisoprolol has lipophilic properties and deserves testing in hypertensive trials.
- Cigarette smoking: Cigarette smoking decreases blood levels of propranolol and cardioprotective effect are lost. The drug did not cause a decrease in mortality or morbidity in postinfarction patients who were smokers.
- Potassium balance: β -blockade causes a mild increase in serum potassium because of blockade of the β_2 -mediated epinephrine activation of the Na K⁺ ATPase pump, which transports potassium from extracellular fluid into the cells. During stress, serum potassium has been observed to decrease 1.0 mEq/L, and this can be prevented by blockade of β_2 receptors. Non-cardioselective β -blockers are superior to selective agents in preventing fluctuations of serum potassium concentration during stress and possibly during acute MI and may be more cardioprotective than cardioselective agents.
- Carvedilol has important differences from atenolol, metoprolol, and other β -blockers. This lipophilic β_1 , β_2 blocking agent is a very mild α_1 -blocker and causes arteriolar dilatation; also, antioxidant and antiproliferative properties have been noted; the drug lowers plasma endothelin levels.

Clinicians should use a β -blocker that has proven effective in RCTs and these include:

- Carvedilol (proven for early use in acute MI and over 2 years) and the COPENICUS study indicate decreased mortality and morbidity in patients with HF.
- Metoprolol (Toprol XL), timolol, and propranolol are proven agents.
- The commonly used agent, atenolol, is unproven in patients with MI and its use should be curtailed; β -blockers have subtle and important differences. Sotalolol is reserved for the management of paroxysmal atrial fibrillation and potentially malignant ventricular arrhythmias. **Other β -blockers should be rendered obsolete.**

Adverse Effects and Cautions

β -Blockers are safe cardioactive agents if their warnings and contraindications are followed.

- They are not advisable in patients with severe class IV HF. They are however, indicated in class I to III HF; class IV patients who have been stabilized are no longer decompensated.

sated, and have no evidence of the pulmonary edema and of fluid retention can be started on very small doses of carvedilol (3.5 mg).

- They are contraindicated in patients with bronchial asthma and in patients with severe COPD, including emphysema. Patients with mild chronic bronchitis may be given a cardioselective β_1 agent and may require supplemental salbutamol.
- Complete heart block and varying grades of heart block are contraindications.
- Severe bradycardia < 48 BPM.
- Relative contraindications include allergic rhinitis and insulin-dependent diabetics who are in prone to hypoglycemia.
- Raynaud's phenomenon.
- Adverse effects include: tiredness and fatigue in about 10% of patients; and erectile dysfunction in about 10%; precipitation of HF in patients with poor left ventricular function, slowing of the heart rate causing bradycardia < 45 BPM; depression in $\leq 5\%$; and cold extremities.
- β -blockers need to be discontinued the day prior to dipyridamole cardiac nuclear scans because they reduce the steal phenomenon caused by dipyridamole; importantly, the β -blocker may be necessary for stabilizing the patient's cardiac condition, so caution is required.

NITROGLYCERIN

In patients with anterior infarction, there is evidence to suggest that IV nitroglycerin causes a slight decrease in mortality. ISIS-4 indicates that nitrates administered from day 1 for 4 weeks do not improve survival.

The ACC/AHA Task Force considers the data inadequate to recommend the routine use of IV nitroglycerin in patients with uncomplicated acute MI.

IV nitroglycerin may be selected for patients with:

- Chest pain unresponsive to morphine and β -blockers.
- Stuttering pattern of pain, indicating continued ischemia.
- Moderate-to-severe heart failure or pulmonary edema complicating acute MI and PCWP more than 20 mmHg.
- Hypertension.

Contraindications include:

- Hypovolemia.
- Inferior infarction. Nitroglycerin is used cautiously only when needed to manage postinfarction angina and/or pulmonary edema, because hypotension may be precipitated.
- Right ventricular infarction.
- Cardiac tamponade.
- Significant hypoxemia. IV nitroglycerin may accentuate hypoxemia by increasing ventilation perfusion mismatch.

Adverse effects include worsening of hypoxemia and severe hypotension that may increase ischemia. Preload decrease may cause hypotension. Rarely, nitrates precipitate bradycardia and hypotension responsive to atropine. Oral, cutaneous, and other nitrates, including interaction with heparin, are discussed further in Chapter 4 (for dosage, *see* Infusion Pump Chart in [Table 4.2.](#)). Commence with a 5- or 10- μ g bolus injection and then increase the dose by 5–10 μ g/minute every 5 or 10 minutes to abolish chest pain and/or to achieve a mean arterial pressure decrease of 10% and a maximal decrease of 20% in hypertensive patients. The SBP must not be allowed to fall under 95 mmHg or diastolic

less than 60 mmHg. Heart rate should be maintained less than 110 BPM. Nitrate tolerance develops after about 48 hours of IV nitroglycerin use, but in unstable patients, the dose is titrated up as required rather than leaving a nitrate-free interval. Interaction occurs with tPA at very high doses of IV nitroglycerin to accelerate tPA clearance by altering hepatic blood flow.

ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS

The ACC/AHA class 1 (highest) recommendation is selective: After the routine administration of aspirin and β -blockers, followed by thrombolytics or PCI patients with acute MI should be considered for ACE inhibitor therapy. High-risk patients: anterior MI, HF or the absence of HF and EF less than 40% should be commenced on ACE inhibitor therapy. Patients with uncomplicated acute MI, particularly inferior MI, with EF greater than 40%, are not expected to benefit significantly.

ACE inhibitors are contraindicated in patients with hypotension, SBP less than 100 mmHg, renal failure, aortic stenosis or bilateral renal artery stenosis.

Therapies preferably commence with ramipril 2.5 mg daily, increasing to 5–10 mg before discharge or a short-acting agents captopril, 6.25 mg around increased to 12.5 mg twice daily and titrated to 25 to the 75.5 mg twice daily. Prior to discharge, captopril may be replaced by a once daily ACE inhibitor, such as ramipril or lisinopril.

Clinical studies that substantiated the beneficial effect of ACE inhibitors and angiotensin receptor blockers (ARBs) in patients with acute MI include:

- SMILE: Zofenopril commenced approximately 15 hours after an acute anterior MI and continued for 6 weeks caused a significant reduction in mortality and occurrence of HF at 6 weeks and at 1 year follow-up.
- ISIS- 4 showed that captopril is effective in improving survival.
- VALIANT: This large randomized trial of 14,703 patients with MI and radiological or clinical evidence of heart failure showed that the ARB, Valsartan, is as beneficial as captopril in reducing mortality. Valsartan 80 mg titrated to a target dose of 160 mg was compared with 50 mg of captopril three times daily. After a median follow-up of 24.7 months, old-cause mortality was similar in patients treated with valsartan or, captopril, or both, in addition to standard therapy. Estimates of death at 1 year were 12.5% for Valsartan-treated patients, 12.3% for patients administered combination therapy, versus 13.3% for those receiving captopril monotherapy. Rates of recurrent MI and hospitalization for HF were similar; a similar beneficial effect was observed for candesartan in CHARM.

Thus ARBs, particularly Valsartan or Candesartan, can replace ACE inhibitors for this group of patients because of superior compliance owing to absence of cough and the very rare occurrence of angioedema. Not all experts agree that ARBs are appropriate replacement to ACE inhibitors. Clear answers are awaited from RCTs.

The SAVE, TRACE, and AIRE trials evaluated patients with LV dysfunction or clinical heart failure with therapy commenced a few days following infarction.

CALCIUM ANTAGONISTS

In a very small study of 288 postinfarction patients treated with diltiazem, 11 patients died, as opposed to 9 patients in the placebo group; diltiazem decreased infarction rates at 2 weeks but was not compared with aspirin. This small, short-term study was used to

advance the claim that diltiazem is the drug of choice in the management of non-Q-wave infarction prior to the current use of PCI. Physicians extended the drug's use to other ischemic syndromes with the hope that the drug will prevent reinfarction but without bearing in mind that the drug does not significantly decrease the cardiac death rate.

A second large, well-run study of 2466 postinfarction patients treated with diltiazem showed an increase in total mortality caused by diltiazem in patients with left ventricular dysfunction. Thus, diltiazem is not recommended in acute MI, Q-wave or non-Q-wave, if signs of left ventricular dysfunction are present or if the EF is less than 40%. There was a trend in favor of a decrease in total events (death and/or reinfarction) in the small number of patients with non-Q-wave infarction treated for 1 year with diltiazem, but the evidence from this overall negative study is not sound enough to recommend diltiazem to patients with non-Q-wave infarction. In the absence of ongoing chest pain, diltiazem has an uncertain role in the management of non-Q-wave infarction in patients with good left ventricular function who are unable to take a β -blocking drug and in whom further interventional therapy in the form of angioplasty or bypass surgery is contraindicated because of underlying ill health or age (*see* Chapter 4).

It is clear that calcium antagonists have no role in the routine management of acute MI. Meta-analysis indicates that this group of drugs does not significantly decrease infarct size, infarction rates, or mortality in patients with acute MI. Nifedipine used without a β -blocking drug in patients with unstable angina may increase chest pain and shows no beneficial trend in mortality.

- Dihydropyridines should be avoided in patients with acute MI because they may increase heart rate and vasodilation may cause a decrease in blood pressure. Also, calcium antagonists may decrease blood pressure during the early hours of infarction.
- Importantly, a decrease in blood pressure may contraindicate the use of life-saving medications: β -blockers, thrombolytic agents, IV nitroglycerin, and/or ACE inhibitors; if chest pain is not relieved or recurrence of pain suggests ongoing ischemia despite the use of these four vaso-active agents, it is wise to proceed with angiography and PCI rather than adding amlodipine.
- Verapamil should not be used in patients with acute MI because of its negative inotropic effect and strong propensity to precipitate heart failure, sinus arrest, or asystole.
- Diltiazem is not indicated in acute MI because it increases mortality in patients who manifest left ventricular dysfunction or in those with an EF less than 40%.

Magnesium

The Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) studied 2316 patients with suspected acute MI. Only 60% of patients (1390) had proven infarction, and 52% of these did not receive a thrombolytic agent. Thirty-five percent of all trial patients were given a thrombolytic agent, and only 66% were administered aspirin. The study is thus not a comparison between magnesium and thrombolytic therapy. Furthermore, no indication is given as to the number of patients who had probable Q and non-Q wave infarction. Thrombolytic therapy is not indicated in patients with non-Q wave infarcts. The study results thus have limited application.

- ISIS-4 randomized 85,000 patients (median 8 hours) after the onset of symptoms of infarction to captopril, mononitrate, and 24 hours of IV magnesium sulfate (8-mmol bolus followed by 72 mmol). Magnesium therapy showed no reduction in 35-day mortality. There were 2216 deaths (7.6%) in the magnesium group versus 2103 (7.2%) in the

control group. There was no decrease in mortality in patients treated early or late or in the presence or absence of fibrinolytic therapy or in those at high risk of death. Regarding LIMIT-2 and ISIS-4 patients, although only 40% of the ISIS-4 group was treated within 6 hours of symptom onset, the number of patients studied was much larger than that in LIMIT-2. ISIS-4 patients randomized within 3 hours and administered magnesium showed no reduction in mortality. There were 342 deaths in 4847 magnesium-treated patients (7.1%) versus 345 deaths in 4865 patients not treated with magnesium (7.1%).

- ISIS-4 conclusively showed that magnesium therapy does not improve survival. IV magnesium was associated with small but significant increases in HF, hypotension, bradycardia, and in deaths attributed to cardiogenic shock.
- In 6213 randomized patients, the MAGIC trial showed that magnesium administered IV within 6 hours of the onset of symptoms in high-risk patients with ST elevation MI has no effect on 30-day mortality. Thus, magnesium is not recommended in the management of acute MI.

NON-ST ELEVATION MI (NON-Q-WAVE MI)

The term “non-Q-wave infarction” was used in the past to embrace nontransmural infarction and the term “Q-wave infarction” to denote transmural infarction. Because of anatomical inconsistencies, however, the use of the terms “transmural” and “nontransmural” are no longer recommended. In addition, during the past decade a new term acute coronary syndrome has been introduced to describe acute chest pain resulting in acute phases of CAD: ST elevation MI, non-ST elevation, and unstable angina. The term non-Q-wave MI has been largely replaced by non-ST elevation MI that qualifies patients with acute chest pain ST segment changes but without ST elevations accompanied by elevation of cardiac enzymes: troponin or CK-MB.

The troponins are more sensitive than CK-MB and are elevated from 6 hours from the onset of infarction to approximately 10 days postinfarction.

The mortality and reinfarction rates of non-Q-wave and Q-wave infarctions are given in [Tables 1.2](#), and [2.2](#). It is established that patients with non-Q-wave infarction represent a group at high risk for the occurrence of reinfarction within 3 months of hospital discharge.

High-Risk Patients

Patients with non-ST elevation MI and postinfarction angina or those who continue to have transient ischemic ECG changes, or considered non-low risk, require urgent coronary angiography with a view to PCI. Patients should be stratified as low risk, and all others are considered as high risk. It makes little sense from a practical standpoint to grade some patients as intermediate risk. All patients with elevated troponin are high risk. Renal dysfunction impairs the clearance of troponins; nevertheless, troponin levels remain valuable predictors of outcome in these subjects.

Features in addition to elevated troponin and CK-MB levels that indicate high risk include:

- Recurrent ischemia: ST depression or deviation.
- Hemodynamic instability.
- Postinfarction angina.
- Arrhythmias.
- High-risk finding on stress testing.
- Depressed LV function; EF less than 40%.
- PCI within 6 months.

- Previous coronary artery bypass grafting (CABG).
- Diabetes.

All patients with non-Q wave infarction should be treated with aspirin and a β -blocker (metoprolol or carvedilol) if no contraindication exists to β -blockade. Enoxaparin, platelet receptor blockers, clopidogrel, and statins play major roles in treatment along with PCI. β -Blockers remain first-line drug therapy along with aspirin, enoxaparin, and clopidogrel, in the management of non-ST elevation MI up to the moment of PCI. In the CREDO trial, 2116 patients were randomized. Clopidogrel (300 mg) and aspirin were administered from 6–24 hours prior to PCI. At 1 year follow-up, this therapy caused a 26.9% reduction in the risk of death, MI, or stroke ($p = 0.02$). Atorvastatin 60 to 80 mg or other statin is advisable to achieve LDL goal of <80 mg/dL (2 mmol/L) and achieve low CPR levels regardless of lowered LDL levels.

Low-Risk Patients

Patients with uncomplicated non-Q wave infarction that are considered low risk (EF $>40\%$, acceptable stress test) are discharged on aspirin, a β -blocker, ACE inhibitor, and a statin to maintain a low-density lipoprotein (LDL) cholesterol 2.0 mg/dL (<80 mg/dL). Clopidogrel 75 mg daily is given for 1–9 months. Patients who have good left ventricular function with an EF greater than 40% and in whom β -blockers are contraindicated should receive diltiazem instead until stress testing and nuclear studies are completed (within 4 to 6 weeks).

TIMI RISK SCORE

The seven TIMI risk score is a risk-assessment model: event rates have been noted to rise from 4.7% when no or one risk factor was present to 40.9% when six or seven risk factors were present. The seven risk factors are:

1. Age >65 .
2. Three risk factors for CAD.
3. Prior coronary stenosis $>50\%$.
4. ST segment deviation on ECG on presentation.
5. Two anginal events in <24 hours.
6. Use of ASPIRIN in prior 7 days.
7. Elevated troponin or CK-MB.

ANTIPLATELET AGENTS FOR ACUTE CORONARY SYNDROME

Clopidogrel

Clopidogrel is a thienopyridine derivative, an analog of ticlopidine; the drug inhibits platelet aggregation by inhibiting adenosine diphosphate, (ADP)-induced platelet activation and platelet fibrinogen binding. Clopidogrel is more effective than ticlopidine but has considerably less toxicity. Clopidogrel prevents platelet degranulation and the release reaction that produces prothrombotic substances. The drug selectively and irreversibly prevents ADP from binding to the platelet-ADP receptor and inhibits the transformation of the GP 11b/11a receptor to the form that binds fibrinogen and links platelets.

The following clinical studies confirm the drug's effectiveness.

CURE Trial

The clopidogrel in unstable angina recurrent events (CURE) trial was a double-blind, placebo-controlled, RCT with clopidogrel versus placebo in addition to aspirin and other optimal therapy for patients with unstable angina and non-ST elevation MI. Of the 12,652 patients, 16.5% (2072) had CABG and 21% (2658) had PCI. At 12 months follow-up, clopidogrel treatment caused a 20% relative risk reduction in the outcome of MI, stroke or cardiovascular death ($p = 0.00009$). Total cardiac deaths were not significantly decreased, however. Excessive bleeding occurred in the clopidogrel group (3.7% versus 2.7%; $p = 0.001$). The major risk of bleeding with clopidogrel has been noted in patients with non-ST elevation MI and unstable angina undergoing immediate CABG. In the CURE study, patients undergoing CABG had the clopidogrel discontinued a few days before surgery.

PCI Cure

The PCI CURE study was a prospectively planned substudy of CURE. The study was confined to the 2658 patients who underwent PCI and randomized to clopidogrel and aspirin versus aspirin alone. At 30 days, there was a significant benefit of clopidogrel, aspirin combination versus aspirin alone. Most important, clopidogrel therapy was significantly beneficial regardless of whether patients received PCI on an emergency basis or days following discharge.

CREDO Trial

This trial randomized 2116 patients. Clopidogrel (300 or 600 mg) plus aspirin was administered from 3–24 hours before PCI. At 1 year, for patients who received clopidogrel more than 6 hours before PCI, the combination caused a 26.9% reduction in the risk of death, MI, or stroke ($p = 0.02$). A 600-mg loading dose given 12–24 hours (at least 6 hours) prior to PCI and stenting is a recommended regimen. Clopidogrel has replaced ticlopidine.

- In patients scheduled for urgent coronary artery bypass surgery, clopidogrel should be withheld for at least 5–7 days to avoid bleeding.
- Clopidogrel should be administered ad hoc prior to PCI but after diagnostic coronary angiograms.
- Clopidogrel and platelet receptor blockers compliment the beneficial antiplatelet effects of each other. Both agents should be administered prior to PCI in all high-risk patients; neither agent is a complete substitute for the other. Platelet activation is inhibited by thienopyridine; clopidogrel is not affected by platelet GP IIb/IIIa blockade, and platelet aggregation, suppressed by blockade of the platelet GP IIb/IIIa integrin, is only modestly inhibited by thienopyridine therapy. In the 2064 patient ESPRIT stent PCI study, an additional 35% relative risk reduction in the composite endpoint of death, MI, and urgent target vessel revascularization was obtained with eptifibatide and concurrent thienopyridine therapy.
- Clopidogrel should be continued for 1 year post-PCI. The beneficial effects of clopidogrel on instant restenosis appear to be partly nullified by hepatic metabolized statins such as atorvastatin. CYP3A4 activates clopidogrel; atorvastatin, another CYP3A4 substrate, competitively inhibits this activation. Rosuvastatin does not interact unfavorably. Presently there is some controversy as to the importance of the interaction that may be modest; further studies should clarify this important interaction.

Platelet Glycoprotein IIb/ IIIa Receptor Blockers

There are approximately 75,000 GP IIb/IIIa receptors on the surface of each platelet. Antagonism of these receptors blocks the final common pathway for platelet aggregation—the binding of fibrinogen to the platelet glycoprotein receptors; platelet aggregation caused by thrombin, thromboxane A₂, ADP, collagen and shear-induced platelet aggregation is prevented. Unfortunately, these agents do not affect platelet activation and degranulation, unlike ADP receptor antagonists, which are active at much earlier stages of the atherothrombotic cascade.

Abciximab (ReoPRO)

This widely used platelet receptor blocker inhibits both α 11b3 receptor and α v β 3 receptors. Several RCTs have documented the beneficial effects when used for patients undergoing urgent PCI. The drug is not recommended for patients who are not scheduled for urgent PCI.

Dosage: 0.25 mg per kg IV bolus over at least 1 minute, immediately followed by IV infusion: 0.125 μ g/kg/minute for 18 to 24 hours, concluding 1 hour after PCI.

The major beneficial effects observed in the ACE trial (*see* section under angioplasty/stent for ST elevation MI, p. 45) should pave the way for the selection of this agent over eptifibatide and tirofiban for non-ST elevation MI patients undergoing angiography and PCI.

Eptifibatide (Integrilin)

This platelet receptor blocker has actions that are similar to abciximab. In one RCT (PURSUIT), a significant benefit was observed in patients who underwent PCI within 72 hours with no benefit at 30 days in those without PCI. In another large RCT (TACTICS), the drug was beneficial only in patients with ACS treated with early invasive PCI. In TARGET, the drug caused less protection from major ischemic events than abciximab. In another trial (PRISM-PLUS), the drug reduced events at 7 days but not at 6 months.

Dosage: intravenous bolus of 135 μ g/kg followed by an infusion of 0.5 μ g/kg/minute for a further 20 to 24 hours after PCI.

Tirofiban (Aggrastat)

This platelet receptor blocker shows specificity toward α I1bB3 receptor and has a shorter biological half-life than abciximab and eptifibatide. This agent and eptifibatide are indicated only in patients at high risk in whom immediate PCI is not immediately planned.

- A meta-analysis of RCTs with these three agents, with the exception of abciximab, used as indicated for PCI planned within 24 hours indicates that nondiabetic patients had no survival benefit.
- In TACTICS, patients were treated with tirofiban for 48 hours plus aspirin and heparin, and randomized to either invasive therapy (coronary angiography and revascularization) or conservative strategy. It is claimed that at 6 months there was a significant reduction in death or MI ($p = 0.0498$), a modestly significant result.

The ACC/AHA Guideline Committee advises the following:

- High-risk patients, especially troponin-positive patients in whom coronary angiography is planned, should receive a GP IIb/IIIa antagonist. The two small-molecule agents,

eptifibatide and tirofiban, may be started “upstream,” i.e., hours to 2 days before, and continued during the procedure. Any of the three available GP IIb/IIIa antagonists may be started immediately before or in the course of the procedure.

- In accord with the findings of GUSTO-IV ACS, abciximab is not indicated in patients in whom PCI is not planned.
- None of the GP IIb/IIIa antagonists appear to be effective or indicated in the routine management of low-risk, troponin-negative patients in whom early angiography is not intended.
- Clopidogrel has proven to be of highly significant benefit in patients undergoing stenting, regardless of the clinical indication.
- A crucial question remains unanswered: What should be done regarding combination therapy with platelet receptor blockers and clopidogrel between the time that a patient is identified as high risk and the performance of coronary angiography?

Braunwald advises that clopidogrel should be held until the coronary anatomy is known, because of the increased risk of bleeding if CABG surgery is done within 5 days of discontinuation of clopidogrel. Although this strategy is rational, many experts in the field believe that it is preferable to begin a clopidogrel loading dose immediately in anticipation of catheterization and PCI.

Some centers use upstream small-molecule GP IIb/IIIa inhibition until a large outcome trial of upstream use compared with targeted use provides answers.

Kereiakes points out that GP IIb/IIIa inhibitors should be withheld until the coronary anatomy is established and PCI is to be commenced because the data for medical treatment with GP IIb/IIIa inhibitors is considered weak. Although, the ACC/AHA guidelines allow for early treatment with either clopidogrel or small-molecule GP IIb/IIIa inhibitors as a class I indication. Several centers withhold clopidogrel until after arteriography to avoid excessive bleeding if surgery is selected and administer abciximab at the time of PCI because it has the most convincing data in support of clinical benefit including enhanced survival.

Conclusion

If arteriography can be carried out within 24–36 hours, it appears logical to withhold clopidogrel, as Braunwald and Kereiakes suggest, until PCI is chosen and surgery is not required. Most important, because the majority of patients with non-ST elevation MI (troponin positive) are at high risk, immediate angiography is indicated and should be completed within 12–36 hours of admission to the ER. During the short period of waiting for angiogram (6–12 hours), coverage includes aspirin, β -blocker, IV nitroglycerin, ACE inhibitor, statin, and heparin.

After angiography, if PCI is selected (as often as is the case) then a 300–600 mg loading dose of clopidogrel and abciximab bolus and infusion are commenced forthwith. If angiography cannot be obtained for more than 24 hours, then upstream small-molecule platelet receptor blocker therapy and clopidogrel-loading dose of 300–600 mg is commenced; enoxaparin is used if the serum creatinine is <2 mg/dL (176 μ mol/L). If the creatinine indicates significant renal dysfunction, UFH is used and because small molecule platelet blockers (tirofiban, eptifibatide) are renally excreted, they are withheld and abciximab is used prior and during PCI. Because surgery is selected in few patients compared with the majority selected for PCI, the protective clopidogrel used initially in virtually all patients can be stopped 5–7 days prior to surgery.

BIBLIOGRAPHY

- Anderson H, DANAMI-2. The Danish trial in acute coronary angioplasty in acute myocardial infarction. *Clin Cardiol* 2002;301:90–93.
- Andersen HR, Nielsen TT, Vesterlund T, et al. Danish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in acute myocardial infarction: rationale and design of the DANish trial in Acute Myocardial Infarction-2 (DANAMI-2). *Am Heart J* 2003;146:234–241.
- Andersen HR, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *New Eng J Med* 2003;349:733–742.
- Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction—Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction) Management of Patients With STEMI: Executive Summary. *J Am Coll Cardiol* 2004;44:671–719.
- Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1879–1885.
- ASSENT—3: Assessment of the Safety and Efficacy of a New Thrombolytic Regimen Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial of acute myocardial infarction. *Lancet* 2001;358:605–613.
- Blazing MA, de Lemos JA, White HD, et al. for the A to Z Investigators. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin. *JAMA* 2004;292:55–64.
- Braunwald E. Application of current guidelines to the management of unstable angina and non-ST-elevation myocardial infarction. *Circulation* 2003;108(Suppl I):III-37.
- Califf RM, Bengtson JR. Current concepts: cardiogenic shock. *N Engl J Med* 1994;24:1724.
- Califf RM. Supplement on acute coronary syndromes: introduction. *Circulation* 2003;108:III-1.
- Cannon CP, Braunwald E, McCabe CH. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [PROVE IT–TIMI 22 trial]. *N Engl J Med* 2004;350:1495–1504.
- CAPRICORN Investigators. The effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction. The CAPRICORN randomized trial. *Lancet* 2001;357:1385–1390.
- CHARM: Granger CB, McMurray JJV, Yusuf S, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin converting enzyme inhibitors; the CHARM-alternative trial. *Lancet* 2003;362:772–776.
- COPERNICUS: carvedilol Prospective randomized cumulative survival study group effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–1658.
- Corti R, Fuster V, Badimon JJ. Pathogenetic concepts of acute coronary syndromes. *J Am Coll Cardiol* 2003;41:7s–14s.
- CREDO Investigators: Steinhubl SE, Berger BP, Mann JT, et al. Esroy and sustined dual oral antiplatelet therapy following PCI: a randomized controlled trial. *JAMA* 2002;288:2411.
- CURE: The clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med* 2001;345:494–502.
- Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. *Circulation* 1996;94:2013–2020.
- Fibrinolytic Therapy and Trialist (FIT) Cooperative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major mortality results from all randomized trials for more than 1000 patients. *Lancet* 1994;343:311.
- Furberg CD, Psaty BM, FitzGerald GA. Parecoxib, Valdecoxib, and cardiovascular risk. *Circulation* 2005;111:249.
- Grines CL. Clinical debate: primary angioplasty: the strategy of choice. *N Engl J Med* 1996;335:1313–1317.
- Grines CL, Serruys P, O'Neill WW. Fibrinolytic Therapy: Is It A Treatment of the Past? *Circulation* 2003;107:2538–2542.
- Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;328:673.
- Gruppo Italiano per lo Studio della Streptochinasi Nell 'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397.

- GISSI-2: Gruppo Italiano per lo Studio della Sopravvivenza Nell' Infarto Miocardico. A factorial randomised trial of alteplase versus SK and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990;336:65.
- GISSI-3: Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. effects of lisinopril and glyceryl trinitrate singly and together on 6-week mortality and ventricular function. *Lancet* 1994; 343:1115.
- GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673.
- GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, SK, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615.
- Hands ME, Cook EF, Stone PH, et al. Electrocardiographic diagnosis of myocardial infarction in the presence of complete left bundle branch block. *Am Heart J* 1988;16:23.
- HOPE; The Heart Outcomes Prevention Evaluation Study Investigators. Effect of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342: 145–153.
- Horan LG, Flowers NC, Tolleson WJ. The significance of diagnostic Q waves in the presence of bundle branch block. *Chest* 1970;58:214.
- Hurst JW. Right ventricular infarction. *N Engl J Med* 1994;331:681.
- INJECT: International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with SK in acute myocardial infarction : trial to investigate equivalence. *Lancet* 1995;346:329.
- ISIS-2 (Second international study of infarct survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:350.
- ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. A randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:953.
- ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669.
- Jacobs AK. Primary angioplasty for acute myocardial infarction- Is it worth the wait? *N Eng J Med* 2003;349:798.
- Kastrati A , Mehilli J, Schlotterbeck K, et al. for BRAVE Investigators Late-Breaking Clinical Trial Abstracts. A randomized evaluation of early administration of reteplase plus abciximab or abciximab alone prior to percutaneous coronary intervention in patients with acute myocardial infarction. *Circulation* 2003;108:2723.
- Keeley EC, Boura JA, Grines CL. Comparison of primary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13–20.
- Keeley EC, Grines CL. Primary coronary intervention for acute myocardial infarction. *JAMA* 2004;291: 736–739.
- Kereiakes DJ. Adjunctive pharmacotherapy prior to percutaneous coronary intervention in non-ST-elevation acute coronary syndromes: The role of modulating inflammation. *Circulation* 2003;108(Suppl I): III-22–III-27.
- Khan M. Gabriel. Management of acute myocardial infarction. In: *Cardiac Drug Therapy*, sixth edition, WB Saunders, Philadelphia, 2003.
- Khan M Gabriel. Beta blockers: the cornerstone of cardiac drug therapy. In: *Cardiac Drug Therapy*, sixth edition, WB Saunders, Philadelphia, 2003.
- Khunti K, Samani NJ. Coronary heart disease in people of south-Asian origin. Important minority ethnic populations in many countries worldwide are people of south-Asian origin. *Lancet* 2004;364:2077.
- Kloner RA. The "Merry Christmas coronary" and "Happy New Year heart attack." *Phenomenon Circulation* 2004;110:3744–3745.
- Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670.
- Lange RA, Hillis LD. Antiplatelet therapy for ischemic heart disease. *N Engl J Med* 2004;350:277–280
- Lange RA, Hillis LD. Immediate angioplasty for acute myocardial infarction. *N Engl J Med* 1993;328:726.

- LATE Study Group. Late assessment of thrombolytic efficacy study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet* 1993;342:759.
- Lau WC, Waskell LA, Watkins PB. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation. *Circulation* 2003;107:32.
- Maehara A, Mintz GS, Bui AB, et al. The morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. *J Am Coll Cardiol* 2002;40:904–110.
- McMurray JJV, Pfeffer MA, Swedberg K, et al. Which inhibitor of the rennin–angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation* 2004;110:3281–3288.
- McSweeney JC, Cody M, O’Sullivan P, et al. Women’s early warning symptoms of acute myocardial infarction. *Circulation* 2003;108:2619–2623.
- Mehta RH, Granger CB, Alexander KP. Reperfusion strategies for acute myocardial infarction in the elderly. Benefits and risks. *J Am Coll Cardiol* 2005;45:471–478.
- Mehta SR, Yusuf S, Peters RJG, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527–533.
- Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard University Press, 1996.
- Reddy KS. Cardiovascular disease in non-western countries. *N Engl J Med* 2004;350:2438–2440.
- Rumsfeld JS, Ho PM. Depression and cardiovascular disease: a call for recognition. *Circulation* 2005;111:250–253.
- Saia F, Lemos PA, Chi-Hang Lee CH, et al. Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction. *Circulation* 2003;108:1927.
- Salukhe TV, Henein MY, Sutton R. Ischemic mitral regurgitation and its related risk after myocardial infarction. *Circulation* 2005;111:254–256.
- Shah PK. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol* 2003;41:15s–22s.
- TAXUS: Stone GW, Ellis SG, Cox DA, et al. for TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221–231.
- Terrin ML, Williams DO, Kleiman NS, et al. Two- and three-year results of the thrombolysis in myocardial infarction (TIMI) phase II clinical trial. *J Am Coll Cardiol* 1993;22:1763.
- TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. *N Engl J Med* 1989;320:618.
- TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;89:1545.
- Topol EJ. Current Status and Future Prospects for Acute Myocardial Infarction Therapy. *Circulation* 2003;108(Suppl I):III-6–III-13.
- Topol BJ, Califf RM, Lee KL, on behalf of the GUSTO Investigators. More on the GUSTO trial. *N Engl J Med* 1994;31:277.
- Topol EJ, Kereiakes DJ. Regionalization of care for acute ischemic heart disease: a call for specialized centers. *Circulation* 2003;107:1463–1466.
- Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002;105:393–343.
- Yamaji H, Iwaki K, Kusachi S, et al. Prediction of acute left main coronary artery obstruction by 12-lead electrocardiography; ST-segment elevation in AVR with less ST-segment elevation in lead V1. *J Am Coll Cardiol* 2001;38:1348.
- Yusuf S, Hawken S, Ounpuu S, et al. on behalf of the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–952.
- Wang K, Asinger RW, Marriott HJL. ST elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003;349:2128–2135.
- Wong GC, Giugliano RP, Antman EM. Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention. *JAMA* 2003;289:331–342.

2

Complications of Myocardial Infarction and Postinfarction Care

CONTENTS

RISK STRATIFICATION
HEART FAILURE POSTINFARCTION
RIGHT VENTRICULAR INFARCTION
POSTINFARCTION ANGINA
ARRHYTHMIAS
CARDIAC PACING
MECHANICAL COMPLICATIONS
DISCHARGE MEDICATIONS
PSYCHOSOCIAL IMPACT OF THE HEART ATTACK
BIBLIOGRAPHY

RISK STRATIFICATION

Knowledge of the probable outcome after myocardial infarction (MI) is important in formulating an appropriate plan of management, as with ST elevation MI versus non-ST elevation MI (non-Q-wave MI). The following information on risk stratification is relevant to decision making.

Acute MI in-hospital mortality is about 12–14% ([Table 2.1.](#)). Several characteristics alter the in-hospital and postdischarge mortality:

- Age over 70.
- Prior MI, angina, or heart failure (HF) is associated with a twofold or greater increase in mortality.
- Non-ST elevation MI, in contrast to ST elevation MI, has a lower in-hospital mortality (about 2%) but a threefold higher incidence of reinfarction within the following 3 months, and angina occurs in 33–66% of patients during the first year postdischarge;
- On admission to the hospital, 40–50% of patients with ST elevation MI have mild-to-moderate HF, and the presence of this complication carries a twofold early mortality. [Table 2.2.](#) gives comparison outcomes in acute ST elevation MI and non-ST elevation MI (non-Q wave infarction). Overall, increasing age beyond 70 and the degree of HF or reduction in ejection fraction (EF) that relates to the size of infarction are the most telling predictors. Thus, frank pulmonary edema or an EF less than 35% before discharge is most unfavorable.
- Recurrence of ischemic symptoms after day 1 represents an unstable state and carries a high mortality rate if not appropriately managed.

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Table 2.1.
Acute Myocardial Infarction: Mortality Risk Stratification

<i>Parameters</i>	<i>In hospital</i>	<i>Approximate %</i>		
		<i>1 year</i>	<i>3 year</i>	<i>5 year</i>
Overall mortality	12–14	10–15		33 ^a
Uncomplicated				
Anterior infarction	12	15	33	
Inferior infarction	3	5	12	
Complicated				
Anterior infarction				
Moderate HF	30	50	60	
Cardiogenic shock	80			
Ejection fraction				
<30%	30	50	60	
30–40%	15	25		
40–50%	5	15		
>50%	3			
Previous infarct	25	30	50	
Postinfarction angina (day 2–10)	20	20		
Anterior infarct (year)				
Age >70	25			
Age <50	7			

^aunchanged 1960–1969, 1970–1979 (1980–2000 not available).

Table 2.2.
Comparison of Outcomes in Acute ST Elevation MI and Non-ST Elevation MI (Non-Q-Wave Infarction)

<i>Parameters</i>	<i>Approximate %</i>	
	<i>Q-wave</i>	<i>Non-Q-wave</i>
Incidence prehospital fatal infarcts	>50	<10
Incidence in hospital	80	20 ^{a,b}
In-hospital mortality		
All patients	12 (18)	6 (9)
First infarction	10 (15)	3 (5)
Incidence of moderate/severe heart failure	>20	<1
Incidence of arrhythmias	High	Low
Incidence of postinfarction angina (12 months)	<40	>60
Reinfarction < 3 months	6	10; 16 ^c

^a10% in GISSI-2.

^bExcept if previous ST elevation MI .

^cPooled data before the use of aspirin and β -blockers, and diltiazem.

() pooled data, 1962–1988, before thrombolytic therapy and general use of aspirin and β -blockers.

The complications of MI determine prognosis. The outcome can be improved, however, by appropriate pharmacological therapy and by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery in properly selected patients. The complications of acute MI are listed in [Table 2.3](#).

Table 2.3.
Complications of Myocardial Infarction

Heart failure
Cardiogenic shock
Recurrent/ischemia
Angina
Reinfarction
Early mechanical complications
Free-wall rupture
Interventricular septal rupture
Mitral regurgitation
Late mechanical complications
Aneurysm
Electrical
Ventricular fibrillation
Ventricular tachycardia, other tachyarrhythmias
Bradyarrhythmias, complete heart block
Left ventricular thrombus/embolism
Psychological

HEART FAILURE POSTINFARCTION

The degree of HF is related to the size of the infarction. More than 50% of patients with anterior or anterolateral ST elevation MI shows evidence of mild or moderate HF. Less than 10% of inferior infarcts manifests HF that usually dissipates quickly over 1–2 days. Approximately 25% of patients with extensive inferior infarction is complicated by right ventricular involvement, and these patients often show signs of right-sided pump failure.

Mild-to-moderate left ventricular (LV) failure is observed in approximately 40% of patients admitted with acute infarction and is associated with a twofold increase in mortality. Frank pulmonary edema carries a fivefold mortality increase (Table 2.1). Patients over age 70 with large anterior or anterolateral infarcts complicated by moderate-to-severe HF have a particularly poor prognosis.

Patients with severe HF caused by acute MI have three possible outcomes:

- Relief of pulmonary edema achieved over 1–3 days with the use of morphine, diuretics, nitroglycerin intravenous (IV), and angiotensin-converting enzyme (ACE) inhibitors, plus or minus digoxin when mechanical complications are not present.
- HF refractory to drug therapy as outlined above persists, especially in patients with severe global hypokinesia, LV aneurysm, or mechanical complications.
- Death owing to malignant arrhythmias or mechanical complications.

Pathophysiology

Hemodynamic derangements occur as a result of six major determinants:

- Severe LV systolic dysfunction is usually associated with very large areas of myocardial necrosis, especially when superimposed on an old infarction.
- Significant ventricular diastolic dysfunction plays an important role, especially in patients with large infarcts, right ventricular infarction, old infarcts, or aneurysm.

- Mechanical complications include mitral regurgitation, septal, papillary, or, rarely, free wall rupture. In these situations, global LV function is generally well-preserved; otherwise, the patient would have succumbed at the onset of the complication.
- A variable area of mild myocardial ischemia and “stunned” myocardium usually surround the necrotic myocardium and can influence ventricular contractility and relaxation.
- The exact incidence of painless ischemia among patients with HF in the presence of large infarction is unknown, but appears to play a role within the first 48 hours of infarction. Painless ischemia is amenable to pharmacological intervention with IV nitroglycerin and β -blockade.
- Arrhythmias: atrial fibrillation (AF), atrial flutter, or other STs commonly precipitate or aggravate HF. The fast ventricular response reduces the time for ventricular filling and for coronary perfusion. In addition, the loss of atrial transport function reduces preload, especially important in patients with diastolic dysfunction.

Mild interstitial edema is common during the first 12 hours of infarction and responds to bedrest, oxygen administration, morphine, and the judicious use of furosemide. In contrast to the more severe forms of failure discussed earlier, this situation is not associated with a poor outcome.

In the presence of a normal serum albumin, a pulmonary capillary wedge pressure (PCWP) exceeding 25 mmHg results in pulmonary edema. Reduction of venous tone by nitrates, morphine, or the rapid loss of several hundred milliliters of urine with the aid of diuretics can reduce left atrial pressure by 10–15 mmHg, and thus prevent the formation of further pulmonary edema, provided that ventricular function is not too severely impaired by poor contractility or mechanical pump failure and cardiogenic shock does not supervene.

Factors that may precipitate HF and increase mortality risk in the patient with acute MI include:

- Concomitant therapy with a calcium antagonist: negative inotropic effect, lack of cardioprotection, a fall in blood pressure (BP) and, thus, decreased coronary perfusion.
- Antiarrhythmics, disopyramide, procainamide, and those that have a negative inotropic effect.
- Nonsteroidal anti-inflammatory drugs (NSAIDs).

Therapy

Mild HF: Mild interstitial edema occurs in over 40% of patients with acute MI and responds to bedrest, oxygen, morphine, and judicious use of furosemide.

Furosemide

A dosage of 20 mg IV is used; repetition with care to avoid potassium depletion suffices in the majority of cases.

Diuretic therapy improves symptoms, but excessive volume depletion stimulates the renin angiotensin system and may paradoxically increase myocardial wall stress. It is advisable, therefore, to use a small dose of diuretic along with an ACE inhibitor.

Morphine

A dosage of 4–8 mg IV at a rate of 1 mg/minute is used; repeat, if necessary, at a dose of 2–4 mg/minute. It is important to allay anxiety. Patients at this stage may not complain bitterly of chest pain, but mild discomfort increases apprehension, which must be avoided.

Morphine produces venous dilatation and thus reduces preload; in addition, the drug has a modest but important effect on elevating ventricular fibrillation (VF) threshold. Morphine should be avoided in patients with right ventricular infarction because all drugs that reduce preload are contraindicated in this setting.

Patients with mild HF, as discussed, represent about 25% of patients admitted and have about a 10% mortality rate. They do not require hemodynamic monitoring if they respond over a few hours to appropriate doses of furosemide and morphine. Some of these patients may require low-dose IV dobutamine via a peripheral vein, according to clinical status, before resorting to Swan-Ganz catheterization. In this subset of patients, if there is evidence of hypoperfusion with oliguria and/or a fall in systolic blood pressure (SBP) to less than 100 mmHg or a fall greater than 30 mm from baseline, hemodynamic monitoring is necessary to guide pharmacological intervention.

Severe HF: Patients with severe HF or early shock require the prompt insertion of a balloon flotation catheter. The choice of a pharmacological agent based on hemodynamic parameters is indicated in [Table 2.4](#).

Severe HF and pulmonary edema, with PWCP exceeding 22 mmHg and a low cardiac index of less than 2.2 L/minute/m², carry an in-hospital mortality rate of about 30% ([Table 2.1](#)).

Intensive hemodynamic monitoring is essential in patients with severe HF. Large doses of pharmacological agents and combination therapy are usually required:

- 80 mg or more of furosemide in repeated doses if pulmonary edema is present with the wedge pressure greater than 24 mmHg. The subsequent development of hypotension after an IV bolus of furosemide should alert the physician to the possibility of hypovolemia secondary to the diuretic or the presence of right ventricular infarction. Care is required in some patients with severe HF and concomitant cardiogenic shock to maintain a wedge pressure as high as 24 mmHg, provided that fulminant pulmonary edema is absent (*see* Chapter 3).
- IV nitroglycerin is commenced if the SBP is greater than 100 mmHg, PCWP is greater than 20, and right atrial pressure is increased in the absence of right ventricular infarction. Titrate the dose to attain an optimal wedge pressure of 14–18 mmHg without causing a fall in SBP below 95 mmHg or 10% from baseline ([Table 4.9](#)).
- A fall in blood pressure is best managed with the use of dobutamine in combination with nitroglycerin. Other inotropes carry no advantages over dobutamine; if severe hypotension is present, dopamine is added.

ACE Inhibitors

- ACE inhibitors are given on the day of admission to all patients with anterior MI, extensive prior infarction, or pulmonary congestion and manifestation of HF in the absence of hypotension (BP < 100 mmHg). If an ACE inhibitor was not administered on day 1, then on day 2 if HF is present and the BP is stable (>100 mmHg), an ACE inhibitor is commenced.
- Ramipril 2.5 mg or captopril may be chosen because of its short half life. A dosage of captopril 3–6 or 6.25-mg test dose is given; observe for 2 hours. If tolerated without a fall in BP, give 6.25 to 12.5 mg twice daily. The dose is titrated slowly up to 25 mg, three times daily to a maximum 50 mg three times daily over the next 5 days, provided that the SBP is greater than 100 mmHg and the serum potassium and serum creatinine remains within normal range

Table 2.4.
Choice of Pharmacological Agents in Patients With Acute Myocardial Infarction Based on Hemodynamic Parameters

<i>Drug effect</i>	<i>Furosemide</i>	<i>IV nitrates</i>	<i>Dobutamine</i>	<i>Dopamine</i>	<i>Nitroprusside</i>	<i>ACE inhibitors</i>
Preload	↓	↓	—	↑	↓	↓
Afterload	—	Minimal ↓	Minimal ↓	↑	↓	↓
Sinus tachycardia parameters	No	Yes	Minimal	Yes	Yes	No, minimal
Moderate HF	Yes	Yes	Yes, if SBP > 70 ^a	Yes, if SBP < 70 and oliguria (on dobutamine)	SBP > 110 and > 6 hours ^b postinfarction	Oral maintenance weaning nitroprusside
Severe HF						
PCWP > 24 cardiac index > 2.5 L/minute/m ²	Yes	Yes if SBP > 95	Yes if SBP > 70	Yes if SBP > 70 ^c	CI < 6 hour	Yes
Cardiogenic shock if SBP < 95	CI	CI	Yes IABP	Yes	CI	RCI ^d
PCWP > 18 cardiac index < 2.5 L/minute/m ²						
Right ventricular infarction JVP ↑	CI	CI	Useful with titrated volume infusion	Relative CI ↑ PA pressure	CI	CI

^asee Fig. 3.2.

^bcoronary steal during ischemic phase of infarction.

^cdopamine, dobutamine combination (see Chapter 3).

^dsee text.

Yes, useful; ↓, decrease; —, no change; ↑, increase; CI, contraindication; PCWP, pulmonary capillary wedge pressure; RCI, relative contraindication; SPB, systolic blood pressure mmHg.

- Captopril is later switched to enalapril twice daily or to a once-daily ACE inhibitor, such as ramipril, 5–10 mg daily. In the Acute Infarction Ramipril Efficacy (AIRE) trial, 2006 patients with clinical heart failure from 3–10 days after MI were randomized and treated with ramipril: death occurred in 23% of control versus ramipril 17%: a 27% significant reduction in mortality. If an ACE inhibitor causes undesirable adverse effects, an angiotensin receptor blocker (ARB), such as candesartan, 8–32 mg daily should be substituted. The CHARM study has shown the efficacy of this agent.

The CHARM-Alternative trial ($n = 2028$) examined the effects of the ARB candesartan in patients with a reduced left ventricular EF less than 40% who were ACE-inhibitor-intolerant. Treated patients received 4–8 mg of candesartan titrated to 32 mg once daily, plus the treatment given to placebo patients: standard ant-failure therapy that included diuretics, β -blocker, digoxin, and spironolactone (85%, 54%, 45%, and 24% respectively).

Results of this study showed that after 33.7 months, patients given candesartan were 23% less likely to experience cardiovascular death or HF hospitalization compared with those who received placebo (40% versus 33%, $p = 0.0004$).

There is no unfavorable interaction when candesartan and a β -blocker are used in combination, as opposed to that shown for the valsartan– β -blocker combination. It appears that ARBs, like β -blockers, have subtle and important clinical differences.

ACE inhibitors have proven effective in the management of acute MI for the modification of remodeling, preservation of LV function, and prevention of HF. These agents produce symptomatic improvement, decrease mortality, and prevent the recurrence of HF in postinfarction patients with HF or an EF below 40%. They cause a modest decrease in mortality in patients with HF with chronic ischemic heart disease when used in conjunction with digoxin and diuretics (*see* Chapter 5).

The renin angiotensin system is activated during the early hours of MI and appears to be an important compensatory mechanism that serves to maintain BP. The arterial vasoconstrictor effects of angiotensin II cause an unnecessarily great increase in afterload and ventricular wall stress, which initiate and perpetuate ventricular enlargement and an associated change in geometry with consequent further LV dysfunction. ACE inhibitors have been shown to attenuate these processes.

Studies that support the salutary effect of ACE inhibitors administered within a few days postinfarction include the following:

- The survival and ventricular enlargement (SAVE) trial randomized 2231 patients postinfarction several weeks with EF less than 40% and no evidence of HF. Captopril-treated patients followed-up for an average of 42 months experienced a significant decrease in mortality ($p = 0.019$) and recurrence of nonfatal infarction.
- The AIRE study randomized 2006 patients 3–10 days postinfarction with clinical evidence of heart failure new york heart association class II and III. At a minimum follow-up of 6 months and an average of 15 months, there were 170 deaths in the ramipril group and 222 deaths in the placebo group ($p = 0.002$), an observed risk reduction of 27%.
- In the survival of MI long-term evaluation (SMILE) study, zofenopril was commenced approximately 15 hours postinfarction and continued for 6 weeks in patients with acute anterior infarction. This therapy resulted in a significant decrease in the risk of severe HF. This beneficial effect occurred mainly in patients with previous infarction. Mortality at 1 year in the group treated for only 6 weeks was 10% versus 14% in the placebo group ($p = 0.011$). Thetrandolapril study confirms the beneficial effects of ACE inhibitors when begun 3–7 days in postinfarction patients with EF less than 35%.

ACE inhibitors are indicated maintenance therapy in the following categories of postinfarction patients:

- From the first day, postinfarction if HF was manifest.
- From the second day, postinfarction in patients with large anterior infarction, or in all patients with acute anterior infarction with previous infarction. If the EF at 6 weeks is more than 40%, ACE inhibitors can be discontinued but continued indefinitely in virtually all patients with EF less than 40%.
- From the second or third hospital day in virtually all postinfarction patients not in HF but with EF less than 40%.

ACE inhibitors must be used with caution, however, in patients who develop postinfarction angina or other manifestations of worsening ischemia, because coronary artery perfusion beyond a critical stenosis may be reduced by these and other vasodilators. These agents, as with other preload reducing agents, are contraindicated in patients with right ventricular infarction. ACE inhibitors reduce both preload and afterload.

Contraindications include the following:

- Severe anemia.
- Unilateral renal artery stenosis in a solitary kidney or severe bilateral renal artery stenosis.
- Hypotension.
- Aortic stenosis.

Interactions between ACE inhibitors and other therapies include the following:

- Except when the patient requires additional significant doses of loop diuretics, potassium supplements and potassium-sparing diuretics should not be given con-comitantly with ACE inhibitors or ARBs because severe hyperkalemia may ensue. Potassium supplementation may be hazardous, and close monitoring of serum potassium and serum creatinine is required because a sharp decline in renal function is sometimes seen. Spironolactone or eplerenone are usual additive agents and have been shown to decrease mortality and recurrent HF but should be avoided in patients with a creatinine clearance <60 mL/min or serum creatinine equal to or greater than 1.3 mg/dL (115 μ mol/L) because life-threatening hyperkalemia may occur.
- Both nitrates and ACE inhibitors decrease preload and may precipitate presyncope or syncope.

Digoxin

Digoxin may increase oxygen demand, but in this situation with high mortality, there's little reason to withhold digoxin if HF is severe and unresponsive to standard therapy. The area of infarction is a necrotic zone, and there is little evidence to support the notion that digoxin increases infarct size. Improvement in cardiac function and hemodynamics may have salutary effects on the peripheral ischemic zone. The concern of increasing infarct size is irrelevant if severe HF persists on the second day postinfarction in the absence of recurrent chest pain or echocardiogram (ECG) signs of worsening ischemia or if mechanical complications are absent. Digoxin is usually not advisable within the first 12 hours of infarction, when the risk of the ischemia and arrhythmia is at its highest.

If the ECG shows no mechanical defect, digoxin is advisable for the management of severe HF, pulmonary edema, or for controlling the ventricular rate if AF develops. Also, when the patient is weaned off dobutamine or other inotropes, the action of digoxin is manifest. Although the effect of digoxin on long-term survival post-MI remains con-

troversial, the risk of precipitating an arrhythmia with digoxin is remote, as long as the dose is kept low enough to maintain a digoxin level less than 1 nmol/L. It is now appreciated that low-dose digoxin with low serum levels produces hemodynamic effects that are beneficial and provide safety compared with larger doses that were used over the past 50 years or more. In patients who have been previously treated with diuretics, magnesium and potassium depletion must be corrected to avoid digoxin-induced arrhythmias.

Digoxin IV is not normally required, except where AF with a fast ventricular response requires control. With sinus rhythm and severe HF, give orally 0.5 mg immediately and then 0.25 mg at bedtime in patients under age 70 with normal renal function and in the absence of conditions in which there is an increased sensitivity to digoxin (Table 5.4); follow with 0.25 mg daily. In patients over age 70 and those with slight elevation of serum creatinine, 1.3–2 mg/dL (115–160 $\mu\text{mol/L}$), the maintenance dose should be reduced to 0.125 mg daily after the second day (*see* Chapter 5). Digoxin is not advisable in patients with severe renal failure (serum creatinine >2 mg/dL [$160 \mu\text{mol/L}$]).

Digoxin is particularly useful in postinfarction patients with HF who have SBP less than 105 mmHg. In these patients, nitrates or ACE inhibitors combined with diuretics and β -blockers may further reduce SBP and preload, causing decreased coronary and cerebral perfusion that may induce ischemia or presyncope.

Intubation

Patients who manifest florid pulmonary edema and respond poorly to furosemide and IV nitroglycerin, with an arterial O_2 (paO_2) less than 50 or arterial CO_2 (paCO_2) greater than 50 mmHg, require mechanical ventilation and positive-end expiratory pressure (PEEP) in addition to the other measures described. Caution: PEEP may decrease cardiac output and precipitate hypotension.

Pump Failure and Shock

There are two hemodynamic subsets of pump failure, and patients may move from one subset to another. This chapter deals briefly with subset I. Chapter 3 presents a more detailed discussion of cardiogenic shock. The clinical spectrum of pump failure and shock embraces:

- Poor peripheral perfusion with cold cyanotic extremities.
- Obtundation.
- Oliguria.
- Weak pulse.
- Cuff SBP range: subset I, greater than 100 mmHg and subset II, less than 90 mmHg.
- Patients with systolic pressures between 90 and 100 mmHg may move toward subset I or subset II; close hemodynamic monitoring is necessary.
- Symptoms and signs of LV failure.

Salient therapeutic measures include the following:

- Define the filling pressure of the left ventricle to exclude volume depletion. Various causes of preload reduction must be defined.
- If the LV filling pressure is less than 15 mmHg, give a rapid IV fluid challenge over a very short period to increase the filling pressure to 18–23 mmHg. A prolonged infusion must be avoided, as it can worsen pulmonary congestion without increasing LV filling pressure appreciably.

If volume depletion and preload-reducing factors are absent, management must rapidly progress to:

- Relieving the load on the left ventricle with afterload-reducing agents but without decreasing BP and perfusion to vital areas.
- Improving myocardial oxygen supply: demand ratio with oxygen-sparing agents, reperfusion by thrombolysis, angioplasty, or finally resorting to coronary artery bypass surgery (CABS) if these alternatives are technically feasible, if a substantial amount of viable myocardium is believed to persist in the ischemic region, and if the patient's condition permits. Two hemodynamic subsets in the spectrum of pump failure and shock can be defined by hemodynamic monitoring.

Subset I

- LV filling pressure greater than 15 mmHg.
- SBP greater than 100 mmHg.
- Cardiac index less than 2.5 L/minute/m².
- Evidence of peripheral hypoperfusion and some evidence of pulmonary congestion.

This category of patients have LV failure, and the SBP range of 95–115 mmHg allows the use of afterload- and preload-reducing agents, thus relieving the load on the left ventricle and favorably altering myocardial oxygen supply:demand ratio. Salutory effects are obtained with the administration of nitroglycerin, dobutamine, dopamine, or nitroprusside, depending on hemodynamic parameters ([Table 2.4](#)).

Nitroglycerin

Nitroglycerin has advantages over nitroprusside during the early hours of infarction because, at this stage, ischemia is often present. The drug is reserved for selected cases in which continued ischemia is suspected of causing progression of infarction or LV dysfunction.

The drug reduces preload, which may be beneficial in some patients with severe pulmonary congestion but in whom blood pressure is reasonably well-maintained. However, patients with pump failure and severe shock may have deleterious effects from too great a reduction in preload. Higher doses also reduce afterload. Thus, careful hemodynamic monitoring is essential when using pharmacological agents that alter both preload and afterload.

Commence with 5 µg/minute via pump-controlled infusion (*see* nitroglycerin infusion pump chart, [Table 4.9](#)). Increase by 5 (µg/min every 10 minutes. Do not allow a fall in SBP in excess of 10 mmHg. The SBP should not fall to less than 90 mmHg.

If nitroglycerin alone causes improvement in the pump failure or shock syndrome, achieving an acceptable increase in cardiac output, continue the infusion for 24–48 hours.

If hypotension persists or worsens and preload is high, decrease the nitroglycerin infusion and add 2–5 µg/kg/minute dobutamine ([Table 3.5](#)). If the preload is low or BP decreases more precipitously, dopamine should replace dobutamine (*see* Chapter 3).

Dobutamine

Commence with 2 µg/kg/minute, increase slowly if needed to 5 µg to a maximum of 10 µg/kg/minute. If a 10-µg/kg/minute dose of dobutamine fails to maintain BP, a dopamine infusion should replace the dobutamine or a low-dose dobutamine/dopamine combination should be considered. Dopamine dose: 5–10 µg/kg/minute (*see* [Table 3.6](#), Chapter 3).

Nitroprusside

This drug is a powerful afterload-reducing agent and has a role, especially when the SBP is in the range of 100–120 mmHg, in the presence of pump failure/shock syndrome. The drug can replace nitroglycerin in patients presenting with pump failure or shock syndrome after 6 hours of infarction if ischemia is not present and afterload reduction is considered necessary.

Commence with 0.4 µg/kg/minute with close monitoring of arterial pressure, increase the infusion given by infusion pump, and titrate the dosage in increments of 0.2 µg/kg/minute every 2–5 minutes (*see Table 8.11*). A dose of up to 3 µg/kg/min should suffice to achieve salutary hemodynamic effects.

Caution: severe hypotension is a major risk. Also, the drug may produce a coronary steal, reflex tachycardia, and hypoxemia. These serious adverse effects may worsen ischemia and infarction and increase mortality. Thus, in each patient, the benefits and risks must be weighed before introduction of nitroprusside.

Contraindications include hepatic dysfunction, severe anemia, severe renal failure, and inadequate cerebral circulation.

There are adverse effects. Patients with liver disease may develop cyanide toxicity, and if kidney disease exists, thiocyanate levels must be monitored when treatment is given for more than 2 days. Severe hypotension causing increased shock, retrosternal chest pain, or palpitations may occur. Great care is necessary to avoid accidental acceleration of the infusion. If acute cyanide poisoning occurs, amyl nitrite inhalations and IV sodium thiosulfate should be given. For further information on nitroprusside, *see Chapters 3 and 8*.

Subset II

- SBP less than 90 mmHg.
- LV filling pressure greater than 15 mmHg.
- Cardiac index less than 2.5 L/minute/m².

These parameters define patients with severe cardiogenic shock. Failure to stabilize the patient with dopamine should prompt consideration of IABP and urgent coronary angiograms with a view to PCI or bypass surgery to enhance coronary perfusion or to correct underlying mechanical problems. Randomized trials that include few patients with true cardiogenic shock demonstrated the benefit of angioplasty over thrombolytic therapy for patients with large infarctions or right ventricular infarction.

The IABP is required in some cases when dobutamine, dopamine, and norepinephrine do not halt hemodynamic deterioration and an aggressive approach is considered appropriate. *Table 2.5* shows indications and contraindications for IABP. The IABP improves coronary perfusion through diastolic augmentation and cardiac output through afterload reduction.

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction is usually associated with inferoposterior infarction and, where present, frequently causes right-sided pump failure or shock. Approximately 25% of patients with inferior infarction show varying degrees of right ventricular infarction, but only those with a large affected area develop the characteristic signs. The diagnostic hallmarks of right ventricular infarction are given in *Table 2.6*. The right atrial and right

Table 2.5
Indications and Contraindications for Intra-Aortic Balloon Pump in Acute MI

<i>Indications</i>
Cardiogenic shock (selected cases) Postinfarction angina (selected cases, stabilization for angiography) Right ventricular infarction with refractory hypotension (consider IABP) Early mechanical complications (Table 2.3) (if stabilization is necessary for interventional therapy)
<i>Contraindications</i>
Severe peripheral vascular disease Aortic aneurysm and aortic disease If contraindications to anticoagulants exist

ventricular diastolic pressures are greater than 10 mmHg, the cardiac index is less than 2.5 L/minute/m², and the LV filling pressure is normal or elevated. Approximately 0.2% of acute inferior infarctions are accompanied by right ventricular infarction. Patients with inferior infarction and ST elevation in V_{4R}, indicating right ventricular infarction, were observed to have a 31% mortality rate and 64% in-hospital complications, versus 6% and 28%, respectively, for those with inferior infarction.

The mechanism of shock in right ventricular infarction combines the following:

- Acute right pump failure reduces the venous return to the left ventricle. Thus, decrease in LV preload is the principal mechanism for the decreased LV output.
- Interventricular septal shift toward the left ventricle reduces LV diastolic volume. Also, an increase in intrapericardial pressure occurs, which restricts LV filling and passively increases pulmonary artery pressure, thus increasing right ventricular afterload.

In the presence of severe right-sided HF, it is necessary to exclude cardiac tamponade, which may occasionally give hemodynamic findings resembling those seen with right ventricular infarction, with equalization of diastolic pressures resulting from intrapericardial pressure owing to a distended pericardium.

Therapy of Right Ventricular Infarction

Patients with extensive right ventricular infarction are very sensitive to volume depletion, and titrated volume infusion should be tried. The right ventricle is unable to deliver adequately the venous return to the left ventricle, however, and the reduced LV preload results in decreased systemic output. Thus, volume infusion is often partially or even completely ineffective but must be tried judiciously.

- Dobutamine infusion should be commenced at 2 µg/kg/minute and increased to a maximum of 10 µg/kg/minute if needed (Table 3.5.).
- Failure to respond to volume replacement and dobutamine is a strong indication for the use of IABP.
- Sublingual or IV nitroglycerin is contraindicated in patients with right ventricular infarction because reduction in preload must be avoided.
- Nitroprusside, as well as diuretics and ACE inhibitors, reduce preload and are not recommended.

Table 2.6
Right Ventricular Infarction

High jugular venous pressure with clear lung fields (exclude tamponade)
Kussmaul's sign present >90%
ECG evidence of inferoposterior infarct
ST segment depression V ₁ , V ₂ , elevation in V ₄ R
PCWP normal
Right atrial and right ventricular pressure > 10 mmHg
Ratio right atrial to PCWP >0.8 ^a

^aPresent in <33% of patients

PCWP, pulmonary capillary wedge pressure.

- Dopamine increases pulmonary vascular resistance and may increase right ventricular pump failure. Dobutamine is thus superior to dopamine in patients with right ventricular infarction although the hypotensive effect may limit the dose that can be tolerated.
- Thrombolytic therapy is strongly indicated to ensure a patent infarct-related vessel.
- If hemodynamic deterioration occurs, angioplasty is advisable. Small clinical trials have documented the beneficial effects of angioplasty in patients with right ventricular infarction.

POSTINFARCTION ANGINA

Definite postinfarction angina, occurring after day 1 to discharge, associated with new ECG changes and correctly interpreted as owing to worsening ischemia, is an indication for coronary angiography with a view to PCI of CABS.

Consider and exclude pericarditis, esophagogastric origin of pain owing to stress ulceration, esophagitis, and the effects of aspirin in individuals with so-called sensitive stomachs. Some patients with a stuttering pattern of pain caused by to ischemia or reinfarction respond readily to β -adrenergic blockers and/or IV nitroglycerin therapy that stabilizes patients prior to PCI.

When the EF is below 35%, and perhaps as low as 25% or if the ischemic syndrome persists and lesions of the left main or triple vessel, with left anterior descending proximal occlusion are observed on angiography bypass surgery is preferred over PCI.

A study of 48-hour ECG ambulatory monitoring 5–7 days postinfarction revealed an incidence of myocardial ischemia of 23.4%. The mortality rate in patients with ischemia was 11.6% versus 3.9% among those without ischemia.

ARRHYTHMIAS

The mechanism of early infarction arrhythmias includes disturbances of impulse generation/enhanced automaticity, disturbances of impulse conduction/reentry, and focal conduction slowing; increased sympathetic and parasympathetic tone is a commonly prominent feature that influences the above underlying mechanisms.

Precipitating factors include the following:

- Ischemia with associated tissue acidosis and local increase in extracellular potassium concentration.

- Catecholamine release: may induce arrhythmia, as well as increase ischemia. Arrhythmias worsen ischemia and vice versa. Thus, a dynamic interplay perpetuates ventricular arrhythmias that may terminate in VF.
- Hypokalemia from prior use of diuretics or induced by verapamil.
- Hypomagnesemia resulting from diuretic use.
- Hypoxemia.
- Respiratory or metabolic acidosis or alkalosis.
- Severe HF related to extensive infarction.

Ventricular Premature Beats

During the late hospital phase, frequent ventricular premature beats (VPBS) (more than 10/hour multifocal beats or couplets) may increase risk, but there is only limited evidence that antiarrhythmic therapy, other than β -blocking agents, prolongs life in these patients. The cardiac arrhythmia suppression trial (CAST) indicated an increase in mortality among these patients with the use of flecainide and encainide. Patients with this category of arrhythmia should be given a β -adrenergic blocking agent, such as metoprolol or timolol, if there is no contraindication to the use of this class of drug. A study has shown improved survival among high-risk patients treated with amiodarone, but this finding requires confirmation (*see* Chapter 6).

Sustained Monomorphic Ventricular Tachycardia

- Monomorphic ventricular tachycardia (VT) asymptomatic with the pulse present and BP >100 mmHg occurring during the first 24 hours of MI (rare at this time); give lidocaine (lignocaine) IV 100-mg bolus. IV lidocaine infusion 2–3 mg/minute is given for a time after conversion without waiting for recurrence (*see* Fig. 6.1.). If the drug is ineffective and the patient is hemodynamically stable, give procainamide IV 100-mg bolus at the rate of 20 mg/minute and then 10 mg/minute; maximum 24 mg/minute not to exceed 1 g during the first hour. Procainamide has a negative inotropic effect and is not recommended for patients who manifest HF or with EF less than 40%. The drug is, therefore, reserved for patients who fail to respond to lidocaine or who have recurrent VT but who remain hemodynamically stable.
- The cardioverter should be prepared and connected to the patient while drug therapy is in progress; if conversion fails, apply 50 J of synchronized electrical cardioversion under brief anesthesia.
- Failure to control with lidocaine procainamide or IV amiodarone requires synchronized cardioversion.
- Any breakthrough should be treated by adding a β -blocker (if not already being administered) and, if needed, IV 300 mg of amiodarone in 20 minutes, preferably via a central vein followed by 50 mg/hour for 6–12 hours and then 30 mg/hour if stable (*see* Chapter 6). IV amiodarone may cause hypotension and caution is required. With the availability of IV amiodarone, which is effective and has good tolerability, the use of bretylium has appropriately dwindled and is currently not available. VT with no pulse present or hemodynamically unstable: chest pain, shortness of breath, clouding of consciousness, or obtundation, treat as VF (*see* Fig. 6.4.).
- IV amiodarone is recommended after sustained VT is converted to sinus rhythm.

It is advisable to obtain Holter recordings for all patients at 1–3 weeks post-MI to assist in assessing the risk profile, especially if the EF is less than 40%. A 24- or 48-hour Holter

study is indicated if the patient complains of palpitations, presyncope, syncope, or other symptoms. Holter monitoring is advisable in patients to document the presence of significant ischemia and arrhythmia requiring consideration of drug therapy.

Late-occurring sustained VT is very ominous. Sustained VT occurring after the first 48 hours or weeks after infarction greatly increases the risk of sudden death and indicates poor long-term survival.

Currently, it is not known what pharmacological agent is best for post-MI patients at highest risk. β -Adrenergic blockers are the only antiarrhythmic agents that have been proven to prevent cardiac death or sudden death. There is evidence from one study, however, that amiodarone may improve survival rates.

The basal antiarrhythmic study of infarct survival investigated the effects of prophylactic antiarrhythmic therapy in patients with asymptomatic complex ventricular arrhythmias postinfarction. Low-dose amiodarone, 200 mg daily, was given over 1 year. Cumulative mortality rates were 13% in the control group, 5% in the amiodarone-treated group ($p < 0.05$), and 10% in the individually treated patients who were administered mexiletine, quinidine, propafenone, sotalol, disopyramide, or flecainide. (Treatment failures were given amiodarone.) Arrhythmic events were also reduced in the amiodarone group.

In contrast with the beneficial effects of β -blocking agents and possibly for amiodarone, other antiarrhythmic agents have been shown to increase mortality. Flecainide, encainide, and moricizine caused an increase in cardiac mortality observed in CAST.

Late Ventricular Arrhythmias

The management of patients with late nonsustained VT, at least in short runs or complex ventricular arrhythmias, is presently unsatisfactory. Suggestive steps include the following:

- If a β -blocking drug is being administered as routine β -blocker post-MI prophylaxis, the dose should be increased (e.g., 100 mg metoprolol, 160 mg propranolol daily should be increased to 300 or 240, mg daily, respectively). If Holter monitoring shows persistence of multiform VPBs or rims of nonsustained VT, a change from one of the aforementioned β -blocking agents to sotalol, 160–320 mg daily, may be effective and should be given a trial but the serum potassium must be maintained > 4.5 mmol and with the avoidance of diuretics that cause potassium depletion.

Amiodarone and other antiarrhythmic agents are used only under close supervision by using repeated Holter monitoring, and the usual precautions are observed when prescribing amiodarone (*see* Chapter 6). The combination of amiodarone and a β -blocking agent (except sotalol) has a role in patients with lethal arrhythmias, as discussed in Chapter 6. The combination of amiodarone and sotalol is not advisable because the risk of torsades de pointes is increased.

Failure of this trial therapy should prompt consideration of selecting alternative treatments, such as a combination of antiarrhythmic agents guided by electrophysiologic testing (although the recommendation of antiarrhythmic therapy has several limitations); rare surgical excision of focus; catheter ablative techniques; an implantable implantation cardioverter-defibrillator (ICD), which has antibradycardia pacing and algorithms for pace termination of VT.

Table 2.7.
Incidence of Supraventricular Arrhythmias in Acute MI

	<i>Approximate %</i>
Atrial fibrillation	
Within 3 hours of infarction	3
New onset first week	5
Known prior (chronic)	10
Atrial flutter	1–2
Ectopic atrial tachycardia (benign)	1–5(transient)
Non-paroxysmal AV junctional tachycardia (benign arrhythmia relates to size of infarction)	5–15
Atrioventricular nodal reentrant tachycardia	Rare

Supraventricular Arrhythmias

The incidence of supraventricular arrhythmias in acute MI is shown in [Table 2.7](#).

Atrial Fibrillation

AF occurs in more than 10% of patients with acute MI and precipitated by large infarction of the atrium, chronic atrial enlargement, HF with atrial dilatation, acute mitral regurgitation, increase catecholamines, acute pericarditis, hypoxemia, and inferior infarction more commonly than anterior infarction, with occlusion of the right coronary or circumflex artery.

AF is observed during the first few days of infarction in up to 15% of patients, and in approximately 10%, the onset is before infarction. Acute atrial fibrillation occurs within the first few hours of infarction in approximately 5% of patients and is often of short duration, lasting less than 2, 4, and 24 hours in 50, 75, and 95% of patients, respectively, and is associated with increased risk of death and embolic stroke.

Management of AF depends on the hemodynamic and proischemic effect of a rapid or uncontrolled ventricular response:

- Electrocardioversion: hemodynamic compromise requires immediate electrocardioversion (synchronized cardioversion is usually achieved at 100 J for AF and 50 J for atrial flutter).
- Digoxin: patients with symptomatic HF with a ventricular rate that requires control are usually managed by slow digitalization. However, digoxin may not reach peak effect for 6–12 hours, depending on the dosing schedule:
Dosage: For HF caused by AF intravenous digoxin 10–15 µg/kg lean body weight, with half dose administered initially and 25% of the dose given at 6-hour intervals for 2 doses or 0.75 to 1.0 mg IV infusion over 2 hours or more when rapid control is needed in patients with HF; *caution*, a lower dose is used in the elderly or if renal dysfunction is present indicated by a serum creatinine greater than 1.3 mg/dL (115 µmol/L). An oral dose of 0.125–0.25 mg is then administered depending on the ventricular response and serum creatinine levels.
- Esmolol: in patients with symptomatic HF in whom efforts to convert to sinus rhythm have failed, and rate control has not been achieved by the use of digoxin the short-acting, β-blocker esmolol has a role (half life 2–5 minutes).
- Dosage: loading dose, 0.5 mg/kg over 2–5 minutes followed by infusion of 0.05 mg/kg/minute titrated upward as needed to maximum dosage of 0.2 mg/kg/minute. It is recom-

mended that the loading dose be omitted in unstable patients with hypotension that could be increased. If the degree of heart failure increases, the infusion is discontinued immediately.

- Metoprolol: asymptomatic patients with a fast ventricular rate but no hemodynamic compromise or symptomatic HF are managed with IV metoprolol. Patients not in prominent HF with SBP greater than 110 mmHg and rates of 120–150/min can be managed with a β -blocking drug. A fast rate >120/minute not causing hemodynamic compromise should respond to metoprolol.

Dosage: 5 mg IV followed if needed every 5 minutes, up to 3 doses.

In patients with acute MI and persistent or chronic AF a β -blocking drug, particularly metoprolol, is recommended to control the ventricular rate; if HF is present, digoxin is the treatment of choice

- Diltiazem IV rapidly and effectively slows the ventricular response and is often used in patients with a fast ventricular rate presenting to emergency rooms in the absence of acute MI and HF. Diltiazem's negative inotropic effect is more prominent than that of titrated small doses of esmolol or metoprolol and is not advisable in acute infarction unless the use of a β -blocker is absolutely contraindicated by severe asthma. Dosage: IV 0.25 mg/kg; a second bolus of 0.35 mg/kg can be repeated after 15 minutes if the ventricular response remains >120/minute. Caution is required because diltiazem may precipitate LV failure in patients with known LV dysfunction; an increase in mortality rates with oral therapy in patients with LV dysfunction has been reported.
- Amiodarone administered IV may control the ventricular rate and cause conversion to sinus rhythm in more than 50% of cases.

Bradyarrhythmias

Early occurring sinus bradycardia, symptomatic or associated with hypotension usually with rates less than 45/minute, should be managed with atropine. Similarly, second- or third-degree atrioventricular (AV) block occurring during the first few hours after onset of MI often responds to this agent. Also, patients with asystole should be given atropine.

- Atropine dosage: 0.4–0.6 mg is given IV, repeated if needed every 5 or 10 minutes to a maximum of 2 mg.

Caution: rapid injection or too large a dose may cause unwanted sinus tachycardia and, rarely, VF. The dosage for asystole is 1 mg IV repeated in 2–5 minutes during which cardiopulmonary resuscitation (CPR) should continue. The total dose is 2.5 mg over 30 minutes. In the latter situation, a large dose given promptly is essential, without concern for tachycardia causing increased myocardial oxygen demand.

Indications:

- Sinus bradycardia associated with peripheral hypoperfusion, hemodynamic deterioration.
- Frequent VPBS associated with sinus bradycardia.
- All forms of AV blocks, second or third degree in patients with inferior MI, because they often respond if less than 8 hours postonset.
- Asystole, along with CPR and preparation for pacing.

Adverse effects include hallucination, sinus tachycardia, and, rarely, VT and VF. Severe bradycardia owing to mobitz type 2 or third-degree AV block not responding to atropine requires temporary pacing.

CARDIAC PACING

Temporary Cardiac Pacing

The use of a temporary cardiac pacemaker is an important procedure for establishing an adequate heart rate and, secondarily, cardiac output in patients with symptoms of bradyarrhythmia. It is usually an emergent procedure. Temporary pacing is indicated in a variety of clinical circumstances in which a symptomatic bradycardia is present or is likely to occur. These can include the following:

- Acute MI.
- Drug-induced bradyarrhythmias.
- During cardiac catheterization.
- Immediate treatment of tachyarrhythmia.

The use of temporary cardiac pacemakers in patients with acute MI requires knowledge of the vascular supply of the conduction system.

- The sinoatrial node, which is located near the junction of the right atrium and the superior vena cava, is supplied by the sinoatrial nodal artery. This is a branch of the right coronary artery in 55% of individuals and of the circumflex artery in the remainder.
- The AV node is supplied by the AV nodal branch of the right coronary artery in approximately 90% of individuals and by the left circumflex coronary artery in the remaining 10%. There is very little collateral blood supply for these structures.
- In contrast, the his bundle and proximal portions of both the left and right bundles have a dual blood supply from the AV nodal artery and the septal branch of the left anterior descending coronary artery. This anastomosis can allow retrograde flow into the his bundle and the AV node when the AV nodal artery is blocked.
- The right bundle branch, however, is a compact structure and receives blood supply from the left anterior descending artery. The left bundle branch is anatomically less discrete. The left anterior fascicle receives blood supply from the branches of the left anterior descending artery and the left posterior fascicle receives blood from the AV nodal and posterior descending arteries.

Conduction disturbances associated with right coronary artery occlusion depend on the site of occlusion. Occlusion proximal to the sinoatrial nodal artery can result in sinus node dysfunction, whereas occlusion more distally can result in AV block at the level of AV node. Therefore, AV block might result from occlusion of the AV nodal branch of the right coronary artery alone and is not necessarily associated with a sizable MI. Because the bundle branches are more diffuse, bundle branch block is usually associated with extensive anterior MI.

- The decision to insert a temporary pacemaker in patients with acute MI is dependent on the location of the block, the extent of MI, and the presence of preexisting conduction system presence.
- Inferior infarction is usually associated with conduction disturbances proximal to the his bundle. Escape rhythms usually have a narrow QRS complex, tend to be fast and stable, and respond well to atropine. AV block in these situations is usually but not invariably transient. Indications for temporary pacing in these patients include a heart rate of less than 40 beats/minute (BPM) and symptoms of low cardiac output or bradycardia associated with angina or ventricular irritability. In asymptomatic patients with a stable escape rhythm despite complete AV nodal block, temporary pacemakers need not be inserted. The long-term prognosis of patients with inferior MI and high-degree AV block is worse than in patients without AV block.

- New abnormalities of the conduction system occurring distal to the AV node are usually seen with anterior MI. Both high-degree AV block and bundle branch blocks can be observed. In these cases, the escape rhythms are associated with a wide QRS complex, are slower and less stable, and usually do not respond to atropine. Frequently, they progress to complete AV block. These patients also have extensive MI and often have signs of pump failure. As progression to complete AV block contributes independently to morbidity and mortality, temporary cardiac pacing is performed more promptly than for inferior wall infarction.

Pacing is recommended in patients who are at risk of complete AV block and include:

- Type II second-degree AV block.
- New bifascicular block (right bundle branch block with left anterior or left posterior block) or complete left bundle branch block.
- Left or right bundle branch block with first- or second-degree AV block.
- Alternating left or right bundle branch block.
- Pre-existing right bundle branch block with new left fascicular block or first-degree AV block.

Methods of Temporary Cardiac Pacing

Temporary cardiac pacing can be established by transvenous, transthoracic, transesophageal, and epicardial approaches. The choice of a specific route is dependent on factors such as availability of the device, indications for pacing, expertise of the physician, and the clinical situation. The transvenous approach is the most often used method.

TRANSVENOUS

External or internal jugular, subclavian, antecubital, and femoral venous approaches are most often used for introduction of pacing catheter electrodes. Under radiographic control, the electrode tip is positioned in the right atrial appendage or the right ventricular apex for stable atrial and ventricular pacing, respectively. In an emergency or in the absence of radiologic facilities, a balloon-tipped flotation electrode catheter can be used to enter the right ventricle. A pacing threshold of less than 1 V is usually satisfactory. It increases over the next few days, probably a result of tissue edema around the electrode tip. Although invasive when compared with transthoracic and transesophageal approaches, transvenous pacing is rapidly accomplished and is reliable when instituted. Atrial, ventricular, and dual-chamber pacing can be achieved, and atrial and ventricular ECGs can be selectively recorded for diagnostic purposes.

PERMANENT PACING IN ACUTE MI

The management of bradyarrhythmias related to conduction disturbances in acute MI is determined by the site of the culprit MI, hemodynamic consequences of the arrhythmia, and arrhythmia duration after acute MI. The requirement for temporary pacing does not, by itself, constitute an indication for permanent pacing.

INFERIOR MI

Conduction disturbances are often seen in patients with acute inferior wall MI. These are a result of ischemia of the AV node or the perinodal regions. Sinus node dysfunction may also occur. First-degree AV block and Mobitz type I second-degree AV block, if present, are usually transient, unassociated with hemodynamic disturbances, and do not require pacing therapy. A minority of patients will develop higher degree or symptomatic AV block. Temporary pacing is indicated, particularly if the patient is hemodynamically

unstable. If symptomatic second- or third-degree AV block persists beyond 2–3 weeks after MI, permanent pacemaking may be indicated.

Conduction disturbances in anterior MI are usually related to ischemic necrosis of conduction tissue distal to the AV node, with involvement of the His-Purkinje system and bundle branches. These arrhythmias most often accompany a relatively large anteroseptal MI. Permanent pacing is generally indicated for new onset bifascicular block, persistent mobitz type II second-degree or complete AV block, or transient mobitz type II second-degree or complete AV block when associated bundle branch block (trifascicular block) is present.

This is performed owing to the substantial potential of these conduction disturbances for the development of complete AV block. Patients with anterior wall MI who have AV conduction and intraventricular conduction disturbances, except left anterior hemiblock, have a poor short- and long-term prognosis and an increased incidence of sudden death. The poor prognosis is primarily related to the extent of MI rather than to the AV block itself. Mortality is high even with pacemaker therapy owing to myocardial failure.

Complications include ventricular arrhythmias, especially in patients with acute MI; pericarditis; ventricular perforation; bleeding; pulmonary embolism; air embolism; pneumothorax when the subclavian vein is used for lead introduction; and local and systemic infections.

MECHANICAL COMPLICATIONS

Mechanical complications should be strongly suspected in patients who develop sudden hemodynamic deterioration, especially from the second postinfarct day onward with no new ECG changes occurring. The incidence and associated mortality of these complications are given in [Table 2.8](#).

Severe Acute Mitral Regurgitation

A transient mitral regurgitant Murmur is often present with acute MI. Severe acute mitral regurgitation is uncommon, however, occurring in fewer than 3% of patients with acute MI and is usually owing to papillary muscle rupture (i.e., partial rupture of the tip or rarely the trunk), or rupture of the chordae tendineae.

Strongly suspect severe mitral regurgitation in the presence of acute inferior infarction on the second to fifth days in patients with pulmonary edema and/or hemodynamic deterioration developing out of proportion to the ECG changes. An EF in the normal range is typical of regurgitant flow. The posterior papillary muscle is most commonly affected with inferoposterior infarction.

Physical signs include the following:

- A new murmur of mitral regurgitation may be loud and, rarely, accompanied by a thrill. The murmur is usually loud, in the presence of papillary muscle rupture, but may be soft in patients with low cardiac output or shock syndrome.
- Papillary muscle dysfunction: mitral regurgitation is not usually severe. The systolic murmur may fluctuate in intensity from hour to hour and may be soft, loud, high, or low pitched; the murmur may stop abruptly well before the second heart sound.
- The murmur caused by ischemia of the posterior papillary muscle radiates anteriorly, whereas that of the anterior papillary muscle radiates posteriorly to the axilla.
- The murmur of a flail leaflet may be well-heard over the spine from the skull to the sacrum.

Table 2.8.
Acute Myocardial Infarction-Mechanical Complications Incidence, Timing, and Mortality

	<i>% of total acute infarcts</i>	<i>Incidence and timing</i>	<i>% of total rupture</i>	<i>% of total in-hospital mortality</i>	<i>type of infarct</i>
Cardiac rupture	3–10	Up to 50%; 2–3 days Up to 40%; day 1		8–17 ^a	
Free-wall	2–6 ^{ab}	10%; days 4–7 25%; day 1	85	7–14	lateral ^c
Papillary muscle rupture	1	75%; 3–5 days 25%; day 1–2 or 6–10	5	1	Commonly inferoposterior
Ventricular Septal rupture	1–2	75%; 3–5 days 25%; 1–2 or 6–14	10	1–2	60% anterior 40% inferior
Severe mitral regurgitation	<2%	1–5 days			
LV aneurysm	7–12	3 months			90% anterior 10% inferior

^aAm Heart J 1989; 117:809.

^bamjcardiol 1991; 68:961.

^cSee text.

Diagnosis and management include the following:

- Echocardiography with continuous wave doppler flow study has an important role.
- If the doppler flow study is in keeping with severe mitral regurgitation, proceed with catheterization. Large V-waves on pulmonary capillary wedge and severe mitral regurgitation are observed on left ventriculography.
- Patients with severe acute mitral regurgitation owing to papillary muscle or chordal rupture require surgery. IABP provides support if needed during catheterization and to the operating room.
- Patients with papillary muscle dysfunction and severe mitral regurgitation who are not hypotensive are managed with afterload-reducing agents. IV nitroglycerin has a role in relieving ischemia, as well as reducing preload, and causes minimal afterload reduction (see Chapter 3). Dobutamine and the use of IABP may be necessary to support blood pressure where needed while considering interventional therapy.

Free-Wall Rupture

The two leading causes of in-hospital postinfarction mortality are cardiogenic shock and myocardial rupture. This catastrophic event accounts for between 8 and 17% of total in-hospital postinfarction mortality.

There have been fewer than 100 reported cases of successful surgical repair despite an incidence of 25,000 cases annually in the US. Myocardial rupture has been found in 38% of patients at autopsy in clinical trials of thrombolytic agents. Several clinical trials indicate that late administration, at 8–21 hours from the onset of symptoms, increases the risk of cardiac rupture, especially in patients over age 70. The Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico trial independently confirmed the relation between the risk of cardiac rupture and time to streptokinase therapy. *A meta-analysis of four thrombolytic studies in 1638 patients showed that therapy after the seventh hour was associated with an increased risk of myocardial rupture.*

Peak incidence is within the first 72 hours; up to 40% of cases occur within the first 24 hours of symptoms (Table 2.8.) and about 85% occur within 1 week.

Free-wall rupture presents in four scenarios:

- Acute free rupture.
- Acute limited rupture.
- Subacute rupture.
- Chronic rupture.

Associated factors include the following:

- Vigorous contraction of surviving myocardium appears to be an important contributing factor.
- Most commonly occurs after first infarction.
- Mainly Q-wave transmural infarcts and mainly lateral wall infarction, particularly inferolateral, posterolateral, and anterolateral. Rupture does not usually occur with inferior infarction that does not involve the lateral or posterior wall.
- Patients are usually over age 70.
- Preexisting hypertension.
- More common in women.
- Thrombolytic therapy is given more than 7 hours after the onset of symptoms, when necrosis is complete. Cardiac rupture is caused by extensive infarction and dissection of blood through the regions of transmural necrosis. Thrombolytic therapy may cause hemorrhage into areas of fresh necrosis and may promote dissection that could result in free-wall rupture.
- Use of anticoagulants or NSAIDs. NSAIDs and Cox-2 inhibitors cause vasoconstriction and may alter myocardial healing. Also, sodium and water retention adds to ventricular strain.
- Early ambulation is an unproven association.

Prevention plays a major role:

- Early use of thrombolytic agents to ensure reperfusion in less than 6 hours of onset of symptoms to prevent transmural infarction.
- Avoid late use of thrombolytic agents in patients, particularly women, over age 75 with first infarction seen after the sixth hour with completed Q-wave infarction, except where a stuttering pain pattern persists (*see* Indications for Thrombolytic Therapy in Patients Over Age 75, Chapter 1).
- Reduce the force and velocity of ventricular contractility with the use of β -blocking agents. β -blockers are the only available cardiac medications that have shown modest protection from myocardial free-wall rupture. There are good theoretic reasons to justify their salutary effects in preventing this catastrophic occurrence in patients with first infarction (*see* Fig. 1.1.). In the international study of infarct survival trial, causes of myocardial rupture were over 2.5-fold more frequent in the placebo group than in those

administered IV atenolol. The Goteborg Metoprolol and Miami trials showed a similar trend. The β -blocker heart attack trial (BHAT) showed a 43% decrease in early morning sudden deaths not believed to be caused by arrhythmias. Because it is rare to prevent death after free wall rupture has occurred, prevention of rupture is of utmost importance. An IV β -blocker, such as esmolol, metoprolol, or atenolol, should be given at the earliest opportunity, preferably within the first 2 hours of onset of symptoms particularly to patients with lateral wall involvement.

- ACE inhibitors decrease afterload and may reduce ventricular work; although these agents are reported to favorably alter postinfarction remodeling, the effect in preventing myocardial rupture needs to be confirmed by multicenter randomized clinical trials.
- Nitrates cause moderate yet important sinus tachycardia and an increase in ejection velocity. Thus, these agents are not indicated in prevention and should be avoided after the first 6 hours of infarction, except where recurrence of ischemia is documented.

Acute free-wall rupture is a catastrophic event; death occurs within the hour.

Acute limited rupture of the thick spiral muscular layer may occur, but an intact outer longitudinal layer of muscle causes a precarious containment of the rupture. Transient cracks may occur in the thin longitudinal layer, causing not only pericardial effusion and tamponade, but also closure of the small leak.

Immediate pericardiocentesis with derived benefit excludes the confounding diagnosis of pulmonary embolism, which may occur between days 2 and 8 and may occasionally present catastrophically and with electromechanical dissociation. Hemodynamic support using IABP may be necessary; the patient may be rushed to the operating room for correction of a defect, making survival possible.

Subacute Rupture

Subacute rupture may cause hemorrhagic pericarditis owing to a slow leak of blood and can present during the 2- to 8-day period. In this condition, a few hours are available to rapidly define the underlying lesion. As in other forms of pericarditis, the patient usually complains of severe chest pain increased on inspiration and recumbent posture with some relief by leaning forward. Increasing signs of cardiac tamponade may be manifest (*see* Chapter 13). Initially, this condition may be difficult to differentiate from benign postinfarction pericarditis, but the latter does not cause hemodynamic compromise.

A study of 70 cases reported by Oliva et al. provides the following important observations:

- The most common site of rupture was the mid or basal lateral wall (41%); this is in accordance with other series that show a preponderance of lateral and postero-lateral ruptures. Because only 20–25% of fatal and 15% of nonfatal infarctions involve the lateral wall, there is about a threefold increased tendency of the lateral wall to rupture.
- The wide belief that most ruptures are sudden and cannot be recognized in a timely fashion to allow successful intervention is incorrect.
- This study indicates that subacute rupture is not rare; it presents in a stuttering pattern and can be anticipated because of hallmark symptoms and signs and relevant electrocardiographic findings.

Two of the following three cardinal symptoms occurred in 80% of patients versus 3% of patients without rupture:

- Pleuritic positional chest pain caused by pericarditis.
- Repeated vomiting over 1–24 hours without an obvious cause (not narcotic-induced).
- Agitation and marked restlessness, indicating internal distress similar to that observed in patients with severe pulmonary embolism.

Only one abnormal physical sign was noted: abrupt transient episode of hypotension (SBP <90 mmHg) with bradycardia in 21% of patients with rupture.

Hallmark ECG findings that should be useful in suspecting underlying rupture include a deviation from the expected evolutionary T-wave pattern that occurred in 94% of patients with rupture versus 34% of control patients ($p < 0.02$). Characteristic evolutionary T-wave changes normally expected in the first 48 hours failed to occur; initial T-wave inversion was followed by gradual reversal.

If rupture is suspected, and pericardial fluid is confirmed by echocardiography and pericardiocentesis reveals a bloody effusion, rapid surgical intervention can produce salutary results in these patients. Coronary bypass surgery or angioplasty in selected patients improve survival.

Chronic rupture with or without pseudoaneurysm is a rare occurrence. Circumferential adhesions and a layer of thrombus formation between the visceral and parietal pericardium may cause containment of the hemopericardium for days to weeks.

The abnormal bulge on the cardiac border, chest discomfort, or increasing HF may alert suspicion. Echocardiographic visualization and, occasionally, CT and left ventriculography are indicated on an emergency basis to exclude this potentially correctable lesion.

Papillary Muscle Rupture

Papillary muscle rupture occurs infrequently and accounts for approximately 1% of mortality from acute MI (Table 2.8.). Rupture of one of the smaller heads of the papillary muscle occurs much more commonly than rupture of a main trunk. Diagnosis and therapy include the following:

- Sudden deterioration of the patient's hemodynamic status, with pulmonary edema or cardiogenic shock out of proportion to the extent of ECG changes, is common in patients with inferoposterior infarction. A high index of suspicion is crucial for this diagnosis. This form of rupture can occur with non-ST elevation MI (subendocardial infarction).
- A new mitral regurgitant murmur is usually loud, but may be just audible.
- The catastrophic event is usually fatal, but if severe mitral regurgitation and partial rupture of a papillary muscle are quickly detected by bedside doppler echocardiography or transesophageal echocardiography and catheterization confirms the diagnosis, then surgery is the only hope of survival. Surgical mortality is 10–25%. Hemodynamic support using IABP may be required during catheterization and transport to the operating room.
- Surgery involves replacement of the mitral valve, because the mitral apparatus is usually severely damaged and beyond repair.
- Rupture of a papillary muscle main trunk is a catastrophic event and death ensues within the hour, a situation that is, fortunately, rare.

Ventricular Septal Rupture

Prior to thrombolytic therapy, ventricular septal rupture occurred in 1–3% of patients with acute infarction. Thrombolytic therapy appears to have reduced the incidence to approximately 0.2%.

Associated features and hallmarks include the following:

- Occurs in both anterior and inferior infarctions with concomitant infarction of the inter-ventricular septum.
- More common with first Q-wave anterior or antero-septal infarction.

- Peak occurrence in 2–5 days, but up to 30% occur within 24 hours or up to 2 weeks postinfarction (Table 2.8.).
- Abrupt onset of hemodynamic deterioration often with cardiogenic shock from 12 hours to 14 days postinfarction, in the absence of signs of tamponade or new ECG changes of reinfarction.
- A new, loud, harsh holosystolic murmur maximal at the left and right lower sternal border, often with spoke-wheel radiation.
- A thrill occurs in up to 50% of cases but murmur and thrill are often difficult to identify if cardiogenic shock develops.
- The murmur may be maximal at the apex without a thrill and may be difficult to differentiate from acute mitral regurgitation; an s3 gallop is usually present, but pulmonary edema is not as prominent as with acute mitral regurgitation.
- Rupture usually occurs at the junction of the septum with anterior or posterior LV free wall.
- Right HF is more prominent than pulmonary edema.
- Severe HF, yet a normal, supernormal, or only mild decrease in EF should be a clue to the diagnosis of the cause of cardiogenic shock occurring between days 2 and 14.
- Doppler ECG should confirm the diagnosis particularly with the application of tee.
- Right-sided catheterization with oximetry should show an oxygen step-up in the right ventricle.

The degree of hemodynamic compromise and the general health and age of the patient dictate the urgency and selection of pharmacological and interventional therapy. Patients often come through angioplasty without problems on the IABP. Mortality exceeds 80% with medical therapy.

Surgery should not be delayed for some weeks as was formerly recommended, even if the IABP produces some stability. This improvement is usually temporary, and although surgical mortality is high, repair of the lesion that is causing hemodynamic compromise gives the only hope of survival. Some centers use intraoperative angiography or angioscopy to define coronary occlusions for added management with cabs.

LV Aneurysm

An angiographic LV demarcated diastolic deformity with systolic dyskinesia defines a ventricular aneurysm.

Associated features and implications include the following:

- LV aneurysm is observed in 10–15% of patients within 3 months postinfarction.
- ECG at this stage shows ST segment elevation greater than 1.5 mm in two or more of the following leads: V₁ to V₅ in approximately 33% of cases.
- Usually seen with large Q-wave anterior infarction and absence of LV hypertrophy.
- More than 75% involve the apical anteroseptal region.
- Severe HF is often refractory to intensive cardiac drug therapy. Thus, these patients have a poor quality of life.
- Three-month and 1-year mortalities are greater than 50 and 75%, respectively.
- Most deaths are owing to HF and lethal arrhythmias.
- Low cardiac output state because of steal of stroke volume.
- Elevated LV end diastolic pressure and pulmonary congestion owing to LV diastolic volume overload.
- Increased LV wall stress imposed by global remodeling secondary to aneurysmal dilatation; thus, angina may worsen.

- The thinned myocardial wall is densely fibrotic, and variable calcification occurs.
- Although significant benefit from surgery is far from invariable, aneurysmectomy carries advantages over medical therapy in patients under age 75 who are healthy enough to undergo aneurysmectomy and any necessary CABG if clear indications are present.
- The thin, yet tough, fibrocalcific aneurysmal walls are not prone to rupture.

Aneurysmectomy

Indications:

- Surgery may not attain symptomatic benefit or prolong life and is carefully considered in younger patients with severe angina or intractable HF, refractory to optimal doses of digoxin, furosemide, and ACE inhibitor.
- Patients with lethal or potentially lethal arrhythmias: recurrent sustained VT, VF, patients resuscitated from cardiac arrest. This group will include patients whose arrhythmias have not responded to amiodarone or in whom adverse effects and intolerance to amiodarone exist. Some patients in this category may benefit from multiple programmable pacemaker–cardioverter–defibrillator. Aneurysmectomy and map-guided focus resection are offered at some centers, whereas a few use aneurysmectomy and extensive cryoablation applied to surrounding areas.

Contraindications:

- Elderly patients, infirmity, or underlying disease.
- Large aneurysm with no effective LV cavity to generate adequate stroke volume following aneurysmectomy.
- Poor contractility of the nonaneurysmal LV.

MEDICAL THERAPY FOR VENTRICULAR ANEURYSM

A large percentage of patients with LV aneurysm must be managed with drug therapy because of contraindications to surgery.

- Management entails the judicious use of digoxin, furosemide, and ACE inhibitor, and is discussed in Chapter 5.
- Recurrent sustained VT or resuscitation from VF is best managed with low-dose amiodarone (*see* Chapter 6). All antiarrhythmic agents, with the exception of amiodarone, mexiletine, and quinidine have marked negative inotropic effects and may precipitate HF, especially in patients with poor contractility, poor LV systolic function, and an EF less than 25%. Quinidine is relatively safe in patients with low EF, but has poor efficacy. The unsatisfactory nature of the results obtained with class 1 agents is undoubtedly amplified by a high incidence of proarrhythmic effects with most of these agents, especially in the presence of poor LV function. Amiodarone has low proarrhythmic effects and has a role in patients with life-threatening arrhythmias. The dose of amiodarone and adverse effects are given in Chapter 6.

LV thrombus occurs in over 80% of patients. The thrombus is usually laminated and well-attached to the endocardium, and embolization occurs in less than 3%. If there is no contraindication, warfarin is given to increase the prothrombin time ratio 1.25 to 1.5 times the control or to achieve an international normalized ratio of 2:3, for a period of 6 months in patients with nonlaminated thrombus protruding into the LV cavity and for 3 months with nonlaminated nonprotruding thrombi. Thereafter, enteric-coated aspirin is given. There is some evidence that aspirin can prevent occurrence of atrial and LV mural thrombi and it is advisable to give aspirin to patients with LV aneurysm.

Table 2.9.

Deep Venous Thrombosis, Ventricular Thromboembolism After Acute Myocardial Infarction

<i>Parameters</i>	<i>Approximate incidence (%)</i>
DVT patients	
Age >70 years	72
<50 years	12
Timing of occurrence	
<4 days	15–25
5–15 days	5–15
1–15 days	20–40
Effect of early heparin therapy	<4
Pulmonary embolism	4
Early heparin	<1
Mural thrombus	
Anterior infarcts	30
Large anterior infarcts	50
Systemic embolism	<4
Effect of heparin (10,000–12,500 units SC 12 hourly)	<1
Effects of early aspirin	To be defined

Prevention of Thromboembolism

Antithrombotic therapy is required during the first 5 days of acute MI. Thereafter, aspirin is continued indefinitely.

Antithrombotic therapy is required to prevent deep vein thrombosis (DVT) and pulmonary embolism; LV mural thrombus formation and systemic embolization; reinfarction, especially among patients with non Q-wave infarction, because these patients are at high risk for reinfarction within 3 months; and reocclusion after successful coronary reperfusion with thrombolytic therapy.

Within 4 days of acute MI, DVT occurs in the lower limbs in some 15–25% of patients (Table 2.9.). An additional 10–15% of patients develop DVT in the ensuing 10 days. This early occurrence of DVT suggests the presence of a hypercoagulable state similar to that observed postsurgery. Table 2.10. gives ambulation advice.

The postinfarction incidence of DVT increases with the presence of cardiogenic shock, HF, and prolonged immobilization beyond the fifth day. Age over 70 years carries a sixfold increase with an incidence of about 70%; this may be compared with an incidence of only 12% among patients under age 50.

Three randomized clinical trials with a total of 130 patients using subcutaneous heparin, started within 18 hours of the onset of acute MI and given for 10 days, showed a reduction of DVT from 24 to 4% in the treated patients.

Studies done before the current era of early mobilization and use of aspirin plus or minus thrombolytic therapy have indicated a 4–5% incidence of post-MI pulmonary embolism. Thus, patients considered at low risk for developing DVT or pulmonary embolism (i.e., patients under age 65 with non-Q-wave infarcts, small infarcts, absence of heart failure, and ability to mobilize on day 2) can be given aspirin only to prevent DVT or pulmonary embolism. Patients given IV streptokinase should continue on aspirin; low-

Table 2.10.
Uncomplicated Postmyocardial Infarction Ambulation Day

Day	
2	Lower limb exercises, sit in chair, use bedside commode
3	Bed to chair, walk to shower, walk in room; transfer from CCU
4	Bathroom privileges, walk 100 feet supervised
5	Walk in corridor 200–600 feet; blood pressure pre and post 600 feet and one flight stairs. If stable, discharge on day 5–6. If no contraindications, predischARGE (Naughton or similar protocol) exercise test is done prior to discharge.

dose subcutaneous heparin is continued from day 2 to discharge if the patient is considered at high risk for thromboembolism. Dosage: enoxaparin 1 mg/kg every 12 hours subcutaneously (SC).

Prevention of Systemic Embolism

Mural thrombus occurs in approximately 20% of patients, but large anterior infarcts have an incidence as high as 60%. Systemic embolism occurs in fewer than 4%, and the incidence can be reduced to about 1% with subcutaneous low-molecular weight heparin (LMWH) given SC for 10 days. The incidence of mural thrombus and systemic embolism is reduced by the early use of aspirin and streptokinase. Continued aspirin therapy appears to decrease the incidence of mural thrombus and systemic embolism.

If heparin is not contraindicated and thrombolytic therapy has not been given, it is advisable to give subcutaneous LMWH to patients with large anterior infarcts or infarction, which include the apex of the heart.

Pericarditis

Approximately 40% of fatal MI show acute fibrinous pericarditis. The incidence of clinical pericarditis ranges from 5–25%. Pericarditis usually manifests during the second and fifth day postinfarction, localized in the area overlying the infarct, but may diffusely involve the pericardial sac. Approximately 50% are symptomatic.

CLINICAL HALLMARKS

Diagnostic features include the following:

- Mild-to-moderate pleuritic positional pain. Maximal over the precordium or sub-sternal area with occasional or typical involvement of the trapezius ridges (one or both).
- Pain is made worse with recumbency, deep breathing, and body movement and is improved by leaning forward.
- Pain can be confused superficially with postinfarction angina. It is of paramount importance to distinguish the two conditions because the latter usually requires interventional therapy beginning with coronary angiography, whereas pericarditis requires conservatism, except when it is associated with myocardial rupture (*see* Subacute Rupture). The pain of angina or infarction does not radiate to the trapezius ridges. This is an important differential point because radiation to the trapezius muscles is virtually never seen with myocardial ischemia.
- A pericardial friction rub is heard in 10–30% of cases. The rub is typically evanescent and may come and go over 1–2 days, may increase with inspiration or expiration, coughing,

or swallowing, and is best heard with the diaphragm of the stethoscope with the patient leaning forward. The rub usually has two diastolic components: early, during the early diastolic phase, and late, owing to atrial systole. A third component occurs during ventricular systole. Occasionally, only one component may be heard, and the rub must be distinguished from acute mitral regurgitation, in which a soft murmur is produced as a result of papillary muscle dysfunction. Pericardial friction rub has a superficial scratchy characteristic.

- ECG changes may be difficult to interpret: j-point elevation, concave upward ST elevation, and PR segment depression.
- Echocardiography is helpful in revealing pericardial effusion in over 33% of patients.
- Pericarditis is more common in patients with Q-wave infarction.

THERAPY

- Discontinue heparin.
- Treatment is indicated for pain even when no friction rub is present.
- Aspirin in full doses, 650 mg three times daily, is useful; NSAIDs or corticosteroids should be avoided because indomethacin and similar agents may cause vasoconstriction and alter myocardial healing and appear to increase the incidence of myocardial rupture. Also, these agents cause retention of sodium and water.

Pericarditis, presenting between 2 weeks and 6 months of infarction, and Dressler's syndrome, reported in the 1970s, occur in about 0.1% of patients and is now exceedingly rare. Fever, pleuritic positional pain, increased sedimentation rate, and increased titer of heart reactive antibodies may be present; NSAIDs are best avoided because they cause pericardial vasoconstriction and increase stress on the myocardium. Dressler's syndrome appears to be caused by an autoimmune autoantibody response. This type of pericarditis is currently no longer observed, probably because of the use of aspirin in virtually all patients with acute MI.

This late pericarditis is treated with aspirin. Failure to respond or relapses should be managed with a short course of prednisone with aspirin overlapping at least 2 weeks before prednisone is withdrawn.

DISCHARGE MEDICATIONS

β-Blockers

If β-blockers were commenced during the early hours of MI and no adverse effects were apparent, then β-blockers should be continued. If not given at that time, β-blockers should be administered before discharge and maintained for at least 2 years. Studies indicate that this approach is highly beneficial and cost-effective.

β-BLOCKER CLINICAL TRIAL RESULTS

More than 15 β-blocker trials have been conducted on post-MI patients. Several of these trials, however, lack the methodology that is consistent with current practice in clinical trial design. Unacceptable metaanalyses have been carried out using β-blocker trials that included few patients, some nonrandomized trials, and trials in which β-blocker therapy was commenced later than 1 month postinfarction. Also, the β-blocker used in several trials was inappropriate; oxprenolol has intrinsic sympathomimetic activity that negates cardioprotective effects (*see* discussion: Which β-blockers to choose in Chapter 1, p. 56 and Chapter 4).

Table 2.11.
Mortality Reduction in Long-Term β -Blocker Trials

<i>Trial</i>	<i>Placebo mortality</i>	<i>Drug mortality</i>	<i>Relative reduction (%)</i>	<i>p</i>
Norwegian (1981) 20 mg timolol daily	152/939 16.2%	98/945 10.4%	35.5	<0.001
BHAT 180/240 mg propranolol daily	188/1921 9.8%	138/1916 7.2%	26.5	<0.01
Salathia (1985) 200 mg metoprolol daily	43/364 11.8%	27/391 6.9%	41.5	<0.05
APSI trial (1988) 400 mg acebutolol daily	34/309 11.0%	17/298 5.7%	48	0.019
Capricorn 25 mg carvedilol twice daily	15%	12%	23%	0.031

Clinical trials that meet most current acceptable standards are listed in [Table 2.11](#). These trials indicate an impressive 33% reduction in mortality owing to β -blocker therapy. Mortality reduction with propranolol is significantly less than that observed with timolol in smokers. The efficacy of hepatic-metabolized β -blockers is blunted by cigarette smoking. It is necessary to prescribe metoprolol or timolol to refractory smokers.

If there is no contraindication to β -blockade, virtually all post-MI patients should receive carvedilol 25–50 mg twice daily; 10 mg of timolol twice daily; 400 mg of acebutolol daily, or 100–200 mg of metoprolol daily. Propranolol (180–240 mg daily) is advisable only in nonsmokers. The American College of Cardiology/American Heart Association task force recommends treatment to commence within the first few days of infarction and to continue for at least 2 years in virtually all patients if there are no contraindications to β -blockers. Timolol has been shown to cause a 67% reduction in sudden death in post-MI patients and a 35% reduction in total mortality in patients followed for 2 years postinfarction.

It is estimated that 70% of postinfarction patients are suitable for β -blocker therapy. Up to 20% of postinfarction patients are unable to receive β -blockers because of contraindications, and a further 10% have relative contraindications.

Contraindications to long-term β -adrenergic blockade include:

- Severe LV failure; *see* Chapters 5 and 14, for use in HF.
- SBP less than 100 mmHg.
- Heart rate less than 50/minute.
- Type I, II, or III AV block.
- Asthma or severe chronic obstructive pulmonary disease.

β -Blockers are of particular value in post-MI patients with mild LV dysfunction or mild HF. Because β -blockers are capable of producing about a 28% reduction in reinfarction rates, up to 67% reduction in sudden death, and a 33% decrease in mortality, it is advisable to prescribe these medications to virtually all patients who can tolerate the effects at the dosage indicated previously. Carvedilol, metoprolol, and timolol are better

Table 2.12.

β -Blocker Reduction of Early Morning Sudden Cardiac Death

<i>Sudden deaths</i>	<i>Control</i>	<i>Propranolol</i>	<i>Decrease</i>
Total	78	60	23% ^a
5–8 AM	6	0	
5–11 AM	25	11	56%
11–4 AM	33	31	Similar

^aTimolol; 67% reduction in sudden death.
Modified from β -Blocker Heart Attack Study Data. Am J Cardiol 1989;65:1518.

tolerated than propranolol and are preferred. If mild adverse effects occur, the drug dosage should be decreased slightly or a switch should be made to another β -blocking agent. Subtle but important differences of various β -blockers are discussed in Chapters 4 and 8. Patients should be encouraged to persist with therapy except when adverse effects are bothersome.

Protective effects of β -adrenergic blockade appear to relate to their ability to actuate:

- A decrease in early morning sudden cardiac death (*see Fig. 1.1. and Table 2.12.*).
- A decrease in the incidence of myocardial free-wall rupture.
- A decrease in lethal arrhythmias, causing only a modest suppression of ventricular premature beats (VPBS).
- An increase in VF threshold and a decrease in the incidence of VF.
- Proven decrease in the incidence of fatal and nonfatal MI rates, possibly by decreasing hydraulic stress at the site of atheroma, thus preventing plaque fissuring and subsequent thrombosis. The action of β -blockers to attenuate the hemodynamic effects of catecholamine surges may protect a vulnerable atheromatous plaque from rupture and consequent “coronary thrombosis that leads to fatal MI, sudden death, or nonfatal MI, (*see Fig. 1.1.*).
- Prevention of early morning platelet aggregation induced by catecholamines and decreased early morning peak incidence of acute MI and sudden death (*Table 2.12.*).
- Decreased renin activity. This may have salutary effects on ventricular remodeling. Decreased aneurysmal expansion may occur.

In the United States, β -blocker usage in the postinfarction patient can prevent more than 15,000 deaths in the first year and up to 60,000 deaths over 5 years in patients at medium or high risk. The effectiveness of β -blockers in the low-risk postinfarction population is modest but worthwhile because it is occasionally difficult to correctly assign risks based on prognostic parameters, including postdischarge exercise stress testing and nebulous results provided by spect scintigraphy. In addition, β -blocking agents prevent sudden cardiac death, and it must be emphasized that aspirin has little effect on the prevention of sudden cardiac death. β -Blockers interfere with dipyridamole cardiac nuclear imaging and the β -blocking drug must be slowly discontinued if this test must be performed, so caution is necessary.

Adverse effects and dosage of β -blockers are given in Chapter 4.

Acetyl Salicylic Acid (Aspirin)

With chewable aspirin, patients must be advised that 160–320 mg taken within an hour of the onset of chest pain can prevent the occurrence of MI or death in a significant number of patients, whereas sublingual nitroglycerin does not offer protection. This advice will motivate patients to carry chewable aspirins for use at the crucial period.

Indications for 75–325 mg of daily coated aspirin include:

- Unstable angina.
- Stable angina.
- Post-MI prophylaxis.
- Prevention of systemic embolization from atrial or ventricular thrombi.
- Prevention of pulmonary embolism.
- Prevention of fatal or nonfatal strokes in patients with cerebral transient ischemic attacks or poststroke.
- Post-CABS to prevent graft occlusion.
- Lone AF in patients under age 65.

The action of aspirin irreversibly acetylates the platelet enzyme cyclooxygenase, thus preventing platelets from forming the powerful aggregating agent thromboxane A₂, resulting in a decrease in platelet aggregation. One dose of 80 mg of aspirin inhibits cyclooxygenase for the 1-week lifespan of the circulating platelets. This action abolishes platelet aggregation that would occur in response to stimuli, such as collagen, arachidonate, second-phase aggregation by ADP and epinephrine, and aspirin, which unfortunately reduces the formation of the potent vasodilator prostacyclin, of which the smallest possible dose is advisable—75–160 mg daily—so as not to inhibit prostacyclin. Further studies will clarify the dose range. Currently, a dose of 81–325 mg daily is widely used in post-MI patients.

Aspirin causes a reduction of the early morning incidence of acute MI but does not prevent sudden death (*see* Table 2.13.). The incidence of gastrointestinal bleeding is shown in Table 2.14.

Nitrates

Nitroglycerin is given to all patients upon hospital discharge, including patients with uncomplicated infarction at a dosage of 0.3-mg sublingual tablet or 0.4-mg nitrolingual spray. Two chewable aspirins can be conveniently carried in the cap of the spray. If pain occurs, the patient is advised to take the drug sublingually while sitting or propped up in bed to allow sufficient pooling of blood in the periphery. The drug must not be taken while standing because presyncope or syncope may occur, especially in patients on concomitant therapy with ACE inhibitors, diuretics, or calcium antagonists.

Oral nitrates are not prescribed routinely to post-MI patients, except for patients with postinfarction angina, who are unable to undergo coronary angioplasty or bypass surgery because of contraindications, such as advanced age or serious underlying disease. Where required, oral nitrates are best used in combination with a β -blocker because they do not prevent reinfarction and have not been shown to decrease mortality. Dosage and other effects of nitrates are given in Chapter 4.

Calcium Antagonists

Calcium antagonists do not have a role during the early phase (days 1–4) of acute MI (*see* Chapter 1). Calcium antagonists have not been shown to significantly decrease mortality in the postinfarction patient and are advisable only when β -blockers are contraindicated for the management of postinfarction angina). A meta-analysis indicates that calcium antagonists do not reduce infarct size or mortality, and in some categories of patients, these agents increase the risk of death.

Table 2.13.
Aspirin Reduction of Early Morning Myocardial Infarction
But Not Sudden Death^a

	<i>Aspirin</i>	<i>Placebo</i>	<i>p</i>
Fatal MI	10	26	0.007
Nonfatal MI	129	213	0.0001
Sudden death	22	12	0.08
Other coronary heart disease	24	25	
Stroke death	9	6	
Total cardiovascular death	81	83	

^a22,071 physicians aged 50–80: 325 mg of aspirin alternating days over 5 years.
Modified from The Physician's Health Study. N Engl J Med 1989;321:129.

Table 2.14.
Gastrointestinal Bleeding in the Physicians Study^a

	<i>Aspirin</i>	<i>Placebo</i>	<i>p</i>
Upper gastrointestinal	38	28	
Melena	364	246	0.00001
Transfusion	48	28	

^a22,071 physicians.
Modified from The Physicians' Health Study. N Engl J Med 1989;321:129.

There is no role for routine prophylactic use of diltiazem or verapamil during the first 2 years in patients with non-ST elevation MI.

The Danish study group on verapamil in MI showed an 18-month mortality rate of 11.1% and 13.8% in the verapamil- and placebo-treated groups, respectively ($p = 0.11$).

Numerous postinfarction patients have been given diltiazem. This practice has been based on a small non-Q-waves infarction study. In the 1986 non-Q-wave infarction study, performed on 288 control patients and 288 patients given high-dose diltiazem, 360 showed a 51% reduction in reinfarction rates in patients with non-Q-wave infarction treated from day 1 for 14 days. This small study group did not show a decrease in mortality. A large multicenter study, however, involving 2466 patients, was completed in 1988 (Table 2.15.). This study showed no decrease in total cardiac mortality, and there was no significant decrease in reinfarction rates in patients with Q-wave versus non-Q-wave infarction. A significant increase in mortality attributable to diltiazem was observed in patients with pulmonary congestion and LVEF below 40%. The increase in mortality persisted during long-term therapy beyond 1 year.

In patients with an EF below 40%, HF occurred in 12% (39/326) of patients on placebo and in 21% (61/297) of patients receiving diltiazem ($p = 0.004$).

Only 514 patients with non-Q-wave were enrolled in this study. The cumulative 1-year cardiac event rate (death and/or nonfatal reinfarction) was 9% in diltiazem-treated and 15% in placebo-treated patients. There was a small decrease in reinfarction rates only in patients treated up to 6 months. Reinfarction after 6 months occurred in 13 patients in the

Table 2.15.
Diltiazem in Acute Long-Term Myocardial Infarction

	Placebo patients	Diltiazem patients	Comments
Cardiac deaths	124	127	
Noncardiac deaths	43	38	
Total mortality	167	166	
Reinfarction	116	99	
Total cardiac events	226	202	11% decrease $p = 0.26$
Ejection fraction < 40%			
Heart failure occurrence	39 12%	61 21%	$p < 0.004$ ↑heart failure owing to diltiazem

Modified from N Engl J Med 1988;379:385; and Circulation 1991;83:52.

↑, increase.

placebo group and in 14 in the treated group. Firm conclusions cannot be made from subgroup analysis of an overall negative study. Also, these studies were done before the era of widespread aspirin use in patients with non-Q-wave infarction.

Contraindications to calcium antagonists postinfarction include pulmonary congestion of all grades, EF of less than 40%, bradyarrhythmias, suspected sinus, or AV node disease, hypotension, and dihydropyridine should not be used in the first 6 months post-MI without added β -blocker therapy because survival may be unfavorably influenced.

Caution: do not combine β -blockers with calcium antagonists, except in carefully selected patients, to avoid HF and bradyarrhythmias (*see* Chapter 4). The evidence indicating that diltiazem decreases reinfarction rates and non-Q-wave infarction is weak. Meta-analysis of therapy with calcium antagonists in postinfarction patients has revealed an excess mortality (averaging 6%). This mortality is markedly increased if pulmonary congestion, LV dysfunction, or bradyarrhythmia is present.

ACE Inhibitors and ARBs

The beneficial effects of ACE inhibitors in the acute phase of infarction were discussed earlier in this chapter under HF. A detailed discussion of these agents is given in Chapters 1 and 5. Only their prophylactic role is considered in this section.

The renin angiotension aldosterone system is stimulated during acute infarction, and the degree of stimulation relates to the size of the infarct. Increase in renin activity appears to relate to an increase in mortality. This finding is, of course, to be expected because patients with large infarcts and of less than 35% have high in-hospital and 1-year mortalities. LV dysfunction or concomitant decrease in BP stimulates the renin angiotensin system.

Some degree of ventricular enlargement is detectable in over 40% of patients with Q-wave transmural anterolateral infarction and is observed as early as 1 or 2 weeks after the event. Physical slippage and reorientation of myocyte bundles in the infarcted area occur, causing thinning and expansion. The left ventricle appears to undergo a variable amount of dilatation with some hypertrophy of the noninfarcted area.

Stimulation of the renin angiotensin system plays an important role in augmenting diastolic and systolic wall stresses, producing further LV enlargement. The structural

changes in the left ventricle, termed remodeling, appear to have some detrimental effects that may later increase the incidence of HF.

Fortunately, ACE inhibitors favorably influence remodeling and improve EF, and their use may be considered in postinfarct patients without overt HF, but with EF less than 35%. The results of the SAVE, AIRE,trandolapril, and SMILE studies were discussed earlier.

Ramipril 5 to 10 mg or captopril therapy (25–75 mg daily) is advisable, commencing between day 2 and discharge provided the SBP remains greater than 110 mmHg. ACE inhibitors are continued in patients with HF or in those without HF with anterior infarction, or EF less than 40%. Patients are discharged on an equivalent dose or enalapril 10–20 mg daily, ramipril 5–10 mg, perindopril or other ACE inhibitor; therapy in these patients reduces the incidence of hospitalization for heart failure and improves survival. ARBs (particularly candesartan and valsartan are advisable when there is intolerance to ACE inhibitors.

Cholesterol-Lowering Agents

The in-hospital diet should reflect the dietary advice given to the patient. Instructions on the value and use of a low saturated fat diet with an increase in polyunsaturated fatty acids, as outlined in the AHA guidelines or similar instructions, are appropriate for all patients.

Serum cholesterol and high-density-lipoprotein (HDL) and low-density-lipoprotein (LDL) cholesterol should be evaluated before discharge from hospital. A statin is administered to maintain the LDL cholesterol less than 80 mg/dL (2.0 mmol/L) and C-reactive protein (CRP) at low levels regardless of LDL goal levels.

Dietary measures include a mediterranean-type diet and increased consumption of almonds and walnuts.

PSYCHOSOCIAL IMPACT OF THE HEART ATTACK

The emotional distress to the individual in the months after an acute MI is often as severe as the heart attack itself. The intense apprehension concerning an impaired quality of life, returning to work, and the ability to meet financial obligations poses a threat to the patient's well-being and must be considered of paramount importance by the treating physician and the medical, nursing, and social teams. Thus, psychological intervention should be commenced from day 3 or 4 after admission.

The patient and the family must be given information concerning diagnosis and proposed therapy. The patient should be reassured, especially if HF is not present with uncomplicated MI. The removal of an oxygen mask or nasal prongs if hypoxemia is absent serves to reassure the patient and family that improvement is underway. Anxiety and depression may center around concerns about long-term disability or death and may persist for weeks to months in more than 50% of patients with infarction. It is imperative that the patient be allowed to discuss fears and inner feelings at this early stage and again before discharge. The reassuring tone of the patient's cardiologist or treating physician helps allay anxiety. Information to the patient and family that the damage affected the inferior surface, an inferior MI, and that this indicates a small heart attack, an excellent outcome for now and years to come, are most encouraging news.

Decisions concerning the length of hospital stay and, with uncomplicated infarction, an approximate date of return to work should be given as early as day 3, with the understanding that these are rough estimates of the timing that will materialize as long as

the expected progress is continued. Early ambulation from day 2 also helps to allay anxiety.

A trainee, nurse, or social worker may attend to other aspects of discussion regarding family matters. Stress associated with the patient's employment should be thoroughly explored and advice and assistance should be given. Advice must be consistent to avoid discrepancies between the physician's recommendations and those of trainees or the nursing staff.

Although small doses of anxiolytic agents may be required during the first 2 days post-MI, patients should be quickly weaned off of these agents. Patients can usually overcome their emotional hurdles by clear advice from the nursing staff, and few patients require antidepressant drugs.

Uncomplicated infarct patients are usually discharged on day 4, 5, or 6. Patients with HF usually require more time, and those with complications not requiring PCI are often ready for discharge on the 6th, 7th, or 8th day. Patients with uncomplicated infarction are advised to return to nonstressful work in 6–8 weeks; depending on complications, 10 weeks to 3 months may be required.

Sexual activities should be permitted within 3 weeks of returning home. Risk stratification should suffice to assure the patient that sexual activity can be resumed within weeks of discharge. Further advice should be given after the results of the 3- or 6-week post-MI exercise test.

For most sexually active individuals, intercourse is one of the most enjoyable, satisfying, and stress-relieving activities that life provides. The treating physician should encourage sexual activity, except in the obviously complicated cases, because this advice may convince the patient that all is proceeding well. This reassurance serves to control the fear of impending doom. Males must be reassured that heart attacks do not cause impotence and that the lack of intercourse for 3–6 weeks will not alter later sexual performance. It is important to explain to the patient that there is no reason to change to a different position; the most familiar position is usually best. This advice increases confidence in the male and allays anxiety in the female. The patient may also be reassured to learn that by 3 months after infarction, more than 80% of patients are able to engage in sexual performance with normal intensity and frequency.

Rehabilitation

Some patients require vocational and stress management counseling. Resumption of prior physical and sexual activity and engagement in some form of exercise program improves the patient's morale and emotional, psychological, and vocational status.

Walking is the most commonly prescribed exercise activity for patients. Uncomplicated infarct patients are expected to increase from 0.25 mile at week 2 to 1 mile at 3 weeks and, after a 3-month period, to have regular 1–2-mile brisk walks at least 6 days a week, in addition to normal activities. A brisk 1-mile walk twice daily, climbing three flights of stairs, and stretching exercises are advisable. Also advised is a 1-mile walk in 20–30 minutes over the first few weeks, followed, in energetic individuals, by the same distance covered in about 15 minutes. Healthy patients up to age 75 have improved their peak oxygen consumption status by walking outdoors and/or in shopping or rehabilitation centers.

Riding a stationary bike, simulated cross-country skiing, stretching exercises, or similar activities are common inexpensive modes of exercise. Many patients take pride in their ability to exercise, and this must be encouraged. The 3- or 6-week exercise test helps reassure the patient and indicates the level of activity desired and its safety.

Table 2.16.
Contraindications to Exercise Training Programs for Postmyocardial Infarction Patients^a

Patients with suspected ischemia are deferred pending interventional therapy
Inability to manage about 5 METS at 3 or 6 weeks exercise stress testing
Overt or treated heart failure ^a
Suspect left ventricular systolic dysfunction, ejection fraction <35% ^a
Systolic blood pressure <100 mmHg
Bradyarrhythmia pulse <60 mmHg not owing to β -blockade, sinus, or atrioventricular node dysfunction
New left bundle branch block during recent infarction; difficult to assess ischemic changes ^a
Ventricular arrhythmias (uncontrolled)
Uncontrolled systolic hypertension: systolic > 200, diastolic hypertension > 105 mmHg
Significant valVular heart disease ^a

^aindividual exercise prescriptions.

Jogging and swimming, for interested patients, should commence after a 6-week exercise test. Jogging is built up slowly, 1 mile daily, increasing over months to 3 miles daily. Regular exercise is encouraged for at least 4 days per week. Patients should refrain from weight lifting, rowing, and other static exercises.

SUPERVISED REHABILITATION PROGRAMS

These important programs require the services of a physician, a nurse coordinator, a physical therapist, and a social worker/psychiatrist.

There is no proof from randomized trials that exercise training programs improve survival. Improvement of muscle tone and the ability to perform employment activities and engage in a sporting hobby, however, enhance quality of life.

Patients with ST elevation MI who are able to do greater than 6 metabolic equivalents (METs) at 3 or 6 weeks exercise testing may participate in rehabilitation exercise programs. The patient should achieve 20 BPM above heart rate resting.

Peak blood pressure should not exceed 140 mmHg, and heart rate should not exceed 140 BPM.

Only patients with moderate to severe HF, angina, inability to manage about 6 METs, VT, or complex ventricular arrhythmias are denied access to exercise programs (Table 2.16.). Participation is not allowed until residual ischemia has been managed by angioplasty or CABS, if feasible, and hypertension or arrhythmia has been controlled.

Patients should learn to take their pulse rate. An increase in pulse rate to 120–130 BPM should suffice. Patients on β -blockers should be advised not to exercise beyond the point of shortness of breath. The physician should also recognize the minority of patients in whom a very gradual program with only mild exercise is appropriate (see Table 2.16. for these categories and contraindications to exercise training programs).

BIBLIOGRAPHY

- AIRE: The acute infarction ramipril efficacy (AIRE) study investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821.
- Ambrosioni E, Borghi C, Magnani B. For the survival of myocardial infarction longterm evaluation (SMILE) study investigators. *N Engl J Med* 1995;332:80.
- Aronow WS, Ahn C, Mercado AD, et al. Circadian variation of sudden cardiac death or fatal MI is abolished by propranolol in patients with heart disease and complex ventricular arrhythmias. *Am J Cardiol* 1994;74:819.

- Becker RC, Charlesworth A, Wilcox RG, et al. Cardiac rupture associated with thrombolytic therapy: impact of time to treatment in the late assessment of thrombolytic efficacy (late) study. *J Am Coll Cardiol* 1995;25:1063.
- BHAT: Peters RW, Muller JE, Goldstein S, et al. For the BHAT study group. Propranolol and the morning increase in the frequency of sudden cardiac deaths. *Am J Cardiol* 1989;63:1518.
- Birnbaum Y, Fischbein MC, Blanche C, et al. Ventricular septal rupture after myocardial infarction. *N Engl J Med* 2002;347:1426–1431.
- Brand DA, Newcomer LN, Freiburger A, et al. Cardiologists' practices compared with practice guidelines: use of beta-blockade after acute myocardial infarction. *J Am Coll Cardiol* 1995;26:1432.
- Burkart F, Pfisterer, Kiowski W, et al. Effects of antiarrhythmic therapy on mortality in basal antiarrhythmic study of infarct survival (BASIS). *J Am Coll Cardiol* 1990;16:1711.
- Cannon CP, Braunwald E, McCabe CH. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [PROVE IT—TIMI 22 trial]. *N Engl J Med* 2004;350:1495–1504.
- CAPRICORN Investigators. The effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction. The CAPRICORN randomized trial. *Lancet* 2001;237:1385–1390.
- CHARM: Granger CB, McMurray JJV, Yusuf S, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin converting enzyme inhibitors; the CHARM alternative trial. *Lancet* 2003;362:772–776.
- COPERNICUS: carvedilol Prospective randomized cumulative survival study group effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–1658.
- The Danish study group on verapamil in myocardial infarction. Secondary prevention with verapamil after myocardial infarction. *Am J Cardiol* 1990;66:331.
- Granger CB, McMurray JJV, Yusuf S, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin converting enzyme inhibitors; the CHARM-alternative trial. *Lancet* 2003;362:772–776.
- Gruppo italiano per lo studio della sopravvivenza nell'infarto miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the Gissi-3 trial. *J Am Coll Cardiol* 1996;27:337.
- Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;285:190–192.
- HOPE: The heart outcomes prevention evaluation (HOPE) study investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients *N Engl J Med* 2000;342:145.
- Jensen GVH, Torp-Pedersen C, Kober L, et al. Prognosis of late versus early ventricular fibrillation in acute myocardial infarction. *Am J Cardiol* 1990;66:10.
- Lane D, Carroll D, Lip GYH. Anxiety, depression, and prognosis after myocardial infarction: Is there a causal association? *J Am Coll Cardiol* 2003;42:1808–1810.
- Macmahon S, Collins R, Peto R, et al. Effects of prophylactic lidocaine in suspected acute myocardial infarction. *JAMA* 1988;260:1910.
- McMurray JJV, Pfeffer MA, Swedberg K, et al. Which inhibitor of the renin–angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation* 2004;110:3281–3288.
- Oliva PB, Hammili SC, Edwards WD. Cardiac rupture, a clinically predictable complication of acute myocardial infarction: report of 70 cases with clinical pathologic correlations. *J Am Coll Cardiol* 1993;22:720.
- Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. *Circulation* 1990;81:1161.
- Pitt B. ACE inhibitors for patients with vascular disease without left ventricular dysfunction—may they rest in PEACE? *N Engl J Med* 2004;351:2115–2117.
- Pitt B. A new HOPE for aldosterone blockade? *Circulation* 2004;110:1714–1716.
- Pitt B. Aldosterone blockade in patients with systolic left ventricular dysfunction. *Circulation* 2003;108:1790–1794.
- Pitt B. Aldosterone blockade in patients with acute myocardial infarction. *Circulation* 2003;107:2525–2527.
- Pitt B, Remme W, Zannad F, et al. for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators (EPHESUS). Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321.
- Pohjola-Sintonen S, Muller JE, Stone PH, et al. Milis study group: ventricular septal and freewall rupture complicating acute myocardial infarction: experience in the multicenter investigation of limitation of infarct size. *Am Heart J* 1989;117:809.

- Szmitko PE, Verma S. Red wine and your heart. *Circulation* 2005;111:e10–e11.
- Topol EJ. Arthritis medicines and cardiovascular events—"House of Coxibs." *JAMA* 2005;293:366–368.
- Valiant: Pfeffer MA, McMurray JJ, Velazquez EJ, et al. for the valsartan in acute myocardial infarction trial investigators. Valsartan captopril or both in myocardial infarction complicated by heart failure left ventricular dysfunction or both. *N Eng J Med* 2003;349:1893–1906.

3

Cardiogenic Shock

CONTENTS

PATHOPHYSIOLOGY OF SHOCK
NEW CONCEPTS
CAUSES OF SHOCK
INCIDENCE AND IMPLICATIONS
CLINICAL FEATURES
THERAPY
BIBLIOGRAPHY

PATHOPHYSIOLOGY OF SHOCK

Shock is a clinical state in which target tissue perfusion is inadequate to supply vital substrates and remove metabolic waste. Inadequate cellular oxygenation leads to marked generalized impairment of cellular function and multiorgan failure. Autopsy studies indicate that combined new and old extensive myocardial infarctions (MIs) consistently involve more than 40% of the left ventricular (LV) myocardium.

The underlying pathophysiology of cardiogenic shock is:

- Profound depression of myocardial contractility, resulting in a vicious spiral of reduced cardiac output and low blood pressure.
- Further coronary insufficiency, and further reduction in contractility and cardiac output occurs.
- In response to the severe reduction of cardiac output (CO) compensatory systemic vasoconstriction with increased systemic vascular resistance occurs.
- The dogma that acute reduction in CO causes marked compensatory vasoconstriction was not confirmed, however, in many patients in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) registry and trial.

Over time, myocardial hypercontractility ceases because of utilization of glucose over fatty acids, loss of Krebs cycle intermediates, and depletion of substrate required for adenosine triphosphate (ATP) production.

NEW CONCEPTS

- Hochman points out that data from the shock trial and registry indicate that cardiogenic shock is often not simply a result of extensive MI with pump failure “but also involves inflammatory mediators. These mediators induce nitric oxide synthase (iNOS) expres-

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Edited by: M. Gabriel Khan © Humana Press Inc., Totowa, NJ

sion, increasing nitric oxide (NO) and peroxynitrite levels, resulting in further myocardial dysfunction and failure of an appropriate peripheral circulatory response.”

- Massive infarction evokes a nonspecific inflammatory response, complement activation, release of inflammatory cytokines, expression of iNOS and inappropriate vasodilation that play a role in the genesis of shock and in outcome after shock.
- The ability to vasoconstrict vascular beds that supply nonvital organs is an important compensatory response to a reduction in cardiac output. Endogenous vasodilators appear to interfere with this compensatory response that becomes severely deranged as shock progresses. Vasoconstrictor drugs do not target specific vascular beds and, thus, do not reverse the abnormality in nonvital vascular beds.
- Cardiogenic shock basically results from profound reduction in cardiac output usually caused by marked reduction of LV or right ventricular (RV) systolic function, despite adequate ventricular filling pressures and there is a failure of compensatory vasoconstrictive mechanisms that are overwhelmed by inappropriate vasodilation in large nonvital vascular beds, thus depriving perfusion of critical areas, particularly the heart, brain, and kidney (*see Fig. 3.1.*).

CAUSES OF SHOCK

Cardiogenic shock may be caused, however, by cardiac disorders that result in profound reduction in ventricular filling pressures. These conditions cause a reduction in effective preload, thus resulting in marked reduction in cardiac output. Catastrophic complications of cardiac disorders that cause cardiogenic shock are given in [Table 3.1](#). Cardiac disorders, including massive MI, particularly RV infarction, may cause acute alteration of ventricular compliance, which decreases preload and further decreases cardiac output. Because arterial blood pressure (BP) equals CO multiplied by systemic vascular resistance, marked hypotension occurs, resulting in poor tissue perfusion.

- Noncardiogenic shock results from a marked reduction in CO caused by profound reduction in preload usually owing to hypovolemia ([Fig. 3.1](#)).
- Shock owing to sepsis, anaphylaxis, and metabolic and toxic etiology produces marked vasodilatation, resulting in a large proportion of the vascular volume being distributed to the skin, splanchnic bed, muscles, and other nonvital areas, thus depriving the brain, heart, and kidneys of adequate perfusion. Maldistribution may also occur in some cases of cardiogenic shock. Marked vasodilation and maldistribution of blood flow that occur in noncardiogenic shock causes hypovolemia and reduction in preload, which decreases cardiac output and leads to poor target tissue perfusion. Preload reduction is most commonly resulting from the many causes of hypovolemia ([Table 3.2](#)).

Although the basic difficulty in most patients with cardiogenic shock is a marked decrease in systolic function, a decrease in preload is also implicated. The end diastolic LV volume, as measured by the LV filling pressure, or pulmonary capillary wedge pressure (PCWP), reflects the effective preload, that is, the load or stretch on a sarcomere immediately before contraction, but it must be emphasized that a high PCWP is not always an accurate measure of LV preload. The PCWP is a relatively reliable index of LV preload only when ventricular compliance is normal or unchanging, tight mitral stenosis, myxoma, or obstruction to pulmonary venous drainage are absent, or severe mitral regurgitation is absent, because in this condition, the tall V-wave in the left atrial pressure tracing elevates the mean pressure above LV end diastolic pressure.

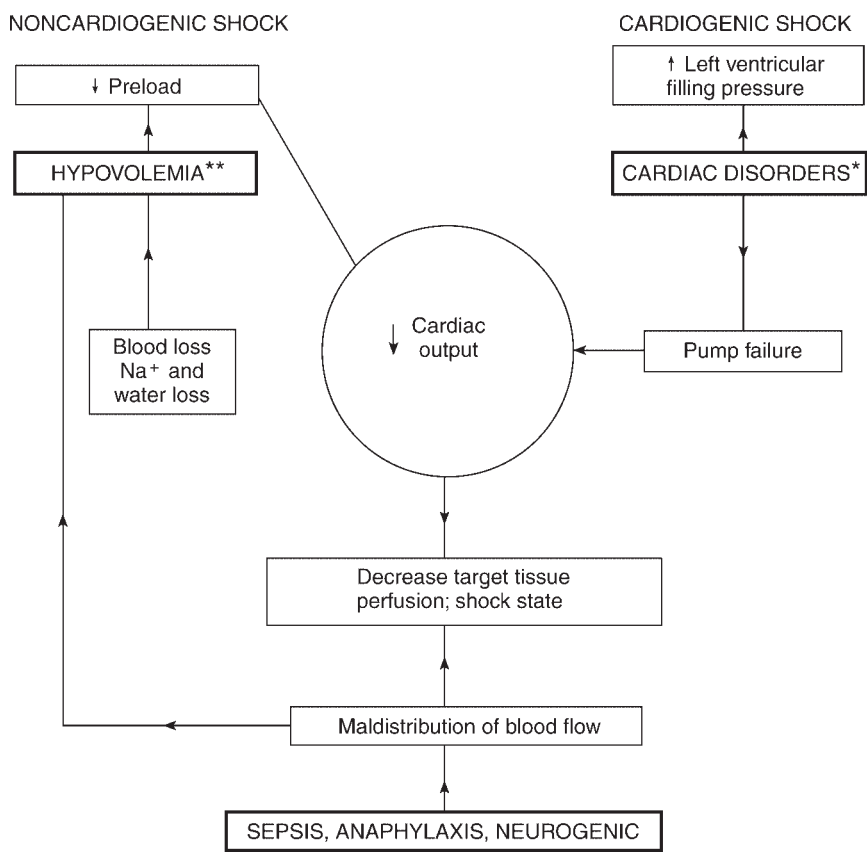


Fig. 3.1. Pathophysiology of shock. ↑, increase; ↓, decrease. *See Table 3.1; **See Table 3.2.

Cardiac causes of preload reduction include alteration of LV or RV compliance because of massive acute MI. RV infarction virtually always causes a decrease in RV preload; thus, volume loading has a role when combined with dobutamine (Fig. 3.2); tight mitral stenosis and atrial myxoma; sudden loss of atrial function, especially important with right ventricular infarction and hypertrophic or restrictive cardiomyopathy; decreased diastolic filling time with tachyarrhythmias; increased intrapericardial pressure causing a high right atrial pressure yet decreased right ventricular preload, as with cardiac tamponade (Fig. 3.2.); and shock complicating acute MI.

In acute MI, early shock is aggravated by pain and arrhythmias, the correction of which can be salutary. Once shock develops, there is a vicious circle of increasing ischemia and decreasing CO. Early treatment with correction of aggravating factors is therefore of great importance. Table 3.3. gives cardiac medications that might worsen the shock state.

INCIDENCE AND IMPLICATIONS

Cardiogenic shock occurs in 6–19% of patients with acute MI that involves more than 40% of the myocardial mass, or in patients with complications of myocardial free-wall rupture, ventricular septal rupture, or severe mitral regurgitation. Mortality rates have been reported to range from 65–80%.

Table 3.1.
Causes of Cardiogenic Shock

Myocardial disorders
Acute myocardial infarction and complications ^a
Dilated and hypertrophic cardiomyopathy
Valvular
Acute mitral regurgitation
Acute aortic regurgitation
Severe aortic stenosis
Prosthetic valve dysfunction
Preload reduction
Restriction to filling
Cardiac tamponade
Mitral stenosis, left atrial myxoma, or thrombus
Alteration of compliance
Acute myocardial infarction, especially in the presence of right ventricular infarction
Hypertrophic cardiomyopathy
Decrease diastolic filling with tachyarrhythmias
Tachyarrhythmias, bradyarrhythmias
Other cardiovascular causes of shock
Aortic dissection
Pulmonary embolism
Primary pulmonary hypertension

^aSee Chapter 2.

Table 3.2.
Causes of Noncardiogenic Shock

Hypovolemia
Blood loss
Effective plasma volume, dehydration, vomiting, diarrhea, burns, acute pancreatitis, peritonitis, diabetic coma, adrenal failure
Latrogenic: excessive diuresis in heart failure patients
Vasodilation and maldistribution of blood flow
Septicemia
Anaphylaxis
Renal failure
Hepatic failure
Acute pancreatitis
Malignant hyperthermia
Neurogenic shock: head or spinal cord injury (often bradycardic)

Although early revascularization is superior to initial aggressive medical therapy, the mortality rate remains higher than 50% despite intervention, and half of the deaths occur within the first 48 hours.

The following clinical trials provided relevant details on cardiogenic shock:

- The Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico trial indicates that cardiogenic shock remains the major cause of death after hospitalization

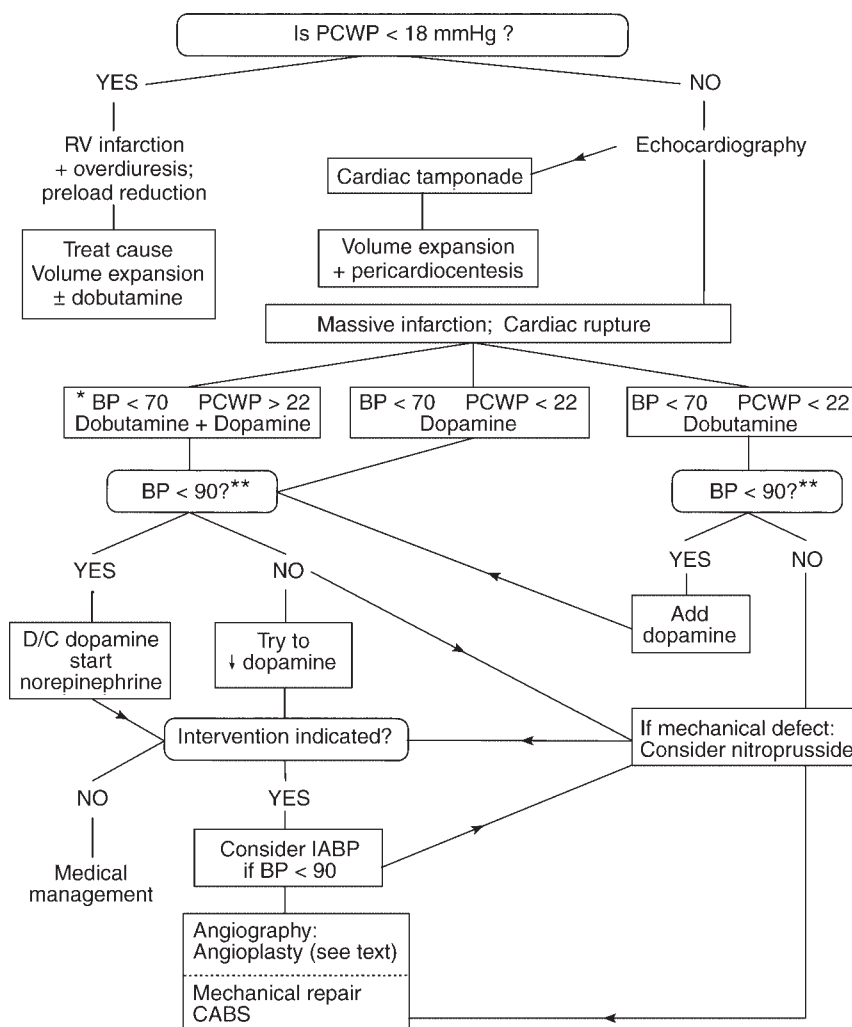


Fig. 3.2. Guidelines for the management of cardiogenic shock complicating MI. ↑, increase; ↓, decrease. *BP, systolic blood pressure in mm Hg. **Goal: BP > 100 mm Hg or mean arterial > 80 mmHg.

for acute MI. From 9–15% of patients with acute MI present to emergency rooms with cardiogenic shock and 6–7% develop cardiogenic shock within 24 hours of hospital admission.

- In an early 1990s prospective multicenter registry of cardiogenic shock that included mechanical causes of shock, the in-hospital mortality rate was 70%. Thus, approximately 40,000 deaths are caused by cardiogenic shock each year in the United States. It is relevant that the estimated incidence of cardiac rupture is 25,000 cases, and most of these succumb to cardiogenic shock and death.
- The Multicenter Investigation of Limitation of Infarct Size study indicates that in patients with cardiogenic shock, fewer than 20% occurred early and was observed on presentation to hospital; over the next 8 days, approximately 10% of cases of cardiogenic shock occurred daily.

Table 3.3.
Cardiac Medications That Might Worsen the Shock State

ACE inhibitors
Renin angiotensin system vital to sustain BP; agents decrease preload
β -blockers
Bradycardia, negative inotropic action, decrease cardiac output and BP
Antiarrhythmics
Negative inotropic action
Calcium antagonists
Negative inotropic action, bradycardia, vasodilation, and profound decrease in BP
Preload-reducing agents
Nitrates, ACE inhibitors, nitroprusside

- The International Study of Infarct Survival found that of 41,299 patients who received thrombolytic therapy, shock was observed in hospital in 7%. This is in accordance with the MILIS study that reported on 845 patients less than age 77 with acute MI in whom cardiogenic shock developed after hospitalization in 7.1%. The incidence of 7% does not include those presenting in shock, which is approximately 3% of acute MI patients.
- In the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) study, the overall incidence of cardiogenic shock was 6.1%, and 10% of these were observed on presentation. Patients treated with streptokinase developed shock more often than those treated with front-loaded tissue plasminogen activator (tPA) (6.6 vs 5.1%, $p > 0.05$).
- In the anisoylated plasminogen streptokinase activator complex (APSAC) Multicenter Trial Group, after the first day, the APSAC-treated group had a lower incidence of shock (3.2 vs 9.5%, $p = 0.03$).

CLINICAL FEATURES

Marked decrease in cardiac output and poor target tissue perfusion give rise to the following clinical findings:

- Severe hypotension that persists beyond 30 minutes: systolic blood pressure (SBP) generally less than 80 mmHg without inotropes, SBP less than 90 mmHg with inotropic support, or in previously hypertensive patients.
- Cool peripheries, often with diaphoresis.
- Clouding of consciousness, progressing to coma.
- Marked reduction in Cardiac index: usually less than 1.8 L/minute/m².
- PCWP greater than 18 mmHg, except in patients with RV infarction. Incorrect estimates of left ventricular filling pressure, based on pulmonary wedge pressure, can occur in the presence of severe mitral regurgitation or ventricular septal defect.
- Oliguria, urine output less than 30 mL/hour.
- A palpable radial pulse usually indicates a SBP greater than 80 mmHg.
- A femoral pulse indicates a SBP greater than 70 mmHg.
- A carotid pulse indicates a SBP greater than 60 mmHg.

A very low cardiac output decreases the intensity of murmurs, and it may be difficult to ascertain the degree of mitral regurgitation at the bedside. Echocardiography (ECG) is a valuable tool to document the presence and significance of mechanical complications of infarction.

RV infarction is rare but must be excluded, because therapy is different from that given to patients with complications of LV infarction. RV infarction usually occurs in association with some degree of LV infarction (inferoposterior), and the PCWP may be less or greater than 18 mmHg (Fig. 3.2).

Signs of RV infarction are:

- Jugular venous pressure elevated with absence of normal inspiratory fall, Kussmaul's sign.
- RV gallop.
- Clear lung fields on examination and on chest x-ray, but interstitial pulmonary edema may be present, caused by LV failure as a result of commonly associated LV infarction.
- ECG evidence of inferoposterior infarction is usually present (ST-segment in right chest leads, elevation in V₃R, V₄R).
- Often the ratio of mean right atrial pressure to mean PCWP is greater than 0.8.

THERAPY

Massive acute MI is the most common cause of cardiogenic shock. The prompt correction of aggravating factors and the use of percutaneous coronary intervention (PCI) or thrombolytic agents within the first 3 hours of onset of anterior, anterolateral, and inferolateral infarction carry the best hope of decreasing the incidence of cardiogenic shock. Recent randomized trials indicate a low incidence of cardiogenic shock in patients treated with thrombolytic agents. In the GUSTO trial, patients treated with front-loaded tPA had a 5.1% incidence of cardiogenic shock versus 6.6% in the streptokinase-treated group. In the APSAC trial, patients treated with APSAC had an incidence of shock of 3.2% versus 9.5% in the placebo group.

Because the in-hospital mortality for cardiogenic shock remains above 70%, even a modest decrease in mortality must be pursued. The addition of hirudin or similar specific thrombin inhibitors to thrombolytic agents may improve prolonged patency of the infarct-related artery. Early recognition of the shock state and an immediate decision to pursue aggressive interventional therapy with coronary angioplasty are necessary to salvage lives.

Recent studies indicate that the very high mortality rate of patients with cardiogenic shock caused by massive evolving infarction is significantly reduced by urgent revascularization in selected patients.

Shock in patients with RV infarction may be reversed by coronary angioplasty done up to 12 hours postonset of the shock state; this salutary effect may be related to a high incidence of reversible ischemia or stunned myocardium in these patients.

Surgical repair for acute severe mitral regurgitation or development of a large ventricular septal defect (VSD) may save a few lives, but a prognosis that depends critically on residual LV function must remain guarded in this subset.

Cardiac tamponade caused by MI and rupture requires immediate volume expansion to maintain an adequate preload and prompt pericardiocentesis, however successful surgical rescue is rare (*see* Chapter 2 for the diagnosis of subacute rupture).

The conversion of acute atrial fibrillation to sinus rhythm in patients with acute MI, particularly RV infarction, and in those with hypertrophic cardiomyopathy is advisable. Prompt electrical cardioversion is required for all arrhythmias if the patient is hemodynamically unstable (*see* Chapter 6). Even mild bradycardia is inappropriate for the patient in shock, and correction of this arrhythmia, too, may be beneficial.

Supportive Therapy

- In shock caused by MI, the shock state is aggravated by pain and arrhythmias, the correction of which can be salutary; morphine is used judiciously.
- Ensure an adequate airway and maintain an alveolar oxygen (PaO_2) rate of 75–120 mmHg.
- Use a well-fitted oxygen mask with a high flow rate of 10–15 L/minute. Patients with clouding of consciousness or coma should be intubated if the decision is made to pursue interventional therapy.
- Insert two large-bore 16-gage catheters; one catheter is placed centrally under sterile conditions. Use a venous sheath with sidearm attachment and a balloon flotation catheter. Obtain duplicate blood samples from the superior vena cava, right atrium, and pulmonary artery for oximetric assessment.
- Insert an indwelling arterial line, preferably femoral, for BP and oximetric monitoring.
- An indwelling catheter is necessary to monitor urinary output greater than 30 mL/hour.
- Determine the PCWP. If less than 15 mmHg, commence fluid challenge to bring the filling pressure of the LV to 18 mmHg (Fig. 3.2).
- Obtain arterial blood gas analysis, electrolytes, creatinine, hemoglobin liver function tests, prothrombin time, and activated partial thromboplastin time with creatine kinase and creatine kinase-MB.
- Determine the CO by thermodilution technique and indirectly by assessment of arterial mixed venous oxygen content difference.
- Monitor the cardiac rhythm and obtain rhythm strips every half-hour.
- Morphine is given in aliquots of 2–5 mg if the patient is in pain or is very uncomfortable.
- Obtain right atrial, RV, and pulmonary arterial pressures and PCWP.
- Check for elevated diastolic pressures and equalization of right atrial (greater than 10 mmHg), pulmonary artery, and PCWP that would indicate cardiac tamponade.
- Obtain reliable end-expiratory pressure tracings.
- Determine the ratio of mean right atrial to mean PCWP; greater than 0.8 is often present in patients with RV infarction.
- Assess for large V-waves with slow upslope in the wedge position that would indicate severe mitral regurgitation.
- An oxygen stepup indicates intracardiac left-to-right shunt.
- Transesophageal echocardiography (TEE) done urgently has proven very useful in the assessment of aortic dissection and is advisable in assessing patients with cardiogenic shock. TEE allows accurate assessment for dissection, cardiac tamponade, severe mitral regurgitation, interventricular septal rupture, and other lesions and assists with making a decision regarding aggressive therapy. The transthoracic technique may suffice in some patients or when TEE is not available.
- Ensure an effective preload with an infusion of 0.9% saline, if needed, to maintain an LV filling pressure of 18–20 mmHg and as high as 24 mmHg if necessary. It is advisable to err on the side of allowing some lung congestion to occur because left ventricular compliance is poor and requires increased preload to maintain cardiac output (*see* earlier discussion of preload). It is not advisable to give furosemide in an attempt to decrease mild pulmonary congestion because this may cause a decrease in preload and decreased CO; furosemide is required if pulmonary edema with a PCWP greater than 24 mmHg is present.
- Nitroprusside is indicated if there is documented acute severe mitral regurgitation and/or mechanical complications of infarction for which afterload reduction is considered necessary. Nitroprusside is commenced after stabilization of BP with inotropes or intraaortic balloon pump (IABP) (Fig. 3.2.).

Figure 3.2. gives suggested guidelines for the management of cardiogenic shock. Patients with PCWP greater than 18 mmHg and severely impaired stroke volume owing to massive infarction comprise the largest group, and urgent coronary angioplasty carries some hope for salvage. BP and renal perfusion must be maintained during preparation for angioplasty. It must be reemphasized that a wait-and-see policy is not advisable, and prompt angioplasty in selected patients with cardiogenic shock is strongly recommended with 18 hours of onset of infarction. If intervention is not considered advisable, continue medical therapy. The use of the IABP without angioplasty or coronary artery bypass surgery (CABS) does not improve outcome.

This recommendation will change with new information from ongoing prospective randomized trials. Pharmacological agents do not improve survival in patients with cardiogenic shock and should be used mainly with an endeavor to support the patient through coronary angiography and angioplasty or CABS.

Inotropes and vasopressors may have an increased role if thrombolytic therapy, which includes front-loaded tPA or bolus reteplase and the addition of hirudin, proves useful in maintaining patency of the infarct-related artery.

Inotrope/Vasoconstrictor

The pharmacological effects of vasoactive agents are given in Table 3.4. These pharmacological agents are given by IV infusion, preferably using well-maintained infusion pumps and under strict supervision. It is necessary to titrate the dosages of these agents to correct severe hypotension, achieve improvement in cardiac output, maintain an adequate LV filling pressure (18–20 mmHg), and, in some instances, to increase peripheral vascular resistance. In properly selected patients with mechanical defects after stabilization of BP, a reduction in after-load is essential (Fig. 3.2).

An attempt should be made to maintain a SBP greater than 100 mmHg or mean arterial pressure greater than 80 mmHg and a urinary output greater than 30 mL/hour.

Dobutamine

A dosage of 2–10.0 mg/kg/minute is used, titrated to achieve a desired inotropic effect directed by several measurements of CO, arteriovenous oxygen content difference, urine output, and mentation (*see* Infusion Pump Chart, Table 3.5., and Fig. 3.2.). Dobutamine should not be used alone in the severely hypotensive patient. Usually, if a dose in excess of 4–6 µg/kg/minute is required and unacceptable hypotension exists, dopamine infusion is commenced at 5 µg/kg/minute and dobutamine 4–6 µg/kg/minute titrated up to a suggested maximum of 10 µg/kg/minute of each agent. Occasionally, dobutamine titrated to a maximum of 20 µg/kg/minute is necessary, especially if LV filling pressure exceeds 24 mmHg, a situation in which dopamine is relatively contraindicated. Thus, if the SBP is less than 70 mmHg and PCWP is greater than 24 mmHg, a combination of dobutamine and norepinephrine is indicated.

Dopamine

A dosage of 2.5–10 µg/kg/minute is used via a central line (*see* Infusion Pump Chart, Table 3.6.). Dopamine at a dose of 0.5–4 µg/kg/minute causes cardiac β stimulation and also stimulates renal dopaminergic receptors producing renal arteriolar dilatation and an increase in urinary output. A dose of 4–6 µg/kg/minute is initially advised if severe hypotension is present. At doses above 4 µg/kg/minute, beneficial renal effects are lost,

Table 3.4
Pharmacologic Effects of Vasoactive Drugs

<i>Receptors and Parameters</i>	<i>Dobutamine</i>	<i>Dopamine, Ibopramine</i>	<i>Epinephrine</i>	<i>Norepinephrine</i>	<i>Nitroprusside</i>	<i>Nitroglycerin</i>
β_1	+++	+ if dose < 5 $\mu\text{g/kg/minute}$	+++	++++	Nil	Nil
β_2	+	Nil	++	Nil	Nil	Nil
α	Nil	++ if > 5 $\mu\text{g/kg/minute}$ +++ if > 10 $\mu\text{g/kg/minute}$ Dopaminergic ++ if < 5 $\mu\text{g/kg/minute}^a$	++	++++	Nil	Nil
Heart rate \uparrow	+	0/+	++	+	++	+
Inotropic effect	+++	+	++++	++	Nil	Nil
Arterial vasoconstriction	Nil	+++	++	++++	Nil	Nil
SVR \uparrow						
Arterial vasodilatation	0/+	Nil	++	Nil	++++	+
SVR \downarrow		(coronary)				
Venodilation preload \downarrow	Nil	Nil	Nil	Nil	+++	+++
Nil	Nil	Nil	Nil	+++	+++	

^aSalutary renal effects.

+, mild effect; +++++, strong effect; -, mild decrease; \uparrow ; increase; \downarrow decrease.

SVR, systemic vascular resistance.

Table 3.5.
Dobutamine Infusion Pump Chart (Dobutamine 2 amps [500 mg] in 500 mL [1,000 µg/mL])

<i>Dosage</i> µg/kg/min	<i>Rate (mL/h)</i>													
	40 kg	45 kg	50 kg	55 kg	60 kg	65 kg	70 kg	75 kg	80 kg	85 kg	90 kg	95 kg	100 kg	105 kg
1.0	2	3	3	3	4	4	4	5	5	5	5	6	6	6
1.5	4	4	5	5	5	6	6	7	7	8	8	9	9	9
2.0	5	5	6	7	7	8	8	9	10	10	11	11	12	13
2.5	6	7	8	8	9	10	11	11	12	13	14	14	15	16
3.0	7	8	9	10	11	12	13	14	14	15	16	17	18	19
3.5	8	9	11	12	13	14	15	16	17	18	19	20	21	22
4.0	10	11	12	13	14	16	17	18	19	20	22	23	24	25
4.5	11	12	14	15	16	18	19	20	22	23	24	26	27	28
5.0	12	14	15	17	18	20	21	23	24	26	27	29	30	32
5.5	13	15	17	18	20	21	23	25	26	28	30	31	33	35
6.0	14	16	18	20	22	23	25	27	29	31	32	34	36	38
7.0	17	19	21	23	25	27	29	32	34	36	38	40	42	44
8.0	19	22	24	26	29	31	34	36	38	41	43	46	48	50
9.0	22	24	27	30	32	35	38	41	43	46	49	51	54	57
10.0	24	27	30	33	36	39	42	45	48	51	54	57	60	63
12.5	30	34	38	41	45	49	53	56	60	64	68	71	75	79
15.0	36	41	45	50	54	59	63	69	72	77	81	86	90	95
20.0	48	54	60	66	72	78	84	90	96	102	108	114	120	126

The above rates apply only for a 1000 mg/L concentration of dobutamine. If a different concentration must be used, appropriate adjustments in rates should be made. Usual dose range 2.5–10 µg/kg/minute.

From: M. Gabriel Khan. Cardiac Drug Therapy. Sixth ed. Philadelphia: WB Saunders, 2003, with permission from Elsevier.

Table 3.6.
Dopamine Infusion Chart

<i>Dosage</i> $\mu\text{g/kg/minute}$	<i>Rate (mL/hour) (pump)</i>						
	40 kg	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg
1.0	1.5	1.9	2.3	2.6	3	3.4	3.8
2.0	3	3.8	4.5	5.3	6	6.8	7.5
3.0	4.5	5.6	6.8	7.9	9	10.1	11.3
4.0	6	7.5	9	10.5	12	13.5	15
5.0	7.5	9.4	11.3	13.1	15	16.9	18.8
6.0	9	11.3	13.5	15.8	18	20.3	22.5
7.0	10.5	13.1	15.8	18.4	21	23.6	26.3
8.0	12	15	18	21	24	27	30
9.0	13.5	16.9	20.3	23.6	27	30.4	33.8
10.0	15	18.8	22.5	26.3	30	33.8	37.5
12.0	18	22.5	27	31.5	36	40.5	45
15.0	22.5	28.1	33.8	39.4	45	50.6	56.3
20.0	30	37.5	45	52.5	60	67.5	75

Dopamine (800 mg) in 500 mL 5% dextrose/water. Use chart for pump (mL/hour) or microdrip (drops/minute). Example: 60-kg patient at 4.0 $\mu\text{g/kg/minute}$: pump, set pump at 9 mL/hour; microdrip, run solution at 9 drops/minute.

and mainly α -adrenergic vasoconstriction occurs with minimal β stimulation that causes an increase in heart rate, CO, and BP. A dose greater than 5 $\mu\text{g/kg/minute}$ is often required to raise SBP in severely hypotensive patients. In patients with cardiogenic shock, a dose above 15 $\mu\text{g/kg/minute}$ without added dobutamine is seldom advisable, because at this dose, only marked α vasoconstriction occurs. It must be emphasized that although the combination of dopamine (6–10 $\mu\text{g/kg/minute}$) and dobutamine (2–10 $\mu\text{g/kg/minute}$) has several merits, dosages of either drug in excess of 10 $\mu\text{g/kg/minute}$ have major disadvantages. If more than 15 $\mu\text{g/kg/minute}$ is required and the SBP or diastolic blood pressure (DBP) remains very low, with a PCWP greater than 24 mmHg, dopamine should be discontinued and norepinephrine should be tried in combination with dobutamine. Provided that filling pressures are adequate (greater than 18 mmHg), failure of dopamine 15 $\mu\text{g/kg/minute}$ to raise SBP to greater than 80 mmHg, or DBP to greater than 60 mmHg, or both, necessitates the addition of norepinephrine; maximum suggested dose is 20 $\mu\text{g/kg/min}$. The IABP is preferred if the decision is made to proceed with interventional therapy (Fig. 3.2).

Norepinephrine

Norepinephrine is indicated only when dopamine administration and IABP fail to maintain arterial DBP above 50–60 mmHg in previously normotensive individuals. The drug is particularly useful in patients in whom systemic vascular resistance is not elevated (<1800 dyne-sec/cm⁵).

A dosage of titrated 2–10 $\mu\text{g/minute}$ IV infusion is used to achieve desired hemodynamic effect; the patient should then be weaned to dopamine plus or minus dobutamine.

An increase in dosage in the range of 11–20 $\mu\text{g}/\text{minute}$ is advised only after careful consideration. Care is also required to prevent extravasation, which causes necrosis.

Norepinephrine causes intense α -adrenergic vasoconstriction and has relatively modest β -mediated myocardial chronotropic and inotropic effects. α -Mediated vasoconstriction produces an increase in SBP and DBP. Because the coronary arteries fill during diastole, it is imperative to maintain adequate DBPs. Because intense α vasoconstriction has adverse effects on renal and other tissues, norepinephrine should be considered a temporary maneuver until either the patient improves spontaneously or, as is more often the case, the decision is reached to proceed with aggressive therapy and insertion of the IABP before angiography, coronary angioplasty, or surgery. It must be reemphasized that vasoactive drugs and the IABP play a role in the temporary support of patients but do not themselves improve mortality. Because of the adverse effects of sympathomimetic amines, early IABP is recommended for all patients who are candidates for further therapy beyond a conservative strategy.

Nitroprusside

Begin with a very low dose (0.4 $\mu\text{g}/\text{kg}/\text{minute}$) and titrate until a desired hemodynamic effect is achieved (*see* Infusion Pump Chart, [Table 8.11](#)).

Patients with severe mitral regurgitation or ventricular septal rupture require afterload reduction with nitroprusside and avoidance of vasoconstrictor agents. Nitroprusside may cause a coronary steal; DBP may be lowered as well. A Veterans Administration study indicated that efficacy of nitroprusside in patients with acute MI was related to the time of treatment. Nitroprusside had a deleterious effect when administered to patients within 8 hours of onset of pain and a salutary effect in patients whose infusions were begun later. Mechanical complications of acute MI often occur more than 8 hours after the onset of pain, and nitroprusside, therefore, has a role in this category of patients (*see* Chapter 2). Tachycardia and thiocyanate toxicity should be anticipated (*see* Chapter 8). The combination of small dosages of dobutamine (2–6 $\mu\text{g}/\text{kg}/\text{minute}$), dopamine (5–10 $\mu\text{g}/\text{kg}/\text{minute}$), and nitroprusside is advisable when afterload reduction is necessary but without causing a fall in BP. Afterload reduction by nitroprusside is indicated in patients with mechanical complications, VSD, and severe mitral regurgitation after stabilization of arterial diastolic and coronary perfusion pressure by concomitant use of the IABP ([Fig. 3.2](#)). Captopril has been tried in these patients with some beneficial effects.

Nitroglycerin

Nitroglycerin infusion has a minor role in patients with mild cardiogenic shock, especially if there is ongoing ischemia, pulmonary congestion, and PCWP exceeding 22 mmHg. Care is needed, however, to maintain systolic blood pressure greater than 100 mmHg and an adequate preload. The PCWP should be maintained in the 18–20 mmHg range and even as high as 22 mmHg in some patients to achieve optimal cardiac output. Nitroglycerin is preferred to nitroprusside if ischemia is present or during the first 8 hours of infarction (*see* discussion of nitroprusside). IV nitroglycerin is contraindicated in patients with RV infarction, hypovolemia, or PCWP less than 18 mmHg. Also, caution is necessary in all patients with inferior infarction and cardiogenic shock because of the likely presence of RV infarction. A marked fall in BP resulting from a decrease in preload with the commencement of oral or IV nitroglycerin should alert the physician to the

presence of RV infarction. Of course, this agent can be used for the treatment of ongoing ischemia if BP has been stabilized by the use of dobutamine, dopamine, and/or IABP.

Definitive Therapy

A firm decision concerning aggressive therapy, coronary angioplasty, or surgical repair with bypass surgery must be carefully weighed. The risks and tribulations of aggressive therapy must be discussed with the patient and family. The decision to proceed is usually not difficult in the less common situation when there is a structural problem such as a VSD or severe mitral regurgitation and LV function is well-preserved.

Contraindications to an aggressive approach include not only the patients wishes but also the presence of the following serious underlying diseases:

- Pulmonary disease.
- Cancer.
- Cerebrovascular disease, stroke, transient ischemic attack, and severe carotid artery stenosis.
- Intermittent claudication or known severe peripheral vascular disease.
- Psychiatric disorders.
- Renal failure (serum creatinine greater than 2.3 mg/dl (203 μ mol/L), respectively).
- Neurological disease.
- Alcoholism with hepatic dysfunction, hematological disease, or other contraindication to heparin therapy.

Thus, the suitable characteristics that encourage an aggressive approach for revascularization or surgical intervention include:

- Generally healthy individuals, preferably under age 75.
- Supportive therapy and appropriate stabilization has been achieved with IAPB within about 6 hours of onset of symptoms.
- Prior MI.
- Ventricular septal rupture (*see* Chapter 2).
- Subacute cardiac free-wall rupture as a cause of shock needs to be repaired within the hour (*see* Chapter 2).

High operative mortality rates have tempered enthusiasm for surgical intervention. The 2-year survival rate for patients after repair of ventricular septal rupture is about 80%, whereas for severe mitral regurgitation, survival is less than 40%. Thus, decision-making contraindications to IABP include aortic regurgitation, if more than mild; aortic aneurysm, severe atherosclerosis of the aorta, or iliofemoral arteries; and contraindication to heparin therapy.

If no contraindication exists, the IABP is placed from the femoral artery percutaneously over a guidewire and positioned in the thoracic aorta. The balloon is rapidly inflated with inert gas at the onset of diastole, synchronized with the R-wave of the ECG, and rapidly deflated just before the onset of systole. The IABP reduces afterload and increases DPB, thus improving coronary perfusion pressure.

The following complications of IABP occur in 10–30% of patients:

- Death owing to rupture of the balloon.
- Aortic dissection.
- Thrombus formation on the surface of the balloon with embolism.
- Thrombus and cholesterol emboli to the kidneys or lower limbs.

- Bleeding at puncture sites.
- Trauma to the iliofemoral arteries and aorta may require surgery, including amputation of a leg.
- Foot drop.

Once the decision is made to pursue aggressive therapy, preparations should be made for urgent cardiac catheterization within an hour.

Revascularization

In a nonrandomized trial by Eltchaninoff et al. at the Cleveland Clinic, 50 patients presenting with acute MI complicated by cardiogenic shock received intensive medical treatment and IABP support. Thirty-three patients (66%) underwent PCI and 17 patients (34%) remained on medical therapy. The in-hospital survival and 1 year follow-up for the PCI group was 76% and 60% versus 24% and 12% in the medically treated group.

In the SHOCK study, acute MI patients with shock caused by LV failure were randomized to emergency revascularization (152 patients: PCI or coronary artery bypass graft [CABG]) or initial medical stabilization (150 patients). IABP counterpulsation was performed in 86% of the patients in both groups. The primary endpoint was mortality from all causes at 30 days. Six-month survival was a secondary endpoint.

Results: The mean (\pm SD) age of the patients was 66 ± 10 years. The median time to the onset of shock was 5.6 hours following onset of infarction, and most infarcts were anterior in location. Ninety-seven percent of the patients assigned to revascularization underwent early angiography, and 87% were revascularized; only 2.7% of the patients assigned to medical therapy crossed over to early revascularization without clinical indication. Overall mortality at 30 days did not differ significantly between the revascularization and medical-therapy groups (46.7% and 56.0%, respectively; difference, -9.3% ; $p = 0.11$).

Six-month mortality was modestly lower in the revascularization group than in the medical-therapy group, but was observed only in patients <75 years of age and patients with a previous MI randomized in less than 6 hours from onset of infarction.

Hochman et al. for the SHOCK investigators reported on the one-year survival following early revascularization (ERV) for Cardiogenic Shock. The SHOCK trial was an unblinded, randomized, controlled trial from April 1993 through November 1998.

Setting: Thirty-six referral centers with angioplasty and cardiac surgery facilities. Three hundred and two patients with acute MI and cardiogenic shock caused by LV failure who met specified clinical and hemodynamic criteria were randomly assigned to an initial medical stabilization ($n = 150$) group, which included thrombolysis (63% of patients), IABP (86%), and subsequent revascularization (25%), or to an ERV group ($n = 152$), which mandated revascularization within 6 hours of randomization and included angioplasty (55%) and CABG surgery (38%).

Endpoint: All-cause mortality and functional status at 1 year, compared between the ERV and medical groups.

At 1 year, survival was 46.7% for patients in the ERV group compared with 33.6% in the medical group ($p = 0.027$; absolute difference in survival, 13.2%; 95% confidence interval [CI], 2.2–24.1%; $p < 0.03$; relative risk for death, 0.72; 95% CI, 0.54–0.95). Of the 10 prespecified subgroup analyses, only age (<75) interacted significantly ($p < 0.03$) in that treatment benefit was apparent only for patients younger than 75 years. Eighty-three percent of 1-year survivors were in New York Heart Association class I or II.

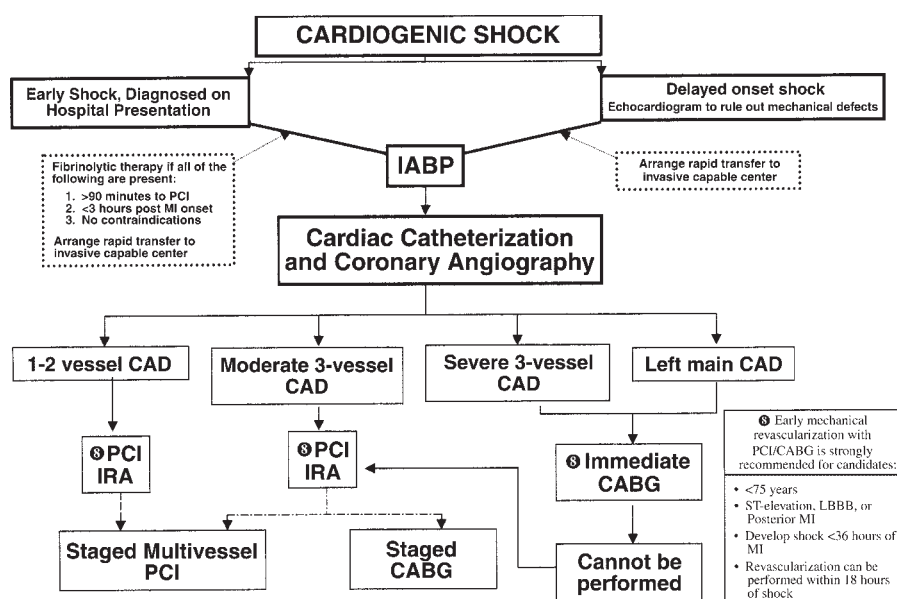


Fig. 3.3. Recommendations for initial reperfusion therapy women cardiogenic shock clumping its acute myocardial infarction (MI). The early mechanical revascularization with percutaneous coronary intervention or coronary artery bypass graft is strongly recommended for suitable candidates less than 75 years of age and for selected elderly patients. 85% of showcases are diagnosed after the initial therapy for acute MI but most patients develop shock within 24 hours. Intra-aortic balloon pump is recommended when shock is not quickly reversed with pharmacological therapy, as a stabilizing measurement for patients who are candidates for further invasive care. Dashed lines indicate that the procedure should be performed in patients with specific indications only. CAD, coronary artery disease; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; IRA, infarct-related artery. LBBB, left bundle-branch block. Reproduced from Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. From *Circulation* 2003;107:2998.

Importantly, at 1-year follow-up in the randomized SHOCK trial, early revascularization resulted in 132 lives saved per 1000 patients treated as compared with initial medical therapy. This benefit is comparable to that of CABG versus medical therapy for patients with left main disease. Because the majority of patients in the SHOCK trial had severe multivessel disease, approximately 40% received CABG.

- Rapid transfer of patients with acute MI complicated by cardiogenic shock is recommended for patients younger than 75 years, to medical centers capable of providing early PCI and CABG.
- Immediate CABG is the recommended strategy for severe 3-vessel or left main disease (see Fig. 3.3.)
- PCI of the infarct-related artery (IRA) is recommended for patients with 1- or 2-vessel disease with lesions suitable for balloon and stent.
- PCI is advisable in selected patients with moderate 3-vessel disease: 100% occlusion of the IRA; less than 90% stenosis in two other major vessels.

Since 2001, mortality from cardiogenic shock has decreased in the United States in hospitals that employ a strategy of early revascularization, but not in those that do not.

- Preliminary studies have shown improved survival when iNOS is absent or inhibited.
- Promising new therapies that target these pathways are being tested in an effort to reduce the high mortality rate that is significantly but only modestly reduced by early revascularization. Many patients with cardiogenic shock are noted to have a low systemic vascular resistance, and the effect of the nitric oxide synthase inhibitor, L-NMMA, has been shown by Cotter et al. in a pilot study to possess favorable therapeutic effects. SHOCK-2 is being designed to test an NO inhibitor, L-NMMA, in a well-powered, randomized trial of patients with persistent shock.

BIBLIOGRAPHY

- Califf RM, Bengtson JR. Current concepts: cardiogenic shock. *N Engl J Med* 1994;24:1724.
- Cotter G, Kaluski E, Milo O, et al. LINCOS: L-NAME (a NO synthase inhibitor) in the treatment of refractory cardiogenic shock: a prospective randomized study. *Eur Heart J* 2003;24:1287–1295.
- Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385–1390.
- Eltchaninoff H, Simpfendorfer C, Whitlow PL. Coronary angioplasty improves early and 1 year survival in acute myocardial infarction complicated by cardiogenic shock. *J Am Coll Cardiol* 1991;17:167A.
- Ghitis A, Flaker GC, Meinhardt S, et al. Early angioplasty in patients with acute myocardial infarction complicated by hypotension. *Am Heart J* 1991;122:380.
- Grines CL, Gowne KF, Marco J, et al. For the primary angioplasty in myocardial infarction study group: a comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;328:673.
- Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 2003;107:2998–3002.
- Hochman J, Sleeper L, Webb J, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999;341:625–634.
- Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;285:190–192.
- Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction: etiologies, management and outcome: overall findings of the SHOCK Trial Registry. *J Am Coll Cardiol* 2000;36:1063–1070.
- Li H, Forstermann U. Nitric oxide in the pathogenesis of vascular disease. *J Pathol* 2000;190:244–254.
- Webb JG, Sanborn TA, Sleeper L, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK Trial Registry. *Am Heart J* 2001;141:964–970.
- Wildhirt SM, Dudek RR, Suzuki H, et al. Involvement of inducible nitric oxide synthase in the inflammatory process of myocardial infarction. *Int J Cardiol* 1995;50:253–261.
- Wollert KC, Drexler H. Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: carvedilol as the sun and center of the β -blocker world? *Circulation* 2002;106:2164–2166.

CONTENTS

CLASSIFICATION
 ATHEROSCLEROTIC PLAQUE
 STABLE ANGINA
 ELECTROCARDIOGRAM
 RADIONUCLIDE MYOCARDIAL PERFUSION IMAGING
 ECHOCARDIOGRAPHY
 ELECTRON BEAM TOMOGRAPHY
 THERAPY
 β -BLOCKERS
 NITRATES
 CALCIUM ANTAGONISTS
 UNSTABLE ANGINA
 RISK STRATIFICATION
 CLOPIDOGREL
 PLATELET-RECEPTOR BLOCKERS
 PRINZMETAL'S (VARIANT) ANGINA
 SILENT ISCHEMIA
 PERCUTANEOUS CORONARY INTERVENTION
 STENTS
 CORONARY ARTERY BYPASS SURGERY
 BIBLIOGRAPHY

CLASSIFICATION

Stable Angina

Stable angina is defined as short duration chest and/or arm discomfort that shows no change in the past 60 days in frequency, duration, or precipitating causes. Most often pain duration is less than 10 minutes, and rarely up to 15 minutes; the mild-to-moderate discomfort is relieved within 1 to 10 minutes by cessation of the precipitating activity or use of sublingual nitroglycerin.

In more than 90% of patients, stable angina is caused by a greater than 70% obstruction in at least one coronary artery. In less than 10% of individuals, a lesser degree of atherosclerotic obstruction, coronary artery spasm, or small vessel disease is present.

From: *Contemporary Cardiology: Heart Disease Diagnosis and Therapy:
 A Practical Approach, Second Edition*
 Edited by: M. Gabriel Khan © Humana Press Inc., Totowa, NJ

Table 4.1.
Classification of Unstable Angina

Severity

Class I New-onset, severe, or accelerated angina

Patients with angina of less than 2 months' duration, severe or occurring three or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion. No rest pain in the last 2 months.

Class II Angina at rest; subacute

Patients with one or more episodes of angina at rest during the preceding month, but not within the preceding 48 hours.

Class III Angina at rest; acute

Patients with one or more episodes at rest within the preceding 48 hours.

Clinical Circumstances

Class A Secondary unstable angina

A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia, e.g., anemia, infection, fever, hypotension, tachyarrhythmia, thyrotoxicosis, hypoxemia secondary to respiratory failure.

Class B Primary unstable angina

Class C Postinfarction unstable angina (within 2 weeks of documented MI).

Intensity of Treatment

Absence of treatment or minimal treatment.

Occurring in presence of standard therapy for chronic stable angina (conventional doses of oral β -blockers, nitrates, and calcium antagonists).

Occurring despite maximally tolerated doses of all three categories of oral therapy, including intravenous nitroglycerin.

Modified from Braunwald E. Unstable angina: a classification. *Circulation* 1989; 80:410, by permission of the American Heart Association, Inc.

The Canadian Cardiovascular Society grading of angina is widely used to differentiate mild, moderate, or severe stable angina:

- Class 1 Angina: Pain is precipitated only by severe and usually prolonged exertion.
- Class 2 Angina: Pain on moderate effort, for example, precipitated by walking uphill or by walking briskly for more than three blocks on the level in the cold, against a wind, or provoked by emotional stress. There is "slight limitation of ordinary activity."
- Class 3 Angina: Marked limitation of ordinary activity; pain occurs on mild exertion, usually restricting daily chores. Unable to walk two blocks on the level at comfortable temperatures and at a normal pace.
- Class 4 Angina: Chest discomfort on almost any physical activity, for example, dressing, shaving, walking less than 100 feet indoors. Pain may be present at rest.

Unstable Angina

SUBSET I: IN PATIENTS WITH PREVIOUS STABLE ANGINA

Pain, mainly on exertion, with a change in pattern from existing stable angina: increasing frequency, severity, and/or duration of pain and a lesser degree of known precipitating factors; there is worsening of previously stable angina that can be termed progressive, crescendo angina; moderate-to-severe pain at rest and on minor activities or minimal exertion.

SUBSET II: NEW ONSET ANGINA PRESENT LESS THAN 30 DAYS

New onset of exertional angina with moderate-to-severe pain lasting usually more than 10 minutes (*see* Table 4.1); pain at rest with or without exertional pain usually lasting more than 20 minutes. Several of these patients show elevated enzyme levels (troponins or creatine kinase MB [CK-MB]) and are reclassified as non-ST elevation myocardial infarction (MI).

Prinzmetal's (Variant) Angina

This condition is rare and is caused by coronary artery spasm. When it does occur, there are often dynamic changes in arterial radius at a point in which there is already eccentric organic stenosis. Pain typically occurs at rest. The electrocardiogram (ECG) reveals ST-segment elevation during the minutes of pain.

ATHEROSCLEROTIC PLAQUE

Obstruction of arteries by plaques of atheroma, atherosclerosis is the basis for cardiovascular disease (CVD) that accounts for approximately 40% of all deaths in the western world and Europe. This single disease is the most common cause of death, particularly premature death, in industrialized countries. Although during the past decade the incidence of coronary artery disease (CAD) has shown a slight decline in most developed countries, there has been an increased incidence in many countries in Eastern Europe and Asia.

In the 1990s the annual mortality from CVD worldwide was approximately 12 million in a population of 6.4 billion. It is estimated that mortality will exceed 24 million in 2025 in a population of approximately 7.4 billion.

Historical

- Rokitansky theory (1841–1852): Atheroma is caused by slow deposition of small thrombi at focal point on the arterial intima, with subsequent organization into the wall of the artery.
- Virchow: In 1858 the German pathologist recognized the participation of cells and proliferative nature of atheroma formation.
- Anitschkow: In 1933 produced fatty lesions in the arteries of rabbits fed with a high cholesterol diet. He emerged as one of the influential figures in the field of experimental atherosclerosis. He considered atherosclerosis an infiltrative rather than a degenerative process that begins with the accumulation of lipid substances in the deep intima. He, however, warned that cholesterol was not the only factor.
- Winternitz: In 1938 indicated that atheroma occur partly from rupture of small capillaries within the arterial wall; hemorrhage into the plaque and organization of this material increased the size of atheroma.
- Dugid: In 1949, some 100 years later, he revised the older theory of Rokitansky to say that atheromatous lesions of the aorta and coronary arteries may result from the slow deposition of thrombus at focal points on the intima with subsequent organization and infiltration with lipid. Dugid pointed out that small thrombi on the arterial lining are more common than is realized and that they are quickly incorporated into the intima by growth of the endothelium over the surface and are later converted into fibrous tissue in which variable degrees of fatty degeneration occur in the deeper layers
- Lipoproteins, (low-density lipoprotein [LDL] cholesterol): The characterization of lipoprotein particles in the 1950s strengthened the cholesterol concept. Cholesterol, how-

ever, as the culprit for atheroma formation and CAD remained controversial worldwide in the minds of many cardiologists, researchers, and the public.

- Lober: In 1953 provided the earliest provocative proof that diet could cause CAD.
- Ross and Glomsett: In 1976 merged the concepts of earlier investigators, that atherosclerotic lesions develop only after chronic injury of the endothelial lining. The mechanisms of injury could be derived from three sources: hemodynamic (turbulence), immunologic, and biochemical.
- Ross: In 1986 summarized the pathogenesis of atherosclerosis: fluid dynamics, at certain sites, create an area of turbulence which in turn injures the endothelial lining so that they become more permeable to circulating lipoproteins. Circulating platelets clump together at the denuded site to form a microclot; smooth muscles proliferate in this area probably under the stimulus of platelet-derived growth factor (PDGF).
- Statins, the Scandinavian Simvastatin Study: The controversial question of the important involvement of cholesterol, particularly LDL-cholesterol however, was only settled in 1994, when statins were shown in the hallmark Scandinavian Simvastatin Survival Study to cause a significant decrease in CAD mortality that was based on the reduction of total cholesterol and LDL-cholesterol blood levels. This ended a 100-year-old controversy and start of a new era in the prevention of atherosclerosis.

An understanding of the pathogenesis of the atherosclerotic plaque is essential because atheroma is the underlying lesion in most patients with acute coronary syndromes, stable angina, unstable angina, acute MI, and sudden cardiac death. These clinical manifestations result from plaques that partially or almost totally occlude the lumen of the affected artery or because the plaque ruptures and the intensely thrombogenic material triggers thrombosis (Fig. 4.1.) *see* Chapter 1, pp. 3–6.

The atherosclerotic plaque consists of a soft central core that has a variable lipid-laden content, covered by a fibrous cap that varies in thickness, smoothness, and fragility. The surface of some plaques is smooth or rough and bumpy. Plaques project into the lumen of the artery causing variable obstruction, and over time the surface of plaques may ulcerate or become fissured. Plaques tend to occur at bending points, bifurcations of arteries, and in regions of oscillating shear stress, which results in endothelial injury or dysfunction.

Response to Injury Hypothesis

The initiating event in the development of the atherosclerotic plaque is believed to be injury to the endothelium of the artery. Endothelial dysfunction/injury incites a host of intricate biological reactions that eventually lead, over several years, to the development of plaque. These reactions appear to occur as a healing response to the injury, but the response becomes counterproductive.

The principal cells and elements involved in atheroma formation include the following:

- Endothelium: The injured endothelium appears to secrete chemotactic factors that attract leukocytes, monocytes, and smooth muscle cells to protect the endothelial monolayer.
- In leukocytes, several β -integrins, which bind to extracellular matrix proteins, are expressed in T and B lymphocytes.
- Platelets.
- T and B lymphocytes in cells are transformed to proliferative smooth muscle cells by cytokine and growth factors. β_1 -integrins are implicated in smooth muscle cell migration.
- Smooth muscle cells.

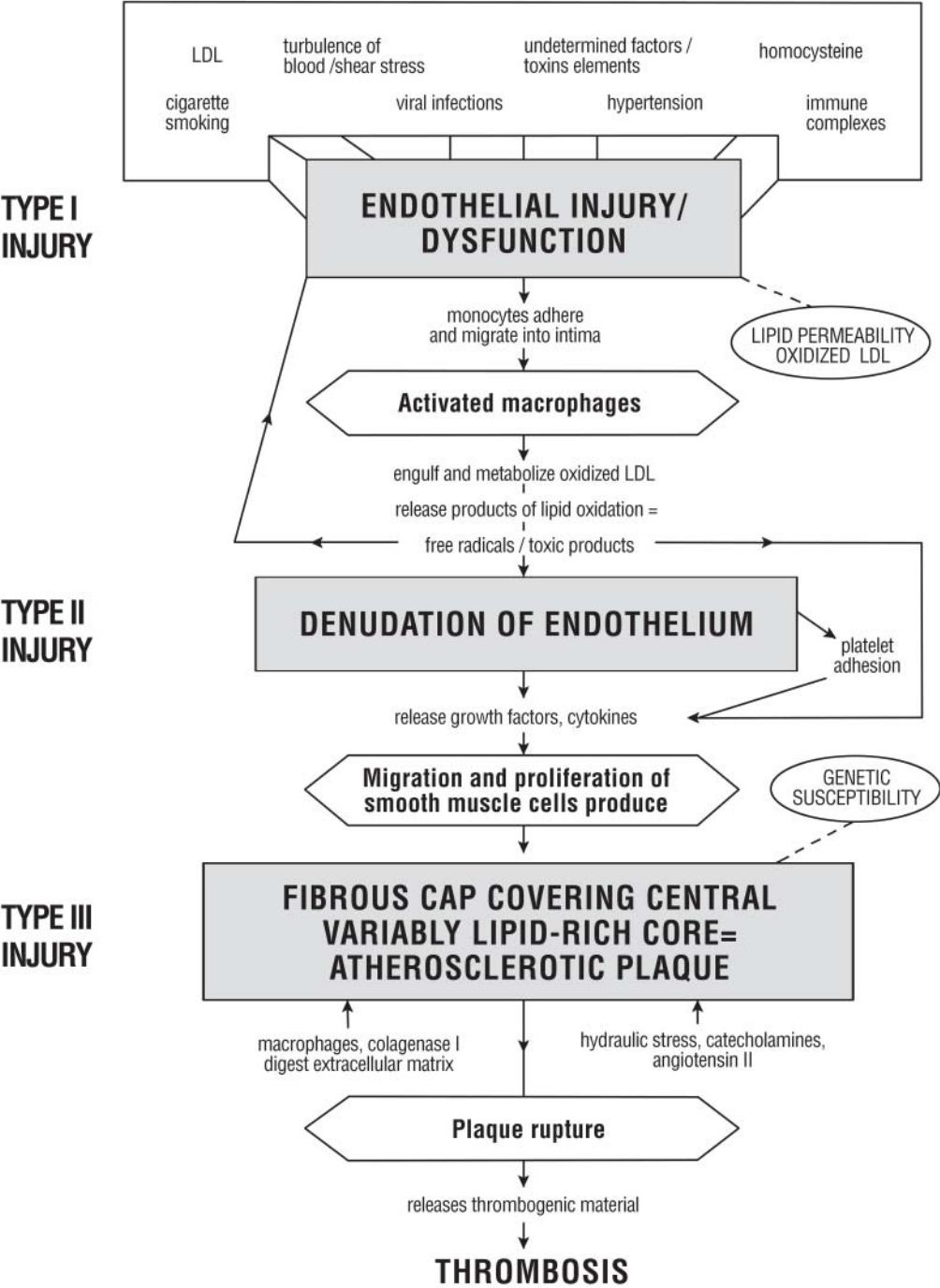


Fig. 4.1. Pathogenesis of the artherosclerotic plaque. From Khan, M. Gabriel. Encyclopedia of Heart Disease, San Diego, Academic Press, 2005, with permission from Elsevier.

- Oxidized LDL cholesterol.
- Free radicals, products of lipid oxidation.
- Cytokines.
- Mitogenic factors, such as PDGF, released from injured endothelial cells, platelets, and macrophages.
- Angiotensin II.

The endothelium forms a protective monolayer lining the arterial tree and produces vasoactive substances such as, Prostacyclin (PGI_2), a potent vasodilator; endothelial-derived relaxing factor (EDRF), a form of nitric oxide (NO) that causes vasodilation; surface molecules (e.g., heparin sulfate, $\text{PGI}_2 > \text{plasminogen}$) that lyse fibrin clot to ensure a nonthrombogenic surface; and procoagulant materials (e.g., Von Willebrand factor).

The endothelium grows only in an obligate monolayer and cannot crawl over one another. Thus, at sites of endothelial injury, monocytes, platelets, and smooth muscle cells play a crucial role in the repair reaction.

Type I Injury

Turbulence of blood, oscillatory shear stress at arterial bifurcations, and/or bending points result in endothelial injury/dysfunction, which appears to be provoked by atherogenic factors: LDL cholesterol, diabetes, hypertension, cigarette smoking, viral infection, immune complexes, undefined toxins, and elements (Fig. 4.1.). Endothelial injury provokes the surface expression of adhesive molecules with monocyte and platelet-vessel wall interaction. Monocytes migrate between endothelial cells into the subendothelial space; they convert to macrophages that engulf and become laden with oxidized LDL.

The initial lesion is a small focus of injury of the intima caused by increased turbulence of blood at special arterial sites, such as the orifice of branches, that of the aorta as mentioned earlier, and bifurcations and curvatures that cause characteristic alterations in blood flow. The small area of injury incites a unique protective nonspecific inflammatory response. But nature's healing has to contend with further turbulent blood flow and further injury to the intima.

From observations in young adults dying acutely of trauma, and in rabbits fed a high cholesterol diet and saturated fat, the accumulation of small lipoprotein particles in the intima has been noted to be one of the first ultrastructural alterations. Microscopic examination reveals fatty material in stellate cells of the intima and macrophages, and, to a certain extent, in the endothelial cells. This fatty deposit is cholesterol and glycerol fat. Such patches have been found in children dying acutely of trauma. Fat is prone to accumulate within the intimal cells, but the reason for this is obscure.

Endothelial injury or activation is followed by an inflammatory process that commences with adherence of leukocytes to the endothelium and diapedese between endothelial cell junctions to enter the intima where they begin to accumulate lipids and transform into foam cells. In addition to the monocyte, T lymphocytes also tend to accumulate.

Turbulence of blood, initiate endothelial injury and dysfunction that calls forth activated white blood cells, macrophages to the scene of injury followed by accumulation of oxidized LDL-cholesterol and a nonspecific inflammatory response occurs. This response is similar to that observed following allergic reactions, autoimmune processes and trauma, but with the unique features imposed by the silky, smooth endothelial lining of arteries that has a protective strong muscular middle wall, the media.

Hydrodynamic forces/pulsatile blood flow:

There are three types of mechanical forces on the walls of arteries:

- The tangential frictional force from the flow of blood across the endothelial surface.
- Transmural pressure, the direct effect of pressure.
- Wall stress as a result of pressure-induced wall deformation and subsequent cyclic strain. Increased blood pressure (BP) appears to promote atherogenesis through biomechanical effects of pulsatile blood flow, or cyclic strain, which has been observed to affect endothelial cell gene expression and function. Okada et al. have shown that changes in shear stress regulate endothelial production of several factors that include vasodilators, such as NO and PGI₂; and vasoconstrictors, such as endothelin 1, that increased cyclic stretch augments production of interleukin (IL)-8 and monocyte chemoattractant protein-1 in a dose-dependent fashion.

Linear shear stress forces appear to be atheroprotective and associated with reduced production of reactive oxygen species (ROS). Oxidative stress results from the production of ROS and superoxide anion and hydrogen peroxide, molecules that cause oxidative damage and trigger intracellular signaling cascades. The muscular wall of arteries is a rich source of ROS; the constituents of atheromatous plaques produce and use ROS. Hypercholesterolemia induced in rabbits causes an increase in ROS in rabbit aorta. Treatment with the antioxidant polyethyleneglycol superoxide appears to reverse impaired endothelial-dependent relaxation observed in rabbit aortic tissue. Dietary lowering of cholesterol reduces ROS production in rabbits.

Low shear stress and disturbed flow are associated with increased production of ROS and redox sensitive up regulation of chemoattractants vascular cell adhesion molecules. Cyclic strain increases vascular cell adhesion molecules expression by human endothelial cells in a time- and strain-dependent manner, resulting in increased monocyte adhesion.

In vitro studies with animal models of hypertension have shown increased production of ROS in arterial tissues. Increased cyclic biomechanical strain modifies macrophage function by increasing expression of scavenger receptor that participates in the deposit of lipid in the arterial wall.

It has been noted that increased turbulence of blood at specific arterial sites causes rolling and adherence of monocytes and T cells that is believed to be the result of upregulation of adhesion molecules on both the endothelium and leukocytes.

Intracellular lipid accumulation and foam cell formation occurs when white blood cells, monocytes once trapped in the arterial intima, imbibe lipid substances. This lipid laden macrophage is called a foam cell. These macrophages are stimulated to divide under the influence of a comitogen, macrophage colony-stimulating factor, and IL-3.

Type II Injury

Activated macrophages metabolize oxidized LDLs and release products of lipid oxidation and free radicals. These toxic products may cause denudation of the endothelium and platelet adhesion. Macrophages, platelets, and endothelial cells release growth factors and cytokines that cause the proliferation of smooth muscle cells and their migration from the media to the intima.

The media contains smooth muscle cells that migrate into the injured area to assist in healing the minute wound. Much research has been conducted on the smooth muscle cell

and its important contribution to the atherosclerotic process. The contribution of the smooth muscle cells, however, commences long after the injury has been inflicted.

Smooth muscle cells have the capacity to contract and have receptors for several substances, including LDLs, angiotensin 11, and chemotactic and mitogenic factors. Smooth muscle cells can produce their own mitogenic factors. Their proliferation forms, elastin and collagen, play a major role in producing a fibrous cap that covers the core of the lipid-laden atherosclerotic plaque. Smooth muscle cells migrate from the middle wall of the artery, the media, into the intima, probably to strengthen the injured area. The chemoattractants for smooth muscle cells appear to be PDGF secreted by activated macrophages. The smooth muscle cells also divide vigorously but some cell death occurs.

LDL activates foam cells and cause injury to these cells within the intimal lesion. It appears that LDL cholesterol is chemotactic for other monocytes and enhances the inflammatory response by stimulating replication of monocyte-derived macrophages and the attraction of new monocytes into the early atheromatous lesion. This activity further stimulates migration and proliferation of smooth muscle cells into the intimal area of injury. The tough smooth muscle cells, along with other cellular and non-cellular components, assume a protective role in an endeavor to form a fibroproliferative barrier that thickens the arterial wall at the site of injury. This is nature's way of healing, which is occasionally counterproductive.

There is evidence accumulating that certain infectious organisms, particularly *Chlamydia pneumoniae*, cytomegalovirus, and *Helicobacter pylori*, may be involved in inflammatory process and evolution of plaque rupture. Increased antibody titers to these organisms have been used as predictors of further cardiac events in patients following a heart attack. Examination of atheromatous lesions has occasionally identified *Chlamydia pneumoniae*. Clinical trials using antibiotics so far have not been beneficial, but this organism may contribute to destabilization of atheromatous plaques, and may play a role in initiating plaque rupture.

Circulating markers of inflammation, such as C-reactive protein (CRP), are higher in patients with unstable CAD than in those with stable coronary disease. Persistent elevation of CRP in patients with unstable angina strongly predicts further serious cardiac events. The precise mechanisms by which atherosclerosis initiates an inflammatory response remain unclear.

Type III Injury

Fuster et al. observed that plaques, which cause less than 50% coronary stenosis but are lipid-rich, especially with relatively increased ratios of monounsaturated to polyunsaturated fatty acids, are prone to rupture.

Type III injuries include plaque rupture/fissuring, ulceration, and thrombosis. The mechanisms underlying plaque rupture are not clearly understood. It appears that in soft centered lesions, macrophages release collagenase-1, which digests extracellular matrix, predisposing to rupture.

The mechanisms by which hypercholesterolemia promote the formation of plaques is now being understood. It is not clearly understood how the other risk factors (hypertension, diabetes, smoking, and genetic) relate to the aforementioned cells and elements to produce the atherosclerotic lesion. There is little doubt that there is a genetic predisposition to the development of plaques, especially those that are prone to rupture. It is not surprising that patients, who do not have angina or silent ischemia and have plaques that

cause less than 60% stenosis, succumb to heart attack or fatal infarction. It must be reemphasized that lesions prone to rupture often cause less than 60% stenosis and have a high lipid core filled with inflammatory foam cells with a thin protective fibrous cap.

Vessels Predilection

VEINS

Atheroma does not occur in veins because the thin-walled veins do not contain an appreciable middle wall—the media—and are not exposed to the same hemodynamic stress and turbulence of blood that occurs in the rapidly circulating arterial blood that is pumped at high velocity and at high pressures by the heart.

PULMONARY ARTERIES

Atheroma is virtually never seen in the pulmonary arteries. These arteries are large and medium-sized. The pulmonary artery receives blood that is ejected from the right ventricle and circulates the blood to the lungs. That is similar to blood being ejected from the left ventricle into the aorta. The only difference is that the left ventricle pumps blood more vigorously and at higher pressures and velocity and therefore submits the arteries to turbulent flow. Thus, the tendency for atheroma to be most marked in the lower part of the aorta is probably owing to the increased hydrostatic pressure in that position. The right ventricle ejects blood into the pulmonary artery at a low pressure (25 mmHg vs >120 mmHg in the aorta). The resistance to flow of blood through the lungs is low, thus the right ventricle ejects blood at a much lower velocity than the left ventricle. Atheroma in the pulmonary arteries is virtually absent, except in the presence of severe pulmonary hypertension. This finding has not been mentioned in the scientific literature over the past 15 years. The author was intrigued by this finding more than 25 years ago. This occurrence then supports the hypothesis that turbulent flow may initiate the lesions of atheroma in arteries at points at which maximum turbulence occurs.

When injury to the intima occurs, the natural inflammatory response and flooding of the area with atherogenic LDL cholesterol contribute greatly to the atheromatous process.

ARTERIES OF THE UPPER LIMBS

The arteries of the upper limbs, the subclavian and brachial arteries and medium-sized arteries, are similar to the ones in the legs or the carotid arteries of the head, and yet atheroma is not seen. The reason why these arteries are not involved may hold the key to the puzzle of atheroma formation. The kidney arteries circulate the entire blood volume to be filtered by the kidney. Atheromatous lesions occurring in these arteries are relatively rare compared to the involvement of the aorta, coronary, and carotid arteries.

AORTA AND ILIAC VESSELS

These vessels withstand the entire hemodynamic force transmitted directly by ejection of blood into the aorta from the powerful heart muscle. The velocity and turbulence is excessive at branching points, including the bifurcation of the aorta and iliac arteries and in individuals who have high circulating LDL-cholesterol lesions are expected to be more aggressive.

Coronary Arteries

The coronary arteries are commonly involved, and this is not surprising. These are unique arteries. It is important to stress that these arteries collapse and are not filled during

the systolic contraction of the heart. They fill intermittently during diastole when the heart is relaxed. This intermittent flow to muscles that work harder and longer than any muscles in the body probably takes its toll.

Turbulence is excessive and in individuals at risk because of high LDL-cholesterol, diabetes, and age are prone to development of atheromatous lesions.

Excessive turbulence of blood, and hemodynamic and hydrodynamic forces particularly in individuals older than 30 years, sets up injury in arteries that possess a predilection for atheroma. Agents that reduced turbulence and velocity of flow particularly the β -blocking drugs may prove beneficial in clinical trials when used in conjunction with statins to reduce LDL-cholesterol levels less than 80 mg/dL, in younger individuals at risk. It is of interest that in the management of patients with ruptured aortic aneurysms or dissecting aneurysms, a β -blocking drug is given immediately to quell the ejection velocity of blood that further tears the ruptured artery.

Angiogenesis in Plaques

During the past decade, therapeutic angiogenesis has come into vogue. The use of angiogenic peptides is believed to produce therapeutic angiogenesis, or functional new blood vessel growth in the heart to improve blood supply and oxygen to muscles deprived of blood.

Unfortunately this may not be such a good therapeutic strategy. Around 1850, Winternitz observed that atheromatous patches may contain new capillaries, and these delicate vessels are exposed to the fluctuations in blood pressure. It is not surprising, therefore, that hemorrhage into such patches should sometimes follow exertion with its consequent rise of BP. Thereafter thrombosis often occurs during sleep. Thus, in some cases of MI and sudden death, sudden occlusion of the artery occurs because of hemorrhage into the plaque followed by rupture of the plaque and subsequent thrombosis. The initiating event in these cases is not the usual cause of a heart attack: rupture of plaque with thrombosis that can be partially ameliorated by immediate aspirin use. Unfortunately, because microvessels within the plaque are friable and prone to burst, attempts to augment myocardial blood flow by enhancing new vessel growth by transfer of angiogenic proteins or their genes might have deleterious effects on lesion growth and may initiate hemorrhage and plaque rupture, a disaster that we are trying desperately to prevent.

STABLE ANGINA

Pathophysiology

Myocardial ischemia is a dynamic process. It is now clear that three, not two, determinants play a major role in the pathogenesis of myocardial ischemia, which may manifest as the chest pain of angina or remain painless as with silent ischemia.

The three determinants of myocardial ischemia are as follows:

- Concentric or eccentric coronary atheroma causing greater than about 70% stenosis; concentric plaques are observed mainly with stable angina and there is a tendency for them to be eccentric in patients with frequent rest pain and in those with unstable angina.
- Increased myocardial oxygen demand.
- Release of catecholamines occurring at the onset of angina and during the episode in most patients with stable angina. Release of catecholamines may actually initiate ischemia, which stimulates further catecholamine release, and a vicious circle perpetuates the oxygen lack (Fig. 4.2.).

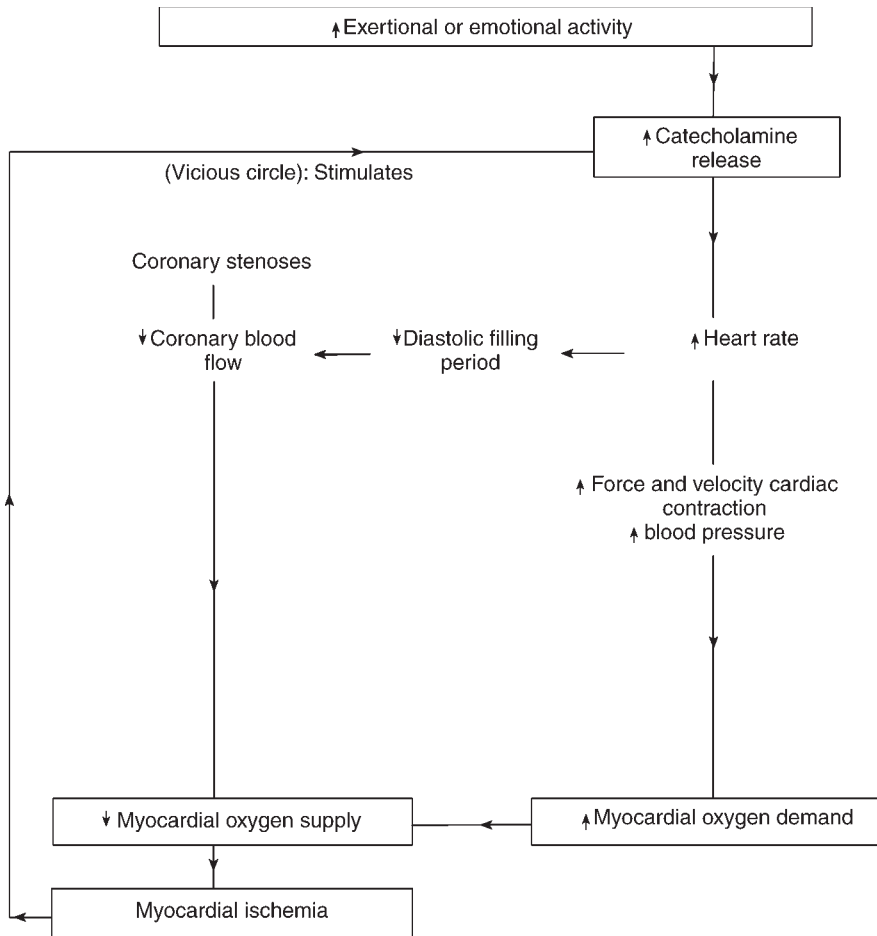


Fig. 4.2. Pathophysiology of angina, ↑, increase; ↓, decrease. From Khan, M. Gabriel, *Encyclopedia of Heart Disease*, San Diego, Academic Press, 2005, with permission from Elsevier.

When angina is manifest, at least one coronary artery is expected to show a greater than 70% stenosis on angiography. The obstructive plaque of atheroma is often focal, and usually occurs in the proximal portion of a coronary artery; this combination of proximal and focal lesions dictates the success of angioplasty and bypass surgery. In fewer than 10% of individuals, and especially in diabetics, multi-focal longer segmental or diffuse disease exists in the distal coronary tree.

An obstructive lesion in the left anterior descending (LAD) artery before the septal or first diagonal branch is considered proximal and highly significant because it can jeopardize more than 50% of the left ventricular (LV) myocardium. LAD lesions after the first diagonal affect only about 20% of the myocardium. In approximately 85% and 15% of individuals, the right coronary or left circumflex artery supplies the posterior diaphragmatic portion of the interventricular septum and the diaphragmatic surface of the left ventricle, respectively, and is referred to as the dominant artery. The term “dominant” does not imply a more important artery but does have some clinical bearing on decision-making in the management of angina.

A 25% decrease in the outer radius of a normal coronary artery results in about a 60% decrease in a cross-sectional area. In an artery with 75% stenosis, a 10% decrease in the outer radius would produce a complete occlusion.

During periods of exercise or exertion, catecholamine release causes an increase in heart rate, an increase in the velocity and force of myocardial contraction producing an elevation in BP, and an increase in myocardial oxygen demand. In the presence of significant coronary artery stenosis, an oxygen deficit occurs. Myocardial ischemia increases catecholamine release, resulting in an additional increase in heart rate and BP, with further oxygen lack, and the vicious cycle ensues. In addition, the coronary arteries fill during the diastolic period, which is shortened during tachycardia.

Pharmacological agents that inhibit the initiation or interrupt the dynamic process described earlier provide rational therapy for myocardial ischemia. It is therefore not surprising that β -adrenergic blocking drugs produce salutary effects in most patients with stable angina and represent first-choice oral medications for the management of angina. In contrast to the β -blocking drugs, dihydropyridine calcium antagonists, when used alone, tend to increase heart rate and, along with other calcium antagonists, do not inhibit the cardiovascular actions of catecholamines. Nitrates also increase heart rate. An important consideration in relation to coronary artery spasm is that ischemia from this cause also triggers catecholamine release and worsening of angina. Coronary artery spasm is, however, a rare cause of myocardial ischemia.

Diagnosis

Diagnosis is based on a careful relevant history. The pain of angina has certain distinctive characteristics:

- A retrosternal discomfort precipitated by a particular activity, especially walking quickly up an incline or against the wind. Pain or discomfort disappears within 1 to 5 minutes of stopping the precipitating activity, in keeping with the concept of oxygen supply vs myocardial demand. Discomfort may start in the lower, middle, or upper substernal area, the lower jaw, or the arm (Fig. 4.3.).
- The discomfort is a tightness, constriction, squeezing, heaviness, pressure, strangulation, burning, nausea, or an indigestion-like feeling of gradual onset that disappears at rest, except with unstable anginal syndromes. Occasionally, the pain is described as sharp, and at times discomfort is replaced by shortness of breath on exertion.
- The intensity of pain ranges from a mere discomfort grade 1 out of 10 to 5 out of 10; the mild discomfort is often described by patients as not really a pain but an uncomfortable feeling in the chest.
- The area of pain is usually at least the size of a clenched fist, often occupying most of the central chest area. The patient uses two or more fingers, the entire palm of the hand, or the fist to indicate the pain site. A finger or pencil point area of pain is rarely caused by myocardial ischemia.
- Relief of pain in an individual with stable angina always occurs within minutes of cessation of the precipitating exertional or emotional activity. Relief with sublingual nitroglycerin occurs promptly within 1–2 minutes.

Investigative Evaluation

Patients who manifest the same clinical symptoms may have very different prognoses depending on coronary anatomy; one, two, or three vessel disease and on LV function.

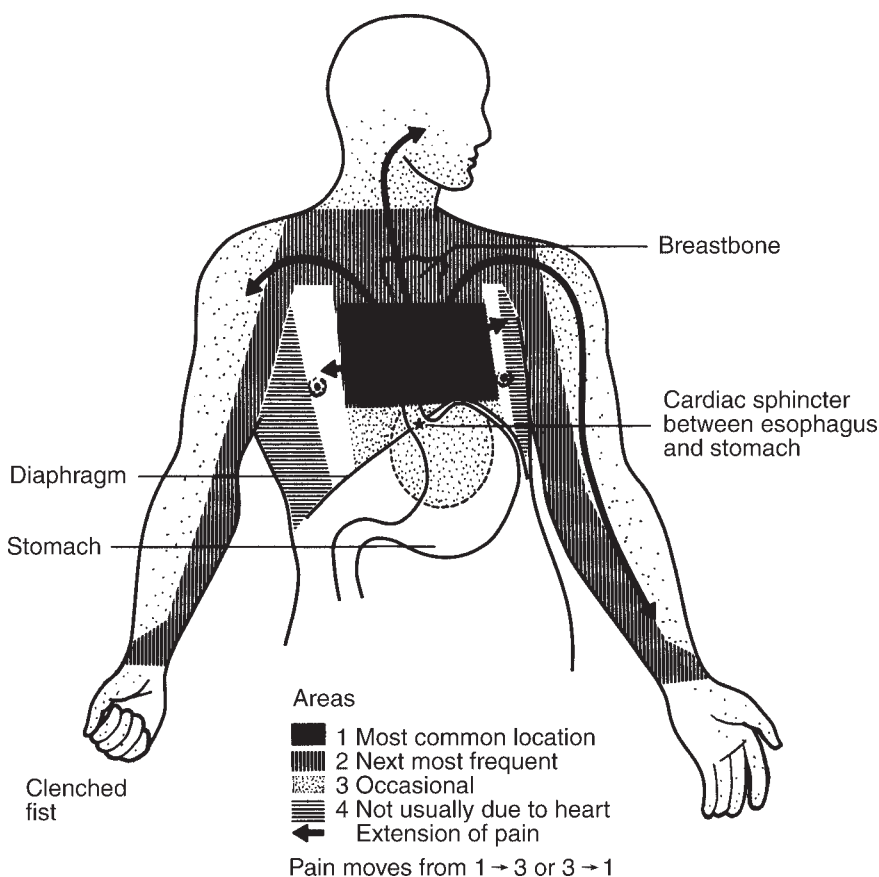


Fig. 4.3. Common locations of cardiac pain. From Khan, M. Gabriel, *Heart Trouble Encyclopedia*, 1996, Toronto, Stoddart, with permission.

The failure to predict outcomes based on the clinical presentation often necessitates evaluation with exercise stress testing to provoke and document electrocardiographic, signs of ischemia, and echocardiography to assess LV wall motion abnormalities and ejection fraction (EF). Cardiac nuclear imaging is required in some. The goal of initial investigations is to stratify the risk so that those at higher risk can progress to angiography early.

Blood Work

- **Lipid levels:** Request total cholesterol, high-density lipoprotein (HDL), LDL, and triglycerides with the patient fasting 14 hours (*see* Chapter 9). Therapeutic decisions are made based on the level of LDL cholesterol in patients with angina. At the initial visit, if the patient is not fasting, the total cholesterol and HDL cholesterol can be estimated because the results are not affected by food intake within the prior hours. Only glucose and triglycerides require testing in the fasting state. Fasting LDL cholesterol is requested because its estimation requires the accurate evaluation of triglycerides. The LDL results are inaccurate if the triglyceride level exceeds 2 mmol/L (176 mg/dL: to convert triglyceride mmol/L $\times 88 =$ mg/dL)

- Fasting and 2 hours glucose are evaluated to exclude diabetes, which carries a high risk in patients with existing ischemic heart disease.
- The hemoglobin is necessary to exclude the rare occurrence of angina precipitated by anemia in patients with atheromatous coronary stenosis.
- Renal function, approximately assessed by the serum creatinine, is relevant to the choice and dosage of medications particularly angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers and low-molecular weight heparin (LMWH) are renally excreted and should be avoided if the serum creatinine is greater than 2 mg/dL.
- CRP levels should be monitored in patients with unstable angina.

ELECTROCARDIOGRAM

- The resting ECG is expected to be normal in over 60% of patients with stable angina. ECG abnormalities are expected in individuals with previous MI, concomitant hypertension, or bundle branch block. In many patients, nonspecific ST-T-wave changes are present, and in less than 30% ST-T-wave changes that are indicative of ischemia are observed. A normal record makes a valuable baseline with which to compare future tracings.
- The normal variant ST-segment elevation that occurs in some individuals of African origin and other ethnic groups should be identified to avoid confusion on presentation to ambulance crews and emergency room staff. Diagnostic errors of acute infarction may be avoided in these individuals if assessed for acute chest pain (*see* ECG section of Chapter 1, pp. 15, 20).
- If the ECG of a patient presenting with typical angina shows evidence of old infarction that was clinically recognized or silent, the prognosis is particularly poor.
- It is important to document the absence of left bundle branch block (LBBB); if the symptoms of infarction supervene and LBBB appear, the diagnosis of block with acute infarction can be made with confidence, and therapy with thrombolytics or PCI can proceed rapidly.

Exercise Stress Test

Exercise stress testing is important in assessing the coronary reserve and in formulating strategies for other therapeutic interventions, especially in patients with class 1 and 2 angina. It is also useful in assessing the effect of medical therapy. The test is not useful in evaluating atypical chest pain, especially in women. The test is not advisable in most patients with documented unstable angina or those with an abnormal ECG, aortic stenosis, and obstructive cardiomyopathy. Patients with stable angina under age 70 with angina who can complete more than 6 minutes of a Bruce protocol treadmill exercise test, achieving more than 85% of maximal heart rate without chest pain or ischemic changes, can usually be managed with medical therapy if angina is significantly ameliorated by antianginal agents and lifestyle changes.

Patients with stable angina who can tolerate 8 minutes of a Bruce protocol appear to have a good prognosis. In this subset, if medical therapy is judged by physician and patient to be yielding adequate control of symptoms, coronary angiography is usually not required.

- A positive exercise stress test is indicated by abnormal horizontal or downsloping ST segment depression.
- Greater than or equal to 1 mm flat or down-sloping ST segment depression, for 80 milliseconds after the J-point occurring in three consecutive isoelectric complexes.

A strongly positive test is indicated by:

- ST-segment depression within the first 3 minutes of exercise, flat or downsloping ST-segment depression of 2 mm or greater, persisting for more than 4 minutes on cessation of exercise or occurring at low work load: onset at heart rate less than 120 beats per minute, or equal to or < 6.5 metabolic equivalents, systolic pressure less than 120 mmHg (i.e., a low rate pressure product).
- Depression in multiple leads: Patients in this category have a poor prognosis and are expected to have a large area of myocardium involved by the ischemic process. Patients with strongly positive tests, ischemia occurring before 6 minutes, and/or hypotension during exercise, have a high probability of having multivessel or left mainstem disease and are, therefore, at significant risk. Coronary angiography is warranted with consideration for PCI or coronary artery bypass graft (CABG).

Patients with class 2 angina who are unable to exercise because of arthritis or peripheral vascular disease should undergo adenosine or dipyridamole-nuclear scintigraphy (*see* Chapter 16). Patients with bothersome stable class 3 angina or unquestionable high-risk unstable angina do not usually require stress testing. Stress testing is particularly hazardous in this last group, and coronary angiography is usually indicated in either situation.

RADIONUCLIDE MYOCARDIAL PERFUSION IMAGING

Radionuclide myocardial perfusion imaging is useful to show the areas of the heart muscle that are poorly perfused with blood in selected patients with angina. The technique is simple and nonpainful. During an exercise stress test, usually on the treadmill, a known minute amount of radioisotope is injected into a vein. The nuclear material reaches the heart and is distributed through the coronary arteries. The areas of the heart muscle that are not receiving adequate blood flow because of blockage of the coronary arteries will receive less, and these areas are assessed by special scanners. Several errors in methods and interpretation limit the usefulness of this test. It is not sufficiently sensitive or specific for coronary heart disease. These tests are expensive and time consuming and the information gained is often not sufficiently accurate. Healthcare costs can be contained if such tests are limited. These tests should be done only when treatment decisions can be appropriately altered by their results.

Single-photon emission computerized tomography (SPECT) uses a scanner plus tomography. Other radioisotopes (e.g., technetium Tc99m / MIBI or similar) have replaced thallium in several laboratories. The test complements exercise treadmill stress testing.

The nuclear isotope perfusing the myocardium is removed by myocardial cells. A positive test, a cold spot on the scan and absent thallium uptake with filling in later views, indicates ischemic myocardium. The test is generally performed in conjunction with an exercise test and is useful in patients with LV hypertrophy and atypical chest pain in which conventional exercise stress testing gives a high rate of false positives. The validity of the test depends on a reasonably high rate pressure product being achieved during the preliminary stress period.

Radionuclide scintigraphy has several limitations:

- Proper methodology is necessary.
- Image artifacts are common and can lead to false-positive interpretation.
- False-positive results may occur because of overlying breast shadows; right ventricular (RV) blood pool may attenuate inferoposterior myocardial activity.

- Myocardial apical thinning causes a local decrease in thallium activity that can be mistaken for ischemic disease.
- LBBB may produce a false-positive scan.
- The sensitivity of radionuclide scintigraphy is lower in women than in men.

Most of these difficulties are important in relation to fixed defects, reversibility being a strong indicator of myocardium at risk.

Radionuclide scintigraphy can give a reasonably reliable estimate of the area of myocardium at risk but does not measure myocardial blood flow in milliliters per gram of myocardium. Negative scans may occur with significant lesions in the circumflex or diagonal branches of the LAD artery. Widespread disease with global reduction in uptake will also, paradoxically, yield a negative result. Accumulation of the thallium in the lungs is a sign of LV dysfunction that should be followed up with echocardiography.

Studies have demonstrated that when the resting ECG is normal in an individual with normal LV function, EF greater than 50%, thallium imaging does not assist with therapeutic decision-making. In a study of 411 patients that used clinical variables, diabetes, sex, age, and typical angina pattern, 46% of patients were correctly classified into low- or high-risk groups, the latter with documented three vessel or left main disease. Thallium imaging resulted in only 3% of the patients being reclassified regarding their particular risk for severe CAD at a cost of \$20,550.

Thallium-201 SPECT is a demanding technique that requires careful quality control. Suboptimal count density, soft tissue attenuation, and technical problems require careful monitoring. Also, distorted images can be incorrectly interpreted as abnormal. SPECT false-positive results are relatively common. Thallium planar imaging has a sensitivity of approximately 80% and specificity of about 68%. The 60–70% specificity of SPECT is not acceptable. Physicians should be cautious when expensive testing is done without meaningful specificity, particularly when other less costly methods of obtaining clinical information that may change therapeutic strategies are available.

Dipyridamole or adenosine thallium scintigraphy is a useful investigation in patients with chest pain, presumed to be angina and in patients with class 2 angina with the absence of pain at rest who are unable to perform an exercise stress test because of arthritis or peripheral vascular disease (*see* Chapter 16). Adenosine or dipyridamole thallium imaging is not indicated in patients with class 3 or 4 angina, because logically these patients require coronary angiograms to direct interventional therapy. Dipyridamole thallium scintigraphy is contraindicated in patients with high-risk unstable angina, postinfarction angina, acute and ST elevation MI. Also, dipyridamole scintigraphy is contraindicated in patients with asthma and chronic obstructive pulmonary disorder (COPD).

- *Persantine nuclear studies are not accurate in patients treated with β -blockers because these agents prevent coronary steal caused by dipyridamole.* Most important, individuals with a negative Persantine scan have had documented infarctions within 6 months of the test results.
- Importantly, nuclear scans give only clues to the presence of cardiac disease and have limited value in making decisions that relate to the choice of treatment for the patient. False positive tests are common particularly in women.
- *Radionuclide imaging is limited by a variable sensitivity and specificity and, unfortunately, exposes the patient to a very high radiation exposure that tends to be forgotten by physicians; in addition the test is a time-consuming protocol.*

Positron Emission Tomography

A positron-emitting tracer, usually rubidium-82, nitrogen-13 ammonia, or fluorine-18, is used and emits two high-energy photons in opposite directions. The positron emission tomography (PET) scanner detects two simultaneously generated photons. Thus, the PET scanner can identify and localize true events and allows improved spatial resolution compared with SPECT. PET can yield information on coronary flow reserve. PET is a very expensive imaging modality, however, and is only available in a few medical centers.

PET achieved a higher specificity than SPECT in a few small studies (82% versus 57%), but these studies have several limitations. The American Heart Association (AHA) has reviewed comparative studies and did not find PET superior to SPECT in diagnostic accuracy, but these were small studies. Further studies are necessary in comparable patients to ascertain the superiority of PET and its role in diagnostic cardiology in the face of escalating health costs. The advantages over SPECT need to be determined by studies to justify the high cost.

- The Persantine rubidium stress test has a role in patients who are unable to perform an exercise treadmill test and walk sufficiently to achieve more than 85% maximal heart rate.

Gated Cardiac Scan

A relatively noninvasive test that gives a good estimation of how much blood the heart ejects with each beat (EF) is the gated cardiac scan. The normal EF is between 50 and 75%. The force of contraction and the motion of the heart muscle wall are visualized on a video screen. If the muscle is contracting poorly or contracting abnormally, as might be expected with an aneurysm, this can be detected in many cases. This test unfortunately does not show structures inside the heart. Visualization of structures, such as valves inside the heart and an EF, can be obtained with echocardiography which is often used instead of a gated scan but is not as accurate for EF measurement. In clinical practice, the EF obtained from echocardiography is a sufficient approximation to gauge therapeutic strategies. The test should not be requested in patients with atrial fibrillation (AF) and, importantly, the EF is erroneously high in patients with mitral regurgitation.

ECHOCARDIOGRAPHY

Echocardiography is not routinely done, but is helpful in patients with stable angina to assess:

- Contractility and LV systolic function in anginal patients. Reduction of EF in patient with class II or III angina may indicate the need for coronary angiography with a view to angioplasty or coronary artery bypass surgery (CABS).
- Left ventricular dysfunction, EF less than 40%, is a relative indication for intervention in patients with bothersome angina and in those with triple vessel disease. Verapamil and diltiazem are contraindicated in patients with EF less than 40% and 35% respectively; these agents are now recognized to influence adversely the prognosis when left ventricular function is compromised (Fig. 4.4).

β -Blocking agents are beneficial but used cautiously in patients with EF less than 30%. Patients with angina and previous heart failure (HF) or suspected LV dysfunction and unstable angina should have echocardiographic assessment.

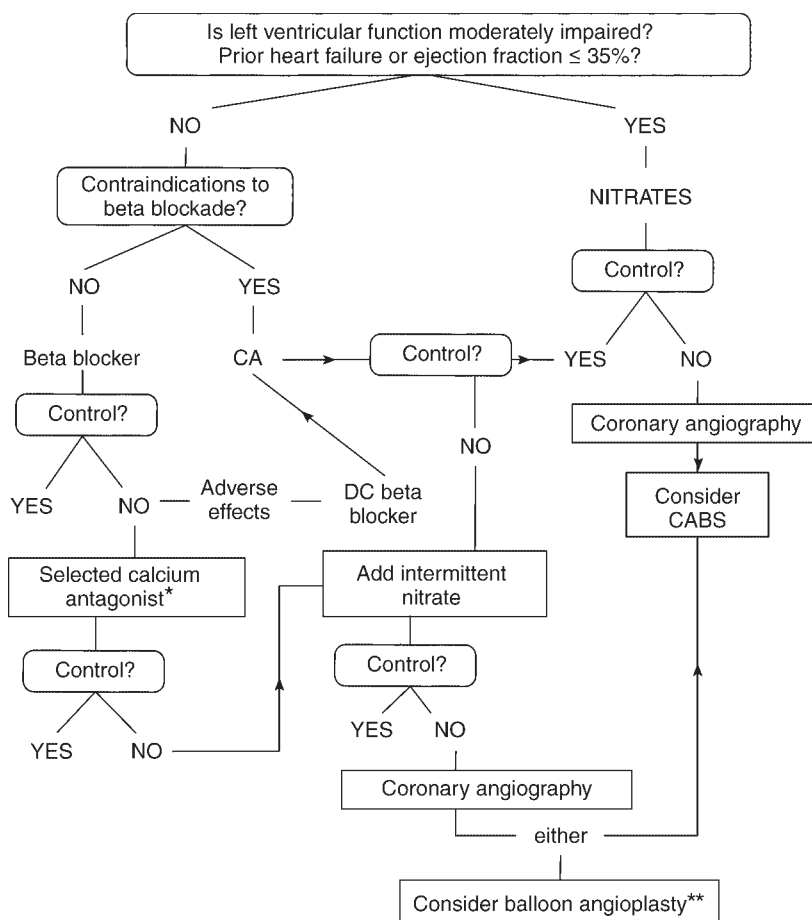


Fig. 4.4. Algorithm for the medical therapy of stable angina. CA, calcium antagonist; verapamil SR first choice (*see text*) or Cardizem CD; DC, discontinue. *Amlodipine. **and stent.

- Shortness of breath on exertion in patients in whom mitral regurgitation is suspected with physical signs masked by a thick chest wall or chronic lung disease. Such patients with significant mitral regurgitation would benefit particularly from angiotensin-converting enzyme (ACE) inhibitors plus or minus valve surgery.
- Stress echocardiography using adenosine or dobutamine is of value in selected patients who are unable to exercise. This test should be done only in laboratories with expertly trained staff. In such centers, results are as good as those obtained with adenosine or dipyridamole thallium scintigraphy.

ELECTRON BEAM TOMOGRAPHY

Coronary computed tomography (CT) scans can detect and quantitate the presence of coronary artery calcium deposits with ECG-gated images obtained with either electron beam computed tomography (EBTC) or helical CT scanners. The entire test takes less than 15 minutes to complete but unfortunately exposes the patient to a moderate amount of ionizing radiation, approximately 10 to 15 standard chest radiographs. EBTC is faster and more accurate for calcium scores than spiral CT. Cardiac motion during imaging

distorts CT-image density and calcium scores by spiral CT are generally higher than those from EBTC, thus potentially corrupting the validity of a zero score. The EBTC uses an electron sweep of stationary tungsten target rings to generate X-ray images that can detect small amounts of calcium with considerable accuracy, whereas helical CT uses a continuously rotating X-ray source.

At the present time, calcium scoring by spiral CT should not be considered comparable to EBTC especially because of the clinical connotation of a zero score. A total calcium score of zero from EBTC should be highly predictive of the absence of obstructive coronary artery disease. But approximately 90% of men and 70% of women age 50 to 75 have coronary calcification that is nonspecific. Thus, in this age group, the search for zero scores is an expensive adventure at the individuals expense.

The amount of calcium in the coronary arteries correlates to some degree with the amount of atherosclerotic plaque. The absence of calcium does not exclude plaque formation, however, because fewer than 50% of plaques are calcified. The specificity of the test is poor, being < 23% in men and < 40% in women.

Most important in the age group where the tests could be most valuable (age 50–70) approximately 90% of men and 70% of women have coronary artery calcification and it is impossible to say if this means anything. The test is unlikely to be of value in young asymptomatic individuals who have no risk factors or in those with multiple risk factors (dyslipidemia, diabetes, hypertension, smoker, strong family history of CAD). The test is not required in patients at high risk for coronary events or those with multiple risk factors because these individuals require cardiac investigations beyond the estimation of calcium scores.

The test adds little to the results of a clearly normal treadmill exercise test with the patient achieving more than 85% maximal heart rate or a clearly abnormal treadmill exercise test. If the treadmill test is equivocal, EBCT may have a role; in such individuals, a negative EBCT (zero calcium score) probably indicates a noncardiac cause for symptoms or low probability risk for coronary events. If the test shows high calcium scores, approximately 20% of men and approximately 40% of women are expected to have significant coronary lesions. The low specificity presents a major obstacle for the development of a strategic algorithm.

The test should be relegated to a small role and should be used in selected individuals only if the initial stress test (treadmill stress test, or stress plus nuclear imaging, pharmacological stress test with nuclear imaging, echocardiographic stress test) results are equivocal or nondiagnostic. The test has been much abused and will continue to be misused at high cost to patients, particularly if used as the initial test in asymptomatic individuals or in low-to-intermediate risk patients. It will be several years before the results of the National Institutes of Health-sponsored Multiethnic Study of Atherosclerosis are published. The study investigates the incremental value of CT coronary calcium scores for prediction of cardiovascular events over both standard and novel coronary risk factors.

- In a patient at intermediate risk, selected use of coronary calcium scores may be appropriate if the results are expected to change treatment strategies. There is presently no indication from the published literature that long-term patient outcomes can be improved by modifying treatment on the basis of coronary calcium scores.
- Which asymptomatic individuals require or will benefit from CT scanning has not yet been determined with certainty.

Holter Monitor

Silent ischemia appears to occur more commonly than painful ischemia. Holter monitoring can be difficult to interpret and is not cost-effective in the assessment of stable class 1 and 2 angina. Patients with unstable angina and those with class 3 angina have a high incidence of silent ischemia. These patients require coronary angiography, however, and Holter monitoring is not indicated unless bothersome or symptomatic arrhythmias are suspected. This occurrence is not common in patients with angina. AF and sustained ventricular tachycardia are uncommon in patients with angina.

Coronary Angiography

Indications include the following:

- Patients who require PCI or CABG. See indications for these interventions.
- Ideally, all patients with bothersome angina in good general health and with absence of severe concomitant disease.
- Purely diagnostic to prevent an incorrect label of ischemic heart disease (IHD) in patients in whom symptoms persist and the diagnosis remains in doubt after careful evaluation, history, and other noninvasive investigations of the heart, lungs, gastrointestinal tract, and chest wall.

THERAPY

- The lowering of LDL cholesterol to less than 80 mg/dL (2.5 mmol/L: conversion; mmol/L \times 38.5) is of paramount importance in the treatment of patients with angina. Aggressive control of LDL cholesterol in patients postinfarction has been shown to be effective in decreasing reinfarction and death.
- It is strongly recommended to attain the goal of LDL <100 mg/dL, close to 80 mg/dL with medium dosage of a statin: 10 mg of Rosuvastatin, 10–40 mg of Simvastatin, 10–40 mg of Atorvastatin, or 40 mg of Pravastatin. If needed, the statin is combined with 10 mg of ezetimibe (Zetia; Ezetrol) to reach the goal less than 80 mg/dL. Combination therapy is advisable because it is effective and fewer adverse effects are observed with lower doses of both agents (*see* Chapter 9).
- General control of other risk factors is a necessary step: weight reduction, cessation of smoking, removal or avoidance of stress, and control of hypertension with suitable agents. For hypertension, a β -blocker (carvedilol or metoprolol) and an ACE inhibitor or angiotensin receptor blocker (ARB) are advisable because they both favorably influence survival and cardiac events.

An algorithm for the medical therapy of stable angina is given in [Fig. 4.4](#). Decision making steps in the management of varying grades of stable angina should be formulated on knowledge derived from:

- The assessment of the patient according to the Canadian Cardiovascular Society functional or similar classification.
- The exercise stress test.
- The anatomic site of atheromatous coronary obstruction, degree of stenosis as determined by coronary angiography, and number of involved vessels ([Fig. 4.5](#)).
- The presence or absence of lesions angiographically acceptable for percutaneous intervention (PCI) (type A) or probably acceptable lesions for PCI.
- Radionuclide or echocardiographic assessment of LV function. Patients with significant proximal coronary stenosis affecting three major vessels or two vessels, including the

LAD and moderate or severe LV dysfunction, EF less than 40% (greater than 20%), show greater benefits from surgery as opposed to medical therapy; surgery is considered to have advantages over angioplasty in these patients. Patients with severe LV dysfunction (EF <20%) without reversible ischemia do not benefit, however, from bypass surgery.

- The patient's age: patients aged 35 to 65 are managed preferably by balloon angioplasty and stent, if the lesions are considered angiographically acceptable. Thus, surgery is deferred as long as possible to avoid the high risk of vein graft occlusion 10 years later. The American College of Cardiology ACC/AHA Task Force Report strongly advises a left internal mammary artery anastomosis to the LAD. The artery remains attached at its origin from the left subclavian. This is the surgical procedure of choice for all patients but especially for the relatively young; the 10-year occlusion rate is 5%, as opposed to 15% for internal mammary graft and 50% for vein graft. Even so, internal mammary graft or anastomosis is deferred, if possible, by PCI in the younger patient.

The algorithm depicted in [Fig. 4.4](#), gives therapeutic guidelines and cannot include all clinical situations. Although bypass surgery is superior to drug therapy when severe proximal stenosis of the LAD artery or triple vessel disease is present, the procedure is not superior to PCI in patients with good LV function (EF greater than 50%) in which the lesion is suitable for PCI. Young patients in this group with EF greater than 45%, should be given a trial of PCI. Bypass is reserved for later use, using left internal mammary artery anastomosis.

Patients suitable for medical management usually have two of the following characteristics:

- Stable, functional class 1 or 2 angina.
- Good effort tolerance, negative or weakly positive treadmill exercise test (e.g., beyond 6 minutes of the Bruce protocol). Patients who are unable to exercise because of intermittent claudication or arthritis cannot be graded as class 1 or 2.
- Good ventricular function, radionuclide EF, or estimate from echocardiography greater than 50%.
- Absence of left main disease.
- Presence of double vessel disease in the absence of severe proximal stenosis of the LAD artery normal EF.
- Concomitant disease and contraindications to bypass surgery.
- Age over 80 and not in good general health.
- Lesions not ideal for intervention.

Most patients with stable class 1 and 2 angina are managed with sublingual nitroglycerin and a one-a-day β -blocker plus aspirin and a statin to keep the LDL less than 2 mmol/L (80 mg/dL).

The rationale for a β -blocking drug as a first-choice oral agent is shown in [Table 4.2](#).

Failure to achieve about a 75% symptomatic relief with an adequate dose of a β -blocker should result in the addition of a second agent or the patient may learn to cope with mild angina that quickly disappears on cessation of a precipitating activity. Either a calcium antagonist or a nitrate is considered second choice ([Fig. 4.4](#)). If a β -blocker is being used, 180–240 mg of Cardizem CD, or 5 mg of amlodipine is advisable. If a β -blocker is contraindicated but verapamil is not, then verapamil should be used as the drug of first choice because verapamil is the most effective calcium antagonist available for the relief of angina in patients with good LV function. Amlodipine is relatively safe if the EF is greater than 40% and a combination with a β -blocker is needed. The rationale for

Table 4.2.
 β -Blocker: First-Line Oral Drug Treatment in Angina Pectoris

<i>Effect on</i>	<i>β-Blocker</i>	<i>Calcium antagonist</i>	<i>Oral nitrate</i>
Heart rate	↓	↓	↑
Diastolic filling of coronary arteries	↑	—	—
Blood pressure	↓ ↓	↓ ↓	—
Rate pressure product	↓	<i>a</i>	—
Relief of angina	Yes	Yes	Variable
Blood flow (subendocardial ischemic area) ^b	↑	↓	Variable
First-line treatment for angina pectoris	Yes	No	No
Prevention of ventricular fibrillation	Proven	No	No
Prevention of cardiac death	Proven	No	No effect
Prevention of pain owing to CAS	No	Yes	Variable
Prevention of death in patient with CAS	No	No	No

^aRPP variable decrease on exercise, but not significant at rest or on maximal exercise.

^bDistal to organic obstruction.

CAS, coronary artery spasm; ↑, increase; ↓, decrease.

From Khan, M. Gabriel. Beta-adrenoceptor blockers. In: Cardiac Drug Therapy. Sixth Edition. Philadelphia, Elsevier, 2003, with permission from Elsevier.

this approach is discussed under calcium antagonists and combination therapy. If a nitrate is selected as second line, a sustained release preparation is selected and given once daily. For preparations and suggested timing of dosing of nitrates, *see* discussion under Nitrates. If symptoms remain bothersome, triple therapy with β -blockers, a selected calcium antagonist, and a nitrate is warranted, but this action should prompt consideration for coronary angiography and interventional therapy. A radionuclide study or PET scan is not indicated because bothersome symptoms require intervention.

β -BLOCKERS

Release of catecholamines plays a major role in the initiation and perpetuation of myocardial ischemia in patients with atheromatous coronary stenosis (Fig. 4.3.). β -Blockers can inhibit the initiation of ischemia, interrupt the dynamic process, and provide rational and effective therapy, as well as prolong life (*see* Fig. 1.1.).

β -Blockers are competitive inhibitors of catecholamines (which they structurally resemble) at β -adrenergic receptors. Their action depends on the ratio of drug to catecholamine concentration at β -adrenoceptor sites. β -Receptors are part of the adenylyl cyclase system situated in the cell membrane. The ventricle contains β_1 - and β_2 -adrenergic receptors in the proportion 70:30. β_2 predominate in the lung. Adenylyl cyclase in the presence of the stimulatory form of the G protein converts adenosine triphosphate to cyclic adenosine monophosphate, the intracellular messenger of β -stimulation.

β -Stimulation causes calcium influx into cells via receptor-operated channels, resulting in a positive inotropic effect; an increase in the pacemaker current in the sinus node, resulting in an increase in heart rate; increased conduction velocity through the atrioventricular (AV) node; increased phase 4 diastolic depolarization results in increased automaticity (*see* Chapter 6).

β -blockade results in the following:

- Decrease in heart rate. Cardiac work is reduced and the increased diastolic interval allows for improved diastolic coronary perfusion especially during exercise.

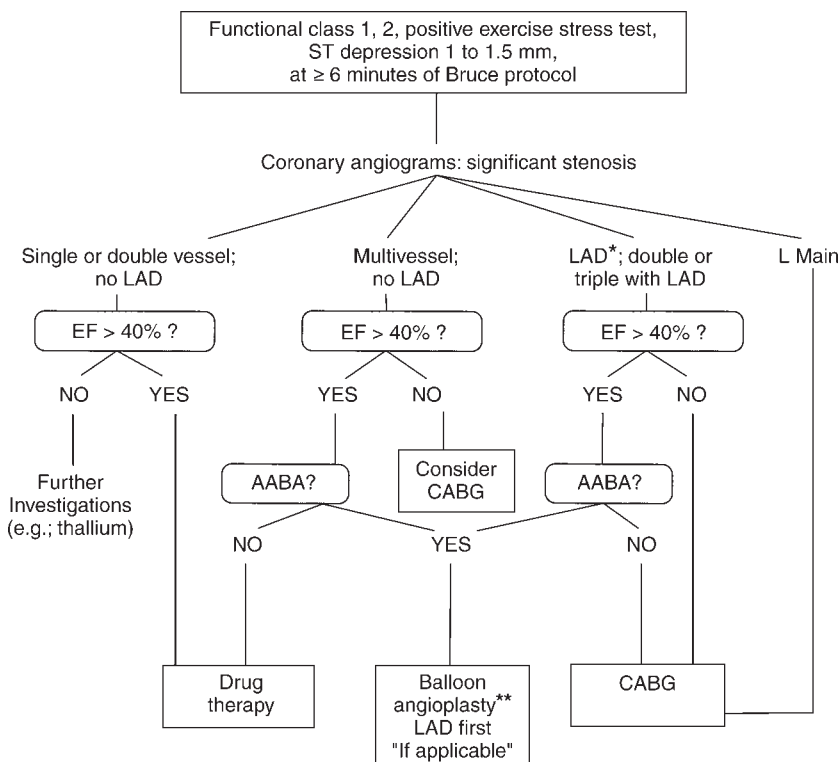


Fig. 4.5. Decision-making in the management of angina (class 1 and 2). AABA, angiographically acceptable for balloon angioplasty. *Proximal stenosis. **and stent.

- Decrease in velocity of cardiac contraction further reduces myocardial oxygen demand, which is particularly important during exertional activities.
- Decrease in cardiac output results in a fall in systolic blood pressure (SBP) and causes a decrease in the rate-pressure product and a reduction in myocardial oxygen requirement (Table 4.2.). The salutary effects of β -adrenergic blockade are shown in Fig. 1.1. These effects are not observed with other antianginal agents.
- A decrease in ejection velocity reduces hyperdynamic shearing forces imposed on the arterial wall; this might be important at the site of atheroma. Thus, it is possible that β -blockers may reduce the incidence of plaque rupture and thus protect from fatal or nonfatal MI. These agents decrease the incidence of myocardial rupture.
- Partial inhibition of exercise-related catecholamines that might initiate vasoconstriction in segments of coronary arteries where atheroma impairs the relaxing effect of the endothelium.
- Increase in ventricular fibrillation (VF) threshold and, thus, a decrease in the incidence of VF, which may be responsible for the high mortality during the early hours of acute MI and also in VF occurring in other ischemic situations. β -blockers are of proven value in the prevention of sudden death in the postinfarction patient.
- A decrease in early-morning platelet aggregation and other salutary effects induced by a decrease in catecholamine surges may eliminate the early-morning peak of transient ischemic periods and decrease the incidence of early-morning mortality and sudden death from MI. β -blockers have been shown to decrease the incidence of sudden death in cardiac patients. This observation has not been documented for any other cardiac medication, including aspirin.

- A decrease in phase 4 diastolic depolarization is important in suppressing arrhythmias induced by catecholamines, which increase diastolic depolarization. This action is opposite to that of digoxin. Thus, β -blockers are useful in the management of digoxin toxicity.
- Decrease impulse traffic through the AV node results in slowing of the ventricular response in AF or in the termination of AV nodal reentrant tachycardia.
- Direct blood flow from the epicardial vessels to subendocardial ischemic areas. In contrast, dipyridamole, a vasodilator used in the management of angina in the early 1960s, is now used to dilate epicardial vessels and produce a “steal.” Experimental evidence suggests that some calcium antagonists may also direct coronary blood flow from the subendocardium to dilated epicardial vessels. Nitrates appear to have an effect similar to calcium antagonists.

The abovementioned points have established β -blocking drugs as first-line oral agents in the management of stable angina and indicate the rationale for the algorithmic approach to drug therapy for stable angina given in [Fig. 4.4](#).

Dosage

Important dosing considerations include the following:

- In the management of stable angina, titrate the dosage over weeks. Some ethnic groups derive β -blockade at lower than conventional doses.
- A concerted effort should be made to get the β -blocker dosage into the important cardioprotective range. β -Blockers protect from fatal and nonfatal MI but may do so only at the correct dose range. Coronary studies in animals have convincingly demonstrated that too large a dose of β -blocker is nonprotective and increases mortality, whereas at a well-defined smaller dose range, fatal and nonfatal infarctions, and VF are prevented by pretreatment with β -blocking drugs.

In the β -Blocker Heart Attack Trial, a 180 or 240 mg dose of propranolol conferred protection. In the timolol Norwegian study, 10–20 mg of timolol offered protection. Carvedilol (50 mg daily) gave protection in the Carvedilol Postinfarction Survival Control in LV Dysfunction (CAPRICORN) and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials. Smaller or larger doses of these agents have not been studied in clinical trials. It may be argued that the patients in the quoted studies were post-MI and the same rules may not apply to patients with angina. The patient with angina or post-MI is at risk for sudden death. Timolol caused a 67% reduction in sudden death in post-MI patients, and it is quite conceivable that β -blockers would decrease sudden death in patients with angina.

Which β -Blocker to Choose

Sufficient attention has not been paid by the medical profession and researchers regarding the subtle differences that exist amongst the available β -blocking drugs.

- Cardioselective agents are safer than nonselective and β -blockers in diabetic patients and in those with mild-to-moderate COPD; this information appears to be well-known worldwide.
- Agents with β -agonist activity (intrinsic sympathomimetic activity, ISA) are not cardioprotective (e.g., pindolol) and should become obsolete.
- Of the cardioselective agents, only metoprolol has been shown in randomized clinical trials to reduce CHD mortality and events significantly. Bisoprolol has not been tried in trials of infarction patients but was beneficial in HF trials. Atenolol, a most popular cardioselective agent, is used worldwide but has never been tested in a randomized trial in post-MI patients followed for 1–2 years, or in patients with LV dysfunction, or HF. It

should not be assumed that this agent has similar cardioprotective properties as shown for metoprolol, carvedilol, propranolol, bisoprolol, and timolol (*see* earlier discussion of clinical trials).

- Brain concentration: Lipophilicity allows high concentration of drug in the brain, and this appears to block sympathetic discharge in the hypothalamus and elevates central vagal tone to a greater extent than water soluble, hydrophilic agents and this may relate to the prevention of sudden cardiac death. Abal et al., in a rabbit model, showed that although both metoprolol (lipophilic) and atenolol (hydrophilic) caused equal β -blockade, only metoprolol caused a reduction in sudden cardiac death. It appears that this information has not reached clinicians or researchers.
- Of the cardioselective agents, only bisoprolol and metoprolol, both with lipophilic properties, have been shown to decrease cardiac mortality. In addition only carvedilol, timolol, and propranolol, all lipophilic agents have been shown to reduce mortality and morbidity in postinfarction patients. Atenolol, a most widely used β -blocker, is nonlipophilic and probably provides less cardioprotection than proven agents and has not been adequately tested in randomized trials; sotalol and nonlipophilic oxprenolol have been tested in randomized clinical trials and have not been shown to reduce mortality or morbidity significantly. Oxprenolol has some β -agonist activity that negates cardioprotection.
- Both nonselectivity and lipophilicity may provide cardioprotection. It is possible that cardioselective agents are not as cardioprotective as β_1 , β_2 -blocking agents. Large randomized clinical trials in the post-MI patients with long-term follow-up have only been carried out with nonselective agents timolol and propranolol, and recently with carvedilol; each agent proved beneficial in reducing cardiac mortality and morbidity. The cardioselective agent, metoprolol, reduced mortality and morbidity in a postinfarction trial, but follow-up was 3 months. The drug was also successful in a HF trial Metoprolol CR Randomized Intervention Trial. The cardioselective agent, Bisoprolol, reduced mortality and morbidity in a HF trial Cardiac Insufficiency Bisoprolol Study II, but this agent is partially lipophilic. Atenolol was used in an early acute MI trial and the result was only modestly significant. The methodology was unsound; patients were admitted 4, 6, and 12 hours following infarction so this was not a genuine trial of a β -blocker during the first few hours of infarction. Unfortunately atenolol is the β -blocking drug most often used in antihypertensive trials comparing β -blocker with the diuretics, calcium antagonists, and ACE inhibitors. A nonselective lipophilic drug, such as carvedilol, that is proven effective in postinfarction patients and in patients with severe HF should be tested in hypertensive patients. The cardioselective agent bisoprolol has lipophilic properties and deserves testing in hypertensive trials.
- Cigarette smoking: Cigarette smoking decreases blood levels of propranolol and cardioprotective effects are lost. The drug did not cause a decrease in mortality or morbidity in postinfarction patients who were smokers.
- Potassium balance: β -Blockade causes a mild increase in serum potassium because of blockade of the β_2 -mediated epinephrine activation of the Na K + adenosine triphosphatase pump, which transports potassium from extracellular fluid into the cells. During stress serum potassium has been observed to decrease 1.0 mEq/L and this can be prevented by blockade of β_2 -receptors. Non-cardioselective β -blockers are superior to selective agents in preventing fluctuations of serum potassium concentration during stress and possibly during acute MI and may be more cardioprotective than cardioselective agents.
- Carevdilol has important differences from atenolol, metoprolol, and other β -blockers. This lipophilic β_1 , β_2 -blocking agent is a very mild α_1 blocker and causes arteriolar

dilatation; also, antioxidant and antiproliferative properties have been noted; the drug lowers plasma endothelin levels. This agent is preferred in patients with HF or LV dysfunction and in those with recent infarction and LV dysfunction as proven to reduce mortality and morbidity in CAPRICORN and COPERNICUS.

- β -Blockers with partial agonist activity, such as pindolol, should be avoided in patients with ischemic heart disease because cardioprotection is not achieved; acebutolol has only weak agonist activity and one study has shown a beneficial effect.
- Do not use hepatic metabolized β -blockers, propranolol, or oxprenolol in smokers who will not quit, as the salutary effects of these agents are blunted by cigarette smoking.
- *Maximum protection occur with proven agents: Carvedilol, timolol, and metoprolol in smokers and in nonsmokers, whereas propranolol is beneficial only in nonsmokers.*
- The subtle differences in β -blockers may provide the solution for the apparent lack of protection of some β -blockers. Lipophilic agents that achieve brain concentration may actuate more effective protection from the brain–heart interaction that appears to be involved in the genesis of sudden death in some subsets. This hypothesis must be tested in clinical trials, but predominantly hepatic metabolized β -blockers should not be given to smokers if all the benefits of β -blockade are to be derived.
- Comianacini et al. have studied nebivolol an interesting highly selective β_1 -receptor antagonist with antioxidant properties. *The findings of the study indicate that nebivolol also increases NO by decreasing its oxidative inactivation.*

Individual β -Blockers

ATENOLOL (TENORMIN)

Atenolol is supplied as 25-, 50-, or 100-mg tablets. The dosage is 50 mg for 1–4 weeks and then 50–100 mg once daily.

Observations have confirmed that in some patients, a once-daily dose of atenolol may not completely cover the 24-hour period and the patient may be at risk between 6 and 8 AM during the early morning period of catecholamine surge. Holter monitoring of patients has documented early morning ischemia in some patients administered atenolol once daily. Thus, it is advisable to give half the dose at 7 AM and half at bedtime. Elderly and nonwhite patients usually require a reduced dose to achieve β -blockade. Reduce the dose and increase the dosing interval in renal failure. Atenolol is a cardioselective agent. The drug is a popular β -blocker but it may have inferior cardioprotective benefits compared with carvedilol and Toprol XL.

CARVEDILOL

Carvedilol is used for HF, hypertension and following acute MI for several years and can be used for angina because the drug has excellent cardioprotective properties.

Dosage: 12.5 mg twice daily increase to 25 mg twice daily.

METOPROLOL (TOPROL XL, LOPRESSOR, BETALOC)

Metoprolol is supplied in tablets of 50- and 100-mg; Toprol XL in 50, 100, or 200 mg; Betaloc-SA in 200 mg; and Lopressor-SA in 200 mg. The dosage used is metoprolol 50–100 mg twice daily, with a maximum of 300 mg daily.

Metoprolol is a cardioselective β -blocker, but this effect is maintained up to a dose of 200 mg daily. A metoprolol dose beyond this dosage or atenolol above 50 mg daily can precipitate bronchospasm. When cardioselective drugs are given, bronchospasm is more easily reversed with albuterol (salbutamol) or other β -agonists than when β_1 and β_2 nonselective β -blockers are used. Toprol XL (metoprolol succinate) extended release tablets are effective when administered once daily at 50–300 mg.

NADOLOL (CORCARD)

Nadolol is supplied in 40-, 80-, 120-, or 160-mg tablets. The dosage is 40 mg once daily for 1–2 weeks and then maintenance 40–160 mg daily. Clinical practice has documented that the maximum dose of nadolol is much less than that recommended by the manufacturer, and the above dosage is less than that given in the package insert.

PROPRANOLOL (INDERAL; ANGILOL, BERKOLOL, UK)

This is supplied as 10-, 40-, 80-, and 120-mg tablets or as 80-, 120-, and 160-mg capsules (Inderal-LA). The dosages are 20–40 mg three times daily for several weeks (increase if needed to 160–240 mg daily) and for Inderal-LA, 80–240 mg once daily. The drug is noncardioselective, lipophilic, and hepatic metabolized.

TIMOLOL (BLOCADREN; BETIM, UK)

This drug is supplied as 5- and 10-mg tablets. Timolol is a noncardioselective β_1 -, β_2 -adrenergic blocking agent that is partially lipophilic and hydrophilic. Thus, the drug causes less central nervous system side effects than metoprolol or propranolol. If vivid dreams occur with metoprolol or propranolol, a switch to timolol is advisable. Because the drug is only partially metabolized in the liver, it is effective in smokers and nonsmokers.

The dosage is 5 mg twice daily for 1–2 weeks and then 10–15 mg twice daily. This dose is much smaller than the maximum dose recommended by the manufacturer.

NITRATES***Mechanism of Antianginal Effect***

The action of nitrates is given in Fig. 4.6. Nitrates act on so-called “nitrate receptors” believed to be structured on the myocyte. The mononitrates are unaffected by the liver, whereas isosorbide dinitrate undergoes extensive hepatic metabolism. Mononitrates, upon entering the walls of veins and arteries, combine with sulfhydryl groups with the formation of NO, which activates guanylate cyclase to produce cyclic guanosine monophosphate, which in turn brings about relaxation of vascular smooth muscle at the doses commonly used, with maximal dilatation of veins and minimal dilatation of arteries. The profound venous dilatation causes reduction in preload and, at high nitrate dosage, a modest decrease in afterload occurs. Sulfhydryl groups become depleted by continued exposure to nitrates, and tolerance develops with little or no resulting venous dilatation. Thus, 24-hour therapy with nitrates is of no value to the patient.

Nitrate tolerance occurs after 24 hours of IV nitroglycerin. Oral and transdermal preparations administered at regular intervals produce tolerance after a few days. A minimum daily 10-hour nitrate-free interval is necessary for the intracellular regeneration of sulfhydryl groups and to maintain the effectiveness of the nitrate preparation.

The “nitrate receptor” is not located in the endothelium and has no relation to the production of EDRF, now recognized as NO. The exact role of EDRF needs clarification. Endothelium-dependent coronary relaxation is impaired by atheroma, and reduced EDRF activity may allow increased smooth muscle response to constrictor agents. It appears that transmitters may stimulate EDRF, producing vasodilatation of large coronary vessels. Nitrates are powerful venous dilators. As indicated, they reduce preload, thus decreasing ventricular volume and myocardial wall stress, and some diminution of myocardial oxygen demand occurs. At high doses, a small reduction in afterload occurs, but an increase in heart rate may then take place and increase oxygen demand. Effort tolerance is somewhat improved by the use of nitrates, especially if the patient with angina has concomitant LV dysfunction.

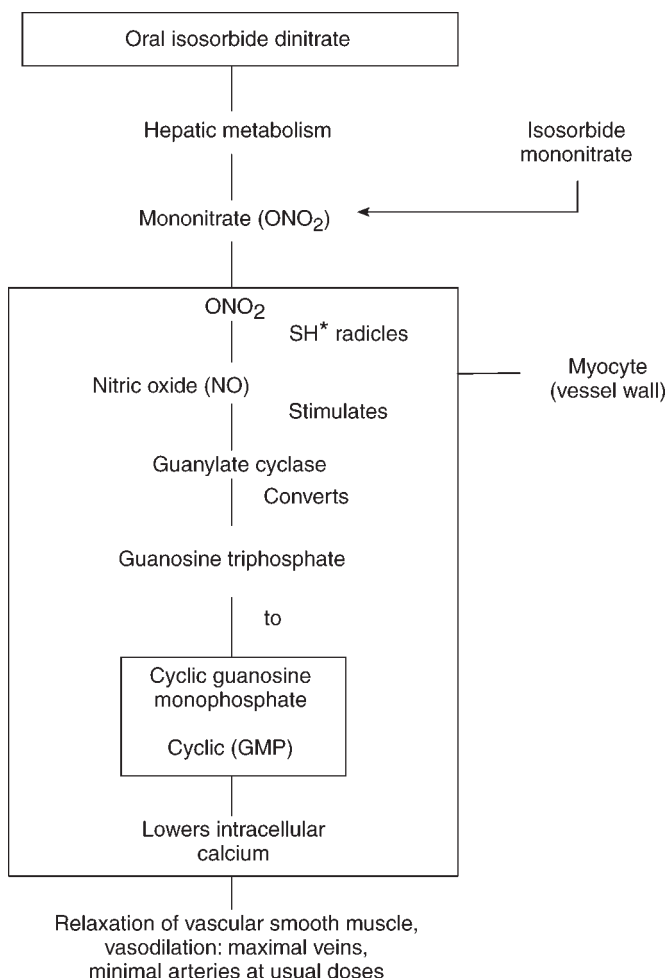


Fig. 4.6. Nitrates' mechanism of action. *SH, sulfhydryl radicles required for formation of NO, oxidized by excess exposure to nitrates become depleted, leading to nitrate tolerance. From Khan M. Gabriel, *Cardiac Drug Therapy*, 6th ed., Philadelphia, Elsevier, 2003, with permission from Elsevier.

Parker indicates that when retrospective analyses have been performed examining the impact of nitrate therapy in the postinfarct period, negative results have been observed, and nitrate therapy appears to have a negative impact on endothelial function; these findings indicate that we should more carefully examine our chronic use of these agents in patients with CAD.

Indications

- Second-choice management of class 2 and 3 stable angina.
- Angina with concomitant LV dysfunction. Shortness of breath and effort tolerance may be improved by nitrate therapy.
- Combination therapy with β -blockers or if β -blockers are contraindicated combined with verapamil or diltiazem.
- Pre- and postoperative management of the cardiac patient undergoing surgery;
- Intraoperative hypertension.

Contraindications

- Hypertrophic cardiomyopathy, constrictive pericarditis, or cardiac tamponade.
- Hypovolemia.
- RV infarction.
- Severe uncontrolled glaucoma with very high nitrate dosing, especially IV nitrates.

Adverse Effects

Adverse effects include syncope, especially in the elderly, and an increased incidence with added ACE inhibitors, diuretics, alcohol, or α -blockers. Tachycardia, mild palpitations, dizziness, and flushing commonly occur. Headaches are often bothersome; more than 25% of patients are intolerant and discontinue the drug. Indigestion and halitosis may occur. High-dose nitrates may cause a decrease in arterial oxygen tension and are relatively contraindicated in severe COPD and hypoxemic situations. Methemoglobinemia has been noted with prolonged high dosage, and withdrawal symptoms have been observed with high-dose long-term use.

Interactions

- Heparin resistance with high nitrate dosage.
- ACE inhibitors, α -blockers, and diuretics also decrease preload.
- An important interaction with tPA has recently been reported (*see* Chapter 1).
- Tachycardia may be increased when nitrates are used with dihydropyridine calcium antagonists.

Advantages

- Moderately effective agents for the management of stable angina.
- Inexpensive, except for transdermal.
- Very few contraindications or serious adverse effects, whereas patients must be carefully selected before the use of β -blockers, verapamil, and diltiazem.

Disadvantages

The development of tolerance is a major disadvantage. Withholding nitrates at night is appropriate and trouble-free in the patient with mild exertional-only angina. All patients may not be protected, however, during the early morning catecholamine surge. The use of a β -blocking drug or, if these agents are contraindicated, a calcium antagonist is advisable to cover the nitrate-free interval in patients with rest angina who require 24-hour antianginal therapy. In patients with unstable angina already on triple therapy, IV nitroglycerin must be continued with titration of the dosage upward as needed for pain control, regardless of concerns of nitrate tolerance.

Nitroglycerin (Sublingual)

This is supplied in sublingual tablets of 0.15, 0.3, and 0.6 mg (in the UK, glyceryl trinitrate: 300, 500, 600 (μ g) or nitrolingual spray, 0.4 mg per metered dose, 200 doses per vial. The dosage of 0.3 mg is given if the SBP is less than 130 mmHg or 0.6 mg if SBP is greater than 150 mmHg. The patient should be instructed on how and when to use nitroglycerin:

- Sit and put one tablet under the tongue or use the sublingual spray. Avoid taking the drug while standing except when accustomed to such usage. Nitroglycerin is less effective when used with the patient lying, because less pooling occurs in the limbs and the drug is thus less effective in relieving pain.

- Take a nitroglycerin tablet before activities that are known to precipitate angina.
- Take a second tablet if pain is not relieved in 2 minutes. After taking the second nitroglycerin tablet, chew and swallow 2 or 3 chewable 80 mg aspirins or regular 325-mg aspirin can be crushed and swallowed if chewable aspirins are not available. Aspirin is used here for its effect in preventing coronary thrombosis.
- Go to the nearest emergency room if pain persists beyond 10 minutes, using a third nitroglycerin during transport if marked weakness or faint-like feeling is not present.
- Take nitroglycerin for acute shortness of breath but not if the symptoms are dizziness or palpitations in the absence of pain.
- Keep nitroglycerin tablets in dark light-protected bottles. If exposed to light, they may only last a few months.
- Use two bottles, one for stock supply with the cotton wool within a well-stoppered bottle and kept in the refrigerator. This will last 1–2 years. The second bottle containing no cotton wool should contain a month's supply and be refilled when needed.
- Alternatively use nitrolingual spray.

Isosorbide Dinitrate (Isordil, Coronex, Cedocard, Iso-Bid, Sorbitrate)

This drug is supplied in 10-, 20-, and 30-mg tablets or 40-mg capsules. The dosage is 10–30 mg three times daily, preferably 1 hour before meals on an empty stomach. Maintenance is at 30 mg at approximately 7 AM, 11 AM, and 3 PM. Allow a 10- to 12-hour nitrate-free interval to prevent tolerance.

Isosorbide Mononitrate

Sustained Release: Elantan La, 50 mg;

Imdur, 60 mg;

The dosage is one tablet at approximately 7 AM and 2 PM daily, with a maximum of 120 mg daily or sustained release (e.g., Imdur half to one tablet once daily; two tablets may be used but nitrate use is limited by headaches and dizziness).

CALCIUM ANTAGONISTS

Verapamil is the most potent antianginal calcium antagonist but is not the safest agent for general use. It is advisable only with stable angina in patients with normal LV function EF greater than 45%. The pharmacological and clinical effects of calcium antagonists are given in [Table 8.8](#). Verapamil is more effective than dihydropyridines or diltiazem because of a more prominent negative inotropic effect; in addition, verapamil causes a greater decrease in systemic vascular resistance than diltiazem. If β -blockers are contraindicated, verapamil is a reasonable choice, provided that there are no contraindications to the use of this agent ([Fig. 4.4](#)).

The rapid-acting nifedipine capsule may cause an increase in heart rate and has been reported to increase anginal episodes. Undoubtedly, early studies were done using nifedipine capsules, which have a rapid onset of action and cause mild provocation of angina in some patients with stable angina. Short-acting nifedipine capsules are no longer recommended for use. The administration of extended release formulations (e.g., Procardia XL [Adalat XL]) virtually abolishes this adverse effect. Dihydropyridines, particularly Procardia XL or amlodipine (Norvasc), are a rational choice for use in conjunction with β -blockers.

Calcium Antagonist β -Blocker Combination

Verapamil should not be combined with a β -blocker because of a high incidence of bradyarrhythmias, including life-threatening sinus arrest and asystole; HF may be precipitated. Diltiazem combined with a β -blocker may cause sinus arrest or asystole. Although the occurrence is rare, caution is necessary and patients should be properly selected before prescribing this combination. Sinus bradycardia is not uncommon; diltiazem is not advisable if the EF is less than 40%.

Dihydropyridines can be safely combined with β -blockers because they have no significant effect on the sinus or AV nodes. Care is needed when dihydropyridines are added to β -blockers in patients with LV dysfunction, because HF can be precipitated.

Advantages

- More effective than nitrates in the management of angina and do not carry the risk posed by a 10-hour drug-free interval.
- One-a-day preparation available.
- Angiographic studies, including the International Nifedipine Trial on Antiatherosclerotic Therapy, have demonstrated that calcium antagonists appear to prevent progression of early atheromatous lesions and may cause some regression. Although the observed effect is quite modest, it could occasionally signify long-term gains for a wide range of patients with IHD. Ongoing studies will clarify this issue.

Disadvantages

- Sinus node dysfunction, AV block with verapamil or diltiazem.
- High incidence of constipation with verapamil.
- Calcium antagonists do not significantly decrease the incidence of fatal MI. Verapamil and diltiazem increase the risk of HF in patients with LV dysfunction and should be avoided in this subset when the EF is less than 40%. Amlodipine may be given a trial in patients without overt HF and EF above 25% if a β -blocker is contraindicated. Calcium antagonists are commonly and inappropriately used in this large group of cardiac patients in whom β -blockers, when used with due caution, are often effective, well-tolerated, and likely to have salutary effects on prognosis. The calcium antagonists may, however, have to be used judiciously when β -blocking agents are contraindicated or produce adverse effects.

Interactions

- Digoxin level is increased with verapamil, diltiazem, and nicardipine.
- Verapamil and diltiazem interact with β -blockers, quinidine, disopyramide, and amiodarone.

Contraindications

- Aortic stenosis if moderate or severe.
- Sick sinus syndrome and AV block with verapamil and diltiazem.
- Congestive HF or suspected LV dysfunction.
- MI with HF. EF less than 40% for verapamil and diltiazem; EF less than 35% for dihydropyridines.
- Presence of marked β -blockade: avoid the use of verapamil or diltiazem.
- Unstable angina: do not use dihydropyridine if a β -blocker cannot be used.
- Wolff-Parkinson-White (WPW) syndrome with antegrade conduction through a bypass tract and/or WPW syndrome with AF.

Nifedipine Extended Release (Procardia XL, 30, 60, and 90 mg, or Adalat XL, 30, 60, and 90 mg in Canada; Adalat Retard, 10 and 20 mg in the UK)

The dosage for nifedipine extended release is 30–60 mg daily, usual maintenance 60 mg daily. As outlined in Chapter 1, an extended release preparation is always prescribed because the capsule formulation causes a quick release and a higher incidence of adverse effects.

Diltiazem (Cardizem CD)

This drug is supplied as follows: Cardizem CD, Tiazac 120-, 180-, 240-, and 300-mg capsules; Adizem SR, 120 mg (Tildiem, UK; Anginyl, Diltzem, Herbesser in other countries). The dosage for Cardizem CD is 120–180 mg with an increase to 240–300 mg as needed. The effective dose range is 240–300 mg daily. In the elderly or patients with renal dysfunction, commence with 120 mg daily. Avoid the use of the rapid-acting tablet formulation.

Caution is required to carefully select patients before giving a combination of diltiazem and a β -blocker. Avoid in patients with HF or with LV dysfunction, EF less than 40%. Reduce dose in hepatic or renal dysfunction.

Pharmacokinetics:

- About 90% absorbed.
- Bioavailability 45%.
- Onset of action after taking orally, 30 minutes.
- Peak 1–2 hours.
- Elimination half-life approximately 5 hours.
- Extensively metabolized in the liver.
- 40% excreted unchanged in the urine.

Adverse effects are bradycardia, AV block, liver dysfunction, hypotension, rarely toxic erythema, depression, psychosis, and mild ataxia.

Verapamil

This is supplied in tablets Isoptin SR 120, 180, and 240 mg (Cordilox 40, 80, and 160 mg; Berkatens 40, 120, and 160 mg, available in the UK). The initial dosage is 120 mg daily, with a maintenance dosage of 120 mg twice daily. Half of the 240-mg tablet every 12 hours gives satisfactory 24 hour coverage and is the most beneficial dose for relief of stable angina; a maximum of 360 mg daily and a higher dose is not advisable in angina. Reduce dose with hepatic dysfunction and renal failure.

Pharmacokinetics:

- After oral dosing, 90% absorption from the gut.
- Extensive first-pass hepatic metabolism.
- 10–20% bioavailability.
- Two hours to act, 3 hours to peak.
- Elimination half-life 3–7 hours, with cirrhosis or renal failure activity prolonged beyond 10–16 hours.
- 70% excreted in the urine as active metabolites, 5% unchanged.
- Increased blood levels with hepatic dysfunction or with reduced hepatic flow, cimetidine use, and renal failure.

Cautions: Avoid in acute MI, AV block, hypotension, LV failure, or LV dysfunction when an EF less than 40% is present. Not advisable in patients taking β -blockers.

Adverse effects include bothersome constipation in more than 20%, hepatic dysfunction, edema, gynecomastia, and bradycardia.

Ranolazine

Chaitman et al. (JAMA 2004;309–316) examined the effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. In the Combination Assessment of Ranolazine in Stable Angina trial, 823 patients with symptomatic chronic angina were randomly assigned to receive placebo or 1 of 2 doses of ranolazine. Intervention patients received twice-daily placebo or 750 mg or 1000 mg of ranolazine. Treadmill exercise 12 hours (trough) and 4 hours (peak) after dosing was assessed after 2, 6 (trough only), and 12 weeks of treatment.

Exercise duration increased by 115.6 seconds from baseline in both ranolazine groups (pooled) vs 91.7 seconds in the placebo group ($p = 0.01$). The times to angina and to ischemia increased in the ranolazine groups. The drug reduced angina attacks and nitroglycerin use by about 1 per week vs placebo ($p < 0.02$). Survival was not affected. The investigators concluded that twice-daily doses of ranolazine increased exercise capacity and provided additional antianginal relief to symptomatic patients administered atenolol, amlodipine, or diltiazem. Again, atenolol, a β -blocker with poor cardioprotective effects, gains use in an RCT.

Although the antianginal effects of ranolazine appear modest, it is real and this new class of antianginal agent will be a welcome addition to our armamentarium if adverse effects are minor and low incidence.

UNSTABLE ANGINA

Pathophysiology

In most cases of unstable angina, atheromatous plaques are eccentric with irregular borders and a narrow neck on angiography. A ruptured or fissured plaque with overlying platelet thrombus is a common finding confirmed on angioscopy and is often suspected from a hazy appearance on the angiogram. In addition, silent ischemia is frequently observed in patients with unstable angina, and prognosis is worse in this subset (*see* earlier discussion of the atherosclerotic plaque).

Therapy

Table 4.1. gives Braunwald's classification of unstable angina.

- Chewable Aspirin, 160–320 mg, chewed for a rapid effect and then 81–325 mg coated aspirin is given daily. Aspirin has proven effective in clinical trials to prevent fatal and nonfatal infarction in patients with unstable angina;
- LMWH is commenced.
- Admission to a CCU or intermediate care area: monitor cardiac rhythm for 24–48 hours, Troponin or CK-MB, ECG every 6 hours for 24 hours and during recurrence of pain.
- Patients with elevation of troponin or CK-MB are classified as non-ST elevation MI.
- Elevation of CRP indicates a worse prognosis. Ridker et al. indicate that patients who have low CRP levels after statin therapy appear to have better clinical outcomes than those with higher CRP levels, regardless of the level of LDL achieved.
- Bedrest with bedside commode, fasting 8 hours, allowed fluids only.

Table 4.3.
IV β -Blocker Dosage

<i>Drug</i>	<i>Dosage</i>
Atenolol	2.5 mg rate of 1 mg/minute repeated if necessary at 5-minute intervals to a maximum of 10 mg
Esmolol (Infusion)	3–6 mg over 1 minute, then 1 to 5 mg/minute; see text
Metoprolol	5 mg rate 1 mg/minute repeated if necessary at 5-minute intervals to a maximum of 10–15 mg. Reevaluate patient and ECG before each dose
Propranolol	1 mg rate of 0.5 mg/min repeated, if necessary, at 5-minute intervals to a maximum of 5–10 mg or 0.025–0.05 mg/kg over 15–30 minutes

Caution: The SBP should not be allowed to fall below 100 mmHg or a 10–15 mm fall from baseline, or up to 25 mmHg in hypertensives.

- BP taken every 30 minutes for a few hours and then every 1–2 hours or as needed for 24–48 hours and more often if IV nitroglycerin is administered.
- IV nitroglycerin is administered, and if not contraindicated, a β -blocker is given.

β -BLOCKERS

If β -blockers are not contraindicated, give 20 mg of propranolol every 4 hours or 50 mg of metoprolol every 8 hours and then titrate quickly to adequate dose, usually 100 mg of metoprolol every 12 hours or equivalent dose of another β -blocker. Hold dose if SBP is less than 100 mmHg or if pulse is less than 50 beats per minute. If pain is present and unrelieved by nitroglycerin, the first dose of a β -blocking drug should be given intravenously; the IV route is currently recommended. The IV dosage of β -blockers is given in [Table 4.3](#).

NITROGLYCERIN

IV nitroglycerin dosage is given in [Table 4.4](#). Commence with 5–10 μ g/min and increase 5–10 μ g/min every 5 or 10 minutes, if needed, to 100–200 μ g/min. Titrate to eliminate all episodes of chest pain and do not lower the SBP below 100 mmHg. The dose is usually sufficient to reduce arterial pressure 10–15 mmHg and up to 20 mmHg in a hypertensive patient. These medications are prescribed with careful monitoring of BP and pulse, and a dose is withheld if the SPB is 100 or less. Occasionally, a SBP of 95 mmHg is acceptable in a patient who was not previously hypertensive. The SPB should not be allowed to drop more than 20 mmHg from baseline levels. Although tolerance to IV nitroglycerin has been shown to occur after 24–48 hours of infusion, concern should not be given to the development of tolerance in patients with unstable angina; the IV nitroglycerin dose is titrated upward. This administration is often successful in controlling pain, especially when time is allowed: 24–48 hours to attain adequate therapeutic dosage of β -blockers and/or calcium antagonists.

CALCIUM ANTAGONISTS

These agents are not recommended as first or second line except when β -blockers are contraindicated. These agents are added if the BP reading allows this addition to be safely

Table 4.4.
Nitroglycerin Infusion Pump Chart^a

<i>Dose (µg/minute)</i>	<i>Infusion Rate (mL/hour)</i>
5	0.75
10	1.5
15	2.3
20	3
25	3.8
30	4.5
40	6
50	7.5
60	9
80	12
100	15
120	18
140	21
160	24
180	27
200	30
220	33
240	36
260	39
280	42
300	45
320	48
340	51
360	54
380	57
400	60

Commence dosing 5–10 µg/minute, increase by 5 µg/minute every 5 minutes until relief of chest pain. Decrease the rate if systolic blood pressure is < 100 mmHg or falls > 20 mmHg below the baseline systolic or diastolic blood pressure < 65 mmHg.

^a100 mg nitroglycerin in 250 mL 5% dextrose/water = 400 µg/mL.

made. If a β -blocker is used, diltiazem is the calcium antagonist of choice. If a β -blocking drug is contraindicated, give diltiazem 30 mg every 6 hours for 24 hours and then 60 mg every 6 hours, increasing if needed to 90 mg every 6 hours. Intravenous administration allows appropriate titration (*see* Chapter 6). Caution is needed when the triple combination is used, because all three drugs (β -blockers, nitrates, and calcium antagonists) can cause excessive reduction in BP, which has the potential to worsen ischemia. Calcium antagonists do not decrease mortality in patients with unstable angina. Diltiazem plus β -blocker may cause excessive bradycardia. Nifedipine or other dihydropyridines should not be used alone or in combination with nitrates in patients with unstable angina because mortality might be increased. Verapamil or diltiazem should not be given if sinus node disease, bradycardia, AV block, HF, or LV dysfunction is present. Verapamil is contraindicated in acute infarction and patients with unstable angina may progress to infarction.

HEPARIN AND ASPIRIN

Intravenous heparin is as effective as aspirin, but LMWH (particularly enoxaparin) has proven more effective than unfractionated heparin (UFH) in several well-run randomized clinical trials (RCTs). Both aspirin and heparin cause a significant decrease in the occurrence of infarction in patients with unstable angina. The combination of IV heparin or LMWH and aspirin is commonly used; LMWH if the creatinine is <2 mg/dL (176 μ mol/L), UFH for creatinine >2 mg/dL.

COMBINATION THERAPY

Combination therapy is used in most centers. A multipronged attack to quell the thrombotic and inflammatory process reinforces the use of combination therapy in high risk patients with β -blocker (metoprolol or carvedilol), aspirin, IV nitroglycerin, ACE inhibitor, LMWH, and a statin followed. Consider PCI with loading clopidogrel and abciximab (bolus and infusion) and CABG in appropriately selected patients.

RISK STRATIFICATION

Risk assessment is crucial to employ logical treatment strategies (*see* Chapter 1, section on TIMI Risk Score, p. 61). Factors associated with a high risk of death or nonfatal MI include the following:

- Prolonged (>20 minutes) rest pain has been documented as a marker for untoward events.
- Accelerated symptoms in the prior 48 hours; crescendo angina.
- Evidence of congestive HF.
- Age over 70 years.
- ST-segment changes (depression or transient elevation).
- Diabetes.
- Elevated troponin are a high-risk group that are clearly non-ST elevation MI and not truly unstable angina which represents a heterogeneous group and it is an error to lump unstable angina high-risk patients with troponin positive patients that are a well-defined group of infarct patients. The error has been compounded by the advent of the unnecessary term acute coronary syndrome (ACS). The syndrome is characterized by acute chest pain caused by ST elevation MI, non-ST elevation MI (troponin, or CK-MB positive patients with chest pain and ST-segment depression on ECG), and a heterogeneous group unstable angina (*see* Chapter 1 for the management of non-ST elevation MI). *It is more logical to separate unstable angina from acute MI (non-ST elevation MI) and stratify these patients into low- and high-risk groups.*

Troponin levels: Several studies have documented that patients with an elevated troponin level are at increased risk. Recurrent MI appears to be unacceptably high in patients with low levels of troponin elevation; the risk of death or MI appears to be equally high in patients with either low or high troponin values.

The European Society of Cardiology (ESC)/ACC guidelines on MI advise a low cut-point for troponin elevation as marker of high-risk and adverse outcome in patients with typical ACS symptomatology. Importantly, increased troponin levels may occur in the absence of infarction being caused by HF, pulmonary embolism, or technical problems with the assay.

Randomized trials have shown that patients with a negative troponin level derived no benefit from LMWH or glycoprotein (GP) IIb/IIIa inhibition as compared with aspirin and heparin. Also, in the Treat angina with Aggrastat and determine Costs of Therapy

with Invasive or Conservative Strategies-Thrombolysis in Myocardial Infarction (TACS-TIMI 18) study, a 40% reduction in recurrent cardiac events was observed in troponin-positive patients treated with an early invasive strategy (troponin T >0.01 or troponin I >0.1 ng/mL); no benefit was observed in patients with a negative troponin. Again note that only non-ST elevation MI patients benefited. There is no proof that high-risk unstable angina patients with negative troponin benefit significantly.

In the Randomized Intervention Trial of Unstable Angina (RITA 3), and Interventional versus Conservative Treatment for Patients with Unstable Angina trials, 1810 patients presenting with chest pain with ischemic ECG changes (ST-segment depression, transient ST elevation, preexisting LBBB, or T-wave inversion), pathological Q-waves indicative of prior MI, or known IHD by prior cardiac angiography were randomized. Patients with acute MI or CK/CK-MB values twice that of normal values were excluded. Troponin elevation occurred in 2% of patients in each study arm. Enoxaparin and aspirin were administered.

At 4 months the follow-up found that 55% underwent revascularization with either PCI (35%) or CABG (21%). A significant reduction in death, MI, or refractory angina was identified within the invasively treated (9.6%) versus the conservatively treated patients (14.5%, $p = 0.001$), but this difference was caused mainly by a reduction in refractory angina with the invasive approach (4.4% vs 9.3%, $p < 0.0001$) rather than by any significant effect of intervention on either mortality (2.9% vs 2.5%, $p = 0.61$) or on nonfatal MI (3.4% vs 3.7%, $p = 0.68$).

The lack of significant reduction in the risk of death or MI with the invasive strategy persisted at 1 year (7.6% vs 8.3%, $p = 0.58$). A decreased rate of refractory angina (readmission for recurrent chest pain associated with new ECG evidence of ischemia) persisted at 1 year in the invasively managed patients (6.5% vs 11.6%, $p = 0.0002$). The trial was done 1997–2001, prior to the widespread use of clopidogrel and platelet-receptor blockers.

CLOPIDOGREL

Use of a loading dose of clopidogrel 6–12 hours prior to PCI and continued for one year plus aspirin has been shown to cause a 26.9% relative reduction in death, MI, or stroke compared with post-PCI clopidogrel therapy for one month (8.5% vs 11.5% [placebo], $p = 0.02$). A decrease in cardiac mortality was not observed in the clopidogrel unstable angina recurrent events or the Clopidogrel for the Reduction of Events During Observation trials. Pretreatment with clopidogrel caused a non-significant 19% risk reduction in events; patients given clopidogrel at least 6 hours before PCI had a significant 38.6% relative risk reduction in events at 1 month ($p = 0.05$) versus no reduction with clopidogrel administered less than 6 hours before PCI.

Significant benefits were observed with or without the concomitant use of GPIIb/IIIa inhibitors. Clopidogrel interacts with statins that use the hepatic cytochrome pathway and beneficial effects may be nullified but this does not appear to occur with rosuvastatin that is renally eliminated; this finding requires further clarification. Clopidogrel is withheld for at least 5–7 days if CABG is selected.

PLATELET-RECEPTOR BLOCKERS

The benefit of “upstream” GPIIb/IIIa inhibitors is limited to patients at high-risk and, notably, to troponin-positive patients non-ST elevation MI. They are not as effective as

abciximab in patients selected for PCI but are more effective than abciximab in high-risk troponin-positive patients (i.e., non-ST elevation MI) not selected for PCI and may be useful protective coverage in this group that are later selected for CABG.

How Useful for Unstable Angina

Because these small molecule platelet blockers are beneficial mainly in troponin positive patients (i.e., non-ST elevation MI) their use in high-risk purely unstable angina patients who have all features of high risk but troponin negative constitutes a grave error in logic. The error by experts has been propagated mainly because of the redundant term ACS.

- In a RCT conducted by Antoniucci et al., abciximab plus stenting of the culprit occluded artery in patients with ST elevation MI was shown to be clearly superior to stenting alone (see Chapter 1). Abciximab is the platelet blocker of choice for ST elevation MI and should be the drug of choice for non-ST elevation MI and for high-risk patients with unstable angina with negative troponin levels undergoing PCI (see Figs. 1.38, 1.39).
- Because of the great benefit of GPIIb/IIIa inhibition during PCI, the ACC/AHA guidelines recommend using GPIIb/IIIa receptor blockers in high-risk patients selected for an invasive strategy. Use of the small molecule GPIIb/IIIa blocker eptifibatide, tirofiban is a class IIa recommendation in high-risk troponin positive patients for whom PCI is not planned (see the section under non-ST elevation MI in Chapter 1). In (TACTICS-TIMI 18): Treat angina with aggrastat and determine costs of therapy with invasive or conservative strategies: the TIMI 18 study, an early invasive strategy caused a 40% reduction in cardiac events only in patients with a positive troponin: patients with unstable angina with negative troponin levels obtain insignificant benefit from small molecule platelet blockers.
- Most importantly, these two hotly touted agents (eptifibatide, tirofiban) have no role in the management of unstable angina once the diagnosis is confirmed by a negative troponin result.
- Abciximab is strongly beneficial in all high-risk patients undergoing PCI, (troponin positive and negative patients) but is not beneficial and thus not recommended if PCI is not an option.
- In stable or unstable angina patients undergoing elective PCI, the combination of aspirin and clopidogrel administered more than 6 hours prior to the procedure has proven beneficial and this effect is not improved by the addition of abciximab, tirofiban, or eptifibatide. Lange and Hillis have indicated, however, that in the United States where often stenting is done immediately after angiography, the need for a 6 hour wait between the administration of clopidogrel and PCI may create logistical problems.
- More than 66% of patients in the United States who undergo PCI are a high-risk subset and abciximab has proven beneficial.
- A study by Mehilli et al. does not support a significant impact of abciximab on the risk of death and MI in diabetic patients undergoing PCI after pretreatment with a 600-mg loading dose of clopidogrel at least 2 hours before the procedure.

Other Therapy

- Treat anemia, hypoxemia, arrhythmia, or sinus tachycardia that can aggravate unstable angina.
- Maintain the LDL cholesterol at less than 80 mg/dL (2.0 mmol/L).
- Administer oxygen by nasal prongs (2–4 L/minute) only if the patient has concomitant shortness of breath or if hypoxemia is proven.

- Thrombolytic therapy does not improve morbidity and mortality and is not indicated.
- Failure to suppress recurrence of pain or ischemia with triple therapy or patients graded as high-risk (*see* TIMI risk score, p. 61) should provoke the consideration of emergent interventional therapy. Coronary angiograms should be done within a few hours, followed by loading dose of clopidogrel 6 hours prior, with preparation for PCI. Clopidogrel is withheld for 5–7 days if CABG is planned.
- Patients with unstable angina, at low or intermediate risk, lack of ECG abnormalities on presentation; relief of pain within a few hours of emergency room treatment with IV nitrates and β -blockers, aspirin, and heparin; or one or two vessel disease and EF greater than 45% are recommended medical therapies.

PRINZMETAL'S (VARIANT) ANGINA

Coronary artery spasm is a rare cause of angina in which spasm of the coronary artery occurs often without identifiable stimuli. In some patients, exposure to cold, smoking, emotional stress, aspirin ingestion, or cocaine use may trigger coronary spasm. Discontinuation of nitrates or calcium antagonists may cause a worsening of spasm. Use of a β -blocker in the absence of vasodilator drugs may allow α -activity with resulting vasoconstriction to predominate. Although β -blockers may increase spasm, the risk of serious complications is likely to be small and is certainly not high enough to justify withholding this form of therapy from most patients with angina or even from those whose symptom pattern includes one or two atypical features, in case spasm is present.

All patients with variant angina should have coronary angiography because a significant number of them have underlying obstructive atheromatous coronary disease with spasm at the site of the lesion.

The clinical hallmarks of Prinzmetal's angina are:

- Pain, usually at rest, often during sleep (between 3 and 7 AM) and described as chronic angina at rest as distinct from unstable angina occurring at rest.
- ECG shows ST-segment elevation during pain.
- Worsening of angina during β -blocker use.
- Variable threshold angina.

Therapy

- Nitroglycerin tablets sublingually.
- Cessation of smoking.
- Aspirin may precipitate spasm and should be avoided if spasm is proven to be the cause of symptoms.
- For chronic management, nitrates at high dosage allowing a 10-hour nitrate-free interval to prevent tolerance; the full 24-hour period at risk may not be covered. Calcium antagonists are preferred. Amlodipine, nifedipine, verapamil, or diltiazem are equally effective. Occasionally, it is necessary to combine both a calcium antagonist and a nitrate.
- If the patient is admitted to the hospital, commence IV nitroglycerin 5–20 $\mu\text{g}/\text{minute}$ (Table 4.4., Nitroglycerin Infusion Pump Chart).
- IV heparin to prevent coronary thrombosis.

A review of all trials using β -blocker monotherapy for coronary artery spasm shows neither exacerbation nor benefit. β -Blockers should not be withheld in patients with unstable angina at rest, except in patients who are known to have proven coronary artery spasm.

Calcium antagonists and nitrates do not appear to prevent death in patients with coronary artery spasm. Verapamil carries the risk of causing severe bradyarrhythmias. Some patients require coronary bypass surgery of their organic stenoses for control of symptoms. Mortality is increased in patients who have double or triple vessel disease with associated spasm compared with those with normal coronary arteries.

Patients with coronary artery spasm have episodes similar to cluster headaches, and these may occur during a couple weeks per year. During this period, transdermal nitrate can be added to maintenance calcium antagonist for 14 hours daily, especially from bedtime to 11 AM if pain has been documented to occur most frequently at these times.

SILENT ISCHEMIA

Symptomless or painless MI is common in patients with IHD. The incidence of silent ischemia is high in patients with unstable angina and outcome is not favorable in this category of patients. Holter monitoring after noncardiac surgery in patients with stable angina and in post-MI patients has documented a high incidence of silent ischemia within the second to fourth day after surgery.

Patients with evidence of silent ischemia should be maintained on a β -blocker and aspirin and evaluated with exercise stress testing. Those with strongly positive exercise tests and/or EF less than 50% should be submitted to coronary angiography for consideration of an appropriate revascularization procedure. Drug treatment of patients with a diagnosis of silent ischemia should commence with enteric-coated aspirin, 160-325 mg daily; β -blockers are advisable to protect from death and infarction, although this therapy has not been proven in clinical trials in patients with silent ischemia. Nitrates and calcium antagonists do not offer this protection, and β -blockers must remain the mainstay of therapy.

In the Total Ischemic Burden Bisoprolol Study, both bisoprolol and nifedipine reduced the number and duration of transient ischemic episodes. Bisoprolol was significantly more effective than nifedipine and reduced the morning peak of ischemic activity. This study is in keeping with others that indicate that β -blocking drugs are superior to calcium antagonists in producing salutary effects in patients with silent ischemia and, in particular, in reducing early morning ischemia that may be related to the peak incidence of early morning heart attacks and death. In the Amlodipine/Atenolol in Silent Ischemic Study, the combination of amlodipine and atenolol was more effective than either single drug in suppressing ischemia during treadmill testing and ischemia during ambulatory monitoring.

Holter monitoring does not add to therapeutic decisions regarding silent ischemia in patients with stable angina. The TIBET (Total Ischemic Burden European) Trial concluded that in patients with stable angina transient ischemia was of no significant prognostic value when assessing either the hard end points of death, MI, or unstable angina, or all endpoints, including revascularization.

PERCUTANEOUS CORONARY INTERVENTION

Interventional therapy in the form of coronary angioplasty/stent or CABG should be strongly considered in virtually all high-risk patients with unstable angina with triple vessel disease or single or double vessel disease with EF less than 45%.

Table 4.5.
Angiographically Acceptable Coronary Balloon Angioplasty Lesions

Proximal 70–95% stenosis ^a
Not totally occluded
Concentric
Discrete < 10 mm length
Readily accessible
Nonostial
Location in nonangulated segment < 45° ^a
Nontortuous
No major branch involvement
Absence of thrombus

^a >60%

In several categories of patients, interventional therapy has advantages over medical therapy in amelioration of angina, a return to a normal lifestyle, and prolongation of life (*see* Veterans Administration study discussion under unstable angina).

Percutaneous transluminal coronary angioplasty (PTCA) and intracoronary stent or CABS each have a definite role. It is advisable, however, to delay surgery for as long as possible in patients under age 65, where PCI plays a major role. This is especially important because more than 10% of patients after bypass surgery require reoperation in 7 years and more than 50% of bypass grafts occlude after the 10th year. Moreover, long-term survival and symptomatic benefit after reoperation are far less favorable with a mortality rate exceeding 3%, as opposed to less than 1% with primary surgery in the best surgical centers.

Because many patients have lesions that are not suitable for PCI, bypass surgery is required for relief of symptoms and prolongation of life in some subsets particularly in diabetics.

In the RITA 3 Trial, 55% of unstable angina patients underwent revascularization as a result of the randomized angiogram with either PCI (35%) or CABG (21%, i.e., 37 % of the revascularized group). More than 30% of patients with non-ST elevation MI and unstable angina troponin negative require CABG as the revascularization procedure.

Coronary angioplasty, when successful, and bypass surgery in similar symptomatic patients with severe proximal single vessel disease appear to give equally excellent 10-year results: mortality, 0.6% per year, and MI rate less than 1%. Patients with single or double vessel disease with 50–70% vessel diameter narrowing and EF greater than 50% have a good outcome with medical therapy, mortality less than 1 % per year. In this subset, angioplasty with its predisposition for restenosis is not advisable unless angina is not controlled with intensive medical therapy: intolerance to drugs, a strongly positive exercise test, or if nuclear scintigraphy reveals a large area of ischemic myocardium.

Patients with proximal LAD lesions and double or triple vessel disease with a normal EF (>50%) have the same survival benefit with angioplasty and CABS. Bypass surgery is not indicated in these individuals solely in an attempt to improve survival.

Restenosis 3–6 months after coronary angioplasty occurs in approximately 30% of patients (Table 4.6.). Fortunately, the second dilatation is often successful. Prevention of

Table 4.6.
Complications and Outcome of Coronary Balloon Angioplasty

Death	<1%
Acute myocardial infarction	<2%
Emergency bypass surgery	<2%
Restenosis at 6 months	30%
Annual mortality rate	1%
Rate of nonfatal MI	2%
5-year follow-up	
Symptomatic improvement	60%
No fatal or nonfatal MI or coronary artery bypass surgery	80%

restenosis presents a major challenge. The process is not significantly prevented by aspirin, dipyridamole, ticlopidine, or σ_3 fatty acids and several test medications.

STENTS

Stents are proven useful in the following situations: avoids CABS for abrupt vessel closure during PTCA; stenosis of saphenous vein grafts and left main coronary artery stenosis, when CABS is not feasible. Restenosis is about 27% less compared with PTCA for new lesions in coronary arteries 3mm or more in diameter. The Stent Restenosis (STRESS) and the Benestent studies indicate that stents will have an increasing role in the management of obstructive coronary lesions, including stenosis of saphenous vein grafts. The Benestent study demonstrated that the primary strategy of elective stenting is superior to that of elective angioplasty and option of bailout stenting.

Coating of stents with antithrombotic materials may decrease the incidence of stent thrombosis. When stents are fully expanded with balloons at high pressures (12–20 atmospheres) the risk of subacute thrombosis is low; the combination of clopidogrel and aspirin is proven superior to anticoagulant/aspirin regimen.

Drug-Eluting Stents

A drug-eluting stent is a device releasing into the circulating blood single or multiple bioactive agents that can deposit in or affect tissues adjacent to the stent. The bioactive agents may be simply linked to the stent surface, embedded and released from within polymer materials, or surrounded by and released through a carrier. Importantly, the carrier may coat or span the stent struts.

Sirolimus-Eluting Stents

Sirolimus (rapamycin) is a natural macrocyclic lactone with potent immunosuppressive and antimitotic action that was approved as an antirejection drug in renal transplant recipients. Sirolimus blocks cell-cycle progression and expression of inflammatory cytokines, thus inhibiting cellular proliferation. On the basis of that the immunosuppressive properties of sirolimus might inhibit neointimal hyperplasia, a stent was made by coating the stent with a mixture of synthetic polymers blended with sirolimus; a second layer of drug free polymers promotes gradual release of the drug in a controlled concentration over 30 days.

The RAVEL Study

A randomized study with the sirolimus-eluting Bx Velocity balloon expandable stent (RAVEL) in the treatment of patients with de novo native coronary arteries. The trial randomized 238 patients with single coronary lesions. Patients with complex coronary lesions were excluded. The angiographic rate of restenosis at six months was 0% in the drug stent group and 26.6% in the standard stent group. There were no reported cases of subacute thrombosis. Long-term beneficial or adverse effects beyond 2 years are not available and caution is required.

The SIRIUS Trial

The trial randomized 1100 patients to treatment with rapamycin-coated versus standard stent and it is investigating long-term safety in complex coronary lesions. Short-term result indicates a reduction of in stent (3.2% drug stent vs 35.4% standard stent) and in segment restenosis (8.9% vs 36.3%) with no difference in adverse effects. The high rate of restenosis with standard stents is alarmingly high. Drug-eluting stents will play a major role if there beneficial effects are proven beyond 5 years.

Paclitaxel-Eluting Stent

Paclitaxel inhibits cell processes that are dependent on a microtubule turnover, including mitosis, cell proliferation, and cell migration, but the cells remain viable and in a cytostatic state. Therapeutic concentration of paclitaxel cause cytostatic inhibition of smooth muscle cells.

The Asian paclitaxel-eluting stent clinical trial tested the safety and effectiveness of this drug-eluting stent system with the safety and effectiveness of uncoated stents of the same type. This small study of 177 patients followed for 6 months effectively inhibited restenosis and neointimal hyperplasia with the safety profile similar to that of standard stent. The long-term effects of drug-eluting stents remain unanswered and the role in more complex lesions requires further large clinical studies.

New Agents

Two new agents are been tested in drug-eluting stents: angiopeptin and everolimus. Angiopeptin is a synthetic cyclic octapeptide analog of somatostatin that inhibits production of growth hormones including PDGF and epithelial growth factor. This agent inhibits smooth muscle cell proliferation but because it is cytostatic it does not appear to cause local toxicity. A phosphorylcholine sponge coating loads the drug onto the stent. Tests are been carried out with stents coated with a somatostatin analog that is human vascular-specific.

Everolimus is a new antiproliferative agent that binds to cytosolic immunophyllin and inhibits growth factor-driven cell hyperplasia. A bioabsorbable polymer matrix is the vehicle in the stent that stays on the sent after the drug is gone. This minimizes the inflammatory response.

Problems to be Resolved

- Polymer coatings have been shown to induce inflammatory responses and fibrinoid deposits. In addition, the stability of polymeric material may degrade over time and delayed intimal hyperplasia may ensue. The perfect carrier for the bioactive material requires substantial search. Biodegradable polymers may prove useful but the length of

drug delivery is a concern; multilayered polymers for multiple drug release and antigen antibody coating to capture endothelial cells and other modalities are being investigated.

- Long-term drug toxicity must be addressed because some drug-eluting stent systems, including dactinomycin, taxane, and batimast, showed delayed thrombosis, delayed restenosis, and aneurysm formation.
- In cases of two stents placed together or overlapping may have local toxic effects that have not been studied.
- Beneficial effects in complex coronary lesions must be shown.
- Long-term effects beyond 5 years must be observed and carefully reported.

Impress Study

This remarkable study in a small group of 83 patients undergoing successful stenting with CRP levels greater than 0.5 mg/dL 72 hours of the procedure were randomized to receive oral prednisone or placebo for 45 days.

Results: 12-Month event-free survival rates were 93% and 65% in patients treated with prednisone and placebo respectively. Six-month restenosis rate was lower in the prednisone treated than in the placebo treated patients (7% vs 33%, $p = 0.001$).

Conclusions: In patients with persistently high CRP levels after successful coronary artery stent implantation, oral immunosuppressive therapy with prednisone results in a striking reduction of events and angiographic restenosis rate.

Perspective: Although adverse effects were low, corticosteroids have undesirable adverse effects and long-term randomized studies are required to clarify the role of prednisone, other corticosteroids and immunosuppressive agents in the management of in-stent restenosis.

- In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial, patients with CAD treated with PCI are being randomized to receive aggressive medical therapy, risk factor modification, and PCI with stent placement or to receive aggressive medical therapy and risk factor modification alone; follow-up will continue until June 2006.

CORONARY ARTERY BYPASS SURGERY

Overall mortality of CABS is about 1–2%, with 96% survival at 1 month and 95, 87, 76, and 60% at 1, 5, 10, and 15 years, respectively.

Approximately 50% of saphenous vein grafts occlude by 10 years postoperatively. This incidence is highest in patients with hypertension, hyperlipidemia, diabetes, and in persistent smokers. Some studies indicate 40% occlusion at 10 years and approximately 25–40% for LAD vein grafts.

Reduction of graft occlusion has resulted from the use of the left internal mammary artery. The artery is left attached to its origin from the left subclavian artery, mobilized, and anastomosed to the LAD artery. The 10-year occlusion rate is only 5%. A 20-year follow-up of internal thoracic artery grafts showed a mean survival of 4.4 years longer than that of vein grafts alone and was associated with fewer reoperations, late infarctions, and lower mortality rates.

CABS appears to protect high-risk unstable angina patients with LV dysfunction from sudden death, with only a 5 and 10% incidence at 10 and 15 years, an important indicator of the role of ischemia in promoting this tragic outcome.

In the 8-year follow-up of the Veterans Administration Cooperative Study, a mortality of 16.8% was observed in medically treated patients, versus 32% in surgically treated patients, in those considered at low risk (patients with one or two vessel disease and EF greater than 58%). In the high-risk patients (i.e., patients with ECG abnormalities, or recurrent pain at rest, triple vessel disease, or EF less than 58%), the mortality in the surgical group was 24.1% versus 35.3% in the medically treated patients. In patients with triple vessel disease, survival of medically treated, but not surgically treated, patients appears to depend on left ventricular EF. Follow-up data at 8 years in the Veterans Administration trial indicate that accumulative mortality in patients with severe rest angina, associated with ST-T changes with LV dysfunction, was significantly lower in surgically treated patients than in those treated medically. Currently, angioplasty with stenting is recommended for many high-risk patients.

Indications

- For relief of angina uncontrolled by intensive medical therapy, especially if symptoms intensely hinder the patient's lifestyle and if obstructive lesions are considered angiographically unacceptable for balloon angioplasty.
To relieve symptoms and prolong life in:
- Left main coronary stenosis with 50% or more reduction in luminal diameter.
- Proximal LAD equal to or greater than 75% plus a second vessel with greater than 60% overall diameter reduction and EF less than 40%.
- EF less than 40% but greater than 25% with two or three vessel disease.
- Three vessel disease with EF less than 50% but higher than 20%.

The European Surgery Study Group indicated that patients with stenosis of the proximal LAD artery and multivessel disease have a poor prognosis with medical therapy and improved survival with CABS. In this category of patients, with normal EF, surgery is not superior, however, to coronary angioplasty. Studies indicate that in patients with normal LV function and three vessel disease, not involving the proximal LAD, CABS should not be done solely in an attempt to improve survival; in diabetics, survival after CABS is superior to PTCA.

In the Emory Angioplasty versus Surgery Trial, 194 patients were randomly assigned to bypass surgery and 198 to coronary angioplasty. Death occurred in 6% of the surgery group versus 7% in the angioplasty group. At 3-year follow-up, there was no difference in the primary end point: death or Q-wave infarction. In the surgery group, repeated bypass surgery was required in 1% and angioplasty in 13% versus the PTCA group that required 22% bypass surgery and 41% repeat coronary angioplasty. Angina was more frequent in the PTCA group, 20% versus 12% in the surgery group. These patients with multivessel disease had a normal EF greater than 50%.

Involvement of the proximal LAD artery and impaired left ventricular systolic function influences the choice of therapy and outcomes. CABG is not superior to medical therapy in patients with double vessel disease and normal EF. Results of well-conducted long-term studies of surgery compared with drug eluting stents in high-risk patients are awaited.

BIBLIOGRAPHY

Åblad B, Bjurö T, Björkman JA, Edström T, Olsson G. Role of central nervous beta-adrenoceptors in the prevention of ventricular fibrillation through augmentation of cardiac vagal tone. *J Am Coll Cardiol* 1991;17(suppl):165.

- Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342–1349.
- Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–842.
- Antooniucci D, Rodriguez A, Hempel A, et al. a randomized trials comparing primary infarct artery stenting with or without abciximab. *J Am Coll Cardiol* 2003;42:1879–1885.
- Barbato E, Piscione F, Bartunek J, et al. Role of β_2 adrenergic receptors in human atherosclerotic coronary arteries. *Circulation* 2005;111:288–294.
- Berger P. Ranolazine and other antianginal therapies in the era of the drug-eluting stent. *JAMA* 2004;291(3):365–367.
- Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Unstable Angina and Non-ST Segment Elevation Myocardial Infarction). *J Am Coll Cardiol* 2000;36:970–1056.
- Budoff MJ, Achenbach S, Duerinck A. clinical utility of computed tomography and magnetic resonance techniques for noninvasive coronary angiography. *J Am Coll Cardiol* 2003;42:1867–1878.
- CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). *Lancet* 1995;346:1179.
- Cameron AA, Green GE, Brogno DA, et al. Internal thoracic artery grafts: 20-year clinical follow-up. *J Am Coll Cardiol* 1995;25:188.
- Cameron AAC, David KB, Rogers WJ, et al. Recurrence of angina after coronary artery bypass surgery: predictors and prognosis (CASS Registry). *J Am Coll Cardiol* 1995;26:895.
- Cameron A, Davis KB, Green G, et al. Coronary bypass surgery with internal-thoracic-artery grafts-effects on survival over 15 year period. *N Engl J Med* 1996;334:216.
- Cannon CP, Braunwald E, McCabe CH. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [PROVE IT–TIMI 22 trial]. *N Engl J Med* 2004;350:1495–1504.
- Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q-wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. *J Am Coll Cardiol* 1997;30:133–140.
- Cannon CP, Turpie AG. Unstable angina and non-ST-elevation myocardial infarction: initial antithrombotic therapy and early invasive strategy. *Circulation* 2003;107:2640–2645.
- CAPRICORN: the CAPRICORN investigators: effect of carvedilol on outcome after myocardial infarction in patients and with left ventricular dysfunction: *Lancet* 2001;357:1385.
- The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
- Chaitman BR, Pepine CJ, Parker JO, et al., Combination Assessment of Ranolazine In Stable Angina (CARISA). Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA* 2004;291:309–316.
- Cheng J-J, Wung BS, Chao Y J, et al. cyclic strain enhances adhesion of monocytes to endothelial cells by increasing intercellular adhesion molecule-1 expression. *Hypertension* 1996;28:386–391.
- Colombo A, Stankovic G, Moses JW. Selection of coronary stents. *J Am Coll Cardiol* 2002;40:1021–1033.
- Cominacini L, Fratta Pasini A, Garbin U, et al. Nebivolol and its 4-keto derivative increase nitric oxide in endothelial cells by reducing its oxidative inactivation. *J Am Coll Cardiol* 2003;42:1838–1844.
- COPERNICUS: Packer M, Coast JS, Fowler MB, et al. for the carvedilol prospective in randomized cumulative survival study group: effect of carvedilol on survival in severe chronic heart failure. *New Engl J Med* 2001;344:1651.
- Cruickshank JM. Beta-blockers continue to surprise us *Eur Heart J* 2000; 21:355.
- Dargie HJ, Ford I, Fox K. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group. *Eur Heart J* 1996;17:104–112
- Fattori R, Piva T. Drug-eluting stents in vascular intervention *Lancet* 361:247-49, 2003
- Fleming SM, O'Byrne L, Finn J, et al. False-positive cardiac troponin I in a routine clinical population. *Am J Cardiol* 2002;89:1212–1215.
- Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery. *J Am Coll Cardiol* 2004;44:2149–2156.
- Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P) H oxidase; role in cardiovascular biology and disease. *Circ Res* 2000;86:494–501.

- Goy J-J, Stauffer J-C, Siegenthaler M, et al. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology, The TAXi trial. *J Am Coll Cardiol* 2004;45:308–311.
- Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;340:1623–1629.
- Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995;333:1267.
- The Joint European Society of Cardiology/American College of Cardiology committee. Myocardial infarction redefined: a consensus document of the joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;21:1502–1513.
- Kastrati A, Mehilli J, Schuhlen H, et al. Intracoronary stenting and antithrombotic regimen-rapid early action for coronary treatment study investigators. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004;350:232–238.
- Khan M Gabriel. β -blockers the cornerstone of cardiac drug therapy. In *Cardiac Drug Therapy*. 6th ed. Philadelphia: WB Saunders/Elsevier, 2003.
- King SB, Lembo NJ, Weintraub WS, et al. For the Emory Angioplasty versus Surgery Trial: A randomized trial comparing coronary angioplasty with coronary bypass surgery. *N Engl J Med* 1994;331:1044.
- Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging—Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging. *Circulation* 2003;108:1404–1418.
- Kramer CM. The comprehensive approach to ischemic heart disease by cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2004;44:2182–2184.
- Lange RA, Hillis LD. Antiplatelet therapy for ischemic heart disease. *N Engl J Med* 2004;350:277–280.
- Loscalzo J, Bonow RO, Jacobs AK. Coronary calcium screening and the American Heart Association news embargo. *Circulation* 2004;110:3504–3505.
- Macaya C, Serruys PW, Ruygrok P, et al. Continued benefit of coronary stenting versus balloon angioplasty: one-year clinical follow-up of Benestent trial. *J Am Coll Cardiol* 1996;27:255.
- Maehara A, Mintz GS, Bui AB, et al. The morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. *J Am Coll Cardiol* 2002;40:904–910.
- Mahoney EM, Jurkovitz CT, Chu H, et al. Cost and cost-effectiveness of an early invasive versus conservative strategy for the treatment of unstable angina and non-ST elevation myocardial infarction. *JAMA* 2002;288:1851–1858.
- Mallik S, Krumholz HM, Lin ZQ, et al. Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. *Circulation* 2005;111:271–277.
- MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure. Metoprolol CR/XL randomized trial in congestive heart failure (MERIT-HF). *Lancet* 1999;353:2001–2007.
- Moreno PR, Fuster V. The year in atherothrombosis. *J Am Coll Cardiol* 2004;44:2099–2110.
- Morice MC, Serruys PW, Sousa JE, et al. for the RAVEL study group. A randomized comparison of a sirolimus eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773–1780.
- Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponin I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA* 2001;286:2405–2412.
- The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1989;319:385.
- Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004;351:1593–1595.
- Münzel T, Sayegh H, Freeman BA, Tarpey MM, Harrison DG Evidence for enhanced vascular superoxide anion production in nitrate tolerance. A novel mechanism underlying tolerance and cross-tolerance. *J Clin Invest* 1995;95:187–194.
- Nemoto S, Hamawaki M, DeFreitas G et al. Differential effects of the angiotensin-converting enzyme inhibitor lisinopril versus the β -adrenergic receptor blocker atenolol on hemodynamics and left ventricular contractile function in experimental mitral regurgitation. *J Am Coll Cardiol* 2002;40:149–154.
- Okada M, Matsumori A, Ono K et al. cyclic stretch upregulates production of interleukin -8 and monocyte chemotactic and activating factor/ monocyte chemoattractant protein-1 in human endothelial cells. *Arterioscler Thromb Vasc Biol* 1998;18:894–901.

- Park SJ, Kim YH, Lee BK, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis. *J Am Coll Cardiol* 2005;45:351–356.
- Park S-J, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med* 2003;348:1537–1545.
- Parker JD. Therapy with nitrates: increasing evidence of vascular toxicity. *J Am Coll Cardiol* 2003;42:1835–1837.
- Peters RW, Muller JE, Goldstein S, et al. For the BHAT Study Group. Propranolol and the morning increase in the frequency of sudden cardiac deaths (BHAT Study). *Am J Cardiol* 1989;63:1518.
- Portegies MCM, Sijbring P, Gobel EJAM, et al. Efficacy of metoprolol and diltizem in treating silent myocardial ischemia. *Am J Cardiol* 1994;74:1095.
- Prakash C, Deedwania PC, Carbajal EV, et al. Anti-ischemic effects of atenolol versus nifedipine in patients with coronary artery disease and ambulatory silent ischemia. *J Am Coll Cardiol* 1991;17:963.
- RITA Trial Participants. Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. *Lancet* 1993;341:573.
- Sakamoto H, Aikawa M, Hill CC. Biomechanical strain induces class A scavenger receptor expression in human monocyte/macrophages and THP-1 cells. *Circulation* 2001;104:109–114.
- Scirica BM, Cannon CP, McCabe CH, et al., Thrombolysis in Myocardial Ischemia III Registry Investigators. Prognosis in the thrombolysis in myocardial ischemia III registry according to the Braunwald unstable angina pectoris classification. *Am J Cardiol* 2002;90:821–826.
- Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489.
- Serruys PW, Ormiston JA, Sianos G, et al. Actinomycin-eluting stent for coronary revascularization. A randomized feasibility and safety study: The ACTION trial. *J Am Coll Cardiol* 2004;44:1363–1367.
- Sharma GVRK, Deupree RH, Luchi RJ, et al. Identification of unstable angina patients who have favorable outcome with medical or surgical therapy (eight-year follow-up of the veterans administration cooperative study). *Am J Cardiol* 1994;74:454.
- Stone GW, Ellis SG, Cox DA, et al., TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221–231.
- Taylor WR. Hypertensive vascular disease and inflammation: mechanical and humoral mechanisms. *Current Hypertens Rep* 1999;1:96–101.
- Topol EJ. A preferred reperfusion strategy for acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1886–1889.
- Thérout P, Ouimet H, McCans J. Aspirin, heparin, or both to treat unstable angina. *N Engl J Med* 1988;319:1105.
- Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002;105:393–343.
- Versaci F, Gaspardone A, Tomai F, et al. immunosuppressive therapy for the prevention of restenosis after coronary artery stent implantation (IMPRESS Study). *J Am Coll Cardiol*. 2002;40:1935–1942.
- von Arnim T. Medical treatment of reduce total ischemic burden: total ischemic burden bisoprolol study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. *J Am Coll Cardiol* 1995;25:231.
- Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease: results from the Emory Angioplasty Versus Surgery Trial (EAST). *Circulation* 1995;92:2831.
- Wong SC, Bairn DS, Schatz RA, et al. Immediate results and late outcomes after stent implantation in saphenous vein graft lesions: the Multicenter U.S. Palmaz-Schatz Stent Experience. *J Am Coll Cardiol* 1995;26:704.
- Wright SA, Sawyer DB, Sacks DB, et al. Elevation of troponin I levels in patients without evidence of myocardial injury. *JAMA* 1997;278:2144.

5

Heart Failure

CONTENTS

DIAGNOSIS
PATHOPHYSIOLOGIC IMPLICATIONS
NONSPECIFIC THERAPY
WHICH DRUG OR DRUG COMBINATION TO CHOOSE
RANDOMIZED CLINICAL TRIALS
DIURETICS
ACE INHIBITORS AND ARBS
 β -BLOCKERS
DIGOXIN (LANOXIN)
CARDIAC RESYNCHRONIZATION THERAPY
DIASTOLIC DYSFUNCTION
PULMONARY EDEMA
BIBLIOGRAPHY

Heart failure (HF) is a syndrome identified by well-defined symptoms and hemodynamic findings caused by an abnormality of cardiac function that results in a relative decrease in cardiac output (CO) that triggers compensatory renal and neurohormonal changes (Fig. 5.1.).

HF is a deadly disease with a prognosis similar to malignant diseases and has reached epidemic proportions in industrialized countries. More than 500,000 individuals die of HF in North America each year, and up to 33% of those die suddenly. HF is the number one cause for admissions to hospitals in individuals older than age 60 in the United States, accounting for over 2.5 million admissions per year. Patients admitted with HF have an increased risk of recurrent hospitalizations with approximately 35% of patients being readmitted within 6 months.

The incidence of HF is rising because of the increase in the aging population, which is predisposed to HF. Also, better management and improved survival after acute myocardial infarction (MI) have created a large population of patients who may succumb to HF. HF, unlike coronary artery disease (CAD), has no territorial boundaries and is reaching epidemic proportions in both developed and in developing countries.

The term “heart failure” is preferred to “congestive heart failure” (CHF), because manifestations of congestion may be absent at rest in some patients with moderate or

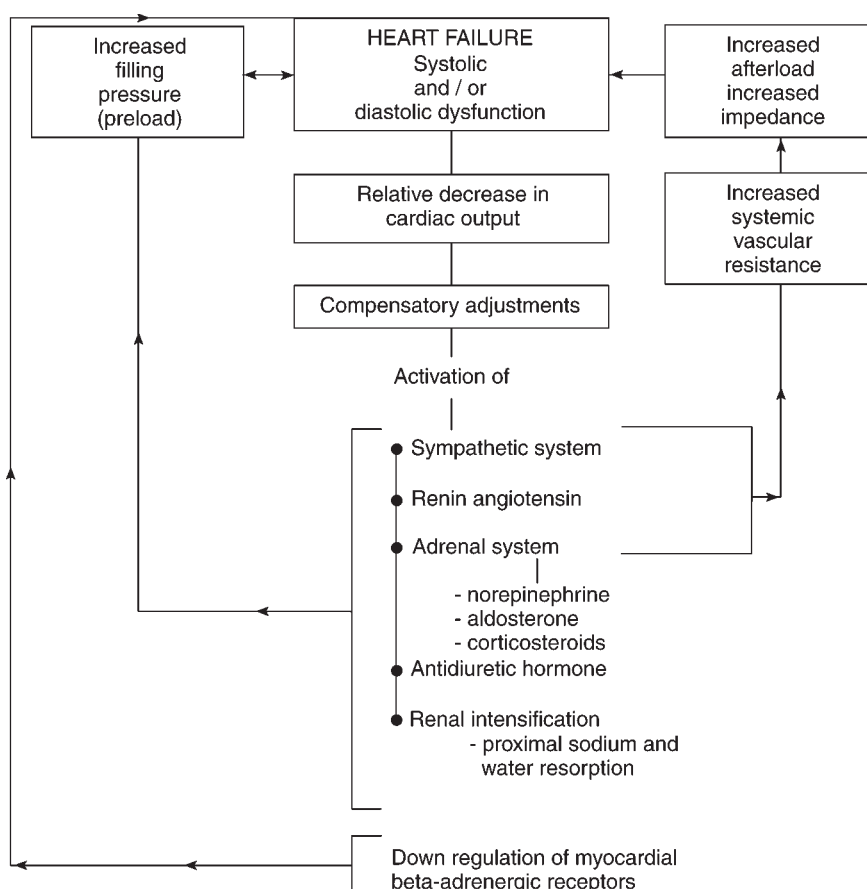


Fig. 5.1. Pathophysiology of heart failure. From Khan, M. Gabriel, Encyclopedia of Heart Disease, San Diego, Academic Press, 2005, with permission from Elsevier.

severe left ventricular (LV) dysfunction. Indeed, there may be no clinical manifestations of forward or backward failure at rest.

The management of HF requires the application of five basic principles to actuate a salutary effect:

- Ensure a correct diagnosis, excluding mimics of HF.
- Determine the underlying heart disease, if possible, and treat.
- Define precipitating factors, because HF can be a result of underlying disease and is often precipitated by conditions that can be prevented or easily corrected.
- Understand the pathophysiology of HF.
- Know the actions of the pharmacological agents and their appropriate indications.

DIAGNOSIS

Symptoms

Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, weakness, fatigue, edema, and an increase in abdominal girth are common complaints. Nocturnal angina may occur if severe ischemic heart disease (IHD) is the underlying cause of heart failure.

PHYSICAL SIGNS

Signs of LV failure include the following:

- Crepitations (crackles) over the lower lung fields. Many patients are treated for HF based on the presence of crepitations. HF may be present without pulmonary crepitations, and, importantly, crepitations may be present in the absence of HF. Crepitations that fail to clear on coughing may be a result of atelectasis, fibrosis and restrictive lung disease, pneumonia, pneumocystis infection, lymphangitic carcinomatosis, and other causes of noncardiogenic pulmonary edema.
- S₃ gallop or summation gallop (S₃ and S₄). An S₃ gallop may elude auscultation in patients with CAD, although a corresponding movement associated with rapid diastolic filling may be visible on careful inspection of the precordium. An S₃ or summation gallop is virtually always present in patients with dilated cardiomyopathy, even in the absence of HF.

Signs of right ventricular (RV) failure include the following:

- An increase in jugular venous pressure (JVP) greater than 2 cm above the sternal angle. Importantly, the most common cause of RV failure is left HF, and signs of this should be sought.
- A prominent V-wave of tricuspid regurgitation or an A-wave of atrial hypertrophy.
- A positive hepatojugular reflux usually indicates a right atrial pressure greater than 9 mmHg and a pulmonary capillary wedge pressure (PCWP) greater than 15 mmHg in which right HF is secondary to left HF.
- Bilateral leg or sacral edema. Edema may be absent with severe HF, and when present, edema is often assumed to be a result of HF. If a diagnosis of HF is not confirmed by other findings and a basic cause for HF is not present, consider the edema to be owing to stasis, venous insufficiency, or deep venous thrombosis of lymphangitic origin, or induced by drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) or calcium antagonists.

Chest X-Ray Verification

Look for:

- Constriction of lower lobe vessels with dilatation of those in the upper lobes. This sign is observed with pulmonary venous hypertension in LV failure, mitral stenosis, severe obstructive lung disease, or X-ray taken in the recumbent position.
- Interstitial pulmonary edema: Pulmonary clouding, perihilar haze, Kerley B or A lines caused by edema, and thickening of interlobular septa. Kerley B lines usually are localized to the periphery of the lower zones and appear as horizontal lines 1–3 cm in length and no wider than 0.1–0.2 cm. They occur transiently when pulmonary venous pressure exceeds about 22 mmHg. A lines are less common, reflect thickened intercommunicating lymphatics, and appear as thin nonbranching lines, several inches in length, extending from the hilar region. The transient appearance of A and B lines is caused by LV failure and may persist if the lymphatic channels are obstructed by tumor, choked by dust particles in pneumoconiosis, or thickened by fibrosing alveolitis or hemochromatosis. They may be caused by viral infections or drug hypersensitivity.
- Pleural effusions: subpleural or free pleural, blunting of the costophrenic angle, the right usually greater than the left.
- Alveolar pulmonary edema, a butterfly pattern, may be unilateral.
- Interlobar fissure thickening owing to accumulation of fluid, seen best on the lateral film.
- Dilatation of the central right and left pulmonary arteries.
- Cardiomegaly.

The heart size may be normal on chest X-ray, in many instances, with HF present because of:

- Acute MI in patients with IHD. Cardiac dilatation may not take place in a transverse direction and patients with one or more old infarcts may present with HF and a normal heart size on chest radiograph. Hypokinetic, dyskinetic areas may be observed on inspection or palpitation of the chest wall and are readily observed on echocardiography.
- Mitral stenosis.
- Aortic stenosis in some patients.
- HF owing to predominant diastolic dysfunction.
- Cor pulmonale.

The following radiological mimics of HF should be excluded:

- Lung infection, including all causes of adult respiratory distress syndrome.
- Allergic pulmonary edema (heroin, nitrofurantoin).
- Lymphangitic carcinomatosis.
- Uremia.
- Increased cerebrospinal fluid pressure.
- High-altitude pulmonary edema.
- Alveolar proteinosis.

B-Type Natriuretic Peptide

In patients in whom the diagnosis of HF as the cause for acute shortness of breath is in doubt the B-type natriuretic peptide (BNP) level serves a useful purpose. More important, the BNP test clarifies whether severe shortness of breath is caused by HF or by pulmonary disease.

BNP is released by cardiac myocytes of the ventricles in response to myocardial wall stress that is brought on by:

- Increased transmural wall tension.
- Elevations of end-diastolic pressure and volume.

The secretion of this important peptide serves to regulate sodium and water balance by the kidneys and cause vasodilatation of arteries that benefits the failing heart.

HF is readily diagnosed by the symptoms of severe shortness of breath on minimal effort, shortness of breath in bed, swelling of the ankles caused by accumulation of fluid, edema, and radiologic confirmation.

In a clinical study of 1586 patients who visited the emergency with acute shortness of breath, dyspnea, and whose BNP level was measured with a bedside assay. The diagnoses of HF were confirmed by two independent cardiologists. Dyspnea was caused by HF in 744 patients 47%, shortness of breath owing to noncardiac causes, in 72 patients with a history of LV dysfunction, 5%, and no finding of HF in 770 patients, 49%. The BNP levels were more accurate than historical or physical findings in establishing the diagnosis of HF. At a cut off 100 pg/mL the diagnostic accuracy of BNP was 83%. A level of BNP less than 50 pg/mL indicates the absence of heart failure. Patients with the diagnoses over HF had mean BNP level results ± 675 . The severity of HF appears to be reflected by the height of BNP levels.

Electrocardiogram Assessment

Scrutinize the electrocardiogram (ECG) for:

- Acute or old infarctions.
- Recent ischemia (assess by serial ECGs).
- LV aneurysm: ST-segment elevation in two contiguous leads present more than 3 months postinfarction.
- Bradyarrhythmias or tachyarrhythmias, particularly atrial fibrillation (AF) with a fast ventricular response.
- LV or RV hypertrophy.
- Left atrial abnormality; this indicates left atrial hypertrophy, increased left atrial volume, left atrial pressure or enlargement. All of these are early signs of altered LV compliance from LV hypertrophy, LV failure, and a common feature of mitral regurgitation and/or mitral stenosis.

Echocardiographic Evaluation

Echocardiography provides many diagnostic aids:

- Decreased systolic function: an ejection fraction (EF) less than 40% is often seen in patients with moderate HF. The EF may not be decreased in patients with HF caused by mitral regurgitation or ventricular septal defect (VSD) and in patients with ventricular diastolic dysfunction. The radionuclide evaluation of EF is more accurate but more expensive than that of echocardiography if AF is absent, but the latter is superior in detecting the presence and significance of valvular lesions and specific chamber enlargement. Echocardiography provides a sufficiently accurate EF for the guidance of therapy.
- Ventricular wall motion abnormalities, global hypokinesia, and chamber enlargement.
- Gives accurate cardiac dimensions; replaces radiology for cardiac chamber dilatation.
- Assess regional LV wall motion abnormalities that indicate ischemia and significant CAD.
- An approximate assessment of pulmonary artery pressure and pulmonary hypertension is extremely useful.
- Valvular abnormalities: reasonably accurate assessment of the severity of mitral regurgitation and obstructive lesions can be ascertained by continuous wave Doppler (*see* Chapter 11).
- Exclude cardiac tamponade.
- Assess pericardial effusion and pericardial calcification; diastolic dysfunction abnormalities.
- Assess left ventricular hypertrophy (LVH), left atrial enlargement, and right ventricular hypertrophy (RVH).
- The diagnosis of hypertrophic, dilated, or restrictive cardiomyopathy.
- For the diagnosis of congenital heart disease.
- Diagnosis of left atrial myxomas.
- Diastolic dysfunction assess after known normal systolic function (EF > 55%), and no regurgitant valvular disease.

Assess For Underlying Causes of HF

A complete cure may be a rare reward if a surgically correctable lesion is uncovered:

- Left atrial myxoma.
- Significant mitral regurgitation: may be missed because of the presence of a poorly audible murmur owing to low CO, thick chest wall, or chronic obstructive pulmonary disease (COPD).
- Atrial septal defect (ASD).
- Atrioventricular (AV) fistula.
- Constrictive pericarditis.
- Cardiac tamponade: may simulate HF and must be excluded because usual HF medications, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or nitrates can cause marked hemodynamic deterioration in patients with tamponade.
- Pulmonary edema or HF is not a complete diagnosis. The basic cause must be stated as part of the diagnosis and an associated precipitant must be defined, if present.

Approximately 60% of adult patients with HF have severe LV dysfunction secondary to IHD. Dilated cardiomyopathy accounts for approximately 15%, valvular heart disease 10%, and hypertensive heart disease is associated in more than 15%.

It is necessary to make a systematic search for the following basic causes of heart disease.

MYOCARDIAL DAMAGE

- CAD and its complications.
- Myocarditis (*see* Chapter 13).
- Cardiomyopathy (*see* Chapter 14).
- Ventricular overload.
- Pressure overload.
- Systemic hypertension.
- Coarctation of the aorta.
- Aortic stenosis.
- Pulmonary hypertension.
- Volume overload.
- Mitral regurgitation.
- Aortic regurgitation.
- VSD.
- ASD.
- Patent ductus arteriosus.

RESTRICTION AND OBSTRUCTION TO VENTRICULAR FILLING

- RV infarction.
- Constrictive pericarditis.
- Cardiac tamponade (although not truly HF).
- Restrictive cardiomyopathies (*see* Chapter 14).
- Specific heart muscle diseases (*see* Chapter 14).
- Hypertensive, hypertrophic “cardiomyopathy” of the elderly.
- Mitral stenosis and atrial myxoma.

OTHERS

- Cor pulmonale, thyrotoxicosis, high output failure: AV fistula, peripartum cardiomyopathy, and beriberi.

Search for Precipitating Factors

More than 50% of patients present with an acute exacerbation of chronic, underlying, LV dysfunction. In most of these patients, an acute precipitating factor can be identified:

- Reduction or discontinuation of medications, salt binge, increased physical and mental stress.
- Increased cardiac work: increasing hypertension (systemic or pulmonary), arrhythmias, pulmonary embolism, infections, increased activities, thyrotoxicosis, and physical and emotional stress.
- Progression or complications of the underlying disease: acute MI, LV aneurysm, valvular heart disease with progression of stenosis or regurgitation.
- Several drugs may precipitate HF: cocaine, alcohol, NSAIDs, coxibs, β -blockers, corticosteroids, disopyramide, procainamide, propafenone and other antiarrhythmics, verapamil, diltiazem, nifedipine or other dihydropyridine calcium antagonists, adriamycin, daunorubicin, mithramycin. Excessive alcohol intake can significantly decrease LV contractility.

PATHOPHYSIOLOGIC IMPLICATIONS

In most patients with HF, CO is reduced owing to poor LV systolic function. However, LV systolic function may be relatively normal in some patients with valvular regurgitant lesions, hypertensive heart disease, and restrictive cardiomyopathy, in which diastolic dysfunction plays a major role in causing HF (Fig. 5.1.).

HF is a syndrome identified by well-defined symptoms, signs, and/or hemodynamic findings caused by an abnormality of cardiac function that results in a relative decrease in CO and compensatory renal and neurohormonal adjustments (Fig. 5.1.). Improvement in CO causes a favorable alteration of the compensatory responses of HF, including the neurohormonal response.

- CO is the product of stroke volume and heart rate. Stroke volume is modulated by preload, myocardial contractility, and afterload.

Preload

Preload is the extent of fiber stretch during diastole and is clinically represented by the end-diastolic volume. The LV end-diastolic or filling pressure is closely related, although in a nonlinear fashion to end-diastolic volume, and is an indication of LV preload. In the absence of obstruction to blood flow through the pulmonary veins and into the ventricle, the LV end-diastolic pressure is in turn reflected by the PCWP or pulmonary artery end-diastolic pressure.

Decrease Preload and Diastolic Dysfunction

The affected ventricle may contract well if adequately filled but may relax poorly, resulting in a diastolic dysfunction that is more prominent than systolic dysfunction. Diastolic dysfunction is an important mechanism that produces HF. An increase in ventricular diastolic stiffness impedes diastolic stretch and causes failure to adequately fill the ventricle. Conditions that alter ventricular compliance, causing diastolic dysfunction, a decrease in preload, and, thus, a decrease in CO, include:

- MI (although systolic dysfunction is the main abnormality).
- Cardiac tamponade.

- Constrictive pericarditis.
- Hypertensive heart disease.
- Restrictive cardiomyopathy.
- Dilated cardiomyopathy.
- Specific heart muscle disease (e.g., amyloid).
- The aging heart.
- Hypertensive, hypertrophic “cardiomyopathy” of the elderly.

Age and some cardiac diseases appear to cause changes in the cross-linking of intercellular connective tissue. Alteration in myocardial collagen occurs with hypertensive and CAD.

Approximately 20% of patients with HF have mainly diastolic dysfunction with relatively preserved EF greater than 50%. Only small studies that have unsound methodology have addressed the question; the incidence of pure diastolic dysfunction as a cause of HF with preserved systolic function. Over 60% of patients with HF have systolic dysfunction and in about 20%, both systolic and diastolic dysfunction are at work. Many investigators claim that diastolic dysfunction is responsible for greater than 33% of HF cases, but allowance must be made for errors in EF measurement, and concomitant valve disease particularly mitral regurgitation that increases EF assessment and the common finding of AF in these patients with HF and preserved EF.

In patients with predominant diastolic dysfunction, the heart size and EF are often normal. (Use EF > 55% as normal, not 45%, and in the absence of regurgitation.) The heart fills less and empties less, and the percent ejected may be relatively normal, but the stroke and cardiac index are decreased.

Because a decrease in preload exists in the above conditions, the use of preload-reducing agents is relatively contraindicated. Hemodynamic and clinical deterioration may ensue with the use of diuretics, nitrates, ACE inhibitors (if the dosage is high), nitroprusside, or prazosin.

Afterload

Afterload is represented by LV wall end-systolic stress, which must be overcome to allow ejection of blood from the ventricle. An increase in afterload signifies an increase in myocardial oxygen demand. Afterload is determined by

- The radius of the ventricle (A).
- LV end-systolic pressure (B).
- Arteriolar resistance or impedance (C).

Afterload is highly dependent on A and B. In turn, B is dependent on cardiac index and C. A decrease in systolic vascular resistance or a fall in blood pressure (BP) is not identical with a decrease in afterload. Also, a decrease in systemic vascular resistance is not synonymous with a decrease in arterial BP, as a compensatory increase in CO occurs to maintain BP. The peripheral systolic pressure may be maintained because of colliding reflected pressure waves, despite a fall in central systolic blood pressure (SBP).

Conditions causing an increase in afterload include:

- Aortic stenosis.
- Pulmonary stenosis.
- Coarctation.
- Hypertension.

- All causes of HF, because of activation of the renin angiotensin and sympathoadrenal system.

LV dysfunction and HF owing to systolic dysfunction improve with therapy directed at:

- A decrease in afterload, which improves ventricular emptying at a lowered demand for oxygen.
- A judicious decrease in preload to decrease symptoms caused by pulmonary congestion but without bringing about an unwanted fall in CO or a marked stimulation of the renin angiotensin system.

Myocardial Contractility

A decrease in myocardial contractility or systolic dysfunction is commonly caused by CAD, especially in patients with large areas of infarction. Rarely, dilated cardiomyopathy and myocarditis are implicated, and with late-stage volume overload owing to valvular regurgitant lesions, myocardial damage occurs, culminating in pump failure.

Compensatory Adjustments in HF

The body responds to the abnormality of cardiac function and a relative decrease in cardiac output by bringing several homeostatic mechanisms into action (Fig. 5.1.). This situation is similar to the body's reaction to severe bleeding over several hours, but the results are, of course, less than completely appropriate in HF.

- The activation of the sympathetic system causes an increase in heart rate, force, and velocity of myocardial contraction to increase stroke volume and CO. An increase in systemic vascular resistance occurs to maintain BP. The body's homeostatic response (indicated in Fig. 5.1.) is appropriate, but often not sufficient, to compensate for the decrease in cardiac index and increased filling pressures. It is, in fact, counterproductive in some ways. Also, sympathetic stimulation causes sodium and water retention and an increase in venous tone to increase filling pressure that enhances preload, provided that there is no restriction to ventricular filling.
- The renin angiotensin system is stimulated. Patients with mild HF show little or no evidence of stimulation of the renin angiotensin system. Stimulation of the system is observed in response to treatment with diuretics and is seen in untreated patients with more severe degrees of heart failure. The secretion of renin causes angiotensin I to be converted by ACE to the vasoconstrictor angiotensin II. This action occurs in the circulation and in the tissues.

Angiotensin II supports systemic BP and cerebral, renal, and coronary perfusion through:

- Arteriolar vasoconstriction and an increase in systemic vascular resistance.
- Stimulation of central and peripheral effects of the sympathetic system.
- Marked resorption of sodium and water in the proximal nephron.
- Enhanced aldosterone secretion, which brings about sodium and water retention in the renal tubules, distal to the macula densa. Because the distal tubules only handle about 2% of the nephron's sodium load, this latter contribution is small compared with proximal sodium resorption, but is a final tuning of sodium balance.
- Stimulating thirst and vasopressin release, thereby increasing total body water.

Renal blood flow is preserved by selective vasoconstriction of postglomerular efferent arterioles. The adjustments, however, made to maintain BP and cerebral, coronary, and

renal perfusion cause a marked increase in afterload, which unnecessarily increases cardiac work and myocardial oxygen demand. Thus, HF may worsen.

Renal Response to HF

It must be reemphasized that the renal homeostatic mechanisms are similar to those for HF, with a decrease in CO, and for severe bleeding, which lowers BP. The design of nature appears to protect SBP to maintain adequate cerebral and renal perfusion in situations, such as hemorrhage, where this reaction is productive. Sodium and water retention occurs in the proximal tubule. The sensors that activate this response in HF are undetermined. Sensors are possibly linked to baroreceptors in the heart and to aortic arch and low-pressure sensors in the ventricle and atria, as well as at the level of the nephron and macula densa. Failure of the neurohumoral response and renal adjustment would result in a fall in BP and deprivation of cerebral, coronary, and renal perfusion.

The compensatory neurohumoral response thus increases afterload to some extent to maintain adequate systemic BP. The intense sodium and water retention and the increase in venous tone bring about an increase in filling pressure ([Fig. 5.1.](#)) in an attempt to increase myocardial fiber stretch during diastole, that is, an increase in preload.

NONSPECIFIC THERAPY

Bed rest is necessary for patients with New York Heart Association (NYHA) class IV or acute HF requiring admission to the hospital. Most patients are able to walk to the bathroom, with assistance, but some may require a bedside commode for the first 24 hours. It is important to quickly ambulate to avoid deep vein thrombosis and pulmonary embolism.

Subcutaneous low molecular-weight heparin (LMWH) is advisable until the patient is mobilized. This is an effective strategy to prevent thromboembolism and is especially indicated in patients at high-risk.

In patients ill enough to be admitted to the hospital and suspected of having hypoxemia because of a history of orthopnea, paroxysmal nocturnal dyspnea, and symptoms of pulmonary congestion or when hypoxemia is proven by arterial blood gas analysis, oxygen is given for 12–24 hours. Arterial blood gas analysis is not necessary in most patients with HF. Oxygen, 2–3 L/minute, by nasal prongs is usually adequate. When deterioration occurs despite appropriate therapy and in patients with chronic lung disease and HF, arterial blood gas analysis is necessary. In the latter situation, oxygen is given using a controlled low-flow oxygen system, such as a Venturi mask, commencing with 28% oxygen for a few hours with repeat blood gas analysis. If there is no increase in PaCO₂ and the PaO₂ content is satisfactory, a switch can be made to nasal prongs for patient comfort.

Overweight patients with HF benefit from weight reduction. The physician or nurse should advise the patient regarding a weight-reduction diet. Occasionally, the assurances of a weight-loss clinic are rewarding.

The physician must have a basic understanding of salt intake to confidently advise the patient. All patients with HF must be given relevant information on the importance of sodium restriction; a formal diet sheet or dietary consultation is not usually required. Diet sheets are not practical. Booklets prepared by the American Heart Association (AHA) and other organizations should be made available to the patient. Patients must recognize that salt added to meals at the table is only a minor part of the daily salt consumption and

that increased salt in the diet can precipitate heart failure and an expensive admission to hospital. The body requires about 500 mg sodium daily. The average daily intake of salt (sodium chloride) ranges from 8000–12000 mg daily, the sodium content of which is approximately 40% (i.e., 3000–5000 mg). One teaspoon of table salt contains 5000 mg sodium chloride and 2000 mg sodium. Most patients with heart failure can be managed satisfactorily on a diet containing less than 5000 mg sodium chloride and 2000 mg sodium. A 1-g-sodium diet requires the use of a diet sheet and a strict salt intake; this is extremely difficult to follow and is not advisable, except in patients with refractory HF. Instructions to the patient should include the following: No salt should be added in cooking or at the table. The patient should be aware of the sodium content of various foods. [Table 8.1](#) lists a few commonly used foods and their sodium content to indicate the marked differences, for example, 1 teaspoonful of garlic salt contains 2000 mg sodium, garlic powder contains 2 mg sodium, and a large dill pickle contains about 1900 mg sodium. Foods that are not salty to taste may have a high salt content. Fast foods, such as one hamburger or one portion of fried chicken, contain 1000 mg sodium. Canned soups must be avoided, because they usually contain 500–1000 mg sodium per 250 mL. A simple aid in controlling sodium intake is checking product labels. If the salt content is greater than 500 mg or if the word “sodium” is listed among the first four ingredients, then it is a high-sodium product and should be avoided. If the patient cannot avoid the use of canned foods, tuna, salmon, vegetables, and similar products, they should be rinsed under running water and the liquid should be drained. Some high-sodium foods not listed in [Table 8.1](#) include onion salt, celery salt, seasoned salts, soy sauce, salted crackers, rye rolls, salted popcorn, pretzels, waffles, hot dogs, salted pork, TV dinners, sardines, smoked fish, and all smoked meats. Patients are usually motivated by the advice that watching the diet carefully will assist in using fewer pills and may prevent admission to hospital.

WHICH DRUG OR DRUG COMBINATION TO CHOOSE

In clinical practice, an appropriate drug combination for patients with HF caused by ventricular systolic dysfunction requires consideration of the patient’s functional class and EF.

It is no longer acceptable to speak in terms of which drug is considered first-line therapy for HF. The four agents—diuretics, ACE inhibitors, β -blockers and digoxin—are complimentary. Diuretics or digoxin have not been shown to improve survival, but significantly prevent recurrence of HF and hospitalizations. ACE inhibitors, angiotensin-receptor blockers (ARB), and β -blockers have been shown to improve survival in patients treated with digoxin and diuretics. Diuretics are a necessary part of symptomatic therapy and are more effective than ACE inhibitors in preventing hospitalizations or in shortening hospital stay.

It is appropriate to use the NYHA functional class because several major clinical trials have incorporated this parameter in study design. Also, most physicians are conversant with the use of this clinical classification. Objective measurements or metabolic classifications relate well to this functional classification, albeit, not exactly. Indeed, the clinical classification provides a guide to prognosis that is reflected by clinical trials and can be used to compare trial results. Consequently, the following discussion is centered on studies using patients assigned according to NYHA classification and EF. Studies that have a mixture of class II to IV patients clearly distort scientific evaluation.

NYHA Functional Class

- Class I: Asymptomatic on ordinary physical activity associated with maximal oxygen consumption (VO_2) greater than 20 mL/kg/minute.
- Class II: Symptomatic on ordinary physical activity with maximum VO_2 of 16–20 mL/kg/minute.
- Class III: Symptomatic on less than ordinary physical activity with maximum VO_2 of 10–15 mL/kg/minute.
- Class IV: Symptomatic at rest or on any activity with maximum VO_2 of less than 10 mL/kg/minute.

Drug Therapy, NYHA Class IV HF/EF Less Than 30%

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) studied only NYHA class IV HF patients. In 253 randomized patients, the 6-month mortality rate was 44% in patients treated with diuretics and a digoxin combination and 26% in patients given enalapril in addition ($p < 0.002$). Forty-two percent of the group treated with added ACE inhibitors showed an improvement in functional class, compared with 22% in the control group ($p = 0.001$). A significant reduction in mortality attributable to ACE inhibitor therapy was observed mainly for the first 6 months of therapy.

The CONSENSUS trial had too few patients in the placebo group between 6 months and 2 years to allow firm conclusions to be made regarding the beneficial effects of ACE inhibitors beyond 1 year in patients with class IV HF.

In a study by Fonarow et al. in 117 class IV patients enrolled for transplantation, sudden cardiac death occurred in only three captopril-treated patients, compared with 17 of 60 hydralazine-treated patients ($p = 0.01$). At 8 ± 7 months follow-up, the actuarial 1-year survival rate was 81% and 51% in the captopril-treated and hydralazine-treated patients, respectively ($p = 0.05$). Patients in both groups received diuretics, digoxin, and isosorbide dinitrate. It must be emphasized, however, that eight patients in the captopril group and 16 in the hydralazine group received a type 1 antiarrhythmic agent, which could have increased the sudden death rate in the hydralazine group. There were other defects in methodology in this study.

After the acute phase is stabilized for patients who are in compensated class IV, and for those sufficiently improved to classify as class III, maintenance medications must include:

- Loop diuretic, usually furosemide 60 to 120 mg daily.
- ACE inhibitor at a dose equivalent to enalapril 20 to 40 mg or lisinopril 20 to 40 mg.
- β -Blocker if no contraindication: carvedilol or metoprolol.
- Digoxin to maintain a low level of the drug; low dose is strongly advisable in women (0.7 to 1 ng/dL except that a larger dose 0.25 mg daily is often required if AF is present). In this setting, even in elderly patients with a normal serum creatinine a larger dose may be required to maintain a ventricular rate less than 100 beats/minute (BPM), particularly if the dose of a β -blocking drug is limited by intractable HF (decompensated class IV HF).
- Eplerenone 25 mg titrated to 50 mg is strongly recommended; if the drug is not available or cost is of concern, use spironolactone 25–37.5 mg daily and warn the patient to report breast tenderness.

Drug Therapy, NYHA Class II and III HF

- Clinical trials have confirmed that monotherapy with diuretics, digoxin, or ACE inhibitors is not satisfactory for NYHA class II patients in sinus rhythm who have an EF less than 35% and who have had overt HF.

- There are sufficient data that strongly indicate that these patients should be managed with triple therapy: diuretic, digoxin, and ACE inhibitor. It is this combination that has been shown in both the studies of left ventricular dysfunction (SOLVD) and the Veterans Administration Cooperative Vasodilator Heart Failure Trial (VHeFT) II to improve survival, and in the SOLVD, significant reduction in hospitalization for recurrent HF was achieved.
- In patients in whom ACE inhibitors are contraindicated an ARB is administered.
- When exercise performance is not improved by diuretic, digoxin, and ACE inhibitor therapy, the dose of ACE inhibitor should be reduced and intermittent oral nitrate should be administered. Caution is necessary with this combination because a sharp decrease in preload may result in syncope or presyncope. If the SBP remains above 130 mmHg and presyncope is not observed, the dose of ACE inhibitor should be increased to be in the range 37.5–100 mg daily for captopril, 20–30 mg daily for enalapril, and 20–40 mg lisinopril.

Class II patients require treatment with furosemide dosage approximately 20–60 mg daily, ACE inhibitor, and digoxin. If hypertension or IHD is associated, a β -blocker is added.

Class III patients with EF less than 40% require the addition of a β -blocker and eplerenone similar to class IV patients.

RANDOMIZED CLINICAL TRIALS

Randomized clinical trials (RCTs) that support or are relevant to the above recommendations are discussed briefly. These studies include the following:

- CONSENSUS.
- SOLVD: The beneficial results of ACE inhibitors for the treatment of HF in patients with LV dysfunction following acute MI has been well accepted (*see Table 5.1.*).
- VHeFT-I and VHeFT-II.
- Captopril-Digoxin Multicenter Research Group (MRG) Study.
- The Hy-C Trial: effect of direct vasodilation with hydralazine versus ACE inhibition with captopril on mortality in advanced HF was discussed under NYHA class IV HF.
- The Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) study.
- EPHEBUS
- COPERNICUS
- MERIT-HF
- CHARM
- VALIANT

CONSENSUS study showed that triple therapy is life-saving in class IV patients, as discussed earlier.

SOLVD studied HF patients who had EFs equal to or less than 35%; 1284 patients who had overt HF with EF less than 35% were randomly selected to receive 2.5–20 mg of enalapril plus conventional therapy, and 1285 patients were randomly assigned to a control group to receive conventional therapy. Approximately 30% of the study group were in NYHA class III. At an average follow-up of 41 months in class III patients, there were 182 (47%) deaths in the enalapril group and 201 (51%) deaths in the placebo group. Total mortality in the enalapril group was 452 (35%) versus 510 (39.7%) in the placebo arm, a 16% risk reduction ($p = 0.0036$). Enalapril therapy resulted in a significant decrease

in hospitalizations; overall, 971 patients in the placebo group required hospitalization versus 683 patients in the enalapril group. Mortality reduction was highest at 24 months of therapy, when the risk reduction was 23% (Table 5.1.). Although class III VHeFT-II randomized 804 class II and III HF patients who had EF less than 0.45 (mean at baseline 0.29). Enalapril (10–20 mg) added to standard therapy diuretic–digoxin was compared with isosorbide dinitrate (ISDN)-hydralazine added to standard therapy. Enalapril therapy resulted, at the end of 2-year follow-up, in a significant reduction in mortality (18% vs 25% [$p = 0.016$] in the ISDN-hydralazine arm). The incidence of sudden death was reduced mainly in class II patients. Only ISDN-hydralazine therapy, however, resulted in an increased body oxygen consumption at peak exercise. The venodilator effect of ISDN is more potent than enalapril at the dose administered. This may have contributed to the ISDN-hydralazine improvement in exercise performance because hydralazine therapy alone does not improve this parameter.

The RADIANCE study included 178 patients with chronic HF class II and III, EF less than 35% and sinus rhythm who were clinically stable on diuretics, ACE inhibitors, and digoxin. Most patients (70%) were in NYHA class II. In those patients withdrawn from digoxin for 3 months, there was a sixfold worsening of HF. More than 28% of patients taking a placebo, ACE inhibitor, and diuretic deteriorated, compared with 6% receiving digoxin. The dose of digoxin in the RADIANCE study was 0.38 mg daily and serum digoxin levels ranged 0.9–2.0 ng/mL.

The captopril-digoxin MRG study compared the effects of placebo, digoxin, or captopril added to maintenance diuretic therapy at 6 months in 300 class II and III HF patients, LV EF mean of 25%. Digoxin significantly increased EF, compared with diuretics alone or a diuretic–captopril combination. Exercise time was increased and recurrence of HF was reduced by digoxin. The study had several drawbacks, however. In particular, the two groups were not identical: the number of class III patients was twice as high in the digoxin–diuretic group as in the captopril–diuretic group. Also, 30 patients who deteriorated when digoxin was withdrawn were not randomized, thereby biasing the study against digoxin.

Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS): Following the beneficial effects of spironolactone (Aldactone) shown in the well-conducted Randomized Aldactone Evaluation Study (RALES) study eplerenone, a selective aldosterone blocker, added to optimal medical therapy was tested in patients with acute MI and HF, EF <35% significantly reduced mortality and morbidity. The trial randomized 6600 patients. A 25-mg dose of eplerenone was titrated up to 50 mg daily. Gynecomastia was not observed, but significant hyperkalemia occurred in 5.5% and 3.9% of patients in the treated and placebo group respectively ($p = 0.002$). Caution: this useful replacement for spironolactone should not be used in patients with serum creatinine greater than 1.1 mg/dL, or in type 2 diabetics with altered glomerular filtration rates because hyperkalemia may be precipitated. Most important, the serum creatinine does not reflect creatinine clearance, particularly, in the elderly who are most often treated for HF.

The Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS) studied 2289 patients with severe HF, EF 16–24% but free from overt fluid retention or recent treatment with IV diuretics or positive inotropic drugs showed: a highly significant 35% reduction in all-cause mortality with carvedilol. There were 190 placebo deaths and 130 with carvedilol, a 35% decrease in the risk of death, $p = 0.0014$. The dose of carvedilol was 6.25 mg, with slow increase to 25 mg twice daily. ACE inhibitor, digoxin, and spironolactone were used in 97, 66, and 20% of patients, respectively.

The Metoprolol CR Randomized Intervention Trial (MERIT)-HF showed significant benefit for metoprolol in patients with class II and III HF, mean EF 0.28. ACE inhibitor or ARB and digoxin were used in 95% and 64 % of patients respectively. Cardiac Insufficiency Bisoprolol Study (CIBIS)-II trial studied bisoprolol in patients with class III and IV HF and noted a significant beneficial effect.

Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) Program of Trials

The CHARM-Alternative trial ($n = 2028$) examined the effects of the ARB, candesartan in patients with reduced LV EF $< 40\%$ who were ACE-inhibitor intolerant. Treated patients received candesartan 4–8 mg titrated to 32 mg once daily plus the treatment given to placebo patients: standard antifailure therapy that included diuretics, β -blocker, digoxin and spironolactone (85, 54, 45, and 24% respectively).

Results of this study showed that after 33.7 months patients given candesartan were 23% less likely to experience cardiovascular death or heart failure hospitalization compared with those who received placebo (40% vs 33%, $p = 0.0004$).

CHARM-Added, examined the effect of candesartan on patients who were already on an ACE inhibitor, the majority of whom were on a β -blocker.

Results: After 41 months of follow-up, patients receiving candesartan were 15% less likely to experience the primary endpoint compared with those given placebo (42% vs 37.9, $p = 0.0011$). This result occurred regardless of whether or not patients were on a β -blocker and independent of the dose of ACE inhibitor used. Addition of candesartan to an ACE inhibitor plus a β -blocker leads to further clinically important reduction in cardiovascular death and hospitalization for HF. When the combination of candesartan and an ACE inhibitor is administered, monitoring of serum creatinine and for hyperkalemia is necessary, and particularly if spironolactone or eplerenone are used in the HF treatment regimen.

Candesartan demonstrates long-lasting blockade of the AT1 receptor and appears to have the most potent blood pressure-lowering effects in the ARB class. There is no unfavorable interaction when candesartan and a β -blocker are used in combination as opposed to that shown for the valsartan- β -blocker combination. Most important, ARBs, like β -blockers, have subtle and important clinical differences.

Valsartan in Acute MI Trial (VALIANT): this large randomized trial of 14,703 patients with acute MI and radiologic or clinical evidence of HF showed that the ARB valsartan is as beneficial as captopril in reducing mortality. Eighty mg of valsartan titrated to target a dose of 160 mg was compared with 50 mg of captopril three times daily. After a median follow-up of 24.7 months, old-cause mortality was similar in patients treated with valsartan or captopril or the combination in addition to standard therapy. Estimates of death at 1 year were 12.5% for valsartan-treated patients, 12.3% for patients administered combination therapy versus 13.3% for those receiving captopril monotherapy. Rates of recurrent MI and hospitalization for HF were similar.

DIURETICS

The main action of diuretics is to decrease preload. Although this effect does not improve cardiac output or survival, diuretics are essential agents for the management of HF because they ameliorate bothersome congestive symptoms and prevent costly hospitalization. They can be used alone as first-line therapy in patients with NYHA class II HF

with mild systolic dysfunction, especially when HF is precipitated by a reversible cause, such as pneumonia, infection, arrhythmia, or NSAIDs. If the EF is more than 40%, these patients are often controlled with a diuretic only and maintained without ACE inhibitor or digoxin therapy. Further reasons for the choice of diuretics in various grades of HF are given under the previous section regarding which drugs to choose.

FUROSEMIDE

This well-known loop diuretic is the most commonly used agent in the management of HF. The drug has been given to millions of patients worldwide since 1964. It is easy to use orally and intravenously and, other than electrolyte imbalance, has negligible side effects. Indications include the following:

- IV furosemide is indicated for pulmonary edema, severe HF, or failure associated with hypertensive emergencies. In these situations, urgent symptomatic relief is necessary and poor oral absorption is of concern.
- Oral therapy is indicated for NYHA class II HF patients in combination with digoxin and/or ACE inhibitors in selected patients.
- NYHA class III and IV HF patients, in combination with digoxin and ACE inhibitors in virtually all patients.
- HF owing to acute MI (IV or oral).

Contraindications include:

- Cardiac tamponade.
- RV infarction.
- Hepatic failure.
- Uncorrected hypokalemia (less than 3.5 mEq [mmol/L]).
- Hypersensitivity to furosemide, sulfonamides, or sulfur-containing compounds.
- Women of childbearing potential, except in life-threatening situations in which IV furosemide is necessary. Furosemide has caused fetal abnormalities in animal studies and is not recommended for maintenance therapy.

The action of furosemide inhibits sodium and chloride reabsorption from the ascending limb of the loop of Henle, with weak effects in the proximal tubule, which excretes the drug. Intravenous furosemide has a venodilator effect; thus, preload reduction occurs within minutes and relief of symptoms may occur before the appearance of increased urinary flow. The potency of action allows furosemide and other loop diuretics to retain beneficial effects in renal failure patients with glomerular filtration rates as low as 10 mL/minute. Thus, in patients with elevated serum creatinine, greater than 2.3 mg/dL (203 μ mol/L), furosemide retains activity, whereas thiazides, except metolazone, are not effective.

Furosemide is supplied in tablets of 20, 40, 80, and 500 mg. Ampules are available in 10 mg/mL, 20 mg/2 mL, 40 mg/4 mL, and 250 mg/25 mL. The dosage is 20–80 mg given as a slow IV bolus, 20 mg/minute. Caution: if renal failure is present, do not exceed 4 mg/minute to prevent ototoxicity. For acute HF of mild-to-moderate severity in patients with acute MI, small doses are advisable (20–40 mg IV repeated 1–2 hours after careful assessment) so as not to decrease CO or produce further stimulation of the renin angiotensin system.

For acute HF in patients with known NYHA class III or IV, large doses may be required, depending on the extent of pulmonary congestion and the degree of respiratory distress (80 mg IV followed by 80–120 mg in 2–4 hours and repeated every 8 or 12 hours as needed; maintenance 40–120 mg once daily). Larger dosages may be required if

urinary output is poor or if chronic renal failure is present (with serum creatinine greater than 2.3 mg/dL, 203 μ mol/L) or if severe pulmonary congestion with respiratory distress persists (with a JVP greater than 5 cm), having excluded cardiac tamponade or mimics of HF.

Maintenance dose should be given before 9 AM daily. Split doses are rarely needed at 7 AM and 3 PM. The afternoon dose should not be given later than 3 PM so as not to disturb the patient's sleep. It is preferable to give 160 mg once daily rather than 80 mg twice daily because the tubules may be resistant to the 80 mg dose in patients with severe HF. Doses beyond 160 mg are preferably divided into 120 mg in the morning and 80 mg in the early afternoon. Patients with class IV ventricles and graded as NYHA class IV require at least 120 mg in 1 day, alternating with 80 mg the next day to achieve adequate control. Patients who require a dose of furosemide greater than 40 mg daily to prevent pulmonary congestion and shortness of breath should be digitalized and an ACE inhibitor should be prescribed. Patients with class III and class IV NYHA HF require management with furosemide (average 80–120 mg daily), along with digoxin and combined ACE inhibitor therapy: Always maintain the serum potassium above 4 mEq (mmol)/L. Patients who require large doses of furosemide beyond 80 mg daily benefit from ACE inhibitor therapy, which normalizes serum potassium. When the combination is used, potassium supplements or potassium-sparing diuretics should not be given, except with carefully monitored serum potassium levels. Also, salt substitutes contain potassium and can cause hyperkalemia. Periodic measurements of serum potassium are advisable for all patients taking daily diuretics.

Adverse effects are hypokalemia, hypersensitivity in patients allergic to sulfur compounds, and, very rarely leukopenia, thrombocytopenia, precipitation of gout, hypocalcemia, and hypomagnesemia.

Drug interactions of cephalosporin or aminoglycoside antibiotics may show increased nephrotoxicity in patients with renal dysfunction when given large doses of loop diuretics. An increased reabsorption of lithium may occur, resulting in lithium toxicity; with chloral hydrate, hot flushes, sweating, and tachycardia may occur; NSAIDs antagonize the action of loop diuretics, as well as thiazides; the effect of tubocurarine is increased.

BUMETANIDE

This is supplied as 0.5-, 1-, and 5-mg tablets and as 2-, 4-, and 10-mL ampules (500 μ g/mL). The dosage is oral 0.5–1 mg daily, increase if needed to 2–5 mg daily. In patients with renal failure, 5 mg or more may be required. An IV dose of 1–2 mg is used, repeated in 30 minutes to 1 hour if needed.

The drug has similar actions to furosemide but is reported to cause less magnesium loss (1 mg bumetanide is equivalent to 40 mg furosemide). The drug is more nephrotoxic than furosemide, and its use should be avoided with cephalosporins and aminoglycosides.

TORSEMIDE

Torsemide appeared to be more beneficial than furosemide in preventing recurrence of HF in one study.

THIAZIDE DIURETICS

See Chapter 8 for products and dosage. Thiazide diuretics are advisable mainly in patients with NYHA class II HF. However, hypokalemia occurs in up to 20% of patients and as many as 33% with chlorthalidone. Also, hypomagnesemia often occurs and goes

undetected. Potassium-sparing diuretics retain potassium and magnesium and are useful in patients with mild heart failure (NYHA class II). The patient may benefit from a potassium-sparing diuretic given 3–4 days per week only.

MODURETIC (MODURET)

The formulation contains hydrochlorothiazide (50 mg) and amiloride (5 mg) available in the United States, the United Kingdom, and elsewhere. Moduret, which also contains 50 mg of hydrochlorothiazide and 5 mg of amiloride, is available in Canada. Moduret 25, hydrochlorothiazide (25 mg), and amiloride (2.5 mg) is available in the United Kingdom and Europe and the use of one tablet daily sufficiently conserves potassium and magnesium and allows for the use of a small dose of hydrochlorothiazide.

DYAZIDE

This drug is supplied as tablets of 25 mg of hydrochlorothiazide, 50 mg of triamterene. The dosage is one tablet daily. A larger dose is not advisable, because 50 mg of hydrochlorothiazide may cause hypokalemia, even in the presence of a small dose of triamterene. The drug is contraindicated in patients with renal calculi. Caution: potassium-sparing diuretics may cause serious hyperkalemia when used in conjunction with ACE inhibitors, potassium supplements, or salt substitutes. Patients with maturity-onset diabetes may develop hyporeninemic hypoaldosteronism, which causes hyperkalemia in patients with a normal serum creatinine. Potassium-sparing diuretics may increase this effect. Spironolactone may cause gynecomastia, and tumorigenicity in rats has been noted; although this finding may not apply to humans, care is needed with the use of this drug.

METOLAZONE

Metolazone is supplied as 2.5-, 5-, and 10-mg tablets. The prescribed dosage is 2.5–5 mg once daily, with a maximum of 10 mg (rarely indicated). This thiazide diuretic has a unique property of retaining effectiveness when other thiazides become ineffective with glomerular filtration rate less than 30 mL/minute. The combination of metolazone and furosemide is very useful in patients with refractory HF who fail to respond to large doses of furosemide or ethacrynic acid. In one reported study, in 15 of 17 patients with severe failure refractory to loop diuretics, digoxin, and ACE inhibitors, substantial improvement occurred, allowing discharge from the hospital. This potent combination is useful, but hypokalemia is often pronounced. Intermittent therapy (metolazone twice weekly) may help avoid this effect. In this situation, however, combination with an ACE inhibitor or potassium supplement often becomes necessary.

ACETAZOLAMIDE (DIAMOX)

This is supplied as 250-mg tablets. The dosage is 250 mg three times daily for 4 days once or twice monthly. This carbonic anhydrase inhibitor has a weak diuretic action, which dissipates in 3 or 4 days. The drug is useful in the management of hypochloremic metabolic alkalosis in the presence of a normal serum potassium. The patient with refractory HF on furosemide and potassium-sparing diuretics or ACE inhibitors may show a typical electrolyte abnormality: potassium 4–5 mEq (mmol)/L, chlorides less than 92 mEq (mmol)/L, carbon dioxide greater than 30 mEq (mmol)/L. The addition of acetazolamide to furosemide and ACE inhibitors 3 days weekly maintains diuresis with correction of normokalemic, hypochloremic, metabolic alkalosis. The drug is contraindicated in patients with severe cirrhosis, metabolic acidosis, renal failure, and renal calculi.

SPECIAL DIURETICS: SPIRONOLACTONE, EPLERENONE (INSPRA)

Spirolactone Aldactone; Supplied: 25-mg tablets. Dosage: Initial 12.5 mg, Assess K^+ within 1 Week, if less than 5.0 mEq/L, 25 mg Once Daily, Maximum 37.5 mg.

The RALES study assessed the effects of spironolactone in patients with severe HF, EF less than 35% treated with loop diuretics ACE inhibitor, and digoxin. The risk of death was 30% lower among patients in the spironolactone group ($p < 0.001$). Hospitalizations for recurrent HF was significantly reduced. Unfortunately the dosages of ACE inhibitor used were smaller than those used in modern clinical practice: mean dose of 63 mg of captopril, 15 mg of enalapril, and 14.3 mg of lisinopril. Spironolactone causes gynecomastia and other androgenic effects, and a new agent, eplerenone has proven effective in the RCT EPHESUS.

- The dose of spironolactone used in the RALES trial was 25 mg. Serum K^+ levels were 0.3mEq/L (significantly) higher in the treated group.
- *Spirolactone and eplerone are more than just diuretics that enhance the effectiveness of loop diuretics; these agents favorably modify myocardial collagen and the development of fibrosis.*
- Caution is required in patients with abnormal renal function and in type 1 diabetes with hyporeninemic hypoaldosteronism because severe hyperkalemia may ensue. If the serum K^+ reaches 5.2 mEq/L the dose of ACE inhibitor should be decreased and loop diuretic increased, before reducing the 25-mg dose of spironolactone. Serum K^+ should be done 1–2 weeks after starting treatment and monthly. If the K^+ reaches 5.3–5.4 mEq/L, spironolactone or eplerenone should be discontinued. The maximum dose, 50 mg, should be used only in patients with normal renal function and absence of type 2 diabetes. *In patients over 75 years of age, a normal serum creatinine does not indicate normal function.*
- The drug was developed by replacing the 17α -thiacetyl group of spironolactone with a carbomethoxy group. Thus, the drug has a greater selectivity for the mineralo-corticoid receptor than for steroid receptors, and is devoid of sex hormonal effects of spironolactone.
- Eplerenone is a selective aldosterone blocker, and added to optimal medical therapy was tested in patients with acute MI and HF, EF less than 35%; the drug significantly reduced mortality and morbidity (*see clinical trials: EPHESUS discussed earlier*). Dosage 25 mg daily for a few weeks then increase to 50 mg provided that the serum potassium remains less than 5 mmol/L.

ACE INHIBITORS AND ARBS

When HF occurs, sensors in the heart, the aortic arch, and arterioles of the juxtaglomerular apparatus actuate a host of neurohormonal responses that are necessary for the perfusion of vital tissues, especially of the brain, heart, and kidneys. These responses, initiated by sympathoadrenal activation and enhanced by stimulation of the renin angiotensin system, result in marked vasoconstriction, which increases systemic vascular resistance to maintain central BP. Unfortunately, an increase in systemic vascular resistance increases afterload and contractile myocyte energy costs.

Components of the renin angiotensin system are not confined only to the kidney, adrenals, liver, and blood but are also present in several tissues, including the heart, brain, pituitary gland, uterus, gut, salivary glands, ovaries, testes, and placenta. Angiotensin is synthesized in many tissues, as well as in the circulation. Thus, some ACE inhibitors have a tissue site of action, the importance of which requires further evaluation. ACE inhibitors

Table 5.1.
Clinical Trials of ACE Inhibitors in Heart Failure or Left Ventricular Systolic Dysfunction

<i>Trial</i>	<i>NYHA Class or EF</i>	<i>Results</i>
Consensus	IV	36% ↓ in mortality at 6 months
Consensus II	Early acute MI	Trial stopped: IV enalapril hypotension
SOLVD (treatment arm)	II-III, or CHF present EF < 35% 65% of patients > 4 weeks post-MI	16% ↓ mortality risk at 41 months
SOLVD (prevention arm)	I, II EF <35%	8% non-significant ↓ in mortality
VHeFT II	No CHF I, II EF >45%	37% ↓ in incidence of CHF and hospitalization 18% mortality vs hydralazine nitrate 25% $p = 0.016$, 2-year follow-up
SAVE	EF 31% (average), post-MI 3–16 day; <10% of patients screened had EF < 40%	17% ↓ in risk of death at 2 years, 25% ↓ hospitalization
AIRE	CHF post-MI, 3–10 days	27% ↓ in mortality risk
SMILE	CHF large anterior MI, 9–20 hours post	34% ↓ in risk of CHF and mortality at 35 days, mainly in patients with prior infarction

↓, decrease.

prevent formation of the vasoconstrictor angiotensin II and, at the appropriate dose, provide sufficient vasodilatation to bring about reduction in afterload and decrease in systolic ventricular workload. Plasma renin levels are usually normal in patients with HF in NYHA class I, and ACE inhibitors may not be logical therapy in most patients at this stage except if the EF is less than 40%. When these patients are treated, with diuretics, plasma renin increases and ACE inhibitors produce salutary effects. In these situations, not all patients benefit from ACE inhibitor therapy; it is estimated that approximately 50% of patients may benefit in LV function, but survival data are not available except in postinfarction patients with HF (*see* Survival and Ventricular Enlargement [SAVE] and Acute Infarction Ramipril Efficacy [AIRE] studies, [Table 5.1.](#)).

ACE inhibitors decrease LVH, an important cause of diastolic dysfunction that predisposes to the late phase of the failing ventricle. In the last phase of HF, both systolic and diastolic dysfunction prevail. ACE inhibitors play a major role as second-line drug therapy for HF (NYHA class II, III, and IV). Although these agents have greatly improved the management and survival of HF patients, they do not replace loop diuretics as first-line agents and are used in combination with a diuretic, and often with added β -blocker and digoxin therapy (*see* earlier discussion of drug therapy; NYHA class II, III, and IV HF).

ACTION OF ACE INHIBITORS AND ARBs

Renin release causes the conversion of angiotensinogen to angiotensin I. ACE inhibitors are competitive inhibitors of ACE and thus prevent the conversion of angiotensin I to angiotensin II. Two main types of angiotensin II receptors exist: AT1 and AT2. The major actions of angiotensin II are mediated through the AT1 receptor. ARBs specifically block the angiotensin II receptor AT1, and this causes a blockade of the renin–angiotensin–aldosterone system. The blockade is, however not complete so that aldosterone inhibitors have a role.

Blockade of angiotensin II brings about:

- Marked arteriolar vasodilatation, and thus, a fall in systemic vascular resistance, afterload, and BP.
- Decreased sympathetic activity and reduced release of norepinephrine. This action causes further vasodilatation. It also prevents the usual increase in heart rate observed with vasodilators of the non-ACE-inhibitor category.
- Decreased aldosterone secretion, and thus, enhancement of sodium excretion with potassium retention.
- Suppression of vasopressin release with free water loss, resulting in some protection from severe dilutional hyponatremia.
- Accumulation of bradykinin, causing a release of vasodilator prostaglandins and further vasodilatation.
- Angiotensin II blockade causes an increased flux of superoxide that improves nitric oxide (NO) bioactivity.
- AT₂ receptors are not blocked by ARBs. The AT₂ receptors appear to play a physiologic cardioprotective role with the production of bradykinin, NO, prostaglandins in the kidney, inhibition of cell growth, promotion of cell differentiation and apoptosis.
- The ARBs have now been shown to have the beneficial effects of ACE inhibitors in reducing mortality and morbidity in patients with HF. *See* earlier discussion of CHARM and VALIANT randomized trials.
- The major advantage of ARBs is that they do not cause cough, a bothersome complication of ACE inhibitor. Most importantly, the rare but serious occurrence of angioedema with ACE inhibitors has been noted only rarely with ARBs.
- *Most agree that ACE inhibitors should be first choice.* If cough occurs, an ARB can be substituted. The combination of ACE and ARB may provide modest benefits, but it is advisable to try the addition of eplerenone before adding an ARB.

CAPTOPRIL (CAPOTEN)

The dosage is a 6.25-mg test dose (a 3-mg test dose is administered to the elderly or patients considered at risk for hypotension). Observation is necessary for the next 2–4 hours. If there is no occurrence of hypotension or presyncope, give 6.25 mg twice daily for the first day, increase to 12.5 mg twice daily then over days to weeks, increase to maintenance dose of 37.5–50 mg two or three times daily.

ENALAPRIL (VASOTEC; VASOTEC OR INNOVACE, UK)

The dosage is 2.5 mg orally; the patient should then be observed for 2–6 hours. If there is no hypotension, give 2.5 mg twice daily for a few days and increase slowly over days or weeks to 10–30 mg daily. An initial effect of hypotension is usually observed within 1–2 hours after administration of captopril and within 2.5–5 hours with enalapril. Withdrawal of diuretics on initiation of therapy does not always prevent marked hypotension or syncope, so close observation is required for 12 hours.

LISINAPRIL (PRINIVIL, ZESTRIL; ZESTRIL, CARNEE, UK)

For HF, a dosage of 2.5 mg daily under close hospital supervision is used; usual maintenance is 10–30 mg daily for HF. The Assessment of Treatment With Lisinopril and Survival (ATLAS) trial indicated that a 30–35 mg dose is more effective than doses < 10 mg in preventing hospitalization; a 14% decrease was observed. The 30–35 mg dose did not cause a reduction in total mortality.

CILIZAPRIL (INHIBACE)

Dosage: Initial 0.5 mg, maintenance 1–2.5 mg once daily; maximum 5 mg daily.

RAMIPRIL (ALTACE; TRITACE)

An initial dose of 2.5 mg daily is used, which is increased over 1–2 weeks; maintenance dose is 5–10 mg daily.

CAUTIONS FOR ALL ACE INHIBITORS AND ARBs

Stenosis in a solitary kidney or in patients with suspected tight renal artery stenosis because acute renal failure may be precipitated. Renal circulation in patients with severe bilateral renal artery stenosis or stenosis in a solitary kidney is critically dependent on high levels of angiotensin II. In these situations, ACE inhibitors markedly decrease renal blood flow and may worsen renal failure, causing a sharp elevation in serum creatinine. Thus, patients showing a sharp rise in serum creatinine during the first few days after commencement of ACE inhibitors are at high risk for occlusion of the renal circulation, and the drug should be discontinued immediately.

Maturity-onset diabetic patients with hyporeninemic, hypoaldosteronism may develop significant hyperkalemia. ACE inhibitors and ARBs should not be given concurrently with potassium supplements, salt substitutes, or potassium-sparing diuretics (eplerenone, spironolactone) unless measurements of serum potassium levels indicate that it is safe to do so.

Contraindications include the following:

- Significant aortic stenosis.
- Renal artery stenosis of a solitary kidney or severe bilateral renal artery stenosis.
- Severe carotid artery stenosis.
- HF associated with unstable angina restrictive cardiomyopathy or hypertrophic cardiomyopathy with obstruction.
- Severe anemia.
- During pregnancy and breastfeeding.
- Relative contraindications include concomitant use of immunosuppressives, because neutropenia and agranulocytosis observed with ACE inhibitors appear to occur more often in these patients.
- Interactions may occur with acebutolol, allopurinol, hydralazine, and NSAIDs, including aspirin, pindolol, procainamide, tocainide, and immunosuppressives.

Adverse effects include the following:

- Hypotension.
- Hyperkalemia in patients with renal failure and/or type 2 diabetes.
- With ACE/Inhibitors but not ARBs: Cough in about 20% of patients; may be prostaglandin-mediated angioedema of the face, mouth, tongue, or larynx may occur in approximately 0.2% of patients and can be fatal.
- Pruritus and severe rash in about 2% of patients.
- Loss of taste (apparently specific for sulfhydryl compounds) in approximately 5% of patients.
- Mouth ulcers, neurologic dysfunction, and proteinuria in about 1% of patients with preexisting renal disease.
- Neutropenia and agranulocytosis (rare, occur mainly in patients with serious intercurrent illness, particularly immunological disturbances, altered immune response, or collagen vascular disease).

- Occasionally, wheeze, myalgia, muscle cramps, hair loss, impotence, decreased libido, hepatitis, pemphigus, or the occurrence of antinuclear antibodies.

Caution: Increased hepatic enzymes and the rare occurrence of severe hepatic dysfunction with a few fatalities have been reported in association with marketed ARBs. Neutropenia has been reported in 1.9% of valsartan-treated patients.

Angiotensin Receptor Blockers

CANDESARTAN (ATACAND, AMIAS)

Dosage: Initial dose 4–8 mg, then 8–16 mg, max 32 mg once daily. The drug was shown in the CHARM study to be as effective as ACE inhibitors in reducing mortality and hospitalization in patients with HF. Elimination is 60% renal, 40 % bile.

EPROSARTAN (TEVETEN)

Dosage: 300–4000 mg twice daily or 300–800 mg once daily.

IRBESARTAN (AVAPRO, APROVEL)

Dosage: Initial 75 mg then 150–300 mg once daily. Elimination is 80% renal, 20% bile.

LOSARTAN (COZAAR)

Dosage: Initial 25 mg then 50–100 mg once daily. Elimination is renal and hepatic.

TELMISARTAN (MICARDIS)

Dosage: 20–80 mg once daily; elimination is greater than 95% in the feces.

VALSARTAN (DIOVAN)

Dosage: Initial dose 40 mg in the elderly, then 80–160 mg once daily, maximum 320 mg. The drug has been shown to be as effective as ACE inhibitors in the management of patients with HF and in patients with LV dysfunction and HF following acute MI (*see* VALIANT study).

β-BLOCKERS

The failing human heart is exposed to increase adrenergic activity. Because chronic β₁-adrenergic receptor signaling is a dominant cardiotoxic pathway in the failing heart, effective β₁-adrenergic receptor blockade is especially important.

- Chronic adrenergic activation has adverse effects on the natural course of heart muscle disease that can be ameliorated by β-blocker administration.
- It is often forgotten that β-blockers significantly reduce renin secretion from the juxtaglomerular cells of the kidney that causes a decrease in angiotensin levels and aldosterone production is reduced; this action adds to their life-saving potential.

The well-known beneficial anti-ischemic and antiarrhythmic properties, as well as salutary effects on progressive LV remodeling prevents functional cardiac deterioration and causes improved survival.

Recent large randomized trials have exalted them to be on par with ACE inhibitors for the treatment of HF. A similar benefit of 2.3% absolute reduction in risk has been observed in recent β-blocker trials as was observed in SAVE, AIRE, and Trandolapril Cardiac Evaluation (TRACE) trial with ACE inhibitors; thus about 43 patients need to be treated to save one life.

β -Adrenergic blocking drugs play a major role in the management of most patients with heart failure. Post-MI patients with EF less than 40% treated with propranolol in the β -Blocker Heart Attack study carried out in the early 1980s showed an improved survival. Nearly two decades later the COPERNICUS and CAPRICORN studies proved without doubt that carvedilol is an excellent β -blocker that significantly reduces mortality and hospitalization for recurrent HF; the drug can be given with beneficial effects to the majority of patients with varying degrees of HF from NYHA class I through class III and in patients with compensated class IV, including HF following acute MI. Similar salutary results have been shown for sustained release metoprolol, Toprol XL, and bisoprolol.

- *Note: β -blockers are not all alike; they have subtle and important differences (see Chapters 1, p. 55). Also, Wollert et al. make the point that “not all β -blockers are created equal.” Nebivolol is a vasodilatory β -blocker.*
- The highly beneficial survival and reduced recurrence of HF observed with carvedilol, metoprolol CR/XL, and bisoprolol are in deep contrast to the increased mortality observed with xamoterol and the disappointing results recently reported for bucindolol. Results have been poor with pindolol and oxprenolol, agents with β -agonist activity.
- Results have never been substantiated for atenolol a most popular and over prescribed β -blocker with fortunately an excellent adverse risk profile that perpetuates its use in practice; atenolol is a favorite of organizers for hypertension trials.

Carvedilol (Coreg; Eucardic)

Carvedilol is a nonselective β -blocker with β_1 , β_2 , and mild α_1 blocking activity. The drug has vasodilating and significant antioxidant properties. *This is a unique β -blocker with other several beneficial properties.*

Packer et al., in a large randomized trial in patients with NYHA class II and III HF, showed an improvement in exercise time and pulmonary artery wedge pressure; the trial was stopped because of improved survival. Carvedilol therapy caused a 27% reduction in hospitalizations and a 65% reduction in mortality. In COPERNICUS the drug caused a 35% decrease in the risk of death $p = 0.0014$ (see earlier discussion in this chapter and in Chapter 1 for CAPRICORN studies).

Supplied: 3.125, 6.25, 12.5, 25 mg tablet. Dosage: 3.125-mg test dose, then every 12 hours with food for 1–2 weeks; increase to 6.25 mg twice daily; double the dose every week to the highest level tolerated to a maximum 25 mg twice daily. The dose is titrated depending on BP, heart rate and patients tolerance. If dizziness or hypotension occurs, decrease diuretic dose if pulmonary congestion is not causing bothersome shortness of breath; most importantly, the dose of ACE inhibitor should be reduced if needed to allow the necessary continuance of the β -blocker.

Khand et al. have shown that the combination of carvedilol and digoxin appears generally superior to either carvedilol or digoxin alone in the management of AF in patients with HF.

Metoprolol CR/XL (Toprol XL)

It must be emphasized that it is a pure β -adrenergic blockade that actuates the major salutary effects in HF. Metoprolol was shown in several small trials during the 1980s to be beneficial for the management of HF.

MERIT-HF: the metoprolol extended release randomized intervention trial in HF involved patients with class II and III HF mean EF 28%. Metoprolol administration resulted in risk reduction of 33% for total mortality or worsening HF and a significant reduction in sudden death ($p = 0.0002$) and total mortality ($p = 0.0062$).

Dosage: 25 mg once daily increased to 50 then 100–150 mg as tolerated. Adverse effect profile is excellent for this β -blocker.

The Carvedilol or Metoprolol European Trial (COMET) randomized 3029 patients with moderate or severe HF treated with metoprolol tartrate 50 mg twice daily or carvedilol 25 mg twice daily. Carvedilol was more effective than metoprolol tartrate. The trialists, however, have not taken into account that the extended release formulation of metoprolol CR/XL, which was used in MERIT-HF may have beneficial advantages over immediate release metoprolol tartrate.

Bisoprolol (Zebeta, Monacor)

CIBIS-II HF trial in patients with *mainly* class III and IV HF showed improved survival. The trial involved 2647 patients. Study patients received ACE inhibitor diuretic and digoxin for two months prior to bisoprolol or placebo. Dosage: bisoprolol initial dose 1.5 mg daily was titrated at weekly intervals in 1.5-mg increments for 4 weeks up to a maximum 10 mg daily. Bisoprolol administration reduced all cause mortality by 32% ($p = 0.00005$) and sudden death by 45% ($p = 0.0001$). Significant reduction in hospitalization occurred in the treated group.

DIGOXIN (LANOXIN)

After more than 200 years of use and controversies in the 1970s regarding its efficacy and role, digoxin has been fully restored as the only oral positive inotropic agent available that significantly improves symptoms, signs, EF, and other hemodynamic parameters in patients with all grades of acute, recurrent, or chronic HF with salutary effects occurring when combined with a diuretic and/or ACE inhibitor. *Digoxin favorably alters the neurohormonal imbalance that contributes to HF.*

Clinicians who have used this drug for over 30 years in patients with ventricular systolic dysfunction (NYHA class III and IV HF) recognize the effectiveness of the drug when combined with diuretics and have documented the recurrence of HF when digoxin is discontinued. An S_3 or summation gallop, present during several days of treatment with diuretics and ACE inhibitors disappears within days of digitalization. Also, objective hemodynamic data are now available that clearly indicate the drug's salutary effects.

Clinical Studies

Digoxin has been shown to further improve cardiac function in patients with abnormal hemodynamic variables when stabilized on diuretics and ACE inhibitors. In 11 patients in sinus rhythm with severe HF stabilized on digoxin and vasodilators, IV digoxin increased EF by 38% from 0.21 to 0.29, the mean cardiac index rose 30%, and pulmonary wedge pressure decreased by 29%. Six patients who had persistent hemodynamic evidence of LV dysfunction when given appropriate doses of diuretic and vasodilators responded dramatically to digoxin. Patients with the most severe LV dysfunction showed the most hemodynamic improvement.

The RADIANCE study (Randomized Assessment of Digoxin and Inhibitors of Angiotension Converting Enzyme) randomized 178 clinically stable patients in sinus rhythm with class II HF treated with diuretics ACE inhibitor and digoxin. In patients withdrawn from digoxin for 3 months there was a sixfold worsening of HF; patients taking placebo had a higher incidence of deterioration and worsening of HF (23 vs 4 patients).

Gheorghiade et al. completed a double-blind placebo-controlled study of patients with documented HF and no reversible etiology: 16 of the 46 patients deteriorated between 4 days and 3 weeks after discontinuing digoxin.

Digitalis investigation group: digoxin was assigned to 3397 patients, and 3403 received a diuretic and ACE inhibitor; the mean EF was $28\% \pm 9\%$. After 37 months follow-up fewer digoxin patients were hospitalized for HF 26.8% versus 34.7% ($p \leq 0.001$). *The risk associated with the combined outcome of death from HF of hospitalization for HF was significantly lower in the digoxin group than the placebo arm: 1041 versus 1291 patients ($p < 0.01$).*

Most importantly, this reduction was similar to those observed in Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Function (SOLVD) attributed to the benefits of ACE inhibitor. In addition, the study included only 2% patients with class IV HF and 30% class III. It is well-known that digoxin is expected to benefit class IV patients and this subset was not represented in the study. In patients with EF less than 25%, death or hospitalization from HF occurred in 428 of 1127 digoxin treated versus 556 of 1127 in the placebo group, a 23% reduction similar to SAVE and SOLVD. A 22% decrease in death and hospitalization was observed in patients with a cardiothoracic ratio > 0.55 and this reduction in mortality is expected in patients with echocardiographic left ventricular dilation.

Digoxin is strongly indicated in the majority of patients in sinus rhythm with class III and IV HF and in all patients with HF and AF.

CONTRAINDICATIONS

- Patients with sick sinus syndrome or AV block of all grades.

ACTION

- Inotropic effect: digoxin increases the force and velocity of myocardial contraction and improves the EF. It combines with and partially inhibits the sodium pump, the enzyme sodium, and potassium-activated ATPase (Na K ATPase) located in the sarcolemmal membrane of the myocardial cell and increases the availability of intracellular calcium to contractile elements resulting in enhanced myocardial contractility. This effect causes the Frank-Starling function curve to move upward and to the left.
- Increase of vagal activity and a modest decrease in sympathetic activity slow conduction velocity in the AV node. This action is important in slowing the ventricular response in atrial fibrillation and the termination of paroxysmal supraventricular tachycardia. Mild slowing of the sinus rate occurs owing to the mild decrease in sympathetic activity.
- Increase in phase 4 diastolic depolarization increases the activity of ectopic pacemakers.

About 66% of the oral tablet dose is absorbed mainly in the stomach and the upper small bowel. After absorption, the drug is widely distributed, but binding to skeletal muscle is particularly important because a low muscle mass in the elderly calls for a smaller loading dose. The mean serum half-life is approximately 36 hours. It is advisable to wait until equilibrium is reached to obtain a digoxin level that represents myocardial concentration.

Dosing at bedtime is advisable so that an assay during a morning assignment would be appropriate and allows the physician time to reach the patient before the evening.

Bioavailability is reduced as a result of decreased absorption owing to malabsorption syndrome; colestipol, cholestyramine, metamucil (or similar agents); antacids, metoclopramide, phenytoin, phenobarbital.

Digoxin levels are increased by quinidine, some calcium antagonists, amiodarone and ficticiously by spironolactone that interferes with the method. Excretion is by the kidneys. Thus, undetected or unnoticed renal insufficiency is the most common cause of digoxin toxicity.

After 1-mg oral dosing, peak onset of action occurs in 1–6 hours, with serum levels usually exceeding 1 µg/mL; maximum inotropic action is observed in 4–6 hours.

DOSAGE

- Orally: 0.5 mg immediately, 0.25 mg twice daily on second day then 0.25 mg daily at bedtime for 1–2 days then an appropriate maintenance dose depending on age, renal function, and presence or absence of conditions that increase sensitivity to the drug (Table 5.2.). If such conditions are present, halve the initial dose 0.25 mg daily for 2 days then followed by maintenance dosage at bedtime depending on age.
- IV therapy for AF with a fast ventricular response greater than 150 per minute in patients with HF only where urgent digitalization is required in the absence of definite daily digoxin use in the previous week and the exclusion of sick sinus syndrome: 0.5 mg IV slowly over 10 minutes with ECG monitoring, reassess before a second dose of 0.25 mg. A further 0.25 mg may be required in 6 hours, then maintenance. Alternatively, it is recommended (in the UK) that digoxin is given by IV infusion (0.75–1 mg in 50 mL) over 2 or more hours when rapid control of AF is required in patients with HF and AF.
- Importantly, Khand et al. have shown that the combination of carvedilol and digoxin appears generally superior to either carvedilol or digoxin alone in the management of AF in patients with HF.
- Suggested maintenance dosage with normal serum creatinine.
- Age less than 70 (0.25 mg daily, preferably at bedtime).
- Age greater than 70 (0.125 mg at bedtime).

For the treatment of HF in women, a lower dose is recommended to keep the digoxin level less than 1.0 ng/mL. Beneficial effects are observed at levels 0.5 to 0.9 ng/mL. Mortality has been shown to increase with higher levels independent of toxicity.

Saif et al. indicate that higher digoxin levels appear to be associated with increased mortality and suggest that the effectiveness of digoxin therapy in women with HF and EF less than 45% may be optimized in the range of 0.5–0.8 ng/mL; *levels are thus maintained 0.5–1 ng/mL in both men and women.*

DIGITALIS TOXICITY

A decrease in the incidence of definite or serious digitalis intoxication has materialized because lower levels of serum digoxin have been shown to be beneficial and thus, lower doses are being used. In addition, physician awareness of the pharmacokinetics: absorption, binding, distribution, and excretion of the drug has improved. In particular, the hazard in patients with renal dysfunction, including elderly patients with unsuspected impaired renal function with a normal serum creatinine, has sharply curtailed digitalis toxicity. A lean skeletal mass, especially in the elderly, carries two important connotations:

Table 5.2.
Conditions in Which There is an Increased Sensitivity to Digoxin
and Conservative Dosing is Recommended

1. Elderly patients (age >70) or renal dysfunction	7. Hypomagnesemia
2. Hypokalemia	8. Hypercalcemia
3. Hyperkalemia	9. Hypocalcemia
4. Hypoxemia	10. Myocarditis
5. Acidosis	11. Low skeletal mass
6. Acute MI	12. Hypothyroidism
	13. Amyloidosis

From Khan M. Gabriel: Cardiac Drug Therapy. 6th ed. Philadelphia: WB Saunders, 2003, with permission from Elsevier.

- Digoxin binds to skeletal muscle; thus, in individuals with lean skeletal mass, more digoxin is available in the serum for myocardial binding. Therefore, there is a higher probability of toxicity in patients with lean skeletal mass, especially if renal dysfunction inhibits elimination of the drug.
- Low skeletal muscle mass in the elderly reflects a lowered serum creatinine that leads the physician to believe that renal function is normal, when creatinine clearance may be reduced by 50% or more.

Reduction of the maintenance dose in patients with conditions that increase sensitivity to digoxin (Table 5.2.) and the appropriate use of digoxin serum assay are important precautionary measures. Conditions that increase or decrease the bioavailability of digoxin, particularly drugs that cause interactions, are listed in Table 5.3.

Symptoms and signs of digitalis intoxication include:

- Gastrointestinal: nausea, anorexia, vomiting, diarrhea, abdominal pain, weight loss.
- Central nervous system: visual hallucinations; blue, green, or yellow vision. blurring of vision and scotomas; dizziness, headaches, restlessness, insomnia, and, rarely, mental confusion and psychosis.
- Cardiac: there is a spectrum from occurrence of arrhythmia in digoxin free state, through latent arrhythmia precipitated by digoxin, to arrhythmia directly secondary to digoxin. First-, second- or third-degree AV block; sinus pause greater than 2 seconds; paroxysmal atrial tachycardia with block (ventricular rate is often 90–120/minute; the P-waves may be buried in the T-waves); accelerated junctional rhythm; ventricular premature beats, bigeminal or multifocal; ventricular tachycardia (VT); and, rarely, ventricular fibrillation (VF). Table 5.4. shows the incidence of arrhythmias caused by digoxin toxicity. In addition, deterioration in HF may be due to digoxin toxicity.

SERUM DIGOXIN ASSAY

No single serum digoxin concentration drawn at the appropriate time interval, more than 6 hours after oral dosing, can indicate toxicity reliably, but the likelihood increases progressively through the range 1.5–3 ng/mL or $\mu\text{g/L}$ (1.2–3.5 nmol/L). Concentrations above 2 ng/mL must be avoided. Levels less than 1.2 ng/mL drawn at the appropriate time are rarely associated with toxicity, except in patients with myocardial sensitivity as listed in Table 5.2. Reviews indicate that digoxin-intoxicated patients had a mean serum digoxin

Table 5.3.
Digoxin Interactions

Increase serum levels
Quinidine displaces digoxin at binding sites, decreases renal elimination quinine, chloroquine
Verapamil, diltiazem, nifedipine, felodipine, amiodarone, flecainide, propafenone, prazosin, ACE inhibitors may decrease renal elimination
NSAIDs decrease renal elimination
Lomotil, propantholol decrease intestinal motility
Erythromycin, tetracycline eliminate eubacterium lentum
Spironolactone, digoxin assay falsely elevated
Electrophysiologic interactions may occur with amiodarone, diltiazem, verapamil
Decrease serum levels or bioavailability
Antacids, metoclopramide, cholestyramine, colestipol
Metamucil, neomycin, phenytoin, phenobarbital, salicylazosulfapyridine

Table 5.4.
Major Manifestations of Digoxin Toxicity

	Percent
Non-life-threatening arrhythmias	
Multifocal VPCs	30
1° AV Block	15
Supraventricular tachycardia	25
Life-threatening arrhythmias	
3° AV Block	25
2° AV Block	15
Ventricular tachycardia	20
Ventricular fibrillation	10
Asystole	8
Noncardiac	
Nausea and vomiting	50
Hyperkalemia ^a	25

^aOwing to renal failure and/or inhibition of the sodium pump.

level of 3.3 ng/mL. The current recommendation to use low doses, particularly in women, will improve outcomes and drastically curtail toxicity. *Importantly, the drug should be taken in the evening or at bedtime; this allows for accurate digoxin assays.*

MANAGEMENT OF DIGITALIS TOXICITY

- Discontinue digoxin.
- Replace potassium if hypokalemia is present. Hold diuretics until serum potassium is in the normal range.
- Clarify conditions that increase sensitivity to digoxin (Table 5.2.). Toxicity is likely to be present if suggestive symptoms are manifest and if there is a precipitating cause for renal impairment or if the serum creatinine is elevated.
- Assess digoxin level.

- Assess ECG signs: digitalis effect does not mean toxicity (*see* bradyarrhythmias and tachyarrhythmias as listed under Adverse Effects).

Drug therapy is indicated for arrhythmias causing a threat to life, hemodynamic deterioration, or worsening of HF. The incidence of digoxin-induced arrhythmias is given in [Table 5.4](#).

BRADYARRHYTHMIAS

Sinus bradycardia, second-degree AV block, and sinoatrial dysfunction are managed with atropine 0.4, 0.5, or 0.6 mg IV every 5 minutes to maximum of 2 mg. Failure to respond to atropine or the presence of third-degree AV block is an indication for digoxin-specific Fab antibody fragments or temporary pacing.

Caution: potassium chloride is relatively contraindicated with bradyarrhythmias as potassium and digoxin synergistically depress conduction and may precipitate a higher degree of AV block. If the serum potassium is in the range of 3.0–3.8 mEq(mmol)/L, potassium should be given IV at a rate less than 10 mEq(mmol)/hr; a serum potassium less than 3 mEq/L may require an infusion rate greater than 10 mEq(mmol)/hr and continuous monitoring of the cardiac rhythm is necessary.

TACHYARRHYTHMIAS

VT, multifocal ventricular premature beats, or atrial tachycardia with block in the presence of hypokalemia.

Potassium chloride. IV 40–60 mEq(mmol) in 1 L of 0.9% or half normal saline over 4 hours, except in patients with renal insufficiency or in patients with AV block, because an increase in potassium may increase the degree of AV block. Potassium chloride is diluted in 5% dextrose in water if HF is present. Magnesium sulfate may be of value in suppressing some cases of ventricular tachycardia by blocking calcium currents that are involved in after depolarization.

Lidocaine is considered the drug of choice for control of ventricular arrhythmias secondary to digoxin intoxication after the correction of hypokalemia. The short duration of action and relatively low toxicity and availability are major advantages. Lidocaine is not indicated for junctional tachycardias because it is not effective.

The dosage is 1.5 mg/kg, 50–100 mg with a simultaneous infusion of 1–3 mg/minute and repeat bolus in 10 minutes. If lidocaine fails to control the tachyarrhythmia and if there are no contraindications, a β -blocking drug may be tried cautiously (*see* Table 4.8 for IV dosage).

Phenytoin is no longer recommended in the treatment of digitalis toxicity, and the use of β -blockers has dwindled with the availability of digoxin-specific Fab antibody fragments.

DIGOXIN IMMUNE FAB (DIGIBIND)

The treatment of digitalis toxicity has been revolutionized since the value of digoxin immune Fab was proven effective. The entire body load of digoxin is bound and pulled back into the bloodstream; thus, the serum digoxin level may be high but the bound level is inactive. Fab fragments are excreted by the kidneys with a half-life of 16–20 hours.

In a multicenter study of 150 patients with potentially life-threatening digitalis toxicity, administration of digoxin immune Fab (Digibind) caused amelioration of symptoms and signs of digitalis toxicity in 80%; 10% of patients were unimproved and 10% showed no response. A treatment response was observed within 20 minutes, and by 60 minutes, more than 75% of patients showed a salutary response. Most patients showed complete

recovery within 4 hours. Approximately 3% of patients had a recurrence of toxicity within 7 days, especially patients receiving less than the estimated adequate dose of Fab. Patients with severe digoxin toxicity may have hyperkalemia owing to renal failure and/or inhibition of the sodium pump.

Hyperkalemia or an increasing serum potassium level is an important predictor; clinical trials suggest that as potassium levels rise, mortality rates increase. Digitalis-induced hyperkalemia suggests imminent cardiac arrest; in these patients, mortality is high and Fab fragments are urgently advised. If serum potassium exceeds 5 mEq/L (mmol/L) in the presence of signs and symptoms of digitalis intoxication, digoxin-immune Fab is immediately indicated.

In patients with life-threatening tachyarrhythmias or bradyarrhythmias the latter unresponsive to atropine the early use of Digibind is strongly recommended; pacing can be avoided.

Digibind is supplied as a powder for preparation of infusion in vials of 38 mg. The dosage is four to six vials, 152–228 mg infused over 30 minutes. If after 1 hour there is no response and digoxin toxicity is proven, the dose is repeated (*see* product monograph).

Adverse effects are uncommon. Hypokalemia is observed in less than 5% of patients and allergic reaction occurs in less than 1%. Caution: rapid onset of hypokalemia should be anticipated after reversal of toxicity by Digibind. IV potassium chloride should be given as needed to avoid hypokalemia.

CARDIAC RESYNCHRONIZATION THERAPY

HF patients with intraventricular conduction delay have been shown in randomized studies to obtain a decrease in hospitalization for recurrent HF and to have an improved lifestyle when synchrony of contraction has been improved by biventricular pacing.

Mortality reduction has been modest, however, and only small numbers of patients have been studied in randomized trials.

Most important the comparisons were not done with the placebo arm being administered optimal medical therapy using a combination of diuretics, ACE inhibitors, β -blockers, digoxin, and eplerenone.

Cardiac resynchronization therapy (CRT) endeavors to restore contractile coordination in hearts burdened by wall motion dyssynchrony caused by intraventricular conduction delay. This is accomplished by stimulating areas of the ventricle with the most delayed mechanical activation so that it can contract in synchrony with the earlier stimulated region.

The left ventricle is stimulated at or near the time of RV depolarization. Synchronized activation of the ventricles improves cardiac function and appears to diminish myocardial oxygen consumption. The best clinical benefits response are observed in patients with QRS duration exceeding 150 ms. Auricchio et al. have shown that LV pacing significantly improves exercise tolerance and quality of life in patients with chronic HF, LV systolic dysfunction, provided that the QRS interval is over 150 ms. The short QRS group (120–150 ms) studied did not improve in any endpoint with active pacing.

Criteria for resynchronization therapy modified from Saxon et al.:

- Recurrence of HF with hospitalization in the past 6–12 months in the absence of known precipitating factors and despite optimal therapy for HF, loop diuretics and spironolactone or eplerenone; ACE inhibitors or ARB (candesartan) β -blocker therapy (carvedilol or metoprolol CR/XL), and digoxin.
- EF less than 35%, NYHA Class III–IV.

- LV dilation.
- QRS duration greater than 130 ms and left bundle branch block and evidence of dyssynchrony on ECG but Auricchio et al. indicate that more than 150 ms is the cutoff if truly beneficial results are to be gained.
- Normal sinus node function.

Multicenter In Sync Randomized Clinical Evaluation Study

Four hundred fifty-three patients more than 90% with class III HF, EF less than 35%, QRS interval greater than 130 ms were randomized to a CRT group (228 patients) or to a control group (225 patients) for 6 months, while therapy for HF was maintained with diuretics, ACE inhibitors, and digoxin; only approximately 55% received a β -blocker and, unfortunately, spironolactone was not used. The primary end-points were NYHA class, quality-of-life, and the distance walked in 6 minutes.

As compared with the control group, patients assigned to CRT experienced an improvement in the distance walked in 6 minutes (+39 versus +10 m, $p = 0.005$), functional class ($p < 0.001$), quality of life (−18.0 versus −9.0 points, $p = 0.001$). Fewer patients in the treated group than control patients required hospitalization (18 patients 8 % versus 34 patients 15%) but these numbers are small and follow up was only 6 months.

Unfortunately, the procedure is not without risk. Implantation of the device was unsuccessful in 8% of patients and was complicated by refractory hypotension, bradycardia, or asystole in four patients (two of whom died) and by perforation of the coronary sinus requiring pericardiocentesis in two others. CRT requires the insertion of an additional pacing lead into the coronary sinus, to pace the ventricle; this procedure resulted in dissection or perforation of the coronary sinus or cardiac vein (~6%). Other complications included complete heart block, hemopericardium, and cardiac arrest (which together occurred in about 1.2% of patients). The LV lead became dislodged during long-term pacing in approximately 6%.

The Multisite Stimulation in Cardiomyopathy study randomized 58 patients class III, with QRS greater than or equal 150 ms. This small study showed a modest 23% improvement in 6 minute walk.

Other small studies show similar effects, but clear-cut mortality reduction is unproven and large randomized studies must compare optimal medical therapy in both class III and IV patients followed for more than 1 year to justify the considerable cost that exceeds \$20,000.

If right bundle branch block is excluded, less than 25% of HF patients have a QRS > 150 ms; thus CRT therapy in practice may be applicable to less than 15% of HF patients. In approximately 10% therapy is unsuccessful and serious adverse effects are expected in approximately 2%, with less serious adverse effects in approximately 6%. Importantly, in a significant few CRT may defer transplantation until a donor is obtained.

DIASTOLIC DYSFUNCTION

Age and cardiac disorders appear to cause changes in cross-linking of intercellular connective tissue. The heart fills less and empties less, and the % ejected may be relatively normal, but the stroke output and cardiac index are decreased; thus the renin–angiotensin–aldosterone system is stimulated. Systolic dysfunction impairs the ability of the left ventricle to relax and fill at low pressure. Thus, systolic dysfunction is a principal cause of diastolic dysfunction. It appears that blacks may be more susceptible than whites to diastolic HF.

Hallmarks of diastolic dysfunction are impaired relaxation and increased passive stiffness.

The left ventricle has passive compliance and becomes stiffer; these changes are caused mainly by diffuse fibrosis. In patients with focal scar or aneurysm after MI passive stiffness is increased. Similarly, amyloidosis and other infiltrative cardiomyopathies increase passive myocardial stiffness.

The American College of Cardiology (ACC)/AHA guidelines state that it is difficult to be precise about the diagnosis of diastolic HF, and “it is a disease of elderly women, most of whom have hypertension.” Yet the incidence of this imprecise condition is stated to be 20–40% of HF patients with preserved LV systolic function.

The diagnosis of definite diastolic HF is made if typical signs, symptoms and radiological features are present in the presence of normal systolic function within 3 days of the episode, in the absence of valvular disease and objective evidence of diastolic dysfunction obtained at catheterization or with problematic echocardiographic assessment of abnormal LV relaxation, filling, diastolic distensibility or stiffness.

The diagnosis of probable diastolic HF may be made by echocardiography using Vasan and Levy criteria. Zile et al. indicate from a study that it is possible to make the diagnosis of definite diastolic HF provided that there is echocardiographic evidence of mild LVH.

- Clinical and echocardiographic criteria are still imperfect, however. It must be reemphasized that the EF must be more than 55% done within 3 days of the episode, in the absence of mitral regurgitation, and must be obtained from radionuclide imaging in the absence of AF. It must be emphasized that an EF in the normal range may occur in patients with LV systolic dysfunction if mitral regurgitation is present; also, the radionuclide EF is inaccurate in the presence of AF.
- The author concurs with Maurer et al. and others who have used the term heart failure with normal ejection fraction (HFNEF) instead of diastolic heart failure mainly because the diastolic Doppler abnormalities seen in patients with HFNEF are chiefly the result of elevated LV filling pressure and not caused mainly by diastolic dysfunction.
- Maurer et al. emphasize that the finding of abnormal diastolic Doppler echocardiographic patterns should not lead to the conclusion that an intrinsic disorder of myocardial diastolic properties exists and is responsible for the heart failure state.

The European Cardiology Society, establishment of the diagnosis of DHF requires:

- the presence of symptoms and signs of HF with supporting chest X-ray findings.
- demonstration of an ejection >50% in the absence of mitral regurgitation.
- demonstration of diastolic dysfunction by Doppler echocardiography.

Diastolic dysfunction occurs in approximately 20% of patients with HF along with systolic dysfunction. The EF in patients with diastolic HF should be greater than 50% to qualify for this diagnosis. Thus, genuine diastolic HF in the absence of significant systolic dysfunction, mitral regurgitation and AF is not as common as experts contend. The true incidence of this condition is unknown and probably does not exceed 20% of HF hospitalizations. A recent report by Hogg et al. agrees with conclusions given above.

An elevated BNP in a patient with worsening shortness of breath or acute shortness of breath and normal systolic function (EF > 55%) in the absence of mitral regurgitation or atrial fibrillation infers diastolic dysfunction and diastolic HF.

Causes of diastolic dysfunction include:

- Systolic dysfunction is a principal cause of diastolic dysfunction.
- LVH.
- Hypertensive heart disease (systolic and diastolic HF).
- Chronic CAD.
- Diabetes.
- Myocardial fibrosis.
- Cardiomyopathy: hypertrophic and restrictive, amyloid heart disease, sarcoidosis, hemochromatosis, metabolic storage diseases, hypertensive hypertrophic cardiomyopathy of the elderly women age and heart particularly in women.
- Constrictive pericarditis, pericardial effusion, and cardiac tamponade.

Management of Diastolic HF

Drug therapy for diastolic HF must be individualized depending on the cause. Because a decrease in preload exists. The over zealous use of preload reducing agents, including, diuretics, ACE inhibitors and nitrates may cause hemodynamic and clinical deterioration. Usually dosages are 50–75% lower than used for systolic HF and diuretics may not be required except during the symptomatic congestive phase that may last a few weeks. These agents are contraindicated in pericardial diseases, and restrictive cardiomyopathy and relatively contraindicated in hypertrophic cardiomyopathy (HCM). In the absence of a congestive state, diuretics may worsen fatigue and effort dyspnea.

1. Prevention is crucial: aggressive drug therapy to control BP, but also aimed at preventing LVH; ACE inhibitors, β -blockers and diuretics prevent and cause regression. Calcium antagonists and α -blockers do not. Eplerenone has a role instead of loop diuretics.
2. Drug treatment of diastolic HF is governed by the underlying disease: hypertensive LVH and chronic CAD.
 - Diuretic at low dosage: approximately 50% lower than for systolic HF, e.g., 40 mg of furosemide daily for a few days then 20 mg daily during the congestive phase, then alternate day with added eplerenone 12.5–25 mg daily.
 - ACE inhibitor, also at low dosage, approximately 50% less than for systolic HF, can speed the rate of LV relaxation and improve diastolic function.
 - Low-dose β -blocker to decrease heart rate that allows a longer diastolic filling phase. β -blockers are necessary to favorably influence the underlying disease e.g., ongoing ischemia in CAD. Ischemia contributes to diastolic dysfunction. But β -blockers slow the rate of LV relaxation and may impair diastolic function.
4. Spironolactone or elprenolone can favorably modify myocardial collagen and the development of fibrosis and is considered essential therapy. A 12.5–25-mg dose is advisable.
5. Digoxin should be tried because more than 50% of patients with diastolic HF have underlying systolic dysfunction.
6. HCM, restrictive, infiltrative disease, constrictive pericarditis, amyloid and other diseases in the absence of hypertension and LVH are difficult to treat with drugs; hypotension and deterioration may be precipitated by diuretics, nitrates, and ACE inhibitors.

PULMONARY EDEMA

Cardiogenic causes include:

- Pulmonary edema, commonly accompanied by left-sided HF, which may result from or be precipitated by complications of IHD, AF with uncontrolled ventricular response,

other tachyarrhythmias, hypertension, mitral regurgitation or aortic valve disease, and dilated cardiomyopathy.

- Mitral stenosis and, rarely, left atrial myxoma.

Noncardiogenic causes include:

- Adult respiratory distress syndrome owing to pneumonias, severe trauma, toxins, allergens, smoke inhalation, gastric aspiration, hemorrhagic pancreatitis.
- Drugs, narcotic overdose, severe hypoalbuminemia, uremia, and neurogenic causes. Lymphagitic carcinomatosis may mimic LV failure.

Therapy for Cardiogenic Pulmonary Edema

- Oxygen must be given at high concentrations to maintain an adequate PaO₂.
- Furosemide (80–120 mg IV) usually produces an effect in 10 minutes because of the drug's venodilator action, which produces a reduction in preload followed in 30 minutes to 1 hour by diuresis that lasts for about 2 hours. If the response is not adequate, a further dose of 40–120 mg IV is given, provided that hypotension is not present. A higher dose is usually required if severe renal failure is present.
- Morphine remains an extremely useful drug to allay anxiety and relieve discomfort. Also, the drug causes pooling of blood in the periphery. *Morphine is advisable, provided that severe respiratory insufficiency or untreated severe hypothyroidism is absent.* A dosage of 3–5 mg IV at a rate of 1 mg/minute is used. Repeat as needed at 15- to 30-minute intervals to a total dose of 10–15 mg/hour.
- Treat underlying problems, such as severe hypertension: give captopril or nitroprusside (*see Nitroprusside Infusion Pump Chart, Table 8.11.*).
- Manage cardiac arrhythmias and administer digoxin to reduce the ventricular response in AF.
- Nitroglycerin: if the SBP is greater than 100 but less than 120 mmHg, give 0.3 mg sublingually; give 0.4 mg for SBP greater than 120 mmHg. The application of a transdermal preparation or patch formulation is useful after the sublingual dose. However, transdermal application produces variable absorption and must not be relied on within the first hour. Both sublingual and transdermal preparations should be avoided if the SBP is less than 100 mmHg. In severe cases, IV nitroglycerin is recommended (*see Infusion Pump Chart, Table 4.9.*).
- Nitroprusside is indicated if pulmonary edema is owing to severe hypertension or mechanical complications of acute MI (*see Infusion Pump Chart, Table 8.11.*, and Chapter 3).
- Aminophylline should not be used routinely. It has a role if bronchospasm and/or diaphragmatic fatigue are present. The drug increases the diuretic effect of furosemide and has mild anti-ischemic effects. The incidence of life-threatening arrhythmias caused by the judicious use of aminophylline has been exaggerated and has resulted in a decrease in the use of this agent, which has a role when the cardiac adverse effects of albuterol (salbutamol) or other β -agonists must be avoided. A dosage of 2–4 mg/kg IV is used over 20 minutes, and then an infusion 0.3–0.5 mg/kg/hour is used. The smaller dose is used in the elderly or in patients with hepatic dysfunction.
- Rotating venous tourniquets can be temporarily beneficial in patients with severe pulmonary edema unresponsive to standard therapy listed earlier. Tourniquets should be placed several inches distal to the groin and shoulders, and only three of the four tourniquets should be inflated at one time to approximately 10 mmHg below the diastolic pressure; one should be released every 15–20 minutes.
- Dobutamine is indicated if the above measures fail to control pulmonary edema in the presence of mild hypotension and severe left ventricular systolic dysfunction; dobutamine

is superior to amrinone IV (*see* Chapter 3). If respiratory failure complicates pulmonary edema, dopamine should be avoided because this agent may cause constriction of pulmonary veins, which results in an increase in pulmonary capillary hydrostatic pressure and lung fluid accumulation. The dosage used is 2.5–7.5 µg/kg/minute (*see* Infusion Pump Chart, Table 3.5.).

- Digoxin is required if atrial fibrillation or flutter with a rapid ventricular rate is present; slower rates (100–120/minute) may require slowing in patients with severe mitral stenosis and in this situation, a small dose of a β -blocking drug given judiciously may be lifesaving.
- Endotracheal intubation and mechanical ventilation may be required for patients with respiratory failure if PaO₂ cannot be maintained at or near 60 mmHg despite 100% O₂ at 20 L/minute or if there is progressive hypercapnia. Identify and treat precipitating factors, especially acute MI, arrhythmias, and infection.

BIBLIOGRAPHY

- Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *New Engl J Med* 2002;346:18 45–53.
- Abraham WT, Fisher WG, Smith AL, et al., MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–1853.
- The Acute Infarction Ramipril (AIRE) Study Investigators. Effects of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821.
- Adams KF, Gheorghiade M, Uretsky BF, et al. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002;39:946–953.
- Angeja BG, Grossman W. Evaluation and Management of Diastolic Heart Failure. *Circulation* 2003;107:659.
- Auricchio A, Stellbrink C, Butter C, et al., Pacing Therapies in Congestive Heart Failure II Study Group; Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003;42:2109–2116.
- Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–237.
- Bauersachs J, Heck M, Fraccarollo D, et al. additions of spironolactone to angiotensin converting enzyme inhibition in heart failure improves endothelial vasomotor dysfunction. *J Am Coll Cardiol* 2002;39: 351–358.
- Baughman KL. B-type natriuretic peptide—a window to the heart. *N Engl J Med* 2002;347:158–159.
- Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;344:1659–1667.
- Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;289:730–740.
- Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101:558–569.
- The CAPRICORN Investigators: CAPRICORN: effect of CARVEDILOL on outcome after myocardial infarction in patients with left ventricular dysfunction. The CAPRICORN randomized trial. *Lancet* 2001;357:1385–1390.
- CIBIS-II Investigators and committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
- COPERNICUS: Packer M, Coats JS, Fowler MB, et al. for the carvedilol prospective randomized cumulative survival study group: effect of carvedilol on survival in severe chronic heart failure. *New Engl J Med* 2001;344:1651–1658.
- Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303.
- Delyani JA. Mineralocorticoid receptor antagonists. The evolution of utility and pharmacology. *Kidney* 2000;57:1408.
- The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525–533.
- Elkayam U. Tolerance to organic nitrates: evidence, mechanisms, clinical relevance, and strategies for prevention. *Ann Intern Med* 1991;14:667.

- Fowler MB, Vera-Llonch M, Oster G, et al. Influence of carvedilol on hospitalizations in heart failure: incidence, resource utilization and costs. US Carvedilol Heart Failure Study Group. *J Am Coll Cardiol* 2001;37:1692–1699.
- Granger CB, McMurray J, Yusuf S, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin converting enzyme inhibitors; the CHARM- alternative trial. *Lancet* 2003;362:772–776.
- Gheorghiade M, Fergusson D. Digoxin. A neurohormonal modulator in heart failure. *Circulation* 1991;84:2181.
- Gheorghiade M, Hall V, Lakier JB, et al. Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin and their combinations in patients with severe heart failure. *J Am Coll Cardiol* 1989;13:134.
- Goldstein S, Fagerberg B, Hjalmarson A, et al. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. *J Am Coll Cardiol* 2001;38:932–938.
- Grossman W. Defining diastolic dysfunction. *Circulation* 2000;101:2020–2021.
- Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin immune fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol* 1991;17:590.
- Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283:1295–1302.
- Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317–327.
- Hunt SH, Baker DW, Chin MH et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2001;38:2101.
- Jessup M, Brozena S. Heart failure *N Engl J Med* 2003;48:2007–2018.
- Kass DA. Predicting cardiac resynchronization response by QRS duration: the long and short of it. *J Am Coll Cardiol* 2003;42:2125–2127.
- Kazanegra R, Herrmann HC, McCullough PA; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–167.
- Kerwin WF, Botvinick EH, O'Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. *J Am Coll Cardiol* 2000;35:1221–1227.
- Khan M. Gabriel. Heart failure in Cardiac drug therapy, sixth edition, Philadelphia, WB Saunders 2003.
- Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;42:1944–1951.
- Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 2002;105:595–601.
- Maurer MS, Spevack D, Burkhoff D, et al. Diastolic dysfunction. Can it be diagnosed by Doppler echocardiography? *J Am Coll Cardiol* 2004;44:1543–1549.
- McCullough PA, Philbin EW, Spertus JA, et al. confirmation of a heart failure epidemic: findings from the resource utilization among congestive heart failure (REACH) study. *J Am Coll Cardiol* 2002;39:60–69.
- McMurray JJV, Pfeffer MA, Swedberg K, et al. Which inhibitor of the renin–angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation* 2004;110:3281–3288.
- MERIT-HF: the metoprolol CR/XL randomized intervention trial in congestive heart failure. Effects of controlled release METOPROLOL on total mortality HOSPITALIZATIONS AND well being in patients with heart failure *JAMA* 2000;283:1295.
- Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:202–209.
- Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure: US Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349–1355.

- Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002;106:2194–2187.
- Packer M, Gheorghiade M, Young JB, for the RADIANCE study. Withdrawal of digoxin after treatment of chronic heart failure. *N Engl J Med* 1993;329:1.
- Packer M, O'Connor CM, Jalal KG, et al. Effect of Amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107.
- Pina IL. A better survival for women with heart failure? It's not so simple. *J Am Coll Cardiol* 2003;42: 2135–2138.
- Pitt B. A new HOPE for aldosterone blockade? *Circulation* 2004;110:1714–1716.
- Pitt B, Remme W, Zannad F, et al., Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321.
- Poole-Wilson PA, Cleland JG, Di Lenarda A, et al. Rationale and design of the carvedilol or metoprolol European trial in patients with chronic heart failure: COMET. *Eur J Heart Fail* 2002;4:321–329.
- RALES: Pitt B, Zannad F, Remme WJ, et al. for the randomized evaluation study investigators; the effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New Engl J Med* 1999;341:709.
- Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–982.
- Saif S, Rathore, MPH; Jephtha P. Curtis, et al. Association of serum digoxin concentration and outcomes in patients with heart failure *JAMA* 2003;289:871–878.
- Saxon LA, Ellenbogen KA. Resynchronization therapy for the treatment of heart failure. *Circulation* 2003;108:1044–1048.
- Shea JB, Sweeney MO. Cardiology patient page. Cardiac resynchronization therapy: a patient's guide. *Circulation* 2003;108:e64–e66.
- Shekelle PG, Rich MW, Morton SC, et al. efficacy of angiotensin converting enzyme inhibitors and beta-blockers in the management of the left ventricular systolic dysfunction according to race gender, and diabetic status *J Am Coll Cardiol* 2003;41:1529–1538.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
- Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. *J Am Coll Cardiol* 1993;22:955.
- Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000;101:2118–2121.
- Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;342:1441–1446.
- Wikstrand J, Hjalmarson A, Waagstein F, et al. dose of metoprolol CR/ZL and clinical outcomes in patients with heart failure. *J Am Coll Cardiol* 2002;40:491.
- Wollert KC, Drexler H. Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: carvedilol as the sun and center of the beta-blocker world? *Circulation* 2002;106:2164–2166.
- The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990; 336:1–6.
- Young JB, Abraham WT, Smith AL, et al., Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;289: 2685–2694.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I. *Circulation* 2002;105:1387–1393.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part II. *Circulation* 2002;105:1503–1508.

6

Arrhythmias

CONTENTS

DIAGNOSTIC GUIDELINES
MANAGEMENT GUIDELINES
SUPRAVENTRICULAR ARRHYTHMIAS
THERAPY
CHRONIC MANAGEMENT OF AVNRT
ATRIAL FIBRILLATION
VITAMIN K₁
WPW SYNDROME
BRADYARRHYTHMIAS
VENTRICULAR ARRHYTHMIAS
ANTIARRHYTHMIC AGENTS
BIBLIOGRAPHY

DIAGNOSTIC GUIDELINES

Accurate differentiation of ventricular and supraventricular tachycardia (SVT) is essential for appropriate management. The ECG diagnostic points for tachyarrhythmias are shown in [Tables 6.1.](#) and [6.2.](#)

It is important to:

- Designate the tachycardia as narrow QRS or wide QRS.
- Determine whether the rhythm is regular or irregular.

Further diagnostic points and ECG hallmarks are given in this chapter with the discussion of each arrhythmia.

MANAGEMENT GUIDELINES

The common underlying diseases causing arrhythmia are listed in [Table 6.3.](#) The treatment of these conditions may cause amelioration and/or prevention of arrhythmia recurrence. The severity of the underlying diseases, particularly the degree of left ventricular (LV) dysfunction, may dictate the choice of antiarrhythmic agent and the outcome.

The prognosis of ventricular arrhythmias is closely linked to the degree of LV dysfunction:

- An ejection fraction (EF) greater than 50% carries a good prognosis
- 40–50%, a fair prognosis, is commonly associated with benign arrhythmias; 20–30% is often associated with potentially lethal arrhythmias.
- Less than 20% indicates a poor prognosis.

From: *Contemporary Cardiology: Heart Disease Diagnosis and Therapy:
A Practical Approach, Second Edition*
Edited by: M. Gabriel Khan © Humana Press Inc., Totowa, NJ

Table 6.1.
Differential Diagnosis of Narrow QRS Tachycardia

<i>Regular</i>	<i>Irregular</i>
<p>AVNRT Rate = 140–220 P-waves usually buried and not apparent in the QRS or less commonly retrograde P barely visible in terminal QRS or very early ST segment, inverted in II HI aVF</p> <p>WPW with AV re-entry, negative P-wave lead, I suggest left-sided bypass tract Marked alternation in QRS amplitude, highly suspect WPW</p> <p>Sinoatrial tachycardia Average rate, 140/minute Sinus P-waves present: upright P waves in the ST segment</p> <p>Atrial flutter AR, 250–250 often 300/minute VR often 150–160/minute Conduction ratio often 2:1 Sawtooth pattern leads II, aVF Sharp-pointed P-waves in V₁</p> <p>Atrial tachycardia; paroxysmal or nonparoxysmal</p>	<p>1. Atrial fibrillation RR intervals completely irregular Absent P-waves</p> <p>2. Atrial flutter: AR > 250 Variable AV conduction</p> <p>3. Multifocal atrial tachycardia Three different P-wave morphologies in any lead, variable PP, PR, RR intervals AR = 100–200/minute RR intervals completely irregular; may progress to atrial fibrillation</p>

AR, atrial rate; AVNRT, atrioventricular nodal re-entrant tachycardia; VR, ventricular rate; WPW, Wolff-Parkinson-White.

VR, 240–300 suggests WPW.

Adverse effects of drug therapy are clearly related to the degree of LV dysfunction. Drugs that may be used in patients with an EF less than 30%, and other ranges of EFs, are given in [Table 6.4](#). Determining the EF is essential to the management of ventricular arrhythmias. Echocardiographic assessment is useful, because it assists with detection of valvular lesions, segmental areas of hypocontractility, the extent of ischemic heart disease (IHD), cardiomyopathy, and other diseases. Although echocardiographic EF is subject to some error and radionuclide EF is preferred if atrial fibrillation (AF) is absent, the former has practical advantages in assessing structural defects and is cost-effective. In addition, the radionuclide EF is inaccurate in patients with AF, and both methods yield falsely high EFs in patients with mitral regurgitation.

The emergency management of arrhythmias calls for a quick assessment of the following

- The hemodynamic status: is the blood pressure (BP) less than 90 mmHg and are there signs of peripheral hypoperfusion.
- The symptomatic status: chest pain, shortness of breath, presyncope, syncope, or clouding of consciousness.
- Cardiac decompensation: signs of heart failure (HF).

Table 6.2.
Wide QRS Tachycardia

<i>Regular</i>	<i>Irregular</i>
Ventricular tachycardia	Atrial fibrillation and WPW antidromic (anterograde), rate (220–300/minute ^a)
Hallmarks	Atrial fibrillation and prior intraventricular conduction defect on recent ECG
Absence of an RS complex in all precordial leads; totally negative precordial concordance is diagnostic ^b	Atrial flutter with varying AV conduction: bundle branch block, or with WPW antidromic tachycardia
Predominantly negative QRS complexes V ₄ –V ₆ , or QR complex in one or more of V ₂ to V ₆ with QRS in V ₁ being mainly negative	Torsades de pointes
QRS duration:	
R to S interval > 100 ms in one precordial lead	
RBBB pattern QRS > 140 ms	
LBBB QRS > 160 ms	
AV ^c dissociation (cannon waves in neck) excludes atrial but not nodal tachycardia	
Suggestive features	
Positive concordance (except WPW antidromic tachycardia)	
Left axis— 90 to ± 180	
QS or rS in V ₆ (R to S, ratio < 1) or net negative QRS in V ₆	
V ₁ “Left rabbit ear” taller than the right.	
ST with BBB or LBBB	
ST with aberrant conduction	
Atrial flutter: with wide QRS ^d or with WPW antidromic tachycardia	
WPW anterograde (antidromic) through bypass tract ^a (resembles ventricular tachycardia)	

^aRR < 205 ms suggests WPW, treat as ventricular tachycardia.

^bSee Fig. 6.1.

^cAV block or dissociation excludes bypass tract.

^dAtrial fibrillation treated with class IC or IA agents may induce this arrhythmia.

Precipitating Factors and Clinical Settings

An essential step in the management of arrhythmia is to rapidly define the clinical setting and correct a precipitating cause to obviate the need for antiarrhythmic therapy or to appraise and prevent deleterious proarrhythmic effects of these agents.

Precipitating factors and/or clinical settings include:

- Ischemia: as with acute myocardial infarction (MI) or acute myocardial ischemia.
- Those characterized by myocardial reperfusion: postthrombolytic therapy in acute MI, balloon deflation during coronary angioplasty, release of coronary artery spasm.
- Hypotension.
- Sick sinus syndrome or atrioventricular (AV) block.

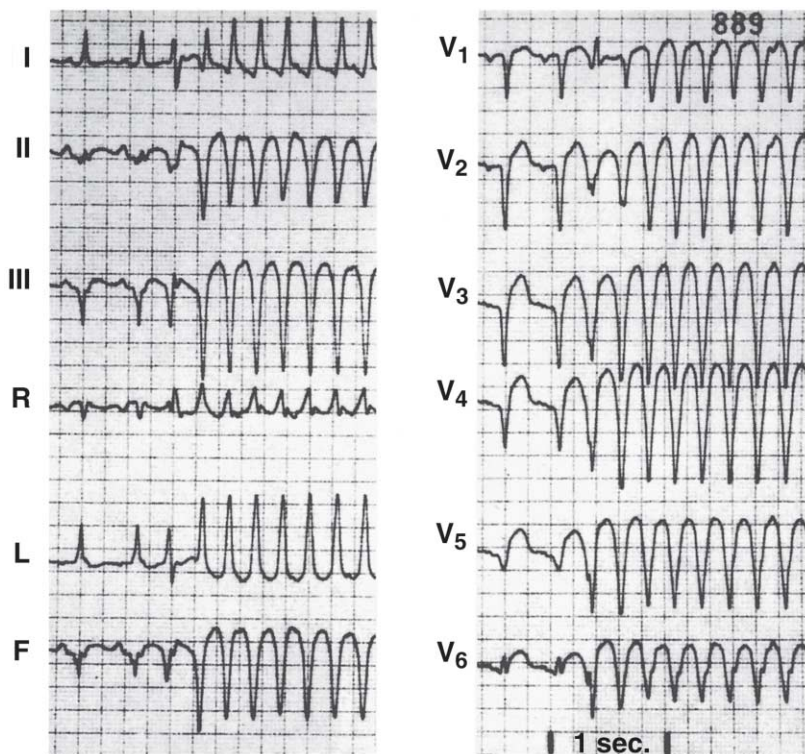


Fig. 6.1. The onset of a tachycardia with negative precordial concordance. Negative precordial concordance indicates ventricular tachycardia because such a pattern does not occur during anterograde conduction over an accessory pathway. From Wellens Hein JJ, Conover MB. The ECG in emergency decision making. Philadelphia, PA: WB Saunders, 1992:60, with permission from Elsevier.

- HF.
- Hypokalemia, hypomagnesemia, hyperkalemia.
- Alkalemia, for example, develops rapidly in ventilated patients.
- Acidemia.
- Hypoxemia.
- Pulmonary disease, cor pulmonale, atelectasis, pneumothorax, and carcinoma of lungs may precipitate atrial flutter or AF.
- Infection.
- Fluctuations in autonomic tone.
- Acute blood loss.
- Thyrotoxicosis.
- Digoxin toxicity.
- Proarrhythmic effects of antiarrhythmic drugs: quinidine and other class IA drugs may cause torsades de pointes, also rarely caused by class III agents and sotalol and extremely rarely caused by amiodarone. More typical monomorphic ventricular tachycardia (VT) and other lethal arrhythmias may be initiated by antiarrhythmic drugs.
- β -agonist.
- Theophylline.
- Ruptured esophagus: may initiate atrial flutter or AF.

Table 6.3.
Common Underlying Diseases Causing Arrhythmias

Ischemic heart disease
Acute MI
Myocardial ischemia
Left ventricular aneurysm
Cardiomyopathies
Rheumatic and other valvular
Myocarditis
Sinus and atrioventricular node diseases
Bypass tract
Congenital heart disease
Pulmonary diseases: all causes of hypoxemia
Endocrine/thyrotoxicosis
Hypokalemia in patients with heart disease and/or concomitant use of antiarrhythmic agents

Table 6.4.
EF May Dictate Choice of Antiarrhythmic Agent

<i>Group I</i>	<i>Group II</i>	<i>Group III</i>
EF < 30% only safe agents ^a	EF > 30%	EF > 40%
Amiodarone	β-blockers and agents used for group I ^a	Agents given under group I, II plus class IA, IB
Mexiletine		
Quinidine		
β-blockers ^b		Propafenone ^c
		Flecainide ^c
		Verapamil
		Diltiazem

EF, ejection fraction.

^aAll other agents: hazard of precipitating heart failure.

^bUsed judiciously in properly selected patients, absence of overt heart failure, EF down to 25%.

^cLimited indications (*see* text).

Mechanism of the Arrhythmia

The mechanism of the arrhythmia is usually a disturbance of impulse generation (enhanced automaticity or ectopic tachyarrhythmia); or a disturbance of impulse conduction (reentrant arrhythmia). Most of the evidence suggests that reentry is the mechanism for sustained VT.

The mechanism often is not known when deciding on treatment. Other prerequisites that may influence the choice of appropriate therapy include: knowledge of the mode of action of the selected antiarrhythmic drug, adverse effects to be anticipated, and possible outcomes of such therapy (salutary, life threatening, or proarrhythmic).

Proarrhythmic Effects of Antiarrhythmic Agents

Proarrhythmia connotes that antiarrhythmic agents can worsen existing arrhythmias or induce new ones. The early and late proarrhythmic effects of the antiarrhythmic drug

to be chosen must be carefully considered. Because proarrhythmia may be life-threatening, the physician must consider the degree of risk and justify the need for antiarrhythmic drug therapy.

Early proarrhythmia is observed in up to 5, 10, and 25% of patients with benign, potentially lethal, and lethal arrhythmia, respectively. Late proarrhythmia is even more worrisome. The incidence of late proarrhythmia for encainide and flecainide is known to be substantial. The incidence for amiodarone is very low, but for other agents (except β -blockers), the incidence is unknown and may be substantial. Most available antiarrhythmic agents have not been studied for the incidence of late proarrhythmia in well-controlled, randomized, multicenter long-term trials.

Factors that increase the incidence of proarrhythmic effects include the following:

- Prior cardiac arrest, ventricular fibrillation (VF), or sustained VT.
- Prolonged QTc.
- Severity of LV dysfunction. Patients with EF less than 30% have a high incidence of early and late proarrhythmia, perhaps because of the propensity for the occurrence of HF. More than 85% of lethal arrhythmias occur in patients with severe underlying heart disease and EF less than 30% and with a 20–40% incidence of recurrence over 2 years.

Basic mechanisms and precipitating factors for proarrhythmia include the following:

- Prolongation of the action potential duration and QTc, particularly in the setting of hypokalemia or bradycardia: commonly seen with class IA agents and with class III agents occurring mainly with sotalol, which prolongs the action potential duration maximally in the presence of bradycardia. Although the QT interval is prolonged by amiodarone, proarrhythmic effect is very low.
- Incessant VT, ventricular flutter, often terminating in VF, usually with class 1C antiarrhythmics. If conduction is severely depressed, class IA agents may induce incessant VT.
- Rapid increase in already high dose of class 1C agents.
- Severe LV dysfunction, EF less than 30%.
- Concomitant administration of potassium-losing diuretic.
- AF treated with class 1A or 1C agent.

The results or outcomes of proarrhythmia during antiarrhythmic therapy include the following:

- Nonserious increase in frequency of nonsustained VT or ventricular premature beats (VPBs) without hemodynamic deterioration.
- Hemodynamic deterioration with nonsustained VT.
- New onset sustained VT or VF.
- Antiarrhythmic death.

It must be reemphasized that the late proarrhythmic characteristics of antiarrhythmic agents are currently unknown and present bothersome problems with decision making concerning the selection of an appropriate agent. The absence of early proarrhythmia bears no relationship to the drug's propensity to produce late deleterious proarrhythmia.

The Multicenter Cardiac Arrhythmia Pilot Study was instituted to ensure the safety and feasibility of chronic suppressive therapy for asymptomatic VPBs after MI in prevention of cardiac arrhythmic death; encainide and flecainide were studied and were determined to be safe and effective in completely suppressing VPBs. Yet, the subsequent Cardiac Arrhythmic Suppression Trial (CAST) showed that in the long-term, encainide

and flecainide produced considerably more deaths than placebo because of serious proarrhythmia that occurred late and progressively throughout the 15 months or more of study. Careful analysis suggests that fresh ischemia in the presence of these agents may have been the major triggering factor for arrhythmia.

Electrophysiological (EP) studies, as well as frequent Holter monitoring, appear to be of little value in predicting late proarrhythmia. Thus, there are few guidelines to direct physicians to avoid late proarrhythmia caused by antiarrhythmic drugs, with the exception of information gleaned from therapy with four agents used extensively for the past 15 or more years: β -blockers (safe), amiodarone and mexiletine (relatively safe), and quinidine (hazardous). In the face of such a dilemma, the physician's assessment of the risk: benefit ratio of initiating antiarrhythmic drug therapy is a worthwhile strategy.

SUPRAVENTRICULAR ARRHYTHMIAS

The differential diagnosis of narrow QRS tachycardia is shown in [Figure 6.2.](#) and [Table 6.1.](#)

Wolff-Parkinson-White (WPW) orthodromic circus movement tachycardia

[Figure 6.3.](#) from Wellens et al. gives a representation of the sites of origin and mechanism of paroxysmal SVT as determined by the position and polarity of the P-waves in relation to the QRS complexes.

- In atrial tachycardia, the P-waves precede the QRS complex and its polarity in leads three depends on its location.
- In atrioventricular nodal reentrant tachycardia (AVNRT), the P-wave is buried within the QRS complex or distort the end of the QRS; that portion of the QRS is then negative in lead I11. In circus movement tachycardia, the P-wave follows the QRS complex.

AV Nodal Reentrant Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is most often caused by AVNRT and is one of the most frequently encountered arrhythmias in clinical practice. In patients under age 35, PSVT usually occurs in an otherwise normal heart and has a good prognosis. However, AVNRT is not uncommon with organic heart disease, resulting from ischemic, rheumatic, or other valvular heart disease, and rarely, can be life threatening. The onset and termination are abrupt; heart rate varies from 140–220/min, with regular rhythm ([Table 6.1.](#)).

DIAGNOSIS

- In AV nodal reentry, the impulse circulates within the AV node. The ventricles are activated from the anterograde path of the circuit and the atria are activated retrogradely.
- In the most common form, more than 50% of AVNRT, the P-waves are hidden within the QRS complex (*see* [Fig. 6.4.](#)).
- The P-wave when visible is inverted. In approximately 40%, the P-wave distorts the terminal QRS causing a pseudo-S in leads II, III and, augmented electrocardiograph leads AVF or accentuated S-waves in these leads, and a pseudo-r in V (*see* [Figs. 6.3., 6.5.](#)), whereas in the common type, WPW orthodromic circus movement tachycardia, the P wave can be observed separate from the QRS in II, III, aVF, and aVL ([Figs. 6.3, 6.6.](#)).
- If a P-wave is present in the ST segment and separated from the QRS by 70 ms, then WPW (AVNRT) is most likely.
- In less than 5% of cases, the P-wave occurs at the onset of the QRS and may be observed as pseudo-Q-waves in leads II, III, and aVF,

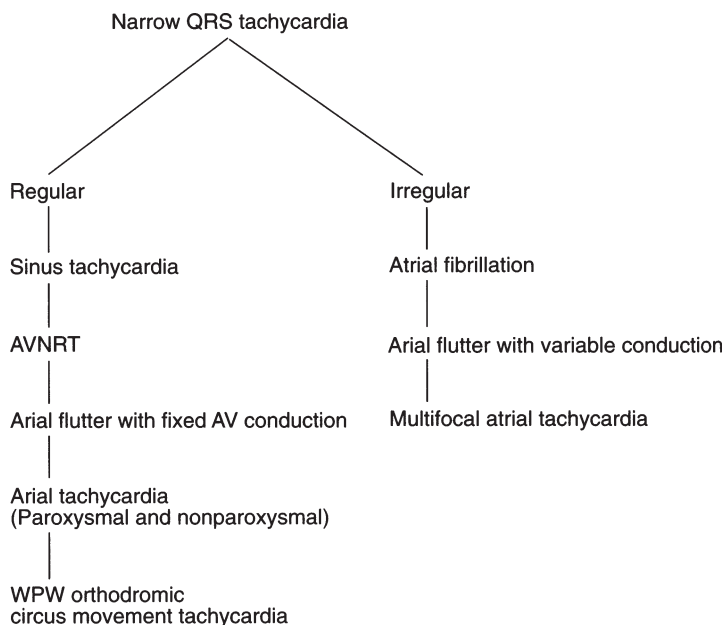


Fig. 6.2. Algorithm for the diagnosis of narrow QRS tachycardia. AVNRT, atrioventricular nodal re-entrant tachycardia; AV, atrioventricular.

- In about 5% of cases, the P-wave is negative in leads II, III, and aVF and follows the QRS with an $RP \geq PR$; this form of AVNRT cannot be differentiated from the rare type WPW orthodromic circus movement tachycardia that uses the retrograde slowly conducting accessory pathway to activate the atria that results in a long RP interval.

CAROTID SINUS MASSAGE, PATIENT RHYTHM MONITORED

Carefully instituted carotid sinus massage is an excellent diagnostic maneuver and may result in termination of AVNRT or circus movement tachycardia.

- Carotid sinus massage is not recommended in the elderly or in patients with known or highly suspected carotid disease or digitalis toxicity; before attempting massage, assess for transient ischemic attacks (TIAs) and carotid artery stenosis.
- Response is either reversion to sinus rhythm or no effect at all, in contrast to atrial flutter, where slowing of heart rate virtually always occurs and atrial activity is exposed, thus confirming the diagnosis of flutter.
- With the patient supine (head slightly hyperextended, turned a little toward the opposite side), locate the right carotid sinus at the angle of the jaw. Apply firm pressure in a circular or massage fashion for 2–6 seconds, using the first and second fingers. It is necessary to monitor the cardiac rhythm and gage exactly when to stop massage because asystole, although rare, can occur. If unsuccessful, massage the left carotid sinus after an interval of 2 minutes to allow acetylcholine to be manufactured in the AV node. (If asystole occurs during the procedure, ask the patient to cough and/or give the patient one or more light chest thumps, which usually reverses transient asystole.)

Caution: never massage for more than 10 seconds.

Other vagal maneuvers include Valsalva maneuver or squatting and Valsalva, putting a finger into the throat to initiate a gag reflex, immersion of the face in cold water, taking

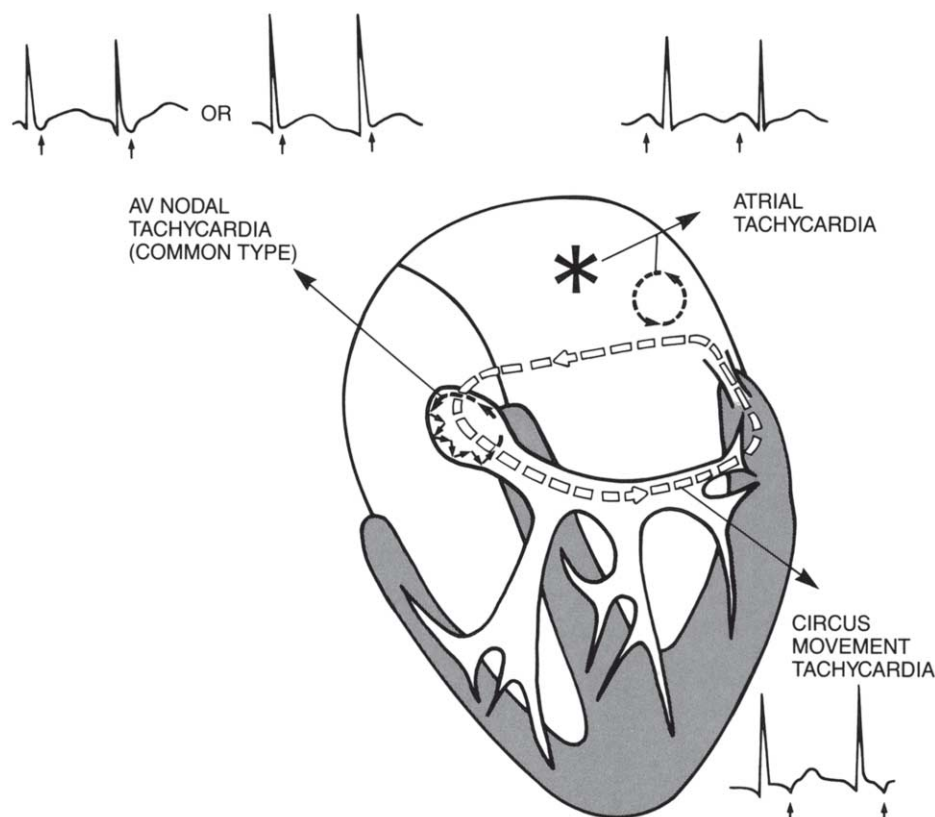


Fig. 6.3. The representation of the sites of origin and mechanism of paroxysmal supraventricular tachycardia as determined by the position and polarity of the P-waves in relation to the QRS complexes. In atrial tachycardia, the wave precedes the QRS; its polarity in lead III depends on its location. In atrioventricular nodal re-entry tachycardia, the P-wave is buried within the QRS or may distort the end of the QRS; that portion of the QRS is then negative in lead III. In circus movement tachycardia, the P-wave follows the QRS. AV, atrioventricular. From Wellens Hein JJ, Conover MB. The ECG in emergency decision making. Philadelphia, PA: WB Saunders, 1992:92, with permission from Elsevier.

a drink of cold water, or elevating the legs against a wall. The Valsalva maneuver is effective in approximately 50% of patients with AVNRT.

Caution: never apply eyeball pressure because retinal detachment may occur.

THERAPY

Advice given on SVTs follows closely the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) Guidelines for the Management of Patients With Supraventricular Arrhythmias.

Suggested steps in treating AVNRT are given in [Figure 6.7](#), and are based on the clinical setting: the presence of cardiac pathology, particularly LV dysfunction, acute MI, or hypotension, which contraindicate the use of verapamil. In patients with acute MI, an intravenous (IV) β -blocking agent, especially short-acting esmolol, or metoprolol is advisable if there is no contraindication to the use of a β -blocking drug.

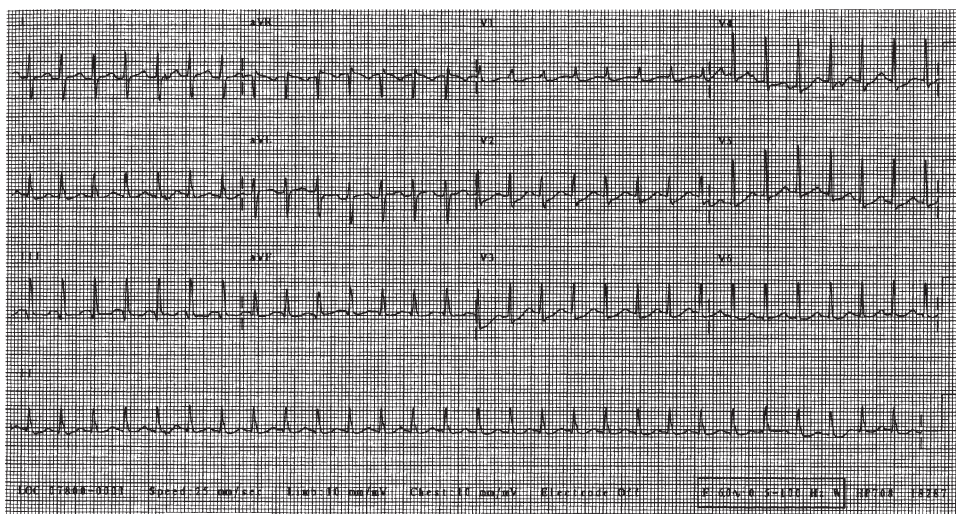


Fig. 6.4. Tracing from a 49-year-old woman with supraventricular tachycardia, the most common form of atrioventricular nodal re-entrant tachycardia. P-waves are not visible because they are hidden in the QRS. Rate: 170/minute.

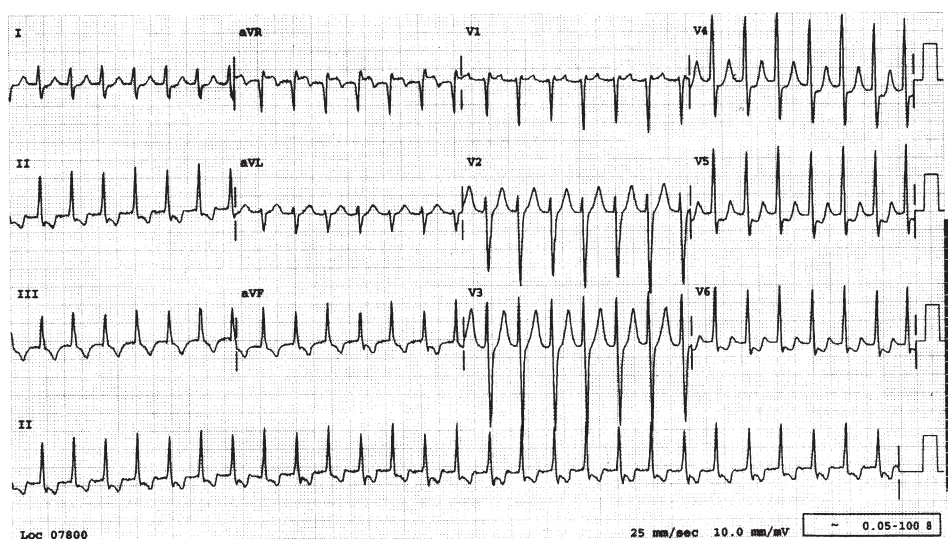


Fig. 6.5. Tracing from a 37-year-old man with supraventricular tachycardia, atrioventricular nodal re-entrant tachycardia. The P-wave distorts the end of the QRS, causing a pseudo-S in leads II, III, and augmented electrocardiographic leads (foot), or accentuated S-waves in these leads, and a pseudo-r₁ in lead V. Rate 170/minute.

Electrical cardioversion is indicated for ST causing hemodynamic compromise. Digoxin is indicated if HF is present. In the absence of acute MI, adenosine can be used for reversion, and, if needed, digoxin can be considered for maintenance therapy; digoxin is an obvious choice in patients with HF. Verapamil is contraindicated with hypotension and if significant cardiac pathology is present, especially in patients with cardiomegaly or known or suspected LV dysfunction.

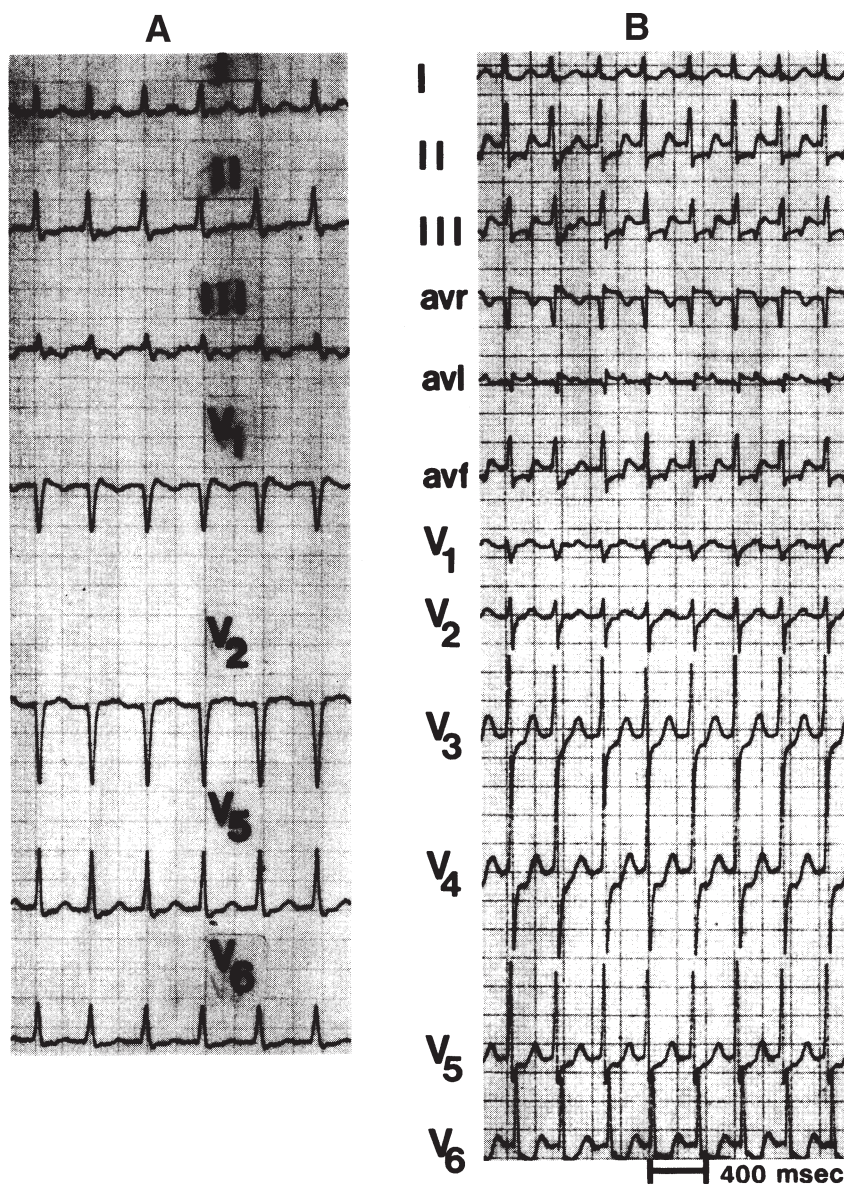


Fig. 6.6. Atrioventricular nodal reentry tachycardia (AVNRT) (A) and circus movement tachycardia (B) are shown for comparison. (A) Note that during AVNRT, the P-wave is distorting the end of the QRS (S in leads II and III and r in lead V). (B) In circus movement tachycardia, the P-waves are clearly separate from the QRS and can easily be seen in leads II, III, augmented electrocardiographic leads (leg) aVL, and aVF (foot). aVR, augmented electrocardiographic leads (arm). From Wellens Hein JJ, Conover MB. The ECG in emergency decision making. Philadelphia, PA: WB Saunders, 1992:92, with permission from Elsevier.

In patients with AVNRT and a virtually normal heart, the arrhythmia is usually well tolerated for 12–24 hours. If no response is obtained from vagal maneuvers, IV verapamil or adenosine is indicated; the choice depends on the presence or absence of hypotension. Verapamil can cause hypotension and is contraindicated if systolic blood pressure (SBP) is less than 90 mmHg. Adenosine has the advantage of not causing hypotension.

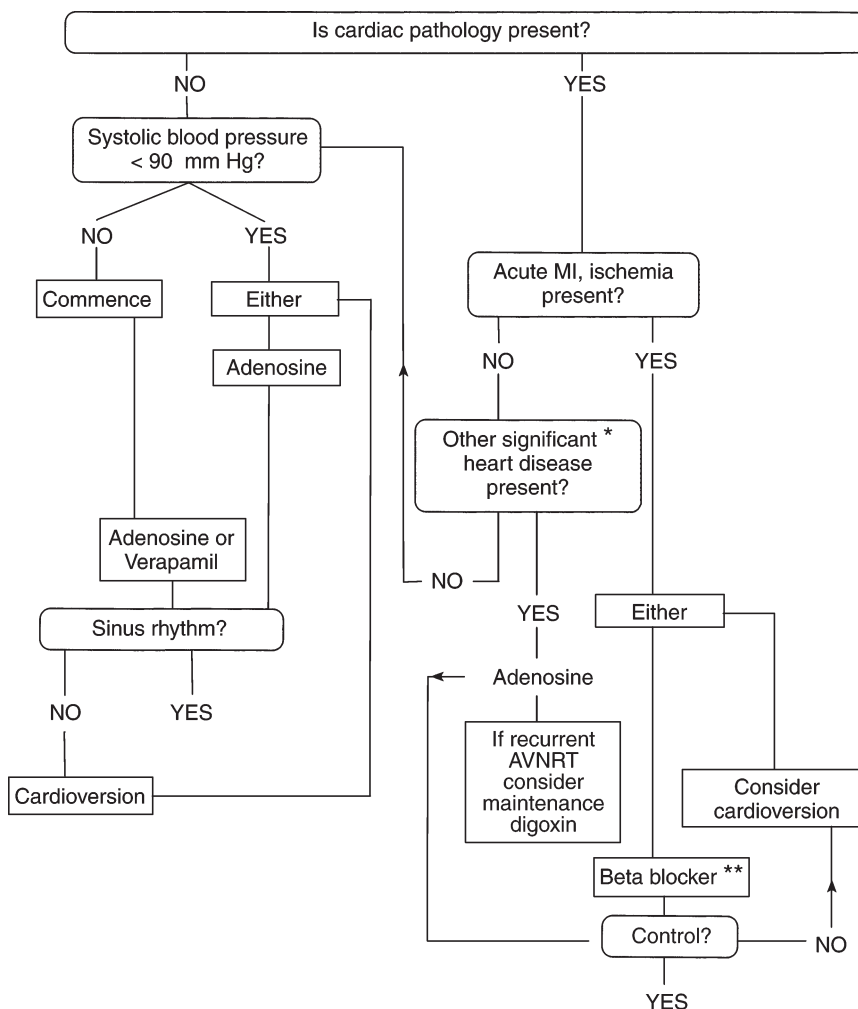


Fig. 6.7. Suggested steps in how to treat atrioventricular nodal re-entrant tachycardia. *For example, heart failure, cardiomegaly. **If heart failure is not present. From Khan M. Gabriel. Cardiac Drug Therapy. 5th ed. London:WB Saunders, 2000.

When adenosine is contraindicated because of the presence of asthma or known sensitivity, then phenylephrine has a role in young patients with PSVT complicated by hypotension but not severely compromised.

Adenosine Versus Verapamil

Adenosine is considered the drug of choice because it is very effective, has a short half-life (<5 seconds) and has no serious adverse effects compared with verapamil. Verapamil is inexpensive, however, and remains a reasonable choice for uncomplicated cases, particularly with known AVNRT and asthmatics (*see* contraindications for verapamil). Adenosine has a major role in patients where contraindications or even relative contraindications exist in the use of verapamil, mainly because of adenosine's short half-life (<2 seconds) as opposed to that of verapamil (6 hours). Although adenosine has a high

incidence of minor adverse effects, serious side effects are rare. [Table 6.5](#) indicates the agent of choice (adenosine versus verapamil) for the management of PSVT.

Median time to termination, 20 seconds for adenosine versus 80 seconds for verapamil, is only important in patients with hemodynamic compromise because PSVT is usually well tolerated. Both drugs are effective, causing reversion to sinus rhythm in up to 90% of patients. Recurrence of tachycardia is slightly more common after the use of adenosine, but a second dose of adenosine often proves effective.

Adenosine assists in the diagnosis of atrial flutter and recording of both lead V_1 and lead 2 is advisable for diagnosis and during attempted conversion, as with all antiarrhythmic agents. Morphology in V_1 ([Tables 6.1.](#) and [6.2.](#)) is vital to arrhythmia diagnosis and has been advocated since the early 1970s. Most hospitals, including teaching centers, however, continue to record mainly lead 2. In the setting of ST, V_1 may reveal type A WPW syndrome. Also, adenosine IV injection during sinus rhythm may reveal latent pre-excitation, usually type A, dominant R-wave in V_1 that highlights the presence of a left-sided bypass tract in this condition.

Patients who have latent preexcitation owing to left-sided pathway are particularly likely to develop rapid ventricular rates, if AF supervenes, with degeneration to VF, a situation that can be precipitated by verapamil. In patients with anterograde conduction over an anomalous pathway, verapamil is known to cause an increase in ventricular response because of reflex sympathetic stimulation and may dangerously accelerate the ventricular response in patients with AF or atrial flutter. Although adenosine can increase the ventricular response to pre-excited arrhythmias, the effect lasts less than 3 seconds owing to the short half-life of the drug.

Verapamil produces some slowing of the ventricular response in AF but does not usually change the rate in patients with atrial flutter. Adenosine usually produces a higher grade of AV block; thus, atrial activity may be exposed, revealing the diagnosis of atrial flutter.

Adenosine (Adenocard)

This ultra-short-acting agent has decreased the need for IV verapamil, digoxin, or β -blockers in the acute management of PSVT.

DOSAGE

Using a peripheral vein, 6 mg by rapid IV bolus injection is given over 2 seconds, rapidly flushed into a peripheral vein; if given via an IV line, the drug should be given as proximal as possible and followed by a rapid saline flush. Termination of the arrhythmia is expected in less than 1 minute, and the action of the drug lasts for less than 30 seconds after injection. A second bolus injection of 12 mg is repeated 2 minutes after the first if the arrhythmia persists or recurs. The 12-mg dose may be repeated in 2–5 minutes, if required, and may be given via a larger vein than used in prior IV injection. Further recurrence of the arrhythmia calls for alternative therapy. In 10–30% of cases, arrhythmia recurs within minutes of the first injection of adenosine. A smaller dose is required if the drug is given through a central vein. A dose of 6 mg administered through a central vein in the same patient may have a potent effect, whereas a 12-mg dose may be ineffective when administered through a small peripheral vein. The drug should be used cautiously in patients with right to left shunting and must not be administered into the distal port of a balloon flotation catheter.

Table 6.5.

Adenosine vs Verapamil for the Management of Paroxysmal Supraventricular Tachycardias

<i>Parameters</i>	<i>First Choice</i>	<i>Second Choice</i>
Uncomplicated cases, known AVNRT Ventricular rate < 220/minute	Adenosine	Verapamil
Hypotension		
Mild	Adenosine	Verapamil after pretreatment with calcium chloride or gluconate
Moderate/severe	Adenosine	Verapamil CI
Left ventricular dysfunction	Adenosine	Verapamil CI
Heart failure cardiomegaly		
Suspect pre-excitation (AVRT)	Adenosine	Verapamil CI
Wide QRS ? aberrancy	Adenosine	Verapamil CI
Atrial tachycardia or multifocal atrial tachycardia	Verapamil	Adenosine ineffective

CI, contraindicated; R, relative.

^aInexpensive, less minor adverse effects.

Action: The drug has a depressant effect on the sinoatrial (SA) node and slows impulse conduction through the AV node. These effects appear to be mediated at the cellular level by an increase in potassium and a decrease in calcium conductance. These EP effects are not antagonized by atropine.

After IV quick bolus injection, adenosine has a rapid onset of action within 5–30 seconds and converts up to 90% of PSVTs to sinus rhythm. The drug has a very short half-life ($1 < 5$ seconds) because it is avidly taken up and metabolized by adenosine deaminase in endothelial and red blood cells. Intracoronary adenosine and papaverine induce a similar degree of coronary vasodilatation. When given a continuous low-dose infusion, adenosine causes coronary vasodilatation without significant effects on the SA or AV nodes and has a role similar to dipyridamole in conjunction with thallium-201 scintigraphy. The coronary vasodilator effect, which is similar to dipyridamole, is the likely explanation for the occurrence of chest pain provoked in patients with angina. Chest pain in patients without significant obstructive coronary disease appears to be owing to abnormalities of adenosine feedback or metabolism. Also, during severe ischemia or MI, the marked release of endogenous adenosine may explain some incidences of bradycardia and AV block resistant to atropine, which, however, responds to theophylline, an adenosine antagonist.

With AVNRT, the reentry circuit is located within or just above the AV node and is formed by a slow pathway with a short refractory period often conducting anterogradely and a fast pathway with a long refractory period conducting retrogradely.

The drug is also effective for AV reciprocating tachycardia in which an extranodal pathway forms the retrograde portion of the circus movement and the AV node constitutes the anterograde limb. Adenosine, as other drugs that are effective for termination of re-entrant supraventricular arrhythmias, delays conduction or increases refractoriness in either the anterograde or retrograde limb of the reentry circuit (usually the former).

INDICATIONS

Adenosine is indicated for the termination of AVNRT and AV re-entrant reciprocating tachycardia. The drug causes termination of these arrhythmias in over 90% of cases. It is the agent of first choice for these arrhythmias in patients with hypotension or other situations where rapid conversion to sinus rhythm is needed or as an alternative to electrical cardioversion. Adenosine is also indicated in patients with PSVT that fail to terminate with a 10-mg dose of verapamil or when contraindications or relative contraindications to verapamil exist.

The drug has advantages over verapamil in patients with AV reentrant tachycardia using an accessory pathway in the reentry circuit; adenosine may unmask latent preexcitation when sinus rhythm is restored and can only produce very transient episodes of rapid pre-excited arrhythmia, as opposed to verapamil, which is contraindicated in these situations. Thus, adenosine is much safer than verapamil for use in patients with WPW or suspected WPW arrhythmias.

Adenosine, in decreasing AV conduction, unmasks atrial flutter and assists with diagnosis. Adenosine also has a role in patients with suspected ST with aberration. In patients with misdiagnosed VT, verapamil may precipitate HF and other life-threatening complications. Adenosine, in this situation, causes reversion if the rhythm is owing to AV nodal reentry, and its effect on VT is transient and not detrimental because of its ultra short half-life. This agent is not effective in ectopic atrial tachycardia (AT) and multifocal AT.

Adenosine appears to have an important role and is relatively safe in infants with rapid PSVT with hemodynamic compromise, because repeat electrical cardioversion with 20 J can cause deleterious effects on the myocardium at this age. Adenosine pediatric dosage: 50 µg/kg increase at 50 µg/kg increments, if needed, to 150 µg/kg (not included in the drug's product monograph but appears to be relatively safe at this dose range). Studies have indicated the drug to be effective for the acute termination of PSVT in children, especially when repeated electrical cardioversion is hazardous.

A multicenter study indicated that a 12-mg dose is usually required to achieve about a 90% success in conversion of the arrhythmia to sinus rhythm at a cost of approximately \$20 compared with approximately \$1.00 for 10 mg of verapamil. Also, there is a high incidence of recurrence of the arrhythmia within minutes of the first successful conversion. The incidence varies from 10 to 33%; a second injection is usually successful. Adenosine has been safely given centrally by means of a catheter positioned in, or near, the right atrium. The initial dose should be 3 mg followed every minute by 6, 9, and 12 mg until the termination of the tachycardia. Chest pain occurs more frequently with central injections than with peripheral administration (17% versus 10%).

CONTRAINDICATIONS

- Second- or third-degree AV block, except in patients with a functioning pacemaker.
- Sinus node disease.
- Known hypersensitivity to adenosine.
- Asthma.
- Chronic pulmonary disease with theophylline usage (may need larger doses of adenosine).
- Unstable angina.
- Acute MI: not given in the product monograph; the drug may cause a steal similar to dipyridamole and is best avoided until further trials document safety.

ADVERSE EFFECTS

Minor adverse effects occur in 30–60% of patients. It is wise to advise the patient that minor transient adverse effects may occur, lasting from 30 seconds to 1 minute. These effects include facial flushing, dyspnea, chest pain or pressure, mild bronchospasm in patients with chronic lung disease, and, less commonly, nausea, vomiting, headache, transient hypotension, and sinus pauses with ventricular standstill of several seconds.

CAUTION

Safety in patients with LV dysfunction owing to coronary artery disease (CAD) is not established and caution is needed. Adenosine should be used with caution in patients with severe CAD when the arrhythmia diagnosis is unclear because VF may be precipitated; also, in patients with pre-excited tachycardia AF, rapid ventricular rates may ensue.

A dose of 12 mg may be ineffective if given through a small peripheral vein, but 6 mg given through a central vein may have a potent effect. Do not administer the 12-mg dose through a central vein or porthole of a balloon flotation catheter. Avoid the use of adenosine in the presence of a prolonged QT interval because induced bradycardia may promote the precipitation of Torsade de pointes.

INTERACTIONS

- Dipyridamole markedly enhances the sinoatrial and AV nodal effects of adenosine. Dipyridamole decreases cellular uptake of adenosine, thereby inhibiting its metabolism. This interaction may be important in patients being given oral dipyridamole.
- Aminophylline, caffeine, and other methyl xanthines completely antagonize adenosine and large doses of adenosine are required.
- Carbamazepine: high rates of heart block may be seen when adenosine is concomitantly administered with carbamazepine.

Verapamil

Verapamil mainly delays conduction in the slow anterograde AV nodal pathway in patients with AVNRT or in the AV node in patients with AVRT. Verapamil is effective in converting these arrhythmias in over 87% of patients.

Dosage: Verapamil (5 mg IV) is given slowly over 2 or 3 minutes in the elderly and with the continuous monitoring of cardiac rhythm and BP. Use 2.5 mg initially if LV function is believed to be slightly impaired. A bolus injection that achieves therapeutic plasma concentration causes reversion to sinus rhythm in 5–10 minutes. Resistance to termination or recurrence of arrhythmia without a marked fall in BP should be managed with an additional 2.5–5-mg dose, 10 minutes after the first dose. Occasionally, an IV infusion is used of 1 mg/minute to a total of 10 mg over 20 minutes with BP monitoring. Mild hypotension is not a contraindication to the use of verapamil, but adenosine, if available, is preferred. If adenosine is not available, further hypotension resulting from verapamil can be avoided by the administration of calcium chloride or calcium gluconate (10 mL of a 10% solution over 5–10 minutes) before verapamil bolus (over 3 minutes or preferably by infusion, 1 mg/minute for 10 minutes). If the patient is taking a β -blocking drug, adenosine is preferred or verapamil should be reduced to 5 mg IV given over 5 minutes in an attempt to avoid severe bradycardia and hypotension. If sinus arrest or AV block occurs, give calcium chloride or gluconate and atropine (0.5–1 mg IV repeated, if required, to a total dose of 2 mg).

- Patients with hypotension, SBP less than 95 mmHg.
- HF of all grades.

- Patients with suspected LV dysfunction, particularly patients with cardiomegaly or an EF less than 40%.
- Sick sinus syndrome.
- Suspected digitalis toxicity.
- β -blockade.
- Concomitant use of disopyramide or amiodarone.
- Wide QRS tachycardia, unless identical complexes of intraventricular conduction delay seen on previous ECG while in sinus rhythm.
- Atrial flutter or AF complicating WPW syndrome; patients with AF and an anterograde conducting accessory pathway. In this situation, verapamil, causing vasodilatation and reflex sympathetic stimulation, may accelerate the ventricular response through the accessory pathway, leading to VF and hemodynamic collapse. The rapidity of the ventricular response 250–300 beats/minute (BPM) should alert the physician to the underlying bypass tract with anterograde conduction.
- Patients with latent pre-excitation, usually type A with dominant R-wave in V. These patients may develop rapid ventricular rates if AF supervenes and verapamil is given intravenously.

Adverse Effects: Hypotension, HF, sinus arrest, AV block, asystole, and acceleration of the ventricular response in patients with AF or atrial flutter complicating WPW syndrome.

Esmolol

Esmolol has an ultrashort action that confers major advantages over propranolol, atenolol, and metoprolol. The onset of action is rapid. The drug is quickly metabolized by esterases of red blood cells and has a half-life of 9 minutes that is unaffected by renal failure, HF, or hepatic dysfunction. The drug is cardioselective and has the same contraindications as other β -blocking agents.

Indications: Management of uncomplicated cases of PSVT not terminated by adenosine and when adenosine or verapamil are contraindicated, especially during acute MI.

Dosage: Initial loading infusion of 3–40 mg (usually 6 mg), IV infusion over 1 minute (30 to maximum 500 μ g/kg given over 1 minute), and then maintenance infusion 1–5 mg/minute (maximum 50 μ g/kg/min). If mild hypotension is present, the maintenance dose should be reduced to 1–3 mg/minute.

Adverse effects: Mild transient hypotension occurs in less than 25% of patients, more commonly in those with SBP less than 100 mmHg, and improvement occurs within minutes of discontinuing the IV infusion.

Propranolol

DOSAGE

One milligram IV given over 2 minutes, repeated every 5 minutes to a maximum of 5 mg.

Metoprolol

DOSAGE

Five-milligram IV bolus over 3 minutes, then, if required, after 5 minutes, an additional bolus is given, and repeated if needed 5–10 minutes later.

Phenylephrine

This α -agonist increases BP, and the ensuing vagal activity results in sinus rhythm and has a role only in young patients with a normal heart when the SBP is less than 90 mmHg,

when adenosine is not available, when contraindications exist to the use of verapamil, or when cardioversion is believed to be undesirable.

DOSAGE

A total of 0.1 mg in 5 mL of 5% dextrose water given IV over 2 minutes. Repeat in 2 or 3 minutes. Allow 1–3 minutes after each bolus for the BP to return to the baseline value before giving an additional bolus. Maximum dose is 0.5 mg. If this fails to produce sinus rhythm but stabilization of BP is achieved, verapamil or esmolol can then be administered.

Digoxin

If rapid restoration of sinus rhythm is not considered essential, digoxin is advisable if there is associated hypotension, cardiomegaly, or signs of HF caused by LV dysfunction. Digoxin takes more than 2 hours, however, to have an effect, and is not recommended where rapid restoration of sinus rhythm is required. Adenosine for termination and digoxin for maintenance therapy are advisable in some patients (Fig. 6.7.).

DOSAGE

In the absence of digoxin use during the previous week, 0.5 mg IV by infusion over 10 minutes followed, if required, in 30 minutes by 0.25 mg, 0.25 mg 4 hours later, and then 0.25 mg orally once daily.

SVT in Pregnancy

For acute management, adenosine, with a short half life of less than 5 seconds is advisable. Metoprolol or propranolol give beneficial results but should be avoided in the first trimester if possible. For prophylactic therapy, digoxin and metoprolol are the safest agents available.

CHRONIC MANAGEMENT OF AVNRT

This is needed only in patients with bothersome episodes (e.g., occurring several times annually). If WPW syndrome and structural heart diseases are excluded, one tablet of verapamil (80 mg) may be taken during acute attacks if vagal maneuvers fail. The earlier the drug is taken, the greater the efficacy. An additional 80-mg tablet may be taken 1 hour later if the arrhythmia persists and is well-tolerated. If this is not effective, the patient is advised to go to the emergency room, where IV verapamil or adenosine can be given safely.

Patients with frequent episodes (e.g., monthly and requiring frequent visits to the emergency room) deserve daily medications; Digoxin is economical and has a role as a one-a-day tablet. A β -blocker usually is effective in over 75% of patients. Verapamil, although widely used, has only a modest prophylactic effect. One-half of a 240-mg sustained release verapamil tablet may be tried and appears to be effective in about 33% of patients. Sotalol may be more effective than the other agents but must not be used concomitantly with diuretics that decrease serum potassium. Flecainide (200–400 mg daily) has been shown to decrease freedom from recurrent tachycardia in up to 80% of patients, compared with 15% in individuals administered placebo. Pooled studies indicate that flecainide is effective in approximately 77% of patients with AVNRT and 70% of those with AVRT. The drug has undesirable side effects. Because an increase in mortality has been observed in patients treated for ventricular arrhythmias, the drug is not

approved by the US Food and Drug Administration (FDA) for PSVT and caution is required. If episodes remain bothersome, catheter modification of the AV junction with radiofrequency energy is indicated.

Catheter Ablation

Catheter ablation is the preferred therapy, over long-term pharmacological therapy, in the following:

- For patients with frequent episodes of tachycardia.
- Related to lifestyle issues: e.g., competitive athletes, recreational pilots; some patients with fast rates greater than 200 BPM, who are not close to emergency room facilities for reversal and other considerations may be offered ablation as first-line therapy particularly because drug efficacy is less than 45%.
- Patients with asthma in whom adenosine is relatively contraindicated, and β -blockers cannot be used chronically.

Although the risk of AV block and pacemaker implantation related to the procedure is low, the patient must be willing to accept this risk. It is advisable to target the slow pathway along the posteroseptal region of the tricuspid annulus initially because this reduces the risk of heart block to approximately 1%. Success is expected in >96%. Fast pathway ablation may cause AV block (~8%), and is advisable only if slow pathway ablation fails. The recurrence rate after ablation is approximately 3–7%.

Atrial Tachycardia

Atrial tachycardia can be paroxysmal, nonparoxysmal, “incessant,” or multifocal. ECG hallmarks include the following:

- The atrial rate is generally 150–200/minute. The P-wave precedes the QRS; the P-wave polarity depends on the site of origin in the atrium (Fig. 6.8.). A positive P-wave in leads 2, 3, and aVF excludes AVNRT or WPW circus movement tachycardia.
- Rhythm is regular but beats may be grouped in pairs, causing some irregularity.
- AV conduction may vary 1:1, 2:1, 3:2.

PERSISTENT (“INCESSANT”) ATRIAL TACHYCARDIA

The rhythm is regular, P-waves are in front of the QRS, and carotid sinus massage increases the AV block.

This very rare persistent arrhythmia of unknown mechanism may cause dilated cardiomyopathy; removal of the area of impulse formation is curative.

Paroxysmal Atrial Tachycardia With Block

ECG hallmarks include the following:

- Isoelectric intervals can be observed between P-waves and the QRS; the T-waves for the hidden P-waves; the atrial rate may be irregular. Figure 6.9. shows a tracing with variable AV block.
- An atrial rate less than 200 excludes atrial flutter except in patients receiving quinidine. If the heart rate is 90–120/minute with a normal serum potassium and symptoms of angina and dyspnea are absent, no immediate treatment is required. If the serum potassium is less than 3.5 mEq(mmol)/L and a high degree of AV block is absent, give potassium chloride IV (60 mEq) in 1 L normal saline over 5 hours. With more intelligent use of digoxin, this arrhythmia has become uncommon with digoxin use. “PAT with block” is not always caused by digitalis toxicity.

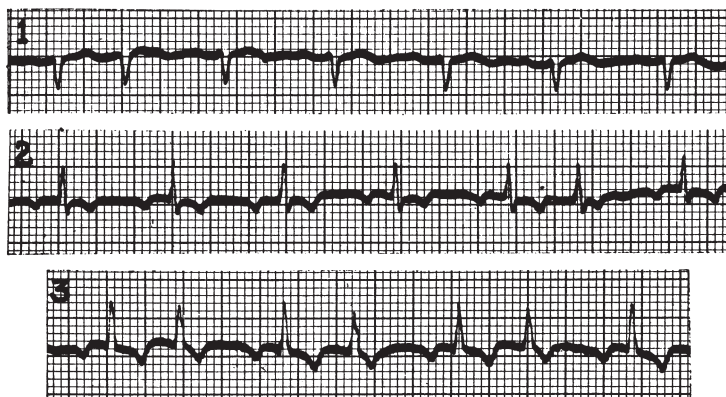


Fig. 6.8. Atrial tachycardia with atrioventricular (AV) block in a patient not receiving digitalis. The P-waves are barely discernible in lead 1 and are inverted in leads 2 and 3. The AV block varies between 2:1 and 3:2. In lead 3, the 3:2 ratio is constant, leaving the ventricular beats grouped in pairs—a common cause of bigeminy. From Marriott HJL. *Practical electrocardiography*. Eighth edition, Baltimore, MD: Williams & Wilkins, 1988:175.

Multifocal atrial tachycardia ECG hallmarks include the following:

- The rhythm is irregular, chaotic atrial rhythm.
- At least three different P-wave morphologies should be recognized in one lead (Fig. 6.9.). The PR interval is variable.

Multifocal atrial tachycardia and other ectopic atrial tachycardias are usually seen in patients with:

- Chronic lung disease.
- Hypoxemia.
- Theophylline toxicity.
- IHD.
- Myocarditis.

THERAPY

Therapy should be directed at the underlying cause. If tachycardia is symptomatic or causes cardiac embarrassment, give verapamil (2.5–5 mg IV, repeated in 30 minutes). IV verapamil is usually successful and 80 mg orally three or four times daily can be administered until the underlying problem resolves. Often, the arrhythmia causes no hemodynamic disturbances, especially at rates of 100–130/minute and requires no drug therapy, or the initial dose of verapamil can be given orally. Magnesium sulfate is effective in some patients. Arrhythmias owing to triggered activity or increased automaticity appear to be partly owing to potassium flux from cells; magnesium has a direct effect on potassium channels and increases intracellular potassium.

A β -blocker, especially metoprolol (IV, then orally), is more effective than verapamil, but caution is necessary to avoid the use of β -blockers in patients with chronic obstructive pulmonary disease (COPD). In patients in whom arrhythmia is not terminated by a β -blocker, verapamil, or treatment of the underlying cause and remains bothersome, amiodarone orally may prove effective after a few weeks of administration. Caution: amiodarone is not generally recommended for non-life-threatening arrhythmias.



Fig. 6.9. Multifocal atrial tachycardia. (A) The patient has chronic obstructive lung disease. Tracing on 3-14-73 shows multifocal atrial tachycardia. The rhythm changes to atrial flutter with varying atrioventricular conduction on 3-23-73. (B) Tracing obtained from an 88-year-old man with mitral insufficiency. The multifocal atrial tachycardia closely resembles atrial fibrillation with a rapid ventricular response. From Chou TC, *Electrocardiography in clinical practice* Fourth edition. Philadelphia: WB Saunders, 1996, with permission from Elsevier.

Atrial Flutter

DIAGNOSIS

- Rhythm is regular if there is a fixed AV conduction ratio and irregular if there is variable AV conduction; the term AV block should be avoided in this context.
- Sawtooth pattern of flutter waves in leads 2, 3, and aVF. Positive P-like waves in V, may be negative in V₅ and V₆, with nearly no atrial activity in lead I V₅ and V₆ (see Figs. 6.10. and 6.11.).
- The downward deflection of the F-waves has a gradual slope followed by an abrupt upward deflection that results in the typical sharp spikes of the sawtooth pattern.
- T-waves may distort the F-wave pattern.
- The heart rate is often 150/minute, because the atrial rate is commonly 300/minute with 2:1 conduction. Conduction ratios of 2:1 and 4:1 occur commonly.
- The atrial rate varies from 250–400 BPM but can be less than 200 BPM in patients taking quinidine.
- If the diagnosis is not obvious, flutter waves can be made visible with carotid sinus massage or adenosine that slows AV conduction .

Atrial flutter is usually owing to underlying cardiac pathology, particularly IHD, MI, and valvular heart disease. Noncardiac disturbances may initiate atrial flutter: hypoxemia caused by pulmonary embolism, pneumothorax, chronic lung disease, and thyrotoxico-

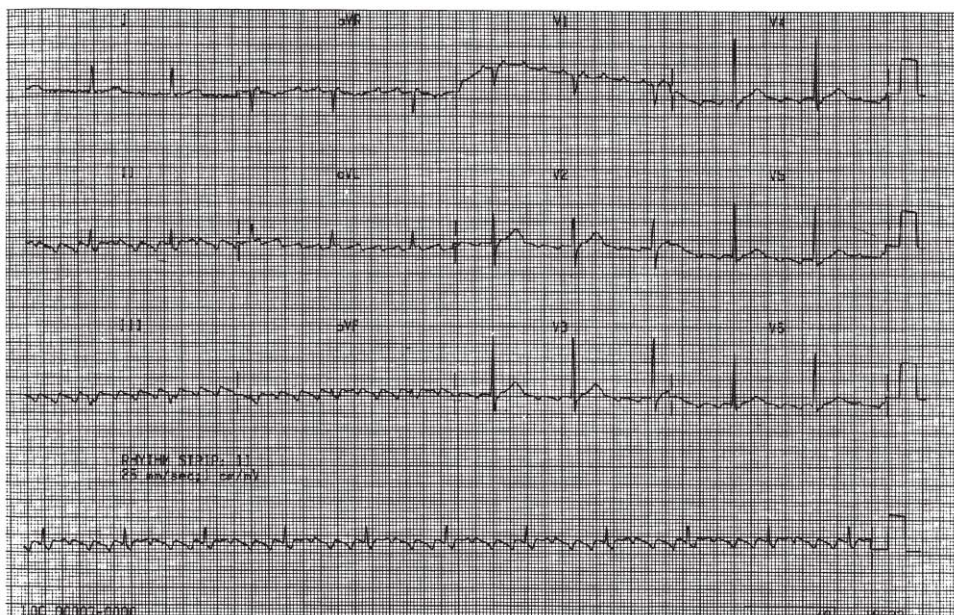


Fig. 6.10. Atrial flutter with fixed 4:1 atrioventricular AV conduction. The zigzag “saw-tooth” waves are readily seen in leads II, III, and avF but assume a P-like form in VI.

sis. Removal of the underlying cause may be followed by spontaneous reversion to sinus rhythm.

In more than 60% of cases, atrial flutter occurs for the first time in association with a specific precipitating event, particularly, major thoracic surgery, pneumonia, acute MI or pneumothorax. In about 33% of cases, atrial flutter is associated with chronic comorbid conditions particularly, HF, hypertension, and chronic lung disease). In fewer than 2% of cases, no cardiac disease or precipitating causes can be defined; lone atrial flutter is thus rare).

The mechanism of this arrhythmia is still not clarified. A re-entrant mechanism in the right atrium is the currently accepted mechanism for the common (type 1) atrial flutter.

THERAPY

Atrial flutter is easily converted to sinus rhythm by synchronized direct current (DC) shock, 20 J increased to 50 J, if required. This should be carried out early if the patient is hemodynamically compromised, has symptoms or signs of ischemia or a ventricular response greater than 200/minute, or is known or suspected of having WPW syndrome. For patients with a ventricular rate less than 200/minute, diltiazem, esmolol, propranolol, or metoprolol may be used to slow the ventricular response. Digoxin often converts atrial flutter to AF and slows the ventricular response. Verapamil may reduce the ventricular response, but conversion to sinus rhythm rarely occurs. Verapamil, digoxin, and β -blockers are contraindicated in patients with WPW presenting with atrial flutter or AF. In this setting, verapamil or digoxin may precipitate VF. Rapid atrial pacing is effective in terminating atrial flutter, but in drug-refractory cases, cardioversion is usually used.

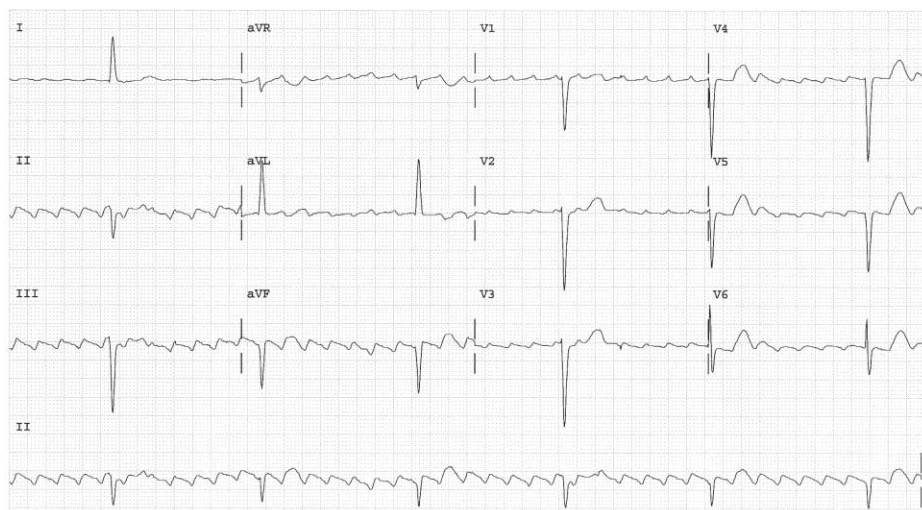


Fig. 6.11. The tracing shows typical atrial flutter.

Flecainide

This drug is expected to convert atrial flutter to sinus rhythm in less than 20% of patients and, therefore, is not sufficiently effective to recommend its use. Caution is needed because doses of 25–50 mg twice daily have precipitated incessant sustained VT, incessant atrial flutter with rapid ventricular rates, VT, HF, and a high incidence of noncardiac adverse effects. The drug is not approved by the FDA for this indication.

IBUTILIDE

This drug is effective for patients with atrial flutter but should not be used in patients with EF of less than 30% because polymorphic VT may be precipitated.

Propafenone

Conversion to sinus rhythm is expected in less than 33% of patients given propafenone. The effect is slightly better than flecainide, with fewer adverse effects, but this agent may cause ventricular acceleration and hemodynamic depression. Propafenone may have a role in a small number of properly selected patients but should be administered under the guidance of a cardiologist and with continuous ECG monitoring in a cardiac care unit.

A dosage of 2 mg/kg IV infusion over 10 minutes is used.

Contraindications

- HF or LV dysfunction.
- Asthma or COPD.
- Conduction defects, bundle branch block, second- or third-degree AV block.
- Sinus node dysfunction, severe bradycardia.
- Electrolyte disturbances.
- Hypotension.
- Myasthenia gravis.
- Pregnancy.

Anticoagulants for Flutter

Observational studies have shown a 2–7% risk of embolization that is only slightly less than observed with nonvalvular AF; risk factors for development of embolization are similar to that of AF.

Although the risk of embolization after DC cardioversion for atrial flutter (2.2%) is lower than that for AF (~6%) the guidelines for anticoagulation for patients with AF should be extended to those with atrial flutter because significant embolization has been observed in negative transesophageal echocardiography (TEE) subjects.

Electrical or chemical cardioversion should be done only in adequately anticoagulated patients. A negative TEE should be followed by anticoagulation, because it by itself it is not protective against thromboembolism.

Catheter Ablation

Techniques for placing lesions between the tricuspid annulus and the inferior vena cava to block the atrial flutter circuit and criteria to prove the existence of bidirectional block are available and can cure patients with isthmus-dependent flutter.

ATRIAL FIBRILLATION

Diagnosis

AF is the most common sustained arrhythmia observed in clinical practice.

The rhythm is completely irregular. RR intervals are irregularly irregular and may vary in amplitude.

Depending on the degree of AV conduction, the ventricular response is described as controlled if the heart rate is less than 100/minute and uncontrolled or fast ventricular response if the rate exceeds 120/minute (Fig. 6.12.). The atrial rate varies from 400–700 BPM and variable AV conduction causes a chaotic ventricular response.

The absence of P-waves, which are replaced by irregular F-waves, also indicates AF. These undulations of the baseline may be gross and distinct, barely perceptible, or invisible in V, where undulations are best visualized. Figure 6.13. shows coarse AF with large irregular undulations in V1.

The heart rate is commonly 100–160 BPM; fast rates beyond this may cause diffuse ST-segment depression (Fig. 6.14.).

A slow regular ventricular response of 40–50 BPM in a patient with known AF on digoxin indicates complete AV dissociation with an independent junctional rhythm that may be caused by digitalis toxicity (Fig. 6.15.). A slow regular ventricular rate less than 40 BPM indicates complete AV block and a junctional escape rhythm.

In patients with cardiac pathology, the overall prevalence rate of AF is 4%. AF is present in more than 50% of patients with mitral stenosis or HF.

Causes of AF include valvular heart disease, hypertension, IHD, cardiomyopathies, cor pulmonale, pulmonary embolism post-thoracotomy, post-coronary bypass graft (CABG), and conditions as diverse as carcinoma of lung thyrotoxicosis, sick sinus syndrome producing tachyarrhythmias and bradyarrhythmias, WPW syndrome, alcohol abuse, postthoracotomy, esophagojejunostomy, ruptured esophagus, carbon monoxide poisoning, and idiopathic.

Investigations should include an echocardiogram to confirm underlying structural heart disease and evaluate left atrial size. Two-dimensional echocardiography may miss

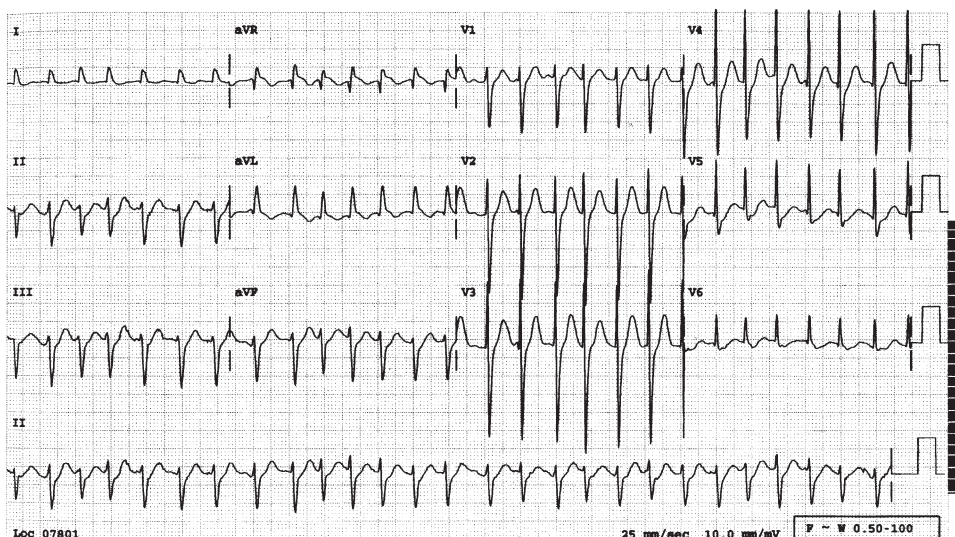


Fig. 6.12. Atrial fibrillation, uncontrolled ventricular response 163/minute.

atrial thrombus detected by TEE. Also, chest X-ray and serum thyrotropin (sTSH) are required.

Approaches to prevent the development of atrial fibrillation is of utmost importance. There is suggested evidence that treatment with statins and ACE inhibitors or angiotensin receptor blockers might reduce the risk of atrial fibrillation.

CAUTION

AF with a fast ventricular rate greater than 240/minute, often with wide QRS complex, occurs in up to 10% of patients with WPW syndrome. In this subset of patients, digoxin, β -blockers, and calcium antagonists and lidocaine are contraindicated because VF may be precipitated (*see* discussion of WPW syndrome).

THERAPY

An algorithm that gives suggestive steps for consideration in the management of AF is depicted in [Figure 6.16](#); algorithms do not cover all scenarios, however, and can be criticized.

DIGOXIN

Digoxin is used in most patients, particularly in those with HF, to control the ventricular response, except when the ventricular rate is greater than 220/minute and WPW syndrome is suspected. Digoxin has a role especially if HF requires digitalis therapy on a chronic basis. In symptomatic patients with ventricular rate of 150–200/minute, give digoxin IV 0.5 mg slowly under ECG monitoring, followed by 0.25 mg IV in 2 hours and repeat if needed 2 to 4 hours to control the ventricular response. A total dose of 1–1.25 mg is usually necessary if the patient has not taken digoxin in the past 2 weeks. For patients who have taken digoxin within 1 week, a dose of 0.125 mg IV should be tried, followed by an additional 0.125 mg after 2 hours if needed, followed by maintenance

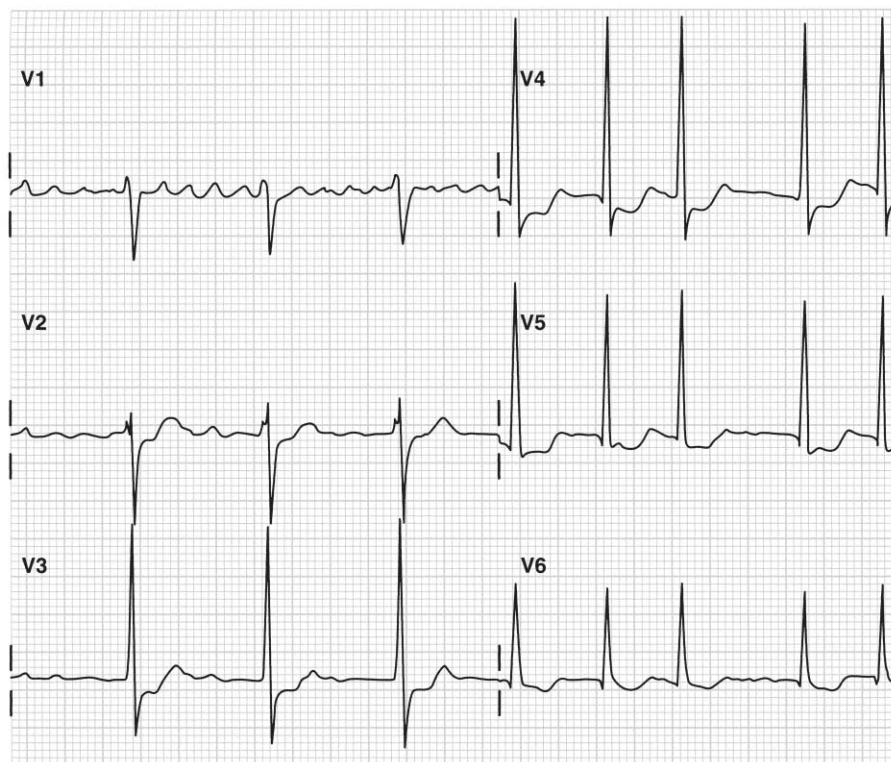


Fig. 6.13. The tracing shows atrial fibrillation with a ventricular response rate of 105 beats/minute; note the coarse atrial fibrillation in lead V1.

doses (0.25–0.375 mg daily). In the elderly or in patients with mild renal dysfunction, give 0.125 mg daily. This dose is stabilized using the apical rate as a guide and not resorting to the inappropriate use of digoxin serum levels (*see* Chapter 5). Digoxin does not cause reversion to sinus rhythm; spontaneous reversion may occur. In some patients, digoxin fails to prevent activity-induced tachycardia and a small dose of a β -blocker (e.g., 25 mg atenolol daily, 50–100 mg metoprolol daily) usually causes a satisfactory reduction of fast heart rates. *In patients with heart failure a combination of a digoxin and carvediol is beneficial.*

DILTIAZEM

Diltiazem IV is useful for the control of fast ventricular rates in patients without HF and in the absence of significant LV dysfunction. The drug has replaced verapamil, which causes a high incidence of HF. Also, a therapeutic response is observed in 3 minutes versus 7 minutes for verapamil. Caution: hypotension may ensue.

Dosage: An initial IV bolus of 20 mg (0.25 mg/kg) is given over 2 minutes, and another bolus of 25 mg (0.35 mg/kg) over 2 minutes 15 minutes later can be given; if necessary, use IV continuous infusion (under medical supervision). A dose of 5–10 mg/hour may be started after the bolus dose to maintain response for 24 hours. Increase to 15 mg/hour if needed. Repeat bolus/infusion sequence if response is lost.

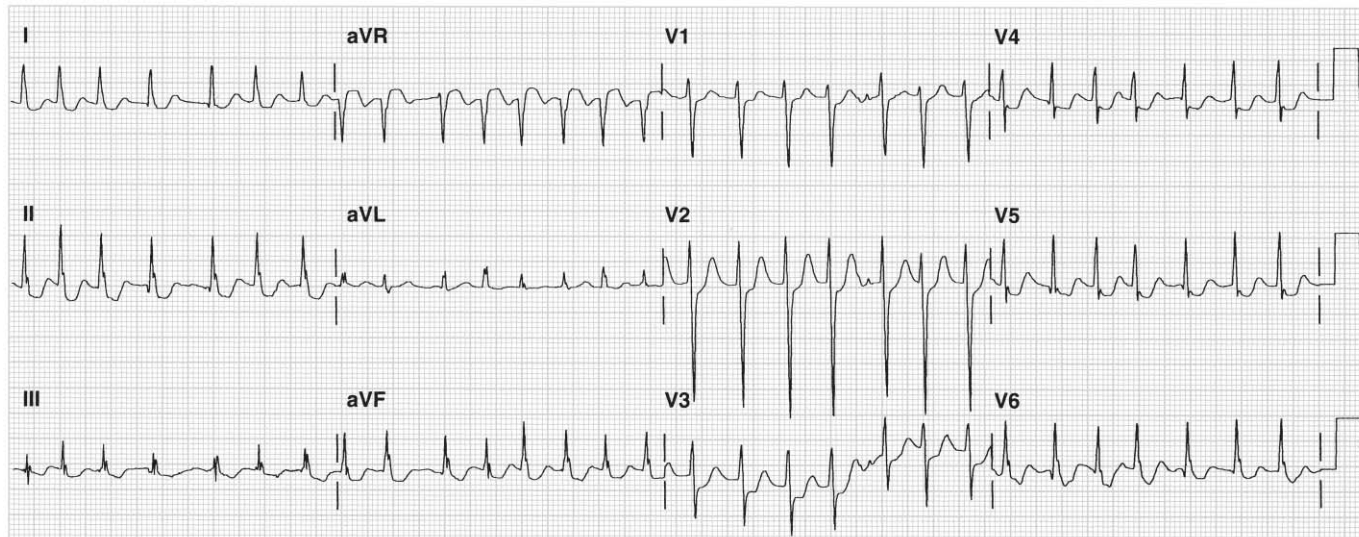


Fig. 6.14. Shows atrial fibrillation with a fast ventricular response of 175 beats per minute and ST-T wave changes likely secondary to the fast rate.

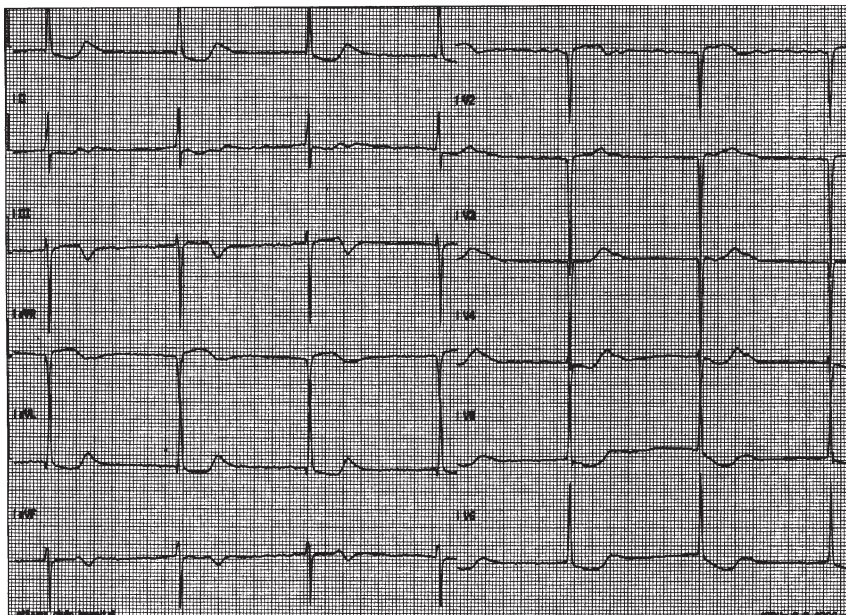


Fig. 6.15. The tracing shows atrial fibrillation with a regular rhythm caused by digitalis toxicity. From Green MS. 1994. *Perspect Cardiology*.

ESMOLOL

Esmolol slows the rate adequately over 20 minutes and sinus rhythm may ensue. The drug causes hypotension in up to 40% of patients. Esmolol and digoxin is effective, and hypotension is much less common than when esmolol alone is used. Digoxin appears to protect from hypotension. In clinical trial 50% of esmolol treated patients with new onset AF converted to sinus rhythm within 30 minutes (*see dosage given earlier for SVT*).

Conversion to Sinus Rhythm. DC cardioversion should be used in individuals with suspected WPW syndrome or heart rate greater than 200, unstable patients, HF, and acute MI with hemodynamic compromise. DC conversion is also deemed necessary in patients with severe aortic stenosis or cardiomyopathy in whom atrial transport function is of great importance. Amiodarone has a role in the latter subset of patients and in others with failed drug therapy or poor LV function.

Ibutilide (Corvert) has been shown to convert up to 48% of patients with AF of recent onset (1–90 days) to sinus rhythm.

Dosage: A 1-mg dose is administered with cardiac monitoring for patients greater than 60 kg; 0.01 mg/kilogram less than 60 kg; a 1-mg dose can be repeated in 20 minutes.

The drug must be avoided in patients with a low serum potassium or a prolonged QT interval because torsades de pointes may be precipitated; the incidence of torsades de pointes is about 5% particularly in patients with coronary artery disease (CAD).

The infusion should be discontinued as soon as AF converts to sinus rhythm or if new or worsening ventricular arrhythmias develop.

Synchronized DC Cardioversion. Consideration of electrical conversion requires careful consideration in properly selected patients. Immediate DC cardioversion is indicated for patients who are hemodynamically unstable:

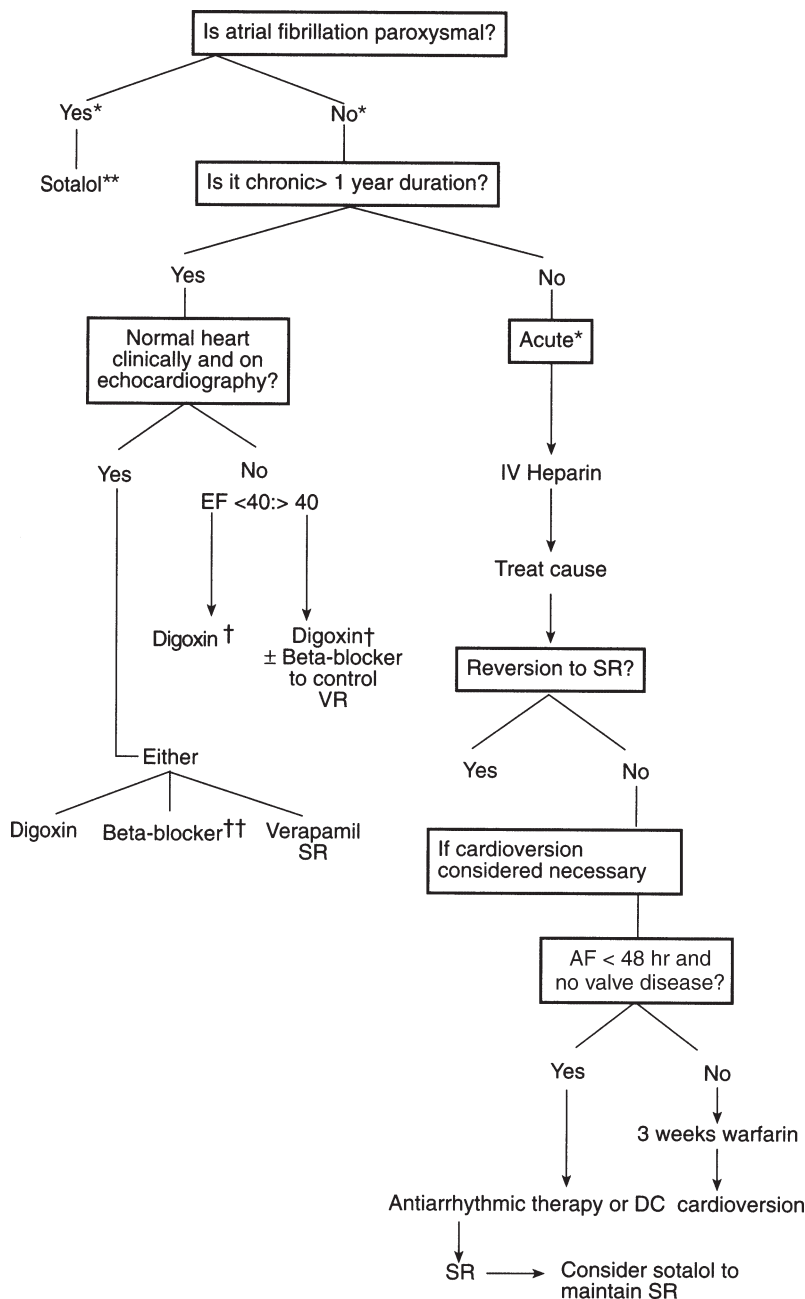


Fig. 6.16. Algorithm for the management of atrial fibrillation. *If hemodynamic compromise or ventricular rate greater than 240/minute, consider urgent cardioversion. **See text for dosage and cautions: if hemodynamically stable, trial of reversion is not indicated because about 60% revert spontaneously over 1–3 days. †Not in obstructive cardiomyopathy or suspected Wolff-Parkinson-White or sick sinus syndrome; ††not sotalol; preferably metoprolol or atenolol to control rate and to avoid risk of torsades de pointes. AF, atrial fibrillation; EF, ejection fraction; IV, intravenous; DC, direct current; VR, ventricular response during activities or exercise (some patients may need β -blocker or verapamil). From Khan M. Gabriel. Cardiac drug therapy. Sixth edition. Philadelphia 2003 WB Saunders, with permission from Elsevier.

- DC cardioversion is usually contraindicated in chronic AF duration greater than 1 year because sinus rhythm is usually not maintained (Fig. 6.16.).
- Patients with AF less than 1 week usually regain AF after conversion.
- If the patient is hemodynamically stable and there is no underlying structural heart disease, a trial of reversion is not indicated because about 60% revert spontaneously over 1–3 days. Control of the ventricular response is readily achieved with the administration of IV esmolol or diltiazem.
- Cardioversion is often not considered worthwhile with chronic AF duration exceeding 1 year because fewer than 60% and 33% of patients remain in sinus rhythm 1 week or 1 year postconversion. But conversion is often attempted where HF or other symptoms of low cardiac output warrant an aggressive approach.
- Embolization occurs in about 2% of patients.
- DC conversion is not advisable in patients with suspected digitalis toxicity because of the risk of precipitating VF, but titrated energy doses are permissible in addition to other measures such as potassium administration.
- Patients with sick sinus syndrome may develop prolonged postconversion pauses, which often can be terminated by a series of chest thumps.
- In patients with left atrial size greater than 5 cm, sinus rhythm is usually not maintained. A report, however, indicates that left atrial size greater than 5 cm does not appear to be a major determinant of failure to maintain sinus rhythm postconversion. Again, the decision depends on the importance of restoring sinus rhythm.
- Amiodarone has been shown to cause reversion and maintenance of sinus rhythm for up to 3 months in approximately 60% of patients with atrial size less than 6 cm.
- For DC conversion, anticoagulants are not generally used if AF has less than 48-hour duration. Because approximately 14% of patients with acute AF reportedly have left atrial thrombus compared with 27% in patients with chronic AF, anticoagulation or TEE is advisable in acute AF, particularly in patients with valvular heart disease before cardioversion.
- If AF is greater than 48 hours duration and conversion is necessary, oral anticoagulants are given. In patients at high risk for embolism with duration slightly over 24 hours, IV heparin for 72 hours and TEE may be an acceptable compromise.

Embolization has been reported postconversion, however, in patients with no visible thrombi on TEE. In a study by Arnold et al. in 454 patients undergoing direct current cardioversion, the incidence rate of embolism in nonanticoagulated patients with AF average duration 6 ± 4 days was 1.32% (6 patients), compared with no embolic complications in patients who received oral anticoagulants to maintain a prothrombin time equal to or greater than 15 seconds. Nonanticoagulated patients with atrial flutter undergoing cardioversion did not have embolic complications, which supports the usual recommendation that patients with atrial flutter do not require anticoagulants during conversion or for long-term therapy. Although embolization has occurred in patients with flutter and caution is required depending on the underlying cause of atrial flutter.

When anticoagulants are commenced in patients with AF undergoing cardioversion, these agents should be continued for at least 3 weeks postconversion because mechanical atrial systole with peak A-wave velocity returns only after about 3 weeks postconversion to sinus rhythm.

- Digoxin is maintained for the period before conversion and is interrupted 24–48 hours before conversion.
- Light anesthesia, IV diazepam, midazolam, or thiopental with a standby anesthesiologist is necessary.

Quinidine given immediately after conversion and continued to increase the chance of perpetuating sinus rhythm is not of proven value. In addition, quinidine is associated with a threefold increase in mortality.

The combination of low-dose quinidine (480 mg/day) and verapamil (240 mg/day) has been shown to maintain sinus rhythm in up to 60% of patients followed for 2 years. Verapamil must not be used in patients with HF or EF less than 40%.

Sotalol

Sotalol appear to be as effective as quinidine in prevention of recurrent AF and for the maintenance of sinus rhythm.

- This unique β -blocking drug is useful for the prevention of recurrent management of paroxysmal AF, but has only about a 33% success rate; other β -blockers are not effective for maintaining sinus rhythm. Postcardioversion, the drug has a definite role.
- For the control of fast ventricular rates caused by AF, sotalol should not be used because all other β -blockers are as effective and do not carry the rare risk of torsades de pointes.
- Patients administered sotalol should not be given potassium losing diuretics and the serum potassium should be maintained greater than 4.5 mmol/L.
- Alboni et al. have suggested outpatient treatment of recent-onset atrial fibrillation with the "Pill-in-the-Pocket" approach.

Amiodarone is reserved for patients with EF less than 30% in whom the maintenance of sinus rhythm is considered essential.

Chronic AF

- Slowing of the ventricular response with digitalis suffices in most elderly patients (>70) because they do usually participate in heart rate increasing activities. A small dose of a β -blocker can be added if rates exceed 100 BPM when on digoxin.
- Younger patients who have a fast ventricular response during daily activities or on exercise are best managed with a β -blocker. If tiredness occurs, the dose is reduced and the old wonderful drug digoxin is added.
- Patients with all grades of HF and AF should be managed with a combination of digoxin and judicious use of carvedilol or metoprolol.
- *Khand et al. have recently shown that the combination of carvedilol and digoxin appears generally superior to either carvedilol or digoxin alone in the management of persistent AF in patients with HF.*

ANTICOAGULANTS FOR AF

Guidelines for the prevention of thromboembolism in patients with chronic AF are given in [Fig. 6.17](#).

- Patients with paroxysmal AF should be anticoagulated to prevent embolization.
- In patients with chronic AF and structural heart disease, systemic embolization is expected in more than 33% of patients over a period of 5 years. Risk of embolization is about 20% higher in patients with rheumatic valvular disease and dilated cardiomyopathy; thus, anticoagulation is strongly recommended in patients with structural heart disease (*see Fig. 6.17*).

In patients under the age of 60 who have lone AF (absence of cardiopulmonary disease or hypertension), the risk of stroke is less than 0.5% per year; if hypertension is included,

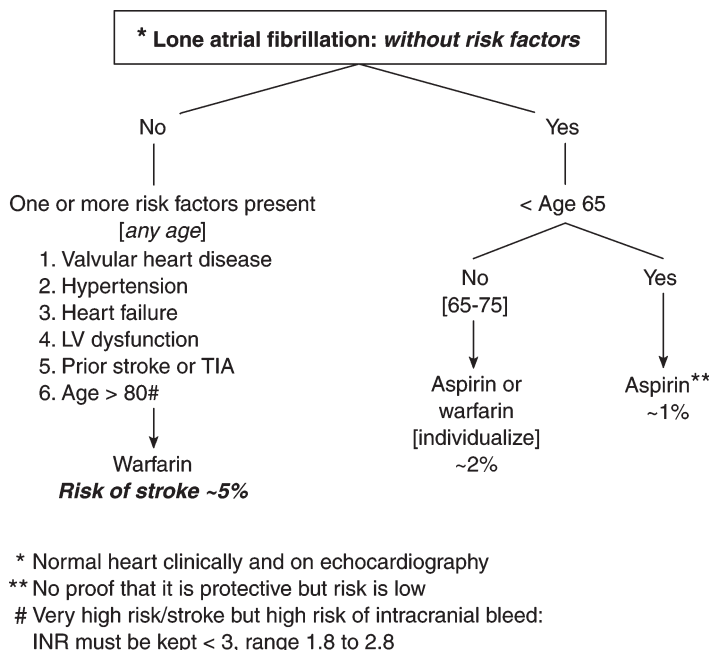


Fig. 6.17. Guidelines for the prevention of thromboembolism in patients with chronic atrial fibrillation. LVD, left ventricular dysfunction. From Khan M Gabriel. Cardiac drug therapy. Sixth edition. Philadelphia: WB Saunders, 2003, with permission from Elsevier.

as in the Framingham Study, the risk of stroke increases to 2.6% per year in older patients (mean age, 70 years).

In the Copenhagen AF, Aspirin, Anticoagulant study of 1000 patients with nonrheumatic AF, the stroke reduction risk was 58% for oral anticoagulants and only 16% for aspirin. In the Stroke Prevention in AF study, stroke risk reduction was 67% for anticoagulants and 42% for aspirin, but this was an interrupted study and a direct comparison of warfarin and aspirin was not done; aspirin reduced the stroke rate mainly in younger patients (under age 60). Aspirin (162–325 mg daily) has a role in patients less than age 70 with lone AF if relative contraindications to anticoagulants exist; 165–325 mg daily is advisable.

Ximelagatran

This oral direct thrombin inhibitor has been shown in two large, randomized trials, Stroke Prevention Using Oral Thrombin Inhibitor in AF (SPORTIF) III and SPORTIF V, to be at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism in a fairly high-risk population of patients with nonvalvular AF. In 3410 patients randomized to 36 mg of ximelagatran twice daily or to controlled warfarin at 17.4 months follow-up there were 56 patients in the warfarin group and 40 patients in the treated group with stroke or systemic embolism ($p=0.10$). Bleeding was significantly higher in the warfarin group than in the treated group $p=0.007$.

Elevation of Transaminases. Three times the upper limit of normal occurred in 6% of the treated group mainly between two and six months. In 3.4% of treated patients, alanine aminotransferase greater than five times the upper limit of normal was observed

but returned to normal upon discontinuation of the drug and death has been reported. It is advisable to check alanine aminotransferase at 2 and 6 months. This drug should replace warfarin in patients with nonvalvular AF because no anticoagulant monitoring is necessary. Further trials would indicate if the drug can replace warfarin in patients with high-risk valvular AF patients. Clopidogrel is also being tested for the management of AF reached here.

VITAMIN K₁

A markedly elevated international normalized ratio (INR) may be lowered by high doses of IV vitamin K₁ (e.g., 10 mg). Unfortunately this may be associated with anaphylactic reactions and may lower the INR more than necessary and lead to warfarin resistance for up to a week. Subcutaneous vitamin K₁ is not advisable because its effect is unpredictable and sometimes delayed. Oral administration is preferred and is predictably effective; it has the advantages of safety over parenteral routes.

Ablation Therapy

PULMONARY VEIN ABLATION

Percutaneous catheters are used to identify the location of arrhythmogenic foci within all four pulmonary veins. Either segmental pulmonary vein isolation or circumferential pulmonary vein ablation techniques are used at different centers. In skilled hands and in patients with one focus, the success rate approaches 80%. Left atrial ablation to encircle the pulmonary veins has been shown to improve survival, reduces the risk of HF and stroke, and improves quality of life when compared with medical therapy. The success rate is low in patients with persistent AF and lower in those with structural heart disease than in those without.

Patients not suitable for pulmonary vein ablation include those with a large left atrium of greater than 60 mm, patients with contraindications to anticoagulants, and the elderly (over 75 years of age). Before considering pulmonary vein ablation, sinus node dysfunction (sick sinus syndrome), thyrotoxicosis, AVNRT, and WPW syndrome must be excluded.

In a study from the University of Michigan (Ann Arbor), segmental pulmonary vein isolation was performed in 93 patients with paroxysmal AF and 17 with persistent AF. At a mean follow-up of 208 days, 28% and 70% of the paroxysmal and persistent AF patients, respectively, experienced recurrent episodes of symptomatic fibrillation in the first 2 weeks after ablation. Good clinical results were achieved in patients with valvular disease, cardiomyopathy, and CAD with or without left ventricle dysfunction. Because of these encouraging results, an algorithm has been proposed by the AHA/ACC.

Nademanee et al. assessed complex fractionated electrograms (CFAEs). The study included 121 patients with refractory AF (57 paroxysmal, 64 chronic).

All patients underwent nonfluoroscopic electroanatomic mapping. Ablations of the areas associated with CFAEs (interatrial septum, pulmonary veins, roof of left atrium, and left posteroseptal mitral annulus and coronary sinus ostium), caused termination of fibrillation without external cardioversion in 115 patients (95%); 32 (28%) needed ibutilide treatment. At the one-year follow-up, 91% were free of AF after one ablation and 18 after two.

Kottkamp et al. studied specific linear left atrial lesions in 70 patients with drug-refractory persistent and paroxysmal AF. Patients underwent intraoperative radiofrequency ablation using video-assisted minimally invasive techniques via minithoracotomy. Mean follow-up was 18 months. Six months following ablation, 93% of patients were in sinus rhythm in both groups and at 12 months, 96% were in sinus rhythm. The linear lesion line concept is not yet practicable when applied percutaneously. The pathophysiological concept is the prevention of anatomically defined left atrial reentrant circuits without mass reduction and without treatment of potential triggers. It is possible that in the future, this intraoperatively validated strategic linear left atrial lesion line concept might be transferred to catheter ablation; new navigation and catheter technologies should allow the transfer to percutaneous ablation techniques.

WPW SYNDROME

Diagnosis

The ECG changes in WPW syndrome are not always typical and depend on the distance between the SA node and the accessory pathway; the resulting conduction times are also important: intraatrial, AV node-His, bundle branch, and accessory pathway. Thus, when AV nodal conduction is slowed, ECG features are more prominent and less apparent during exercise or when the accessory pathway is distant from the SA node.

ECG hallmarks include the following:

- A PR interval less than 0.12 second is observed in up to 80% of cases. In approximately 20% of patients, the PR interval is 0.12 second or slightly longer, especially with advancing age.
- A QRS equal to or greater than 0.12 second is not necessary for the diagnosis; in about 20% of cases, the QRS duration is less than 0.11 second.
- A delta-wave is a distinctive but subtle feature (Figs. 6.1., 6.18., 6.20.). A delta-wave is not always present.
- Occasionally, a pseudoinfarction pattern “Q in leads 2, 3, or aVF” is present (Fig. 6.18.).
- R-wave as the sole or main deflection in V₁ and V₂ referred to as type A (Fig. 6.18.) WPW suggests LV localization of the bypass tract.
- Type A pattern and a negative delta-wave in leads 2, 3, and aVF; consider posteroseptal bypass tract; this mimics inferior MI (Figs. 6.18. and 6.19.).
- Type A and isoelectric or negative delta in one of the following leads: 1, aVL, V₅, V₆, consider a left lateral bypass tract.
- A negative P-wave in lead 1 during tachycardia suggests a left-sided bypass tract.
- In so-called “type B WPW,” an S or rS is the dominant deflection in V₁, V₂ and may be mistaken for incomplete left bundle branch block (LBBB) (or voltage criteria for LV hypertrophy [see Fig. 6.20.]). Type B pattern is more commonly seen with right-sided bypass tracts. The terms “type A” and “type B” are no longer considered important hallmarks, but they are ingrained in history and may serve to remind the physician of certain scenarios, for example, tall R in V₁ is not always owing to right ventricular hypertrophy (RVH) or true posterior MI but may be owing to pre-excitation; also, type B is present in up to 25% of cases of Ebstein’s anomaly.
- During tachycardia, P-waves are always separate from the QRS (see Fig. 6.6.).
- AF occurs in 15–39% of cases and rarely exhibits a fast ventricular response (240–300) that may precipitate VF. Fortunately, the bypass tract pathway usually has a longer refractory period than the AV node. If the refractory period is very short, rapid rates

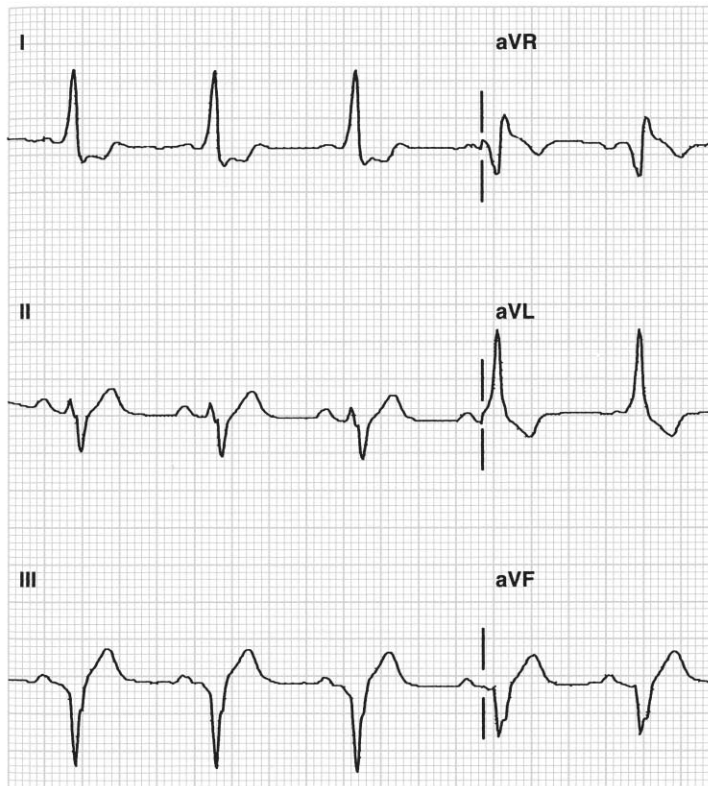


Fig. 6.18. Features of Wolff-Parkinson-White syndrome. Prominent delta-wave in V_2 through V_5 and a very short PR interval. Note how this mimics inferior infarction. From Khan M Gabriel. *Rapid ECG interpretation*. Second Edition. Philadelphia, PA, 2003. WB Saunders, with permission from Elsevier.

(cycle length as short as 0.2 second, ventricular rate of 300/minute) may occur. During spontaneous or induced AF, patients with an increased risk for VF have a mean shortest RR interval less than 205 ms.

- Rarely, atrial flutter is manifest.
- Very rarely, a wide QRS regular tachycardia may be caused by multiple mechanisms, including the antidromic form of tachycardia. AF in this setting causes a wide QRS-irregular tachycardia.
- A clearly observed retrograde inverted P-wave in the ST segment is suggestive of WPW tachyarrhythmia, whereas in AVNRT, the P-wave is usually lost in the QRS complex or causes a pseudo-S in lead 2, aVF, or pseudo-r in V (Fig. 6.6.).
- Rate-related LBBB, consider WPW.
- Patients can have two or more pathways with reciprocation using them and not the AV node.

More than 95% of reentrant tachyarrhythmias associated with an accessory pathway is of the atrioventricular reentrant (AVRT) form and are subclassified as:

- Orthodromic AVRT, or
- Antidromic AVRT.

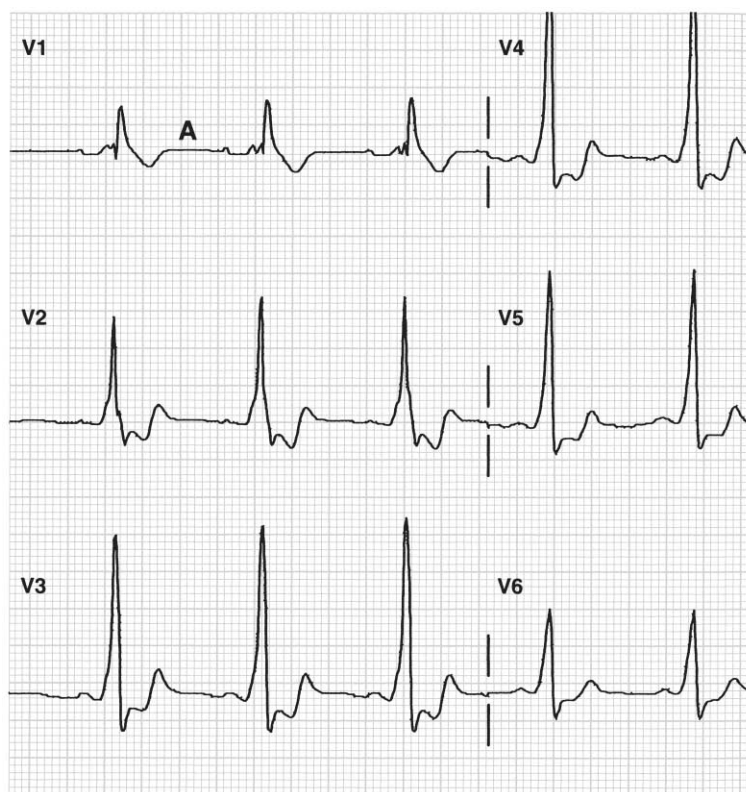


Fig. 6.19. Same tracing as in Fig. 6.18: note the prominent delta-waves and tall R-waves in V₁ and V₂.

Orthodromic Circus Movement Tachycardia

The most common arrhythmia in WPW syndrome is orthodromic AVRT: a circus movement in which the reentrant impulse uses the AV node in the anterograde direction from the atrium to the ventricle and uses the fast accessory pathway in the retrograde direction for conduction from the ventricle to the atrium and is a reciprocating tachycardia.

The RP is less than the PR interval. This situation is present in over 85% of WPW arrhythmia. Rarely, a spontaneous change occurs in some patients from orthodromic to the rare antidromic tachycardia. The presence of QRS alternans during tachycardia suggests orthodromic circus movement tachycardia (Fig. 6.22). In an uncommon type of orthodromic circus movement tachycardia, the RP is \geq PR. The impulse uses retrogradely a slow conducting accessory pathway to activate the atria. The P-wave is negative in leads II, III, aVF, and V₃–V₆ (Fig. 6.22). Studies are necessary to differentiate this circus movement tachycardia from the rare variety of AVNRT that uses a fast pathway for anterograde conduction and the slow pathway for retrograde conduction (see discussion under AVNRT).

Antidromic Circus Movement Tachycardia

This uncommon but clinically important form of tachyarrhythmia occurs in 5–10% of patients with WPW, and over 66% have multiple bypass tracts. In antidromic WPW, the tachycardia uses the accessory pathway in the anterograde direction for conduction from

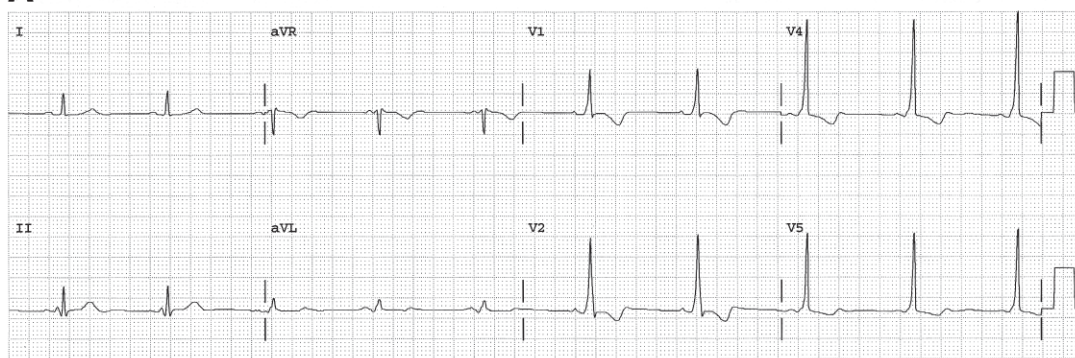
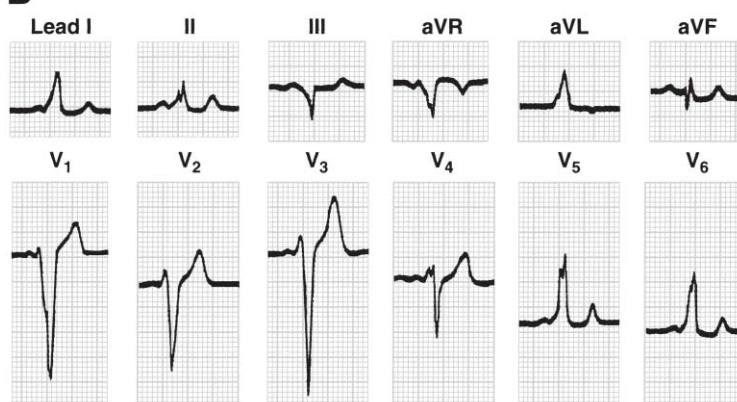
A**B**

Fig. 6.20. (A) Type A Wolff-Parkinson-White syndrome; note the tall R-waves in leads V₁, V₂, and V₃. (B) Type B Wolff-Parkinson-White pattern in healthy 35-year-old man. Note the negative QRS complexes in leads V₁, V₂, and V₃. The tracing resembles closely that of complete left bundle branch block. From Chou TC: *Electrocardiography in clinical practice*; Fourth edition Philadelphia, PA, WB Saunders, 1996, with permission from Elsevier.

the atrium to the ventricle and the AV node or another bypass tract in the retrograde direction to conduct the impulse from the ventricle to the atrium, resulting in rapid wide QRS tachycardia.

Figure 6.23 shows a wide QRS regular tachycardia. The differential diagnosis involves VT (can cause positive concordance) versus WPW antidromic tachycardia; the tracing does not show the diagnostic negative concordance of VT. Positive concordance is a typical feature of WPW antidromic circus movement tachycardia using a left posterior accessory pathway or VT originating in the posterior wall of the left ventricle.

Atié et al. reported dizziness and syncope in 61% and 50% of patients with antidromic tachycardia and in fewer than 10% of patients with orthodromic tachycardia; AF and VF occurred in 16% and 11% of patients. The anterograde refractory period of the bypass tract in patients with VF was less than 200 ms. AF may present with rapid ventricular rates, RR less than 205 ms, with a wide QRS complex. Table 6.6 gives types of tachyarrhythmias observed with WPW and their approximate incidence.

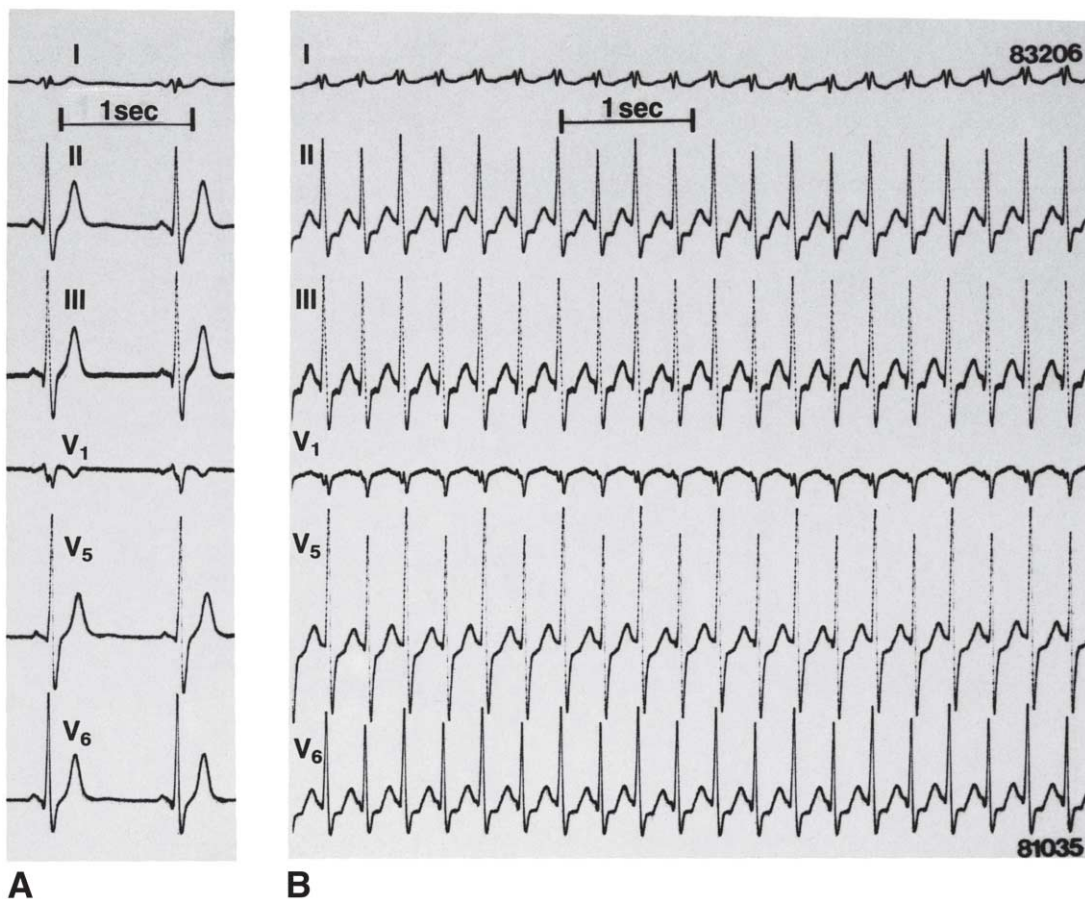


Fig. 6.21. Example of electrical alternans during a circus movement tachycardia. (A) Same patient as in B during sinus rhythm. (B) Several of the leads show alternation in height of successive QRS complexes. Note that the amount of electrical alternans may vary considerably from lead to lead; thus, it is necessary to examine each lead carefully for the presence of this phenomenon. From Wellens JJ, Conover MB. The ECG in emergency decision making. Philadelphia, PA, WB Saunders, 1992:85, with permission from Elsevier.

Associated Diseases and Mimicry

There is an increased incidence of WPW in patients with hypertrophic cardiomyopathy and echocardiographic assessment is advisable in all patients with WPW. Approximately 25% of Ebstein abnormality has a type B ECG pattern. Q-waves in two of the three inferior leads II, III, and aVF may be incorrectly diagnosed as inferior infarction.

- Absence of R in V₁ and initial Q in V₂ simulate anteroseptal infarction.
- Tall R-waves in V₁ may incorrectly suggest RVH or true posterior infarction.
- High QRS voltage may incorrectly suggest LV hypertrophy (LVH).
- Type B or A ECG pattern can be mistaken for incomplete LBBB (Fig. 6.20.) or right bundle branch block (RBBB), respectively.

Risk Stratification

Sudden cardiac death reportedly occurs in approximately 0.27% of patients with WPW syndrome and is unusual to be the first manifestation.

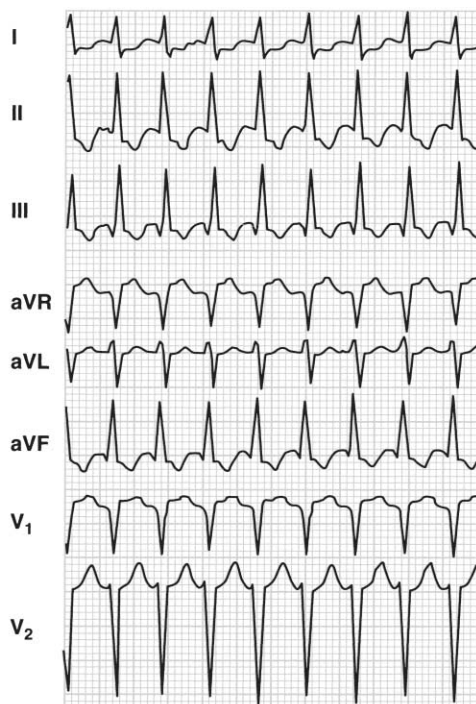


Fig. 6.22. An example of a circus movement tachycardia using a concealed accessory pathway. The diagnosis is based on the position of the P-wave during the tachycardia. Negative P-waves are clearly visible in leads II, III, and aVF following the QRS complex. The P-waves during the tachycardia are positive in leads aVR and aVL, indicating a posteroseptal atrial insertion of the accessory pathway. From Wellens JJ, Conover M.B.: *the ECG in Emergency decision making*. Philadelphia, PA, 1992, WB Saunders, with permission from Elsevier.

WPW patients at high risk for potentially lethal arrhythmias include:

- All patients with PSVT with ventricular rates greater than 240/minute, regular or irregular, narrow or wide QRS. The average heart rate in patients with PSVT owing to AVNRT is about 170/minute and 200/minute with WPW.
- AF with rapid ventricular response. AF occurs in approximately 33% of patients with WPW syndrome and is a potentially life-threatening arrhythmia. Rapid repetitive conduction to the ventricles during AF can result in a rapid ventricular response, pre-excited AF, with subsequent degeneration to VF, in patients with a short anterograde refractory period. There is concern regarding sudden cardiac arrest precipitated by pre-excited AF. Fortunately, catheter ablation eliminates both AVRT and AF.
- Atrial flutter with a rapid ventricular response.
- WPW with hypertrophic cardiomyopathy.
- Ebstein's anomaly.
- Family history of WPW and/or sudden death. Familial WPW syndrome is rare.
- A short anterograde refractory period (<240–270 ms) is a setting for ventricular rates greater than 280 and precipitation of VF if AF supervenes. A refractory period greater than 270 ms is indicated by blockade of conduction through the bypass tract using IV procainamide 10 mg/kg given over 5 minutes with the patient in sinus rhythm. The loss of pre-excitation after IV procainamide has been used to indicate a lowered risk.

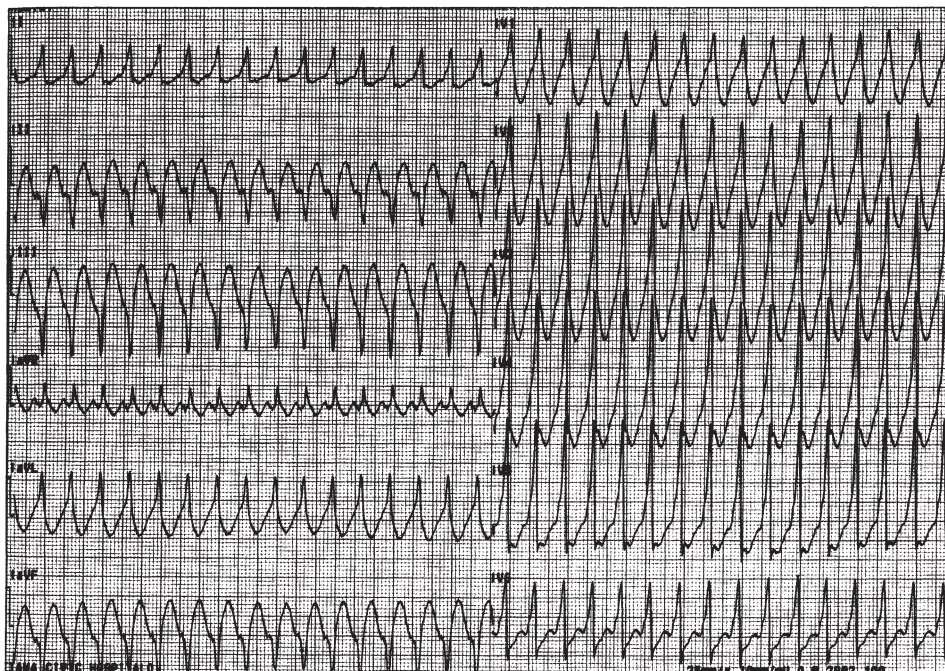


Fig. 6.23. Wide regular QRS tachycardia. The positive concordance suggests ventricular tachycardia or antidromic circus movement tachycardia. This 65-year-old had a long history of palpitations (Wolff-Parkinson-White). From Chandra L, Green MS. *Perspect Cardiol* 1994;13.

- RP less than or equal to PR: This arrhythmia is resistant to drug therapy. Ablation is curative.
- Patients who may have hazardous patterns require EP testing with consideration for ablative therapy.
- If intermittent pre-excitation is observed, characterized by an abrupt loss of the δ wave and normalization of the QRS complex, the accessory pathway virtually always has a relatively long refractory period and is unlikely to precipitate VF.

Drugs and Increased Risk

Digoxin decreases the refractory period of the bypass tract, may increase the ventricular rate in patients with AF or flutter leading to VF, and is best avoided unless the patient has been screened by EP testing. Verapamil may also decrease the refractory period and cause a similar life-threatening situation. Also, verapamil causes vasodilatation and increasing sympathetic stimulation may enhance rapidity of the ventricular response. Lidocaine may also increase sympathetic stimulation and increase the ventricular response.

β -Blockers, digoxin, verapamil, and diltiazem slow conduction in the AV node and should be avoided in patients unless there is proof that the arrhythmia is truly WPW presenting with AVRT orthodromic tachycardia. These agents should not be given unless the diagnosis is clarified, the patient is regarded at low risk of developing anterograde conduction over the bypass tract, and the refractory period of the accessory pathway is greater than 270 ms.

Table 6.6.
Types and Approximate Incidence of Tachyarrhythmias in WPW Syndrome

<i>Tachycardia</i>	<i>Approximate %</i>
AVRT	60
Atrial fibrillation	15–39
Atrial flutter	1
Regular wide complex QRS indistinguishable from VT (antidromic; atrial flutter or BBB during AVRT)	1
Ventricular flutter VF	3

These agents including adenosine are all contraindicated in patients with WPW presenting with AF or atrial flutter or with a wide QRS complex tachycardia. Patients considered at low risk for developing potentially lethal arrhythmias include:

- Intermittent pre-excitation.
- Disappearance of pre-excitation during exercise. A decrease in pre-excitation, however, occurs normally with exercise and must not be taken as an index of low risk;
- The documentation that the refractory period of the bypass tract is greater than 270 ms as indicated by response to IV procainamide or amaline. Procainamide and amaline must not be given to patients with hypertrophic cardiomyopathy and WPW tachyarrhythmia.

Therapy of Orthodromic Tachyarrhythmias

- The emergency room management of AVRT in patients with orthodromic WPW: adenosine rapid bolus injection as indicated in the previous section regarding management of AVNRT. Adenosine is contraindicated with pre-excited tachyarrhythmias.
- Patients with rapid ventricular response greater than 200/minute should be managed with IV procainamide. Caution: avoid in patients with hypertrophic cardiomyopathy. In tachycardia, which could be pre-excited (e.g., AF or flutter), procainamide up to 10 mg/kg IV over 30 minutes, maximum 1 g in 1 hour is advisable, provided that the patient is not hypotensive and does not develop hypotension. Failure to convert the arrhythmia or hemodynamic deterioration is an indication for prompt electrical conversion.
- Patients with the rare type orthodromic circus movement tachycardia require ablation therapy.

Amiodarone has a role in the prevention of paroxysmal AF with rapid rates. Failure to respond is an indication for EP studies with a view to ablative therapy.

Chronic oral β -blocker therapy may be used for treatment of patients with WPW syndrome, particularly if their accessory pathway has been demonstrated during electrophysiological testing to be incapable of rapid anterograde conduction. In a small study of sotalol, 13 of the 16 patients were free of symptomatic recurrences during a median of 36 months of follow-up. Amiodarone has not been shown to be more effective than sotalol and is not advisable.

Propafenone: Experience in small trials of 10–40 cases, including in children, revealed about a 65% effectiveness; combination with a β -blocker improved efficacy and adverse effects were rare. But adverse effects of propafenone have been reported in some studies.

Consideration is required for the use of a pill kept on hand to be used only within minutes of tachyarrhythmia in low-risk patients: 120 mg diltiazem plus 80 mg propranolol appears useful and prevented emergency room visits, being successful in terminating episodes within 2 hours in 81% of patients.

Therapy for Antidromic Tachyarrhythmia

Adenosine should be avoided in the management of pre-excited tachycardias because it may produce AF with a rapid ventricular rate (*see Fig. 6.24.*). Ibutilide, procainamide, or flecainide may be tried in patients with an episode of pre-excited AF or atrial flutter followed by planned ablation.

Catheter Ablation

Patients with orthodromic tachyarrhythmia that is symptomatic or associated with hemodynamic instability, or those with adverse effects or recurrence of arrhythmia during drug therapy should have EP studies and catheter ablation as first-line therapy. Patients with AF or flutter and antidromic tachycardia should have ablation. Catheter ablation carries an approximate 2% risk of a major complication and is not recommended for asymptomatic individuals. Complications include: complete AV block (~0.6%) and cardiac tamponade; perforation of the coronary sinus or myocardial wall, coronary artery dissection, mortality is approximately 0.13%. EP testing is not of value in asymptomatic patients and is not advisable.

Approximately 33% of asymptomatic patients under age 40 found to have pre-excitation are expected to develop symptoms, whereas discovery after age 40 indicates rare symptomatology in later years.

Most patients with asymptomatic pre-excitation have a good prognosis; cardiac arrest is rarely the first manifestation of the disease.

BRADYARRHYTHMIAS

Severe bradycardia producing symptoms is usually treated with 0.5-0.6 mg atropine, repeated every 2 minutes to a maximum of 2–2.4 mg. When atropine is used to treat asystole before pacing, a dose of 1 mg is given, immediately followed by an additional 1 mg after 2 minutes. Mobitz type 2 block or third-degree AV block, as well as sick sinus syndrome, must be managed with pacing.

VENTRICULAR ARRHYTHMIAS

Diagnosis

GRADES OF VENTRICULAR ARRHYTHMIA

The following grades of ventricular arrhythmia determine outcomes from low-risk to high-risk: benign arrhythmias to potentially lethal and lethal arrhythmias. This grading is important for decision-making concerning appropriate therapy.

- VPBs: Unifocal.
- VPBs: Multifocal.
- VPBs: Couplets, runs, or salvos, three to five consecutive beats.
- Nonsustained VT: A run of three or more consecutive beats lasting less than 30 seconds and not associated with hemodynamic deterioration.
- Sustained VT: Runs equal to or greater than 30 seconds or associated with unstable cardiovascular symptoms or signs (chest pain, shortness of breath, syncope, or clouding of consciousness); sustained VT is considered potentially lethal.
- VF or resuscitation from cardiac arrest: lethal arrhythmias.



Fig. 6.24. ECG from a 46-year-old man with a few short bouts of nonbothersome palpitations over 3 years. Onset of rapid tachycardia with presyncope resulted in an emergency room assessment. ECG reveals atrial fibrillation with a rapid ventricular response, and wide QRS indicating conduction down the accessory pathway (antidromic, pre-excited circus movement). Intravenous procainamide caused reversion; the ECG in sinus rhythm showed Wolff-Parkinson-White syndrome. The patient had electrophysiologic studies and successful ablation. From Khan M Gabriel. *On Call Cardiology*. Second Edition. Philadelphia, PA, WB Saunders, 2003, with permission from Elsevier.

The outcome and prognosis of ventricular arrhythmias are clearly related to EF. An arrhythmia associated with an EF less than 30% has a poor prognosis compared with the same arrhythmia and EF greater than 50%.

The differential diagnosis of a wide QRS complex tachycardia includes:

- VT: Coronary and noncoronary; monomorphic and polymorphic.
- ST with pre-existing bundle branch block (BBB).
- ST with functional aberrant conduction.
- Pre-excited tachycardia, ST with anterograde conduction over an accessory pathway.

The approach to the diagnosis of tachyarrhythmias was discussed earlier in this chapter under diagnostic guidelines. Causes of wide complex tachycardia are given in [Fig. 6.25](#). (see also [Table 6.2](#).) The differentiation of VT and wide QRS forms of ST can be difficult. A long rhythm strip using lead 2 is inadequate. A 12-lead tracing is necessary because the precordial leads show distinctive features of VT ([Figs. 6.1](#)., [6.26](#)., [6.27](#).). Several pieces of advice pervade the scientific literature.

Helpful clues from the physical examination of AV dissociation include:

- Irregular cannon A-waves in the jugular venous pulse.
- Varying intensity of the first heart sound.
- Beat-to-beat changes in SBP.

ECG findings that are diagnostic of VT include:

- A totally negative V_1 – V_6 , precordial concordance is always VT because WPW circus movement tachycardia never causes negative precordial concordance (Fig. 6.1.).
- Predominantly negative QRS complexes V_4 to V_6 is virtually always VT (Fig. 6.28.). Fusion complexes are pathognomonic of VT (Fig. 6.29.). These beats are caused by a merger between conducted sinus (or supraventricular complexes) impulses and ventricular depolarization occurring during AV dissociation.

Suggestive features of VT include:

- AV dissociation: AV dissociation with a ventricular rate faster than the atrial rate generally proves the diagnosis of VT but is revealed in less than 30% of all VTs. Assess for P-waves particularly in leads II, III, aVF, and augmented electrocardiographic leads (arm) (aVR). There are more QRS complexes than P-waves (Figs. 6.29., 6.30.). P-waves are often difficult to recognize during a wide QRS tachycardia. Thus, a search for evidence of VA dissociation on physical examination: irregular cannon A-waves in the jugular venous pulse and variability in the loudness of the first heart sound are useful clues.
- Morphology in V_6 : QS or RS (Fig. 6.28.). Any Q in lead V_6 suggests VT, but only if the complex is mainly negative in lead V_1 (Fig. 6.3.). The rule should not be applied if the QRS complex is positive in lead V_1 .
- Morphology in V_1 : If the QRS is positive, with “left rabbit ear” taller than the right VT is assured (Figs. 6.26., 6.28., 6.31.); if the QRS is negative in V_1 , a wide, predominantly negative but clearly slurred or notched downslope suggests VT.
- Positive concordance suggests VT but WPW antidromic circus movement can cause a wide QRS and positive concordance (Fig. 6.23.). Positive concordance therefore does not exclude antidromic (WPW) AVRT over a left posterior accessory pathway. Atrial flutter with antidromic circus movement should be considered if the patient is known to have WPW syndrome.

If after careful analysis of the 12 lead ECG, the differentiation of VT from ST with a wide QRS complex cannot be made, then the patient should be treated for VT.

A separation of VT into monomorphic and polymorphic appearance aids in clinical recognition of the various types of VT.

Monomorphic implies an identical beat-to-beat QRS configuration with the QRS morphology at times being modified by dissociated P-waves (Fig. 6.26.). The substrate for monomorphic VT is usually within the vicinity of a healed MI and sometimes associated with LV aneurysm, dilated cardiomyopathy, and, rarely, in association with no overt structural heart disease.

Polymorphic VT is characterized by beat-to-beat changes in QRS morphology (Fig. 6.26.); at times, the beat-to-beat changes in QRS appearance may be subtle, and a true polymorphic pattern may be revealed only after careful study of rhythm strips from multiple leads. Polymorphic VT is represented by two clinical scenarios that will be discussed later: torsades de pointes and polymorphic VT in the absence of QT prolongation.

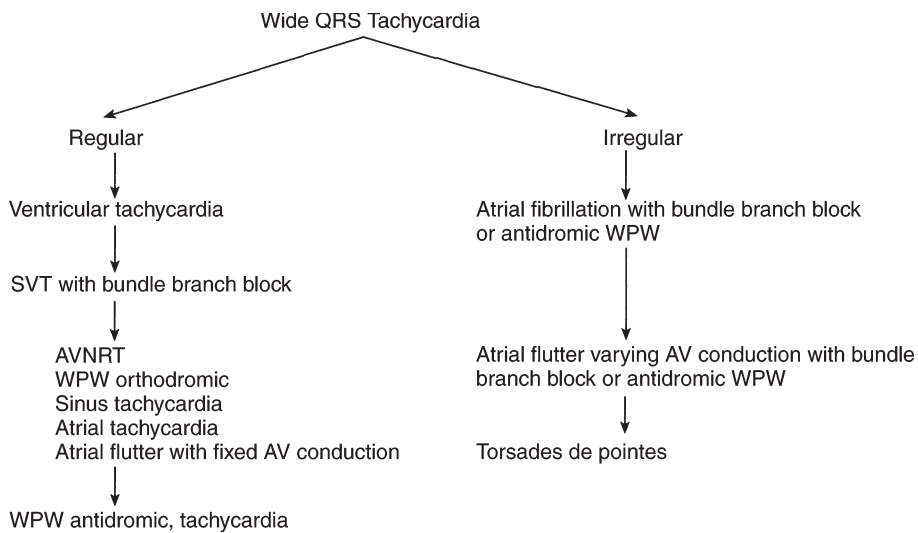


Fig. 6.25. Differential diagnosis of wide QRS tachycardia.

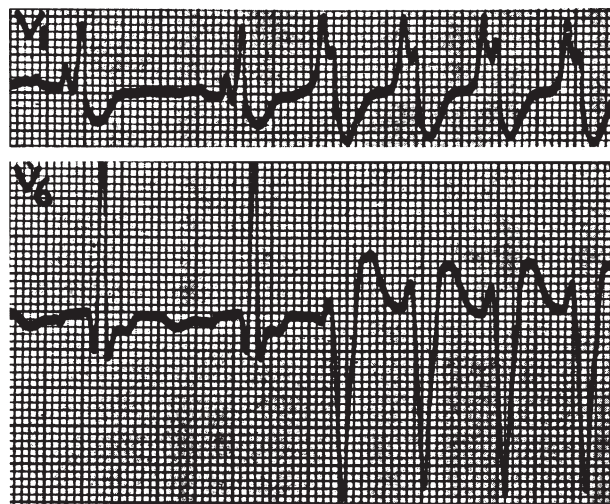


Fig. 6.26. Sinus rhythm with right bundle branch block (RBBB) interrupted by a run of left ventricular tachycardia. Note the “rabbit ears,” with left taller than right in V₁ and rS pattern in V₆ with S-wave almost 25 mm deep. From Marriott HJL. Practical Electrocardiography. Eighth Edition. Baltimore, MD: Williams & Wilkins, 1988:214.

The settings of lethal arrhythmias include sustained VT or VF in patients with severe underlying heart disease. More than 90% of patients in this category have poor LV function with EF less than 35%. Over 80% of these arrhythmias are found in patients with EF less than 30%; there is a high incidence of recurrent lethal arrhythmias. At the other extreme, a few have these arrhythmias in the presence of a structurally normal heart or “primary electrical disease.” ECG tracings depicting VT are given in [Figs. 6.26. to 6.30.](#)

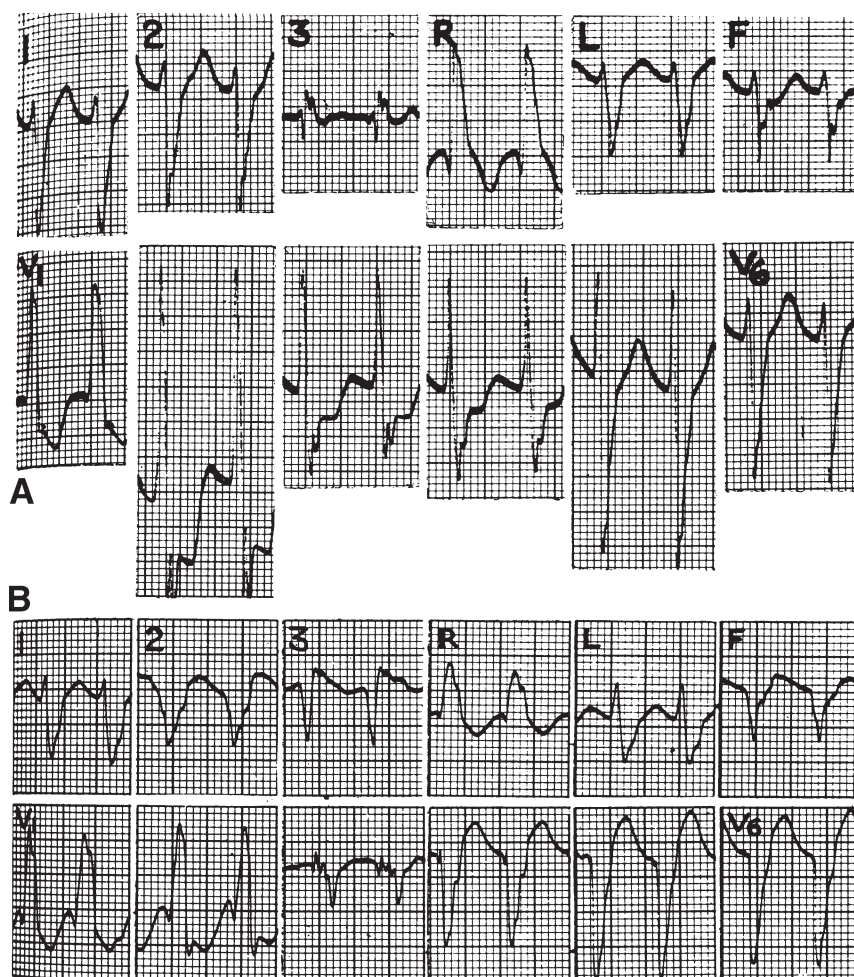


Fig. 6.27. (A) LV tachycardia with axis (-155°) in no-man's land, left rabbit ear taller than right in V_1 and rS in V_6 with S-wave 20 mm deep. (B) LV tachycardia with axis in no-man's land (-135°), taller left rabbit ear in V_1 , and QS complex in V_6 . From Marriott HJL. Practical electrocardiography. Eighth Edition. Baltimore, MD: Williams & Wilkins, 1988:215.

Therapy

A spontaneous significant decrease in benign and potentially lethal VPBs occurs in more than 33% of patients; this favorable outcome should not be ascribed to administered agents.

The use of antiarrhythmic agents to treat ventricular arrhythmias must be justified in the given individual by the presence of life-threatening symptoms or proven benefit on prognosis; this is essential because the occurrence and consequence of late proarrhythmias with antiarrhythmic agents other than encainide, flecainide, moricizine, and propafenone. These four agents, once believed to be relatively safe, are now known to cause an increase in mortality; encainide has been withdrawn. It is the late proarrhythmic effects of antiarrhythmics that are bothersome because the short-term pre-CAST study showed encainide and flecainide to be nearly devoid of early proarrhythmic effects. The subsequent CAST showed long-term therapy to be disastrous in patients eligible for the trial.

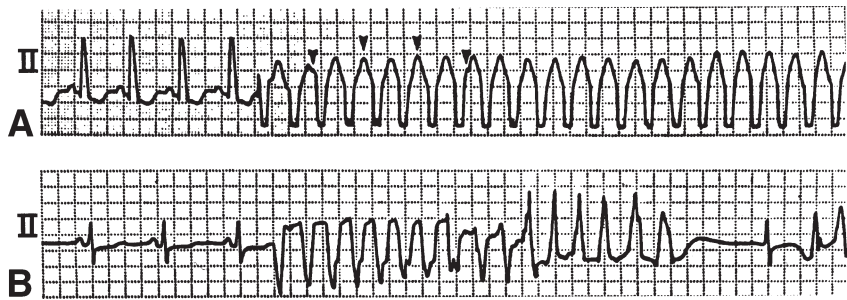


Fig. 6.28. Monomorphic versus polymorphic ventricular tachycardia. Recordings from electrocardiographic bipolar lead II showing monomorphic versus polymorphic QRS morphology. (A) Spontaneous onset of a monomorphic ventricular tachycardia. Note identical beat-to-beat QRS configuration. The arrows depict the dissociated P-waves, which at times modify QRS morphology. (B) Polymorphic ventricular tachycardia characterized by beat-to-beat changes in QRS appearance. From Akhtar M. *Circulation* 1990;82:1562.

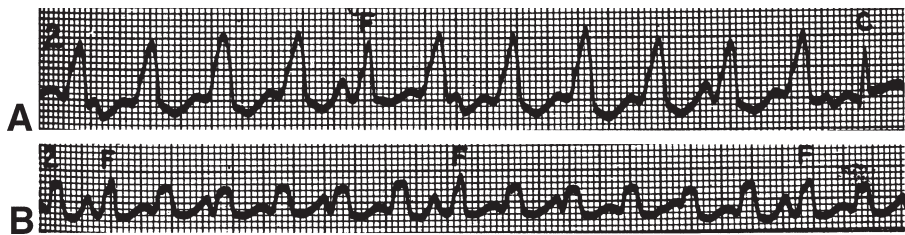


Fig. 6.29. (A) Ventricular tachycardia (rate, 125) showing independent P-waves (atrioventricular dissociation) and capture (C) and fusion (F) beats. (B) Ventricular tachycardia (rate, 155) showing independent P-waves and F beats. From Marriott HJL. *Practical electrocardiography*. Eighth Edition. Baltimore, MD: Williams & Wilkins, 1988:213.

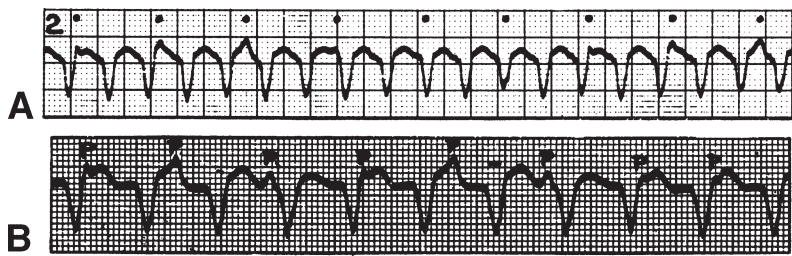


Fig. 6.30. Ventricular tachycardia with independent atrial activity. (A) Ventricular 200/min; atrial activity is indicated by the superposed dots. (B) Relatively slow ventricular rate (120/min) with independent P-waves at slower rate (92/minute). From Marriott HJL. *Practical electrocardiography*. Eighth Edition. Baltimore, MD: Williams & Wilkins, 1988:210.

As well, the study indicates that virtual suppression of VPBs does not prevent sudden cardiac death and the drug may increase the risk of death.

Table 6.7. gives guidelines for the management of ventricular arrhythmias. Arrhythmia in a normal heart rarely requires therapy. VPBs (bigeminy couplets and triplets) do

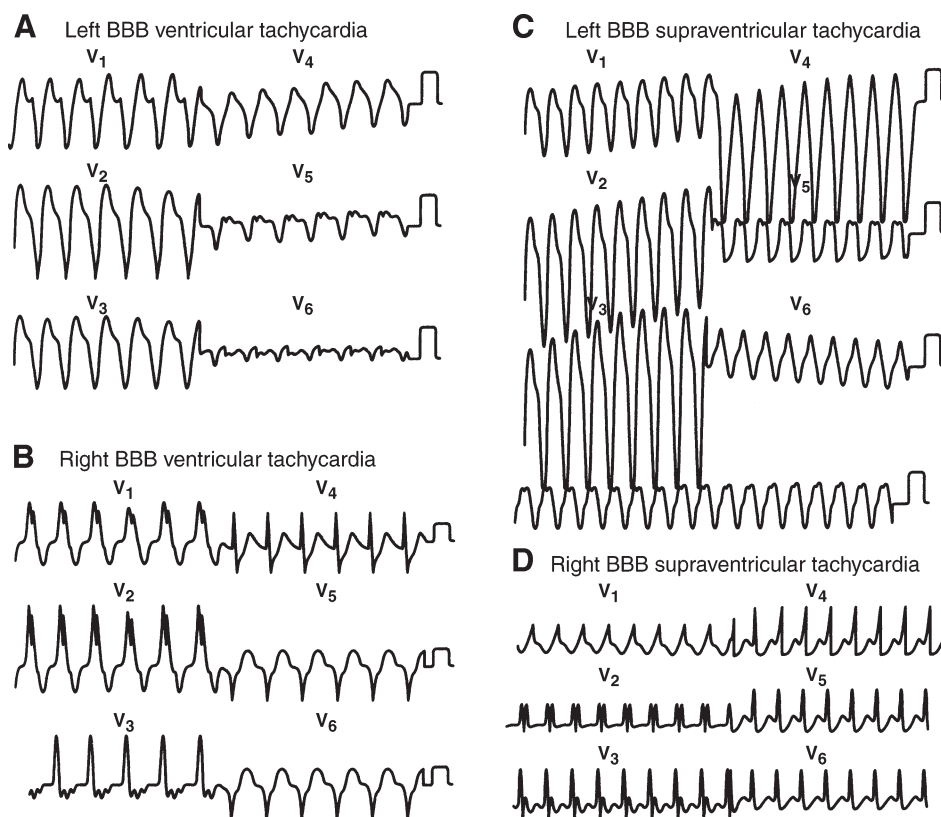


Fig. 6.31. Typical bundle branch block pattern tachycardias. (A) Lead V_1 shows 100 ms to S-wave nadir; lead V_6 has a Q-wave (>40 ms long and >2 mm deep). (B) Lead V_1 has RSR pattern with $R > R'$; lead V_6 has a Q wave (>40 ms long and >2 mm deep). (C) Lead V_1 has QS wave with 50 ms delay to S-wave nadir; lead V_6 has RS wave. (D) Lead V_1 has rSR' pattern with $R' > r$; lead V_6 has RS pattern with $R > S$. BBB, bundle branch block. From Griffiths MJ, Garratt CJ, Mounsey P, et al. *Lancet* 1994;343:386, with permission from Elsevier.

not require drug therapy. If symptoms are bothersome with nonsustained VT, it is advisable to give a trial of a β -blocking drug and to reassure the patient. It is advisable to use metoprolol, timolol, and propranolol in nonsmokers because they are proven effective in clinical trials. If the therapeutic effect is not satisfactory, a trial of sotalol should suffice. Caution is necessary with the use of sotalol because torsades de pointes may be precipitated.

Patients with potentially lethal arrhythmias (arrhythmia in an abnormal heart, e.g., underlying IHD) should be managed with a β -blocking drug. If symptoms are bothersome and are not controlled by adequate doses of sotalol, then substitution or addition of mexiletine, which has a low proarrhythmic effect, is advisable. Sotalol may be helpful when other β -blockers fail.

As emphasized earlier in this chapter, the distinction of VT from ST with aberrant conduction is crucial to appropriate management. Diagnostic steps are given in Fig. 6.1. and Tables 6.1. and 6.2. When doubt exists, a wide QRS tachycardia should be treated as VT.

The management of sustained VT is given in [Fig. 6.32](#). If the pulse is present and the patient is hemodynamically stable, give lidocaine (lignocaine) 100-mg bolus IV and an immediate infusion up to 3 mg/minute (*see* Tables 1.10. and 1.11.). If the arrhythmia is not controlled, repeat a 75-mg bolus of lidocaine; if sinus rhythm is not restored but the patient remains hemodynamically stable, a trial of procainamide is advisable.

In patients with a palpable carotid or femoral pulse who are hemodynamically unstable (BP less than 90 mmHg, chest pain, shortness of breath, or clouding of consciousness), immediate synchronized cardioversion using 100–200 J should be carried out.

In patients with an absent carotid or femoral pulse, prompt defibrillation using 200 J, and 300 J should be carried out, as in treatment of VF ([Fig. 6.32](#)).

[Table 6.8](#) lists the serious adverse effects of antiarrhythmic agents with an emphasis on their role as dictated by negative inotropic effects, their ability to precipitate HF, the propensity for serious adverse effects, and their efficacy with lethal arrhythmias. It must be reemphasized that patients with an EF less than 30% are not able to tolerate most antiarrhythmic agents. Only amiodarone, mexiletine, and quinidine are considered safe. Quinidine has very limited efficacy against lethal arrhythmias, however. The drug decreases the VF threshold, has a strong proarrhythmic potential, and appears to increase mortality. The judicious use of β -blockers has a role in these patients.

[Table 6.9](#) gives drug dosages of antiarrhythmic agents. The maximum doses given are less than that indicated by the manufacturer but are consistent with current clinical practice. A review of the literature indicates that dosages beyond those given in [Table 6.9](#) should be used only under strict supervision with caution in patients with renal dysfunction or in the elderly.

Torsades de Pointes

DIAGNOSIS

Torsades de pointes implies twisting of the QRS points around the baseline:

- There is a typical oscillating morphology of the QRS complexes that vary in amplitude;
- Prolongation of the QT interval is always present.

As with other polymorphic forms of VT, typically there is a beat-to-beat change in QRS morphology ([Fig. 6.26](#)). This life-threatening arrhythmia is also termed “atypical VT.” The short bouts of VT persist for 5–30 seconds, but may last longer than 30 seconds. The arrhythmia is usually initiated by VPBs, with a long coupling time and after a long RR interval but falls on the T-wave because of the prolonged QT interval. Thus, a long-short cycle often initiates torsades de pointes ([Fig. 6.33](#)). Rates of 150–300/minute are not unusual, and the arrhythmia frequently terminates spontaneously, but the arrhythmia is likely to deteriorate into VF or VT. Syncope or clouding of consciousness occurs.

The absolute value of the QTc is inaccurate in predicting the recurrence of torsades de pointes. With reported amiodarone cases, the QTc values range from 0.43–0.87 seconds. With agents other than amiodarone, at a QT interval of 0.60 seconds or more, torsades de pointes is often precipitated by class IA agents or by sotalol.

Precipitating factors include the following:

- Commonly caused by class IA agents: quinidine, disopyramide, procainamide, and rarely sotalol (particularly if hypokalemia or hypomagnesemia are present).
- Amiodarone may cause the arrhythmia, but the occurrence is extremely rare, and fewer than 100 cases have been reported in the literature.

Table 6.7.
Guidelines for the Management of Ventricular Arrhythmias

<i>Benign Arrhythmia</i>	<i>Potentially^a lethal</i>	<i>Lethal (malignant arrhythmia)</i>
Normal heart	Abnormal heart, e.g.,	Cardiovascular collapse
VPBs couplets, Bigeminy	postmyocardial infarction	Postcardiac arrest (VF)
↓	Frequent VPBs multifocal,	↓
No treatment reassurance	Nonsustained VT	EP studies: in approximately
↓	↓	25% of cases, can initiate
If symptoms very	EF >30%; no overt CHF	and suppress with drug
bothersome or recurrent	↓	combination and improve
nonsustained VT	β-blocker ^b	outcome
normal heart	↓	↓
↓	Not controlled and symptomatic	In most EF < 30% trial sotalol ^b
β-blocker and	↓	or
reassurance; consider	Mexiletine (unproven to	Amiodarone or
Mexiletine second	improve survival)	Amiodarone + β-blocker
choice	↓ or	
	Not controlled	Multiprogrammable
	↓ implantable pacemaker-	
	Consider	cardioverter-defibrillator,
	↓ especially if EF ≤ 25%	or
	Amiodarone	ablative treatment torsades de
		pointes (<i>see text</i>)

VPBs, ventricular premature beat; VF, ventricular fibrillation; VT, ventricular tachycardia; EP, electrophysiological; CHF, congestive heart failure; EF, ejection fraction.

^aOnly β-blockers significantly prolong life; amiodarone remains controversial (*see text*).

^bUsed judiciously preferably metoprolol, timolol, or sotalol, EF down to 25% (*see text*).

- Phenothiazines, tricyclic antidepressants, and the commonly used antibiotic, erythromycin.
- Prenylamine, lidoflazine.
- Hypokalemia, hypomagnesemia, hypocalcemia.
- Myocardial ischemia/infarction.
- Congenital long-QT syndromes.
- Myocarditis.
- Bradycardia in association with prolonged QT interval.
- Bepridil.
- Chloroquine, pentamidine.
- Organophosphate insecticides.
- Astemizole, terfenadine.
- Adenosine (*see cautions for the use of adenosine*).
- Liquid protein diets.
- Subarachnoid hemorrhage.
- Chinese herbal remedy (Chui-feng-su-ho-wan) and cocaine abuse.

In most cases of acquired long-QT syndrome, at least two of these factors are required simultaneously.

THERAPY

- Immediately identify and withdraw the offending agent: antiarrhythmics and other drugs known to increase the QT interval.

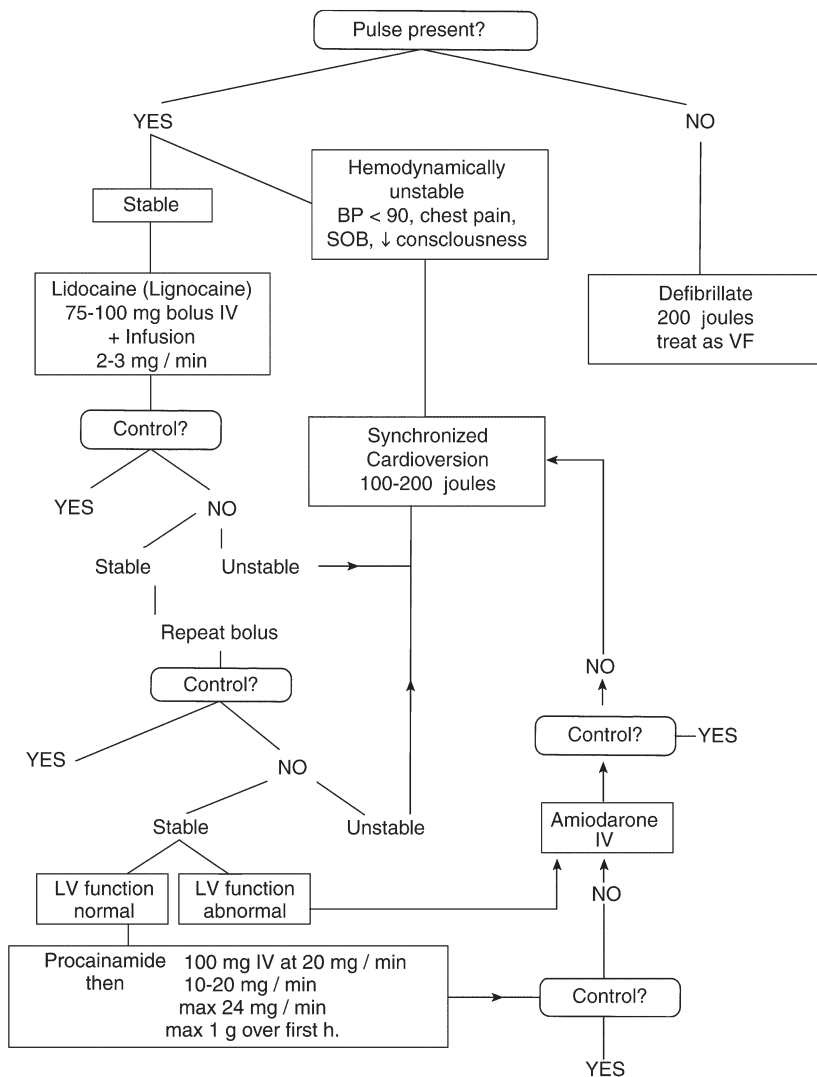


Fig. 6.32. Management of sustained ventricular tachycardia. BP, blood pressure; SOB, shortness of breath; VF, ventricular fibrillation.

- Rapidly correct potassium and magnesium deficiency.
- Magnesium sulfate (1–2 g) is usually highly successful, even in the absence of magnesium deficiency, 2 g (10 mL of a 20% solution) is given IV over 5–10 minutes and is followed by 4 g over 4–8 hours as an infusion of 30 mg/minute. Magnesium chloride is preferred because the sulfate may bind calcium. Also, a low serum potassium is corrected by potassium chloride infusion. Magnesium is a cofactor of membrane sodium, potassium, adenosine, triphosphatase, or sodium pump known to keep the intracellular potassium level constant. Magnesium sulfate given IV at higher doses occasionally causes marked hypotension. The substance also has a mild negative inotropic action. Patients with moderate to severe renal failure generally have high magnesium levels, and great caution is required in this situation.
- Accelerating the heart rate is the simplest and quickest method to shorten the QT interval.

Table 6.8.
Drugs for Ventricular Arrhythmias, Adverse Effects, and Efficacy With Lethal Arrhythmias

<i>Drug</i>	<i>Negative Inotropic Effect</i>	<i>Precipitates heart failure?</i>	<i>Serious side effects</i>	<i>Efficacy with lethal arrhythmia</i>
Quinidine	+	No EF < 25 yes +	Yes proarrhythmic + + + + precipitates torsades, VF, platelets ↓,	Minimal
Procainamide		Yes if EF < 40	Yes agranulocytosis + lupus, torsades	Poor
IV	+ + +			
Oral	++			
Disopyramide	+ + + +	Yes if EF < 40	No precipitates torsades	Poor
Mexiletine	+	No EF < 25, yes	No High minor effects Low proarrhythmic +	Minimal
Tocainide		+ EF < 25 yes +	Yes agranulocytosis + + + pulmonary alveolitis	Poor
Flecainide ^a	+ + +	Yes if EF < 35	No, but proarrhythmic + + + +	Not recommended
Propafenone	+ + +	Yes if EF < 35	Yes rare agranulocytosis + proarrhythmic + +	Not if EF < 35
Amiodarone	+	No EF < 25 yes +	Yes low proarrhythmic +	Yes + + +
β-blocker	++	Yes if EF < 35	No not proarrhythmic ^b	Yes + + +

+ + + +, maximum effect; +, minimal effect.

^aNot recommended for benign or potentially lethal arrhythmias.

^bExcept sotalol mildly proarrhythmic.

Table 6.9.
Antiarrhythmic Drug Dosage

Quinidine	200-mg test dose: if no hypersensitivity, syncope, or ↓ BP, 200–400 mg q 4 hour × 4 doses then q 6 hours, then long-acting forms
Procainamide	375–500 mg q 3 hours × 1 week then, q 4 hours × 2–4 months. RF ^a
Disopyramide	300 mg, then 150 mg q 6 hour. SR 300 mg BID
Mexiletine	200–400 mg then 2 hours later 200–250 mg q 8 hours RP or MI q 12 hour or q 24 hours or elderly: 100–150 mg BID
Flecainide	50–200 mg BID max 400 mg daily RF ^a caution
Sotalol ^b	160–240 mg daily × 1–7 days, then 160–240 mg once or twice daily. (investigational 320–480 mg daily for lethal arrhythmias, <i>see</i> Table 6.8. and text) RF ^a
Amiodarone	200 mg TID or QID × 1–2 weeks then 200 BID × 4–6 week reduce weekly dose ^c by about 400 mg every 4 weeks until patient is taking 200 mg on 5–7 days per week (final maintenance according to Hollers)

BP, blood pressure; SR, sustained release; MI, myocardial infarction; BID, to be taken twice a day; TID, to be taken three times a day; QID, to be taken four times a day.

^aRenal Failure: increase dosage interval.

^bOther β-blocker dosages (*see* Table 4.6).

^cHigher doses previously used in US cause increased pulmonary toxicity.

- Temporary transvenous pacing is the safest and most effective method of management because the heart rate can be quickly and easily controlled for long periods. If available, atrial or atrial ventricular sequential pacing is preferable, but ventricular pacing is a simple procedure and the catheter obtains a more stable position with reliable capture. As an immediate measure, transthoracic pacing may be used while preparations are being made for electrode placement. If there is chronic bradycardia, the patient progresses to permanent atrial sequential pacing.
- An infusion of isoproterenol (2–8 μg/minute) is sometimes used if pacing is not readily available. This agent is carefully infused to increase the heart rate to about 120/minute. Isoproterenol is contraindicated in acute MI, angina, or severe hypertension. However, isoproterenol infusion needs to be carefully monitored to maintain a heart rate of 100–120 BPM. Myocardial ischemia may be precipitated, and the drug may precipitate VT or VF.
- Amiodarone has been successfully used to manage torsades de pointes precipitated by sotalol or class IA agents. This approach requires further confirmation, however.
- Patients with congenital QT prolongation syndrome are best managed with β-adrenergic blockers because these agents reduce mortality. Phenytoin has a role if β-blockers are contraindicated. Resistant cases are managed with permanent pacing plus β₀blockers or left stellate ganglionectomy. Isoproterenol is contraindicated in the congenital QT prolongation syndrome.
- A short-coupled variant of torsades de pointes has been described by Leenhardt et al. This variant responds only to verapamil IV and not to β-blockers or amiodarone. Because of the high incidence of sudden death in this variant of torsades de pointes, automatic implantable cardioverter defibrillator (AICD) is strongly recommended
- Hemodialysis to remove sotalol has been used successfully in a patient with torsades de pointes precipitated by sotalol at therapeutic level and normal serum potassium and with failure to respond to magnesium sulfate, isoproterenol, and overdrive pacing.

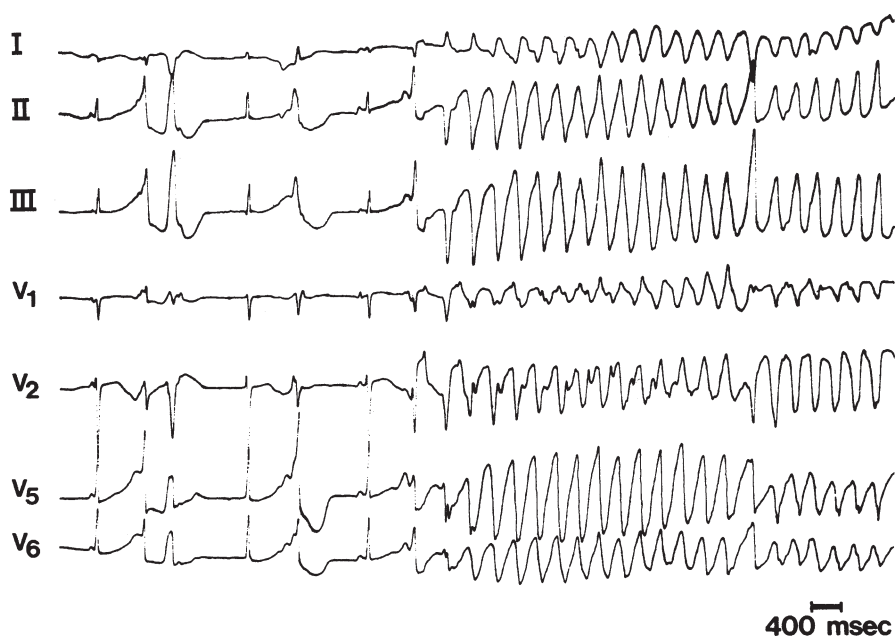


Fig. 6.33. Torsade de pointes. Note (1) the prolonged interval, (2) the long-short cycles preceding the onset of the tachycardia, and (3) the typical oscillating morphology of the ventricular complexes. From Wellens Hein JJ, Conover MB. *The ECG in emergency decision making*. Philadelphia, PA: WB Saunders, 1992:164, with permission from Elsevier.

Prevention of torsades de pointes depends on the removal of the cause and maintenance of normal serum potassium. Amiloride has class III antiarrhythmic activity; the drug retains potassium and is the diuretic of choice in patients treated with agents that have the propensity to prolong the QT interval.

It is important to recognize that polymorphic VT associated with a prolonged QT interval is termed “torsades de pointes” (Fig. 6.33.). When polymorphic VT occurs, however, in the absence of prolonged QT, the condition must not be managed as torsades de pointes (Fig. 6.27.). It is important to differentiate the two conditions. Most patients with polymorphic VT and normal QT intervals have underlying coronary heart disease and are managed in the manner described earlier in this chapter.

Accelerating the heart rate shortens the QT interval. Thus, sympathetic stimulation with physical exertion or excitement often controls the acquired form of torsades de pointes. Sudden acceleration of heart rate, however, tends to provoke the occurrence of torsades de pointes in patients with congenital long QT syndrome. Although β -blockers do not usually shorten the QT interval, they are the agents of choice in this syndrome and have been shown, in symptomatic patients, to reduce mortality. In patients with congenital long QT syndrome, with or without deafness, torsades de pointes represents the predominant form of VT. Agents that shorten the QT (e.g., calcium, potassium, lidocaine, and digitalis) are not effective. Because syncope or sudden death occurs in these patients, consideration must be given for intervention with left cervicothoracic sympathetic ganglionectomy or an AICD if events are not prevented by β -blockade.

Brugada Syndrome

The Brugada syndrome is associated with a high incidence of arrhythmias that cause sudden death in individuals with structurally normal hearts. Typical ECG findings include incomplete or complete RBBB *with a saddle-back type of ST-segment deformity shown in Fig. 6.34.*

ANTIARRHYTHMIC AGENTS

Classification

A knowledge of the EP classification of antiarrhythmics is useful in understanding arrhythmia suppression, drug combinations, proarrhythmia, and some adverse effects.

A modification of Vaughan Williams EP classification of antiarrhythmic drugs is given in [Table 6.10](#). Several EP effects of these agents are not accounted for by their class action and considerable overlap exists.

- Amiodarone has powerful class III and IA actions, as well as significant class II and IV effects. Although the drug prolongs the QT interval, the clinical effect is different from QT prolongation caused by sotalol and class IA agents. Amiodarone brings about a more uniform action potential throughout the myocardium, enhancing EP homogeneity, which appears to protect from lethal arrhythmias. Sotalol placed as a class III or II agent leads to a false notion; it is perhaps preferable to place sotalol in a class of its own (class IIIA) as opposed to an assignment of class II with other β -blockers. The antiarrhythmic effect of bretylium is mainly owing to chemical sympathectomy; the drug does not alter the action potential directly as other class III agents do.
- Class I drugs inhibit influx of sodium into the cardiac myocyte ([Fig. 6.33.](#)). Class IA: Quinidine, disopyramide, and procainamide slow phase 0 and prolong the duration of the action potential.
- Class IB: Lidocaine, mexiletine, and tocainide have relatively little effect on phase 0, cause minimal narrowing of the action potential, and decrease repolarization time. They do slow conduction and delay repolarization in certain situations.
- Class IC: Flecainide and propafenone slow phase 0 but have little or no effect on action potential duration. These agents have a marked inhibitive effect on His-Purkinje conduction, increasing QRS duration. These agents shorten the action potential, but only in Purkinje's fibers, and thus cause marked depression of conduction. Also, repolarization time is unchanged. These latter effects may explain the proarrhythmic effects of these agents.
- Class II agents, the β -adrenergic blocking drugs inhibit sympathetic stimulation. They therefore cause a decrease in phase 4 diastolic depolarization in spontaneously discharging cells, which results in a decrease in automaticity. β -Blockers cause an important increase in VF threshold. Sympathetically mediated acceleration of impulses through the AV node are blocked. These agents have no effect on the action potential or repolarization time. Sotalol is the only β -blocking agent with class III effects.
- Adenosine causes an increase in potassium and a decrease in calcium conductance and should not be associated with class IV calcium antagonists.

Class IA

Class IA agents include disopyramide, procainamide, quinidine.

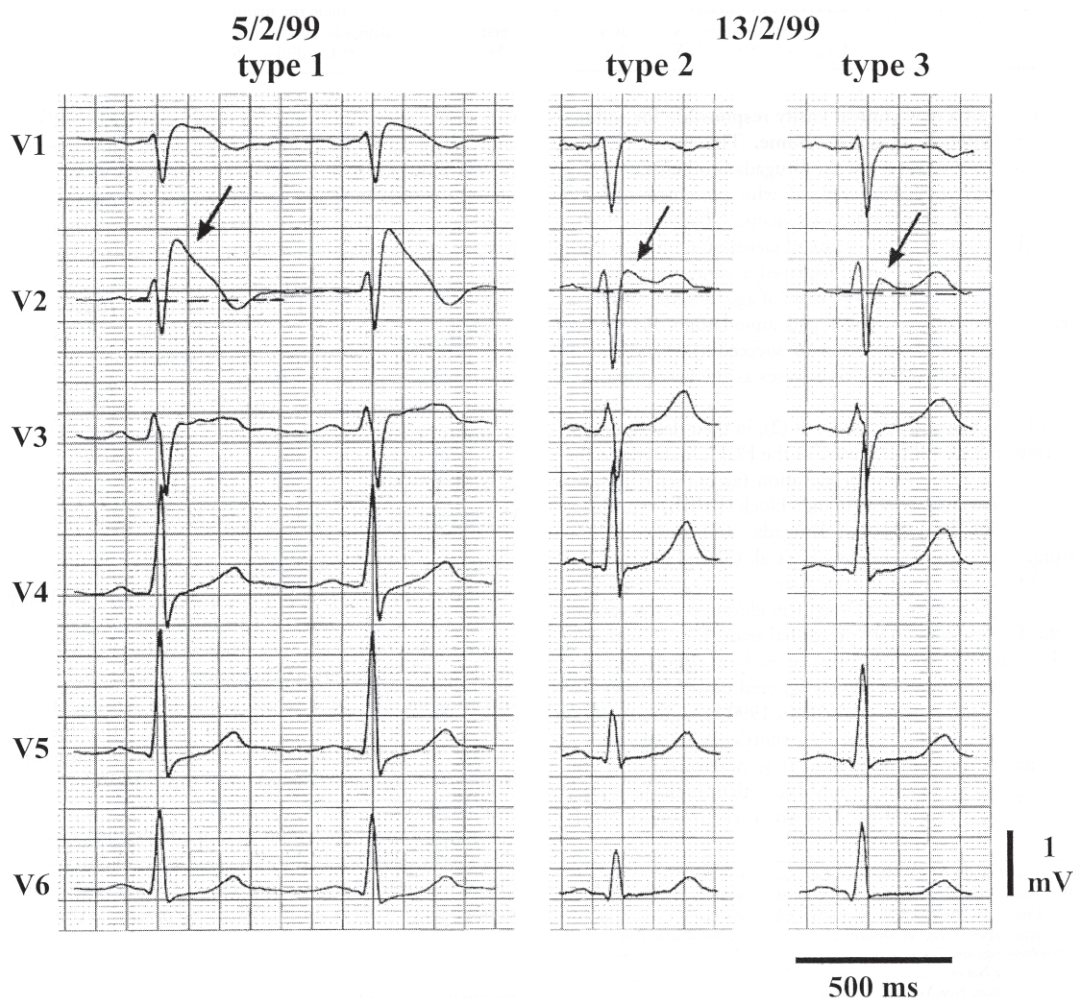


Fig. 6.34. Precordial leads of a patient with Brugada syndrome. Note the dynamic electrocardiographic (ECG) changes in the course of the week. Three distinct patterns are apparent. Arrows denote the J-wave. The left panel shows a type 1 ECG, whereas the middle and right panels depict type 2 and 3 Brugada ECGs. From *J Am Coll Cardiol* 41: 2003, 1665–1671, with permission from the American College of Cardiology Foundation.

DISOPYRAMIDE

Supplied: This drug is supplied in 100- and 150-mg controlled-release capsules: Rythmodan Retard, 250 mg; Norpace CR, 150 mg.

Dosage: A loading dose of 300 mg is used and then 100–150 mg every 6 hours or sustained action 250–300 mg twice daily. IV (not approved in the US): 2 mg/kg over 15 minutes, then 1 to 2 mg/kg by infusion over 45 minutes; maintenance = 0.4 mg/kg/hour.

Caution: The dose should be reduced in severe renal failure, HF, and in the elderly. The action of the drug is given in [Table 6.10](#), and [Fig. 6.35](#). **Adverse effects:** The drug has a powerful negative inotropic effect and may precipitate HF in patients with LV dysfunction. Disopyramide has strong anticholinergic activity, precipitates urinary retention, and is contraindicated in patients with glaucoma, prostate hypertrophy, myasthenia gravis, HF, and renal failure. The drug may cause sinus node depression and torsades de pointes.

Table 6.10.
Electrophysiologic Classification of Antiarrhythmic Drugs^a

Class	Effect on the action potential (AP) ^b
I.	Sodium channel blockers
A.	Sodium channel (+ +); blocks potassium efflux (+) Disopyramide Quinidine Procainamide
	Slows phase zero (+ +) Moderately prolongs the AP: ↑ repolarization time, ↑ QT
B.	Sodium channel (+) Other effects Lidocaine (lignocaine) Mexiletine Tocainide
	Minimal slowing phase zero (+) Minimal narrowing of the AP ↓ repolarization time
C.	Sodium channel (+ + + +) Flecainide Propafenone
	Marked slowing phase zero: Marked depression of upstroke Marked inhibitory effect on His-Purkinje conduction: ↑ QRS duration Shortens AP but only of Purkinje fibers: marked depression on conduction. ^c Repolarization time unchanged. ^c
II.	Inhibition of the effects of sympathetic stimulation β-adrenergic blockers
	No effect on AP or repolarization. ^d ↓, phase 4 spontaneous depolarization: Decrease automaticity
III.	Potassium channel efflux blockade Amiodarone + + + +, also sodium block.
	Slows phase zero (class I effect) Markedly prolongs the AP: Markedly prolongs repolarization time. ↑ QT; Amiodarone brings about a more uniform AP throughout the myocardium:
	Sotalol (+ +) (No sodium block and usual Class II effects)
	Enhances EP homogeneity
	Bretylium partly Class III
IV.	Calcium channel blockers
	No effect

EP, electrophysiological.

^aModified from Vaughan Williams.

^bSee Fig. 6.5.

^cMay explain proarrhythmic effect.

^dExcept sotalol, class III effect.

+, minimal effect; + + + +, maximal effect; K, Potassium.

Indications: Disopyramide may have a role in the management of potentially lethal arrhythmias that are bothersome and not responsive to β-blockers but must only be used in patients with near normal EF and those with no suspicion of LV dysfunction. The drug has a role in the management of antidromic and orthodromic tachycardia or AF and flutter in patients with WPW syndrome because it inhibits anterograde and retrograde conduction in the accessory pathway.

PROCAINAMIDE

Supplied: This is supplied as 250-, 375-, and 500-mg capsules and as 250-, 500-, 750-, and 1000-mg sustained-release tablets. Procanbid extended release 500, 1000 mg: the

controlled delivery system provides sustained 12 hours activity with each dose and is designed to improve compliance. This agent is indicated for treatment of life-threatening ventricular arrhythmias. Dosage: A 500-mg oral loading dose is used, 375–500 mg every 3 hours for 24 hours, and then sustained release 500 mg every 6 hours for a 60-kg patient (750 mg every 6 hours for patients over 60 kg) for a maximum of 6 months. IV dosage: 100 mg bolus at a rate of 20 mg/min, followed by 10–20 mg/minute to a maximum of 1 g over the first hour; maintenance = 1–4 mg/minute. Indications: Management of VT that fails to terminate with a second bolus of lidocaine (lignocaine). Chronic oral therapy is not advisable because the drug does not improve survival in this category of patients with ventricular arrhythmias. If the drug is prescribed, it should generally not be given for longer than 6 months because of the incidence of drug-induced lupus and the occurrence of agranulocytosis, albeit rare. Adverse effects: The IV preparation has moderate negative inotropic effects, and the oral preparation has a mild risk of precipitating HF. torsades de pointes is not uncommon. Lupus occurs in over 33% of patients treated beyond 6 months; agranulocytosis appears to occur more commonly with the sustained release preparation and has been reported in patients as a rate of approximately 0.5%, particularly during the first 2 months of therapy. Complete blood counts with white cells differential and platelet counts should be performed at brief intervals to the first 2 months of therapy. If hematologic abnormalities are identified, procainamide should be discontinued. Blood counts usually return to normal within 1 month of cessation of therapy.

Interactions: angiotensin-converting enzyme (ACE) inhibitors may enhance immune effects; cimetidine increases procainamide levels.

QUINIDINE

Supplied: 200- and 300-mg tablets (Quinidine bisulfate: 250 mg). Dosage: Quinidine sulfate is given as 200-mg test dose; observe for 4 hours, and if there is no hypersensitivity reaction, give 200–400 mg every 3 hours for three or four doses and then every 6 hours. When the arrhythmia is stabilized, a control release preparation can be used: quinidine bisulfate 250 mg, usual maintenance 500 mg twice daily, sustained release tablets 325 mg (one to two tablets twice daily).

Action: The drug is a sodium-channel blocker that slows phase 0 of the action potential, blocks potassium efflux, and moderately prolongs the action potential, resulting in an increase in repolarization time and prolongation of the QT interval. The drug has an anticholinergic effect, facilitates AV conduction, and may cause an increase in the ventricular response in patients with atrial flutter or AF if the AV node has not been previously blocked by digitalis.

Pharmacokinetics

- After oral dosing, peak plasma levels: 1–3 hours.
- Half-life: 7–9 hours.
- Hepatic metabolism with minimal renal elimination.
- Therapeutic blood levels: 2–5 µg/mL (3–5.5 µmol/L).

Indications:

- Occasional use for conversion of AF to sinus rhythm after digitalization in properly selected patients.
- Postelectrical cardioversion, quinidine may be used for maintaining sinus rhythm but is of limited value. Recurrent sustained VT, often in combination with another agent as part of electrophysiologically guided regime. The drug has not been shown to prolong sur-

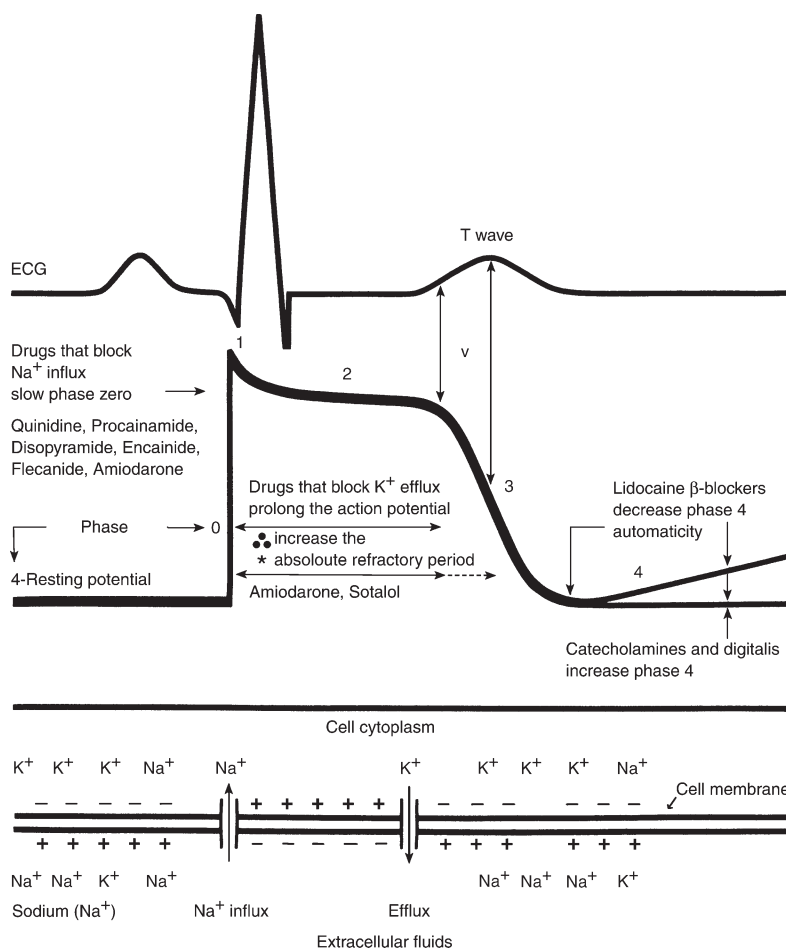


Fig. 6.35. Antiarrhythmic drug action. V, vulnerable period. *Absolute refractory period: during phases 1 and 2, a stimulus evokes no response; an arrhythmia cannot be triggered. From Khan M Gabriel. Cardiovascular system, pharmacology. In: Dulbecco R, ed. Encyclopedia of Human Biology. Vol 2. San Diego, CA: Academic Press, 1997, with permission from Elsevier.

vival in patients with potentially lethal arrhythmias and is rarely indicated in the management of ventricular arrhythmias. A metaanalysis suggests that quinidine has an adverse effect on mortality.

Adverse effects. First-dose idiosyncrasy, diarrhea, nausea, angioedema, thrombocytopenia, hepatitis, agranulocytosis, and torsades de pointes, especially in patients with hypokalemia. The drug decreases VF threshold and increases the risk of VF. Precipitation of sustained VT and cardiac arrest may occur. Quinidine administration is associated with a threefold increase in mortality. Rare hypersensitivity angitis with coronary artery dissection has been reported. For all class IA agents, hypokalemia must be corrected for maximum efficacy and to prevent torsades de pointes.

Contraindications:

- Heart block, torsades de pointes caused by QT prolongation.
- Sick sinus syndrome.

- BBB.
- Myasthenia gravis.
- Hepatic failure.
- WPW with AF or flutter.

Interactions:

- Serum digoxin levels increase.
- Amiodarone and quinidine should not be given concomitantly, because torsades de pointes may be precipitated. Verapamil and diltiazem increase quinidine plasma levels.
- Warfarin action may be enhanced.
- Phenytoin decreases quinidine blood levels.

Class IB

Class IB agents include lidocaine (lignocaine), mexiletine, moricizine, and tocainide.

LIDOCAINE (LIGNOCAINE, UK)

IV lidocaine has remained the mainstay of therapy for the acute management of VT. Dosage: IV bolus 1.0–1.5 mg/kg (75–100 mg) is given over a few minutes with the immediate institution of lidocaine infusion at 2–3 mg/minute. A second bolus of 50–75 mg is given 5 minutes later, and a third bolus is given if arrhythmia recurs with simultaneous increase in the infusion rate. The maximum rate of 4 mg/minute should only be used after careful re-evaluation of the clinical situation and rationale for the use of lidocaine. Infusion rates greater than 2 mg/minute should not be used in the presence of HF and in the elderly (*see* [Table 1.10](#)).

Action: The drug causes minimal slowing of phase 0; causes a minimal narrowing of the action potential, resulting in a decrease in repolarization time; and, as with other class IB agents, does not prolong the QT interval. The drug depresses spontaneous phase 4 depolarization and has no significant negative inotropic effect, a factor that makes this agent extremely useful. The drug acts by slowing conduction selectively on diseased or ischemic tissue and thus has a major role in the management of ventricular arrhythmias during acute MI and ischemia, where enhancement of conduction block appears to interrupt reentry circuit. Prolongation of refractoriness after premature beats has been demonstrated with other drugs in this class (mexiletine), and this may be a useful property. The effectiveness of lidocaine is decreased in the presence of hypokalemia and bradycardia, which must be corrected.

Pharmacokinetics

- After bolus IV injection, the drug acts within minutes and the action lasts only for 5–10 minutes because of rapid de-ethylation by liver microsomes. Thus, plasma levels are increased with liver dysfunction and a decrease in hepatic blood flow, as may occur with HF, the elderly, cimetidine, propranolol, and other hepatic-metabolized β -blockers.
- Therapeutic blood levels: 1.4–5 mg/L (1.4–5 μ g/mL or 6–26 μ mol/L) levels greater than 6 mg/L are associated with seizures and central nervous adverse effects.

Indications:

- Sustained VT.
- Digitalis-induced ventricular arrhythmias.
- Ventricular arrhythmias caused by tricyclic antidepressants and phenothiazine.
- During pregnancy for the management of VT. although it does cross the placenta.
- Indications for use in acute MI are discussed in Chapters 1 and 2.

Contraindications:

- Second- or third-degree AV block.
- Idioventricular rhythm, sinus node dysfunction.
- Bradycardia of less than 50/minute.

Adverse Effects. Sinus arrest may appear in patients with sick sinus syndrome; third-degree AV block may be precipitated in patients with impaired AV conduction, vomiting, twitching, and seizures.

Interactions:

- Cimetidine.
- Hepatic-metabolized β -adrenergic blocking agents.
- Phenytoin decreases lidocaine blood levels.

MEXILETINE (MEXITIL)

This is supplied as 150-, 200-, and 250-mg capsules.

Dosage: An initial oral dose of 200–400 mg is given, followed by 200–250 mg every 8 hours (over 12 hours with severe renal failure, hepatic dysfunction, acute MI, or in the elderly). Mexiletine is a weak antiarrhythmic agent and rarely shows salutary effects in the treatment of lethal arrhythmias. However, because of its weak negative inotropic effect, a low proarrhythmic potential, and the absence of serious adverse effects ([Table 6.10](#)), the drug may be combined, in properly selected cases, with amiodarone, sotalol, or quinidine if sinus node disease, hypotension, bradycardia, AV block, hypokalemia, or other contraindications are absent. The drug can precipitate HF in patients with severe LV dysfunction with EF below 25%.

Action: The drug causes minimal slowing of phase 0, minimal narrowing of the action potential, decreases repolarization time, and does not lengthen the QT interval.

Pharmacokinetics:

- The drug is well-absorbed orally.
- Peak plasma levels in 2–4 hours.
- The drug is lipophilic and high brain concentration accounts for prevalent central nervous system adverse effects.
- Half-life of 9–16 hours may be prolonged to 19–26 hours in patients with HF, acute MI, and liver dysfunction.
- About 15% of the drug is excreted in the urine unchanged. Some unchanged drug is reabsorbed; therefore, in patients with severe renal impairment (creatinine clearance less than 10 mL/minute), the dose interval should be increased.
- Effective plasma concentration: 0.75–2.0 mg/L (0.75–2 μ g/mL or 3.5–9.3 μ mol/L).

Contraindications:

- Severe LV failure.
- Hypotension.
- Bradycardia or sick sinus syndrome.
- AV block.
- Hepatic or severe renal failure and epilepsy.

Adverse Effects. Bradycardia and transient AV block, hypotension, confusional state, seizures, tremor, diplopia, ataxia, nystagmus, dysarthria, paraesthesia, psychiatric disorders, nausea, and gastric irritation may occur in up to 70% of patients, and jaundice,

hepatitis, and blood disorders have been reported. Interactions: Phenytoin is an inducer of hepatic enzymes and decreases mexiletine blood levels; theophylline levels may increase.

Class IC

Class IC agents include: flecainide and propafenone.

Indications for class IC agents include: paroxysmal AF in properly selected cases in combination with digoxin.

The use of class IC agents is limited by their proarrhythmic effects, highlighted by the CAST study, which indicated a significant increase in mortality in patients with postinfarction ventricular arrhythmias treated with encainide or flecainide. Several reports indicate the effectiveness of class IC agents in conversion to sinus rhythm of paroxysmal AF, a bothersome and sometimes incapacitating arrhythmia. Physicians are tempted to use flecainide or propafenone because of their low frequency of noncardiac adverse effects. Their use is fraught with danger, however, because over 15% of patients treated with supraventricular arrhythmias have been reported to develop very serious cardiac adverse effects. These deleterious effects may occur early or several months later, and patients at risk cannot be predicted.

Type IC agents slow atrial conduction with little effect on anterograde AV nodal refractoriness. The atrial rate is slowed and the rhythm may regularize to atrial flutter, resulting in fewer impulses penetrating the AV node, which may permit one-to-one AV conduction with a rapid ventricular response. This may precipitate hypotension, and the resulting sympathetic release further facilitates AV nodal conduction. Hypotension may induce MI, or HF may be precipitated because of a fast ventricular response and negative inotropic effects of the drug.

Class IC agents are not warranted for ventricular arrhythmias because the salutary effects of these agents are poor and adverse effects are hazardous. There is little indication for their use with AF, except in properly selected cases of paroxysmal atrial fibrillation less than 48-hour duration (e.g., postcardiac surgery). Conversion is expected in more than 80% with normal LV function and with prior digitalization to avoid a 1:1 response that is well-recognized with quinidine and class IA agents. Class IC drugs are not sufficiently effective with atrial flutter to justify their use.

Propafenone is slightly less effective than flecainide, causing reversion to sinus rhythm in patients with paroxysmal AF and in about 70% of patients where AF is present for less than 48 hours. Flecainide causes about an 80% reversion to sinus rhythm. Propafenone appears to be safer than flecainide for IV conversion, but the drug must be avoided in patients with bronchospasm.

Propafenone is useful in patients with WPW and anterograde conduction over the bypass tract. Patients with this rare presentation with rapid ventricular rates are best treated with electrical cardioversion followed by EP studies and selection of an appropriate antiarrhythmic agent, usually amiodarone, followed, if needed, by ablative therapy,

FLECAINIDE

The drug is not approved by the FDA for the management of AF and has been implicated in the causation of deaths in postinfarction patients. The drug is approved in the United States only for the management of life-threatening arrhythmias. It is supplied in tablets of 400–600 mg (in the UK, 100–200 mg).

Dosage. For sustained VT, an oral dose of 25 mg is given twice daily, increasing to 50–100 mg twice daily. After several weeks or months, give a maximum of 200 mg twice daily. In the elderly, half of the above dose is advisable; the dose must be reduced with renal or hepatic impairment. IV 2 mg/kg over 30 minutes (maximum 150 mg with continuous cardiac monitoring) followed, if needed, by infusion of 1.5 mg/kg/hour for 1 hour and then reduce to 100–250 µg/kg/hour for up to 24 hours. Do not exceed 600 mg in 24 hours; then, if justifiable, transfer to oral therapy.

Contraindications:

- Sinus node dysfunction.
- AV block.
- HF, LV dysfunction, EF less than 35%.
- History of MI.
- Nonsustained VT.

Adverse Effects. Noncardiac adverse effects are rare (dizziness, visual disturbances, gastrointestinal upset). Serious life-threatening cardiac arrhythmias may be precipitated because of a high proarrhythmic effect and atrial flutter with one-to-one conduction. An increase in mortality was observed in the CAST study.

Interactions:

- β-blocker combinations may increase LV dysfunction.
- Verapamil or diltiazem may increase the incidence of HF, as well as AV disturbances.
- Disopyramide may increase the risk of HF.
- Flecainide plasma levels increase with amiodarone.

PROPAFENONE

This drug is supplied in tablets of 150–300 mg.

Dosage. Give 150 mg three times daily after food and increase after a few weeks, if needed, to 300 mg two or three times daily for individuals over 70 kg. For elderly patients or those under 70 kg, half of the above dose is advisable. Patients should be under direct hospital supervision with ECG monitoring and BP control during institution of therapy.

Indications. Paroxysmal AF and ST associated with WPW syndrome, and life-threatening ventricular arrhythmias are indications of propafenone. The drug is rarely effective, however, with ventricular arrhythmias and safety of long-term use is not established. In the Cardiac Arrest Study Hamburg (CASH) the drug was withdrawn because of increased cardiac arrest recurrence and mortality.

Contraindications:

- HF, patients with moderate or severe LV dysfunction, EF less than 35%.
- Bradycardias, sinus or AV node disease, BBB.
- Asthma or COPD.
- Myasthenia gravis.
- Pregnancy.

Caution. In patients with HF, hepatic and renal impairment, pacemakers, or in elderly patients, propafenone increases thresholds and dramatically widens paced-QRS complex. The drug is not advisable in pregnancy.

Adverse Effects. These include proarrhythmias, fatal VT, HF, taste disturbances, and, rarely, agranulocytosis, hepatitis, and lupus syndrome. An increase in mortality was shown in the CASH study.

Interactions:

- β -Blockers, because propafenone has β -blocking properties.
- Digoxin levels are increased.
- Increased effects of oral anticoagulants.

Class II Drugs

The β -adrenergic blocking agents are effective antiarrhythmic agents that have no proarrhythmic effects, with the exception of sotalol, which has class III effects.

β -BLOCKERS

- Are effective in all grades of ventricular arrhythmias.
- May not completely suppress VPBs; nevertheless, in the same individual, the occurrence of sustained VT or VF may be prevented.
- Are particularly useful for ventricular arrhythmias initiated by ischemia or catecholamine release.
- Are effective for supraventricular arrhythmias (this has been discussed earlier in this chapter).

Atenolol, acebutolol, and nadolol at doses of 100, 600, and 120 mg, respectively, have proven to be effective in suppression of ventricular arrhythmias. Both acebutolol (600 mg) and atenolol (100 mg) have been shown to be as effective as quinidine in controlling ventricular arrhythmias and more effective than quinidine in suppressing exercise-induced ventricular arrhythmias. In one study, sotalol and propranolol caused up to 65% and 44% reduction in VPBs, respectively, but sotalol caused up to 99% reduction of ventricular couplets versus less than 50% reduction with propranolol administration.

Several clinical trials have shown sotalol to be a well-tolerated effective antiarrhythmic agent in patients at high risk for sudden death. The drug is often effective in patients who did not benefit from multiple-drug treatment. A dose of sotalol ranging from 160–720 mg with a mean dose of 240 mg is usually required for suppression that is more frequent in patients with VF, 58 versus 24% in patients with VT. When sotalol is used, it is necessary to maintain a normal serum potassium. Thiazide diuretics should not be used in combination. If a diuretic is necessary, it is advisable to give amiloride (see later discussion in this chapter).

Often, a combination of acebutolol (200–400 mg) or nadolol (40–80 mg) with amiodarone proves effective and safer than amiodarone combined with a class I agent.

In general, β -blockers are used cautiously in patients with EF < 30% because HF may be precipitated. Recent trials indicate, however, the benefit and relative safety of β -blockers in the management of patients with EF as low as 25% who are at high risk for sudden death after episodes of monomorphic VT, and a judicious trial of a β -blocking drug is advisable in these patients. The use of β -adrenergic blocking agents to prevent sudden cardiac deaths in patients at risk will increase because of the failure of antiarrhythmic agents, with the exception of amiodarone, to prevent sudden cardiac death. Also, the use of amiodarone has not resulted in a reduction in sudden cardiac death in patients with a low EF and/or HF. It is appropriate, therefore, that several clinical trials are in progress to document the salutary effects of β -blockers on sudden cardiac death.

Evidence supports the extensive use of β -blockers for the prevention of sudden cardiac death in patients with life-threatening arrhythmias and in patients with LV dysfunction and in others at high risk:

- In the Norwegian MI study, timolol showed an impressive 67% reduction in sudden cardiac death in patients treated from approximately day 7 and followed up for 2 years.
- In the β -Blocker Heart Attack Trial (BHAT), β -blockers caused a greater reduction of sudden cardiac death than placebo in post-MI patients with either a history of prior HF or the emergence of HF. These agents also caused a reduction in early morning sudden cardiac death and infarction, possibly because of their ability to suppress the effects of early morning catecholamine surge and resulting increased platelet aggregation, heart rate, BP, arterial hydraulic stress, and plaque rupture (*see Fig. 1.1.*).
- The incidence of VF in patients with acute MI was significantly reduced in patients treated with metoprolol compared with controls. β -Blockers cause a salutary increase in VF threshold and have been used since the 1960s in the management of recurrent VF.
- In animals with induced myocardial ischemia, β -blockers have been shown to protect against digoxin sensitization of the myocardium to catecholamine-induced ventricular arrhythmias. Animals treated with β -blockers and digoxin revealed a reduction in the incidence of sudden cardiac death, compared with animals treated with digoxin.
- In animal studies of MI, Inoue and Zipes demonstrated that in the areas distal to the zone of infarction, there is a supersensitivity to catecholamines.
- Dellsperger et al. showed that in dogs with induced LV hypertrophy, although ACE inhibitors and β -blockers have similar hemodynamic effects, the incidence of sudden cardiac death caused by ischemia was only decreased by the β -blocking drug.
- Lipophilic β -blockers achieve brain concentration and are superior to hydrophilic agents in the prevention of cardiac death in animals (*see Chapter 8*). Randomized clinical trials support this experimental work. Carvedilol, metoprolol, propranolol, and timolol are the only β -blockers proven effective in reducing the incidence of total deaths and/or sudden cardiac deaths in patients, and these are lipophilic β -blocker agents. Thus, a lipophilic β -blocker with class III effect may find a role in the prevention of death, and further research and clinical trials are required to resolve these important issues.

Class III

Class III agents include amiodarone, sotalol, bretylium, bethanidine, and possibly amiloride. Both amiodarone and sotalol have become widely accepted for use in patients with lethal arrhythmias: their role has increased because of the findings of the CAST. As outlined earlier, sotalol is particularly effective in patients whose presenting arrhythmia was VF and may be given a trial in patients with EF above 30%; some patients without overt heart failure and EF as low as 25% have been successfully treated.

β -Blockers, particularly sotalol with type III activity, are the only antiarrhythmics that have been shown to cause prolongation of life in patients with potentially lethal or lethal arrhythmias. Amiodarone appears to improve survival in postinfarction patients with lethal arrhythmias but not in patients with HF. It is not surprising, therefore, that over 30 class III agents are currently under development. It is appropriate that the role of class III agents, including those with associated β -adrenergic blocking effects, is increasing and that of class I and II agents should dwindle because of proarrhythmia and increased mortality.

AMIODARONE (CORDARONE)

Action. Amiodarone blocks the efflux of potassium from myocytes and markedly prolongs the action potential, thus increasing repolarization time and the effective refractory period.

Although the QT interval is prolonged, torsades de pointes is, in fact, a rare complication of amiodarone, mainly because the drug enhances homogeneity of the action potential throughout the myocardium. Amiodarone does not encourage calcium-mediated oscillations of membrane potential at the end of the action potential (after depolarizations). Undoubtedly, the absolute value of the QTc interval does not predict the occurrence of torsades de pointes, although the amplitude and stability of the TU segments probably do. Amiodarone also blocks sodium channels and slows phase 0 of the action potential. The drug noncompetitively blocks α - and β -receptors, resulting in vasodilatation and mild β -blockade. Fortunately, the drug has a very mild negative inotropic action that allows its use in patients with lethal arrhythmias who often have underlying severe LV dysfunction with EF less than 30%, although the drug does not appear to prolong life in these patients.

The benzofuran derivative has two atoms of iodine and a structure similar to thyroxine. A 200-mg tablet contains more than 50 times the daily requirement of 150 μ g of iodine.

The drug is supplied in 200-mg tablets and in 150-mg ampules.

Dosage. For life-threatening arrhythmias, IV infusion of 150 mg over 10 minutes, 900 mg in 500 mL dextrose water at 1 mg/minute for 6 hours, and then 0.5 mg/minute for 18 hours; if required for the next 24 hours, continue at 0.5 mg/minute. Additional 150-mg boluses can be given if required for breakthrough VT during the infusion. Caution: hypotension may occur.

Oral doses are given at 200 mg three or four times daily for 2 weeks, 200 mg twice daily for 4–6 weeks, and then, if arrhythmia is controlled, reduce the dose by about 400 mg every 4 weeks, that is, decrease from 14 to 10 tablets weekly, reducing from 9 to 5 tablets at intervals of about 4 weeks. Reduction of dosage is guided by 24- or 48-hour Holter monitoring with a goal of five to seven tablets weekly to avoid long-term toxicity.

Pharmacokinetics

- About 50% of the oral dose is absorbed; bioavailability ranges from 20 to 80%.
- Plasma levels occur in 6–12 hours.
- The lipophilic compound is extensively metabolized to desethyl amiodarone, which has pharmacological activity. The drug is highly bound (95%) to protein, and widespread distribution occurs in most tissues, especially the liver, lungs, and adipose tissue. The concentration in the myocardium is about 20–40 times that in plasma.
- The volume of distribution is high; an adequate loading dose is necessary.
- The half-life is about 30–110 days.
- With dosages of 200 mg, three or four times daily, a therapeutic effect is observed in 1–4 days but increases up to 6 months; the action of the drug may persist for more than 50 days after cessation of therapy, although most side effects show a decrease after 4–7 days, depending on the oral loading dose.
- When given IV, a therapeutic effect is observed within a few minutes.
- A therapeutic effect shows poor correlation with the therapeutic plasma levels (0.75–2.0 μ g/mL, up to about 95% of which is bound to plasma proteins). These levels, as well as metabolite levels (desethylamiodarone 1.1 ± 0.5 μ g/mL), however, assist with monitoring of toxicity.

- A loading dose of 10–12 g in the first 2 weeks and maintenance of 400 mg daily 5 days weekly reportedly showed steady-state plasma amiodarone and desethylamiodarone concentrations of 1.7 ± 1.3 and 1.1 ± 0.5 $\mu\text{g/mL}$, respectively, only after about 1 month of therapy. Patients usually experience therapeutic benefits to amiodarone at plasma concentrations less than 1.0 $\mu\text{g/mL}$, and toxicity is not often manifest with concentrations less than 2.0 $\mu\text{g/mL}$.
- The action of the drug appears to relate to tissue stores, and myocardial concentration is important.

Indications:

Lethal ventricular arrhythmias: sustained VT, recovery from VF or cardiac arrest. In the United States, the drug may be used for this indication only if adequate doses of other antiarrhythmics have been tested or are not tolerated. This stipulation makes little sense because other antiarrhythmics except β -blockers (sotalol) have been associated with an alarming increase in mortality; many of these agents have been withdrawn or have restricted use that is not justifiable in view of associated fatalities. IV amiodarone is a most useful addition (*see* Fig. 6.31.).

Patients with a first occurrence of lethal arrhythmias in the absence of precipitating factors have about a 50% mortality. Survivors have a high mortality; some subsets of patients have a mortality of over 90% in 1 year. The overall mortality in survivors of cardiac arrest is about 66% over 5 years. In these high-risk patients, amiodarone has a role. Alternatively, an antiarrhythmic device may be implanted.

Patients who survived an episode of out of hospital VF in the absence of acute infarction were enrolled in the Conventional Versus Amiodarone Drug Evaluation study. The trial comprised 113 patients treated with amiodarone and 115 with conventional antiarrhythmics. At 4-year follow-up, the amiodarone-treated group showed improved survival and received less shocks from an implanted defibrillator; syncope followed by a shock from a defibrillator was less common. Clinical studies support the empiric use of amiodarone and sotalol to prevent recurrent VT and sudden death, especially in patients postinfarction.

Three randomized studies support the value of amiodarone in the management of complex ventricular ectopy in postinfarction patients:

In the Basel Antiarrhythmic Study of Infarct Survival, during 1-year follow-up, there were only 5 deaths in the amiodarone-treated patients, 12 deaths in patients treated with class 1A drugs, and 15 deaths in the control group ($p < 0.05$).

In the pilot Canadian Amiodarone MI Arrhythmia Trial (CAMIAT), sudden cardiac death occurred in 6% of the 48 patients treated with amiodarone and 14% of the 29 placebo-treated patients. The results of the CAMIAT with enrollment of 1200 is awaited.

In a Polish study, Ceremuzynski et al. randomized 305 acute MI patients to receive amiodarone and 308 to placebo. At 1-year follow-up, there were 33 cardiac deaths in the placebo group and 19 cardiac deaths in the amiodarone group; a 42% reduction in cardiac deaths was observed ($p < 0.05$).

Amiodarone does not appear to be as effective in patients with HF or hypertrophic cardiomyopathy and sotalol has not been sufficiently studied. The Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure showed no beneficial effect of amiodarone therapy. The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina study was stopped prematurely because the nonblinded control group had 106 deaths versus only 87 in the amiodarone group (risk reduction 28%).

Indications Outside of the United States:

- For conversion of acute AF to sinus rhythm, especially in patients with hypertrophic cardiomyopathy.
- Paroxysmal AF that is highly symptomatic with rapid ventricular rates refractory to other therapy and deemed bothersome and incapacitating.
- WPW: Management of AF or atrial flutter with rapid ventricular rates because of antero-grade conduction over the accessory pathway. In this subset, the drug is worth a trial before consideration of ablative therapy (*see* Chapter 18).

Contraindications:

- Sinus bradycardia, sinus node disease, or AV block (requires pacing to allow amiodarone therapy).
- Hypokalemia.
- Severe hepatic dysfunction.
- Iodine sensitivity.
- Pregnancy and breastfeeding.
- Porphyria.

Interactions:

- Class IA antiarrhythmic agents prolong the QT interval and may include torsades de pointes; also, erythromycin increases the QT interval and must not be given concomitantly (*see* Table 6.11.).
- Oral anticoagulant activity is increased.
- Verapamil and diltiazem may produce sinus arrest or AV block.
- Digoxin levels increase.
- Quinidine levels increase.
- Sotalol should not be used in combination, but any of the available β -blocking drugs can be combined with amiodarone, provided that contraindications to both drugs are not present.
- Tricyclics and phenothiazines, including moricizine, may induce torsades de pointes.
- Thiazide diuretics should be avoided because they may produce hypokalemia and increase the risk of torsades de pointes, unless covered by potassium supplements or ACE inhibitors.
- β -Blocking agents interact with amiodarone, which has weak β -blocking properties, and mild bradycardia may occur. These two agents, out of necessity, are commonly used in combination, especially if the patient has a pacemaker.

Adverse Effects:

- Cardiac side effects: Severe bradyarrhythmias, asystole, and, rarely, torsades de pointes, especially in patients with a low serum potassium. Approximately 60 cases of torsades de pointes associated with the use of amiodarone have been reported in the literature. Most of these cases were induced by multifactorial causes, the majority having hypokalemia, hypomagnesemia, or the concomitant use of antiarrhythmics, phenothiazines, or tricyclics. The drug has been used in a patient to successfully treat torsades de pointes caused by sotalol–thiazide combination; despite further prolongation of the QT interval from 0.56 to 0.72 seconds, amiodarone was successful in causing reversal to sinus rhythm. The incidence of serious proarrhythmic effects in patients administered amiodarone is less than 1%.
- Hypothyroidism or, less often, hyperthyroidism occurs in about 5% of patients. Asymptomatic corneal microdeposits developed in most patients after about 3 months of therapy.

A few patients complain of halo or blurred vision, which disappears on lowering the dose of amiodarone.

- Hepatitis with grossly elevated transaminase levels occurs very rarely regarding a minimum of the arm, but may progress to cirrhosis, which may be fatal, and immediate discontinuation of amiodarone is necessary if hepatic transaminases rise to greater than three times normal. Mild elevations of liver function tests rarely occur when plasma amiodarone levels are less than 2µg/mL.
- Photosensitivity, metallic taste, nausea, and vomiting.
- Slate gray skin, rarely seen, is related to high loading and maintenance doses.
- Nervous system effects are common, especially sleep disturbances, twitching, paresthesia that usually responds to decreased dosage.
- Pulmonary infiltrates and alveolitis should occur in less than 1% of patients with modern conservative dosing schedules, but the patient should be warned of the risks and the need to obtain chest X-rays in the event that dyspnea develops.
- High loading dose of 800 mg for 6 weeks followed by maintenance of 600 mg daily for several months has been shown to have toxicity in over 50% of patients: pulmonary infiltrates (5%), neurologic involvement (35%), abnormal liver function tests (20%) with high-dose therapy, and pulmonary toxicity may be seen as early as 1–3 months but may be delayed from 1 to 5 years. With low-dose therapy as outlined, adverse effects requiring withdrawal appear to occur in less than 25% of patients. These effects are usually reversible within days to weeks of cessation of amiodarone therapy.
- Severe hypotension during IV bolus injection may be avoided by giving the drug as infusion of 150 mg over 1 hour, although IV infusion given over 10–30 minutes is often required for life-threatening arrhythmias.

Monitoring is necessary. Because of the high potential for adverse effects, the drug should be administered in the hospital or outpatient setting under close supervision. Monitor at 2–4 weeks for 2–4 months, assessing the following:

- Serum potassium and magnesium levels: If a diuretic is necessary, ensure that a potassium-sparing diuretic is being used. In patients with HF on furosemide, supplemental potassium is necessary, or the use of amiloride adequately conserves potassium; also, amiloride has antiarrhythmic properties that appear useful in the suppression of VT.
- ECG for bradyarrhythmias and QT prolongation.
- Liver function tests.
- Free T4, thyroid-stimulating hormone, and T3.
- Digoxin serum assay and the dose of digoxin should be halved. If oral anticoagulants are used concomitantly, the dosage should be halved and a close scrutiny of the international normalized ratio or prothrombin time is necessary.
- Amiodarone and desethylamiodarone plasma levels.
- Request chest X-rays at 3 and 6 months and then every 6 months or annually thereafter, or earlier if dyspnea occurs to detect pulmonary toxicity, peripheral and apical or bilateral diffuse interstitial, or alveolar infiltrates. Baseline pulmonary function tests are advisable and should be repeated if pulmonary symptoms occur. Although the role of pulmonary function tests still appears doubtful, the cost of a baseline test is justifiable in patients who are given a potentially toxic agent that has proven benefits. A greater than 15% decrease in diffusion capacity assists in identifying patients who have amiodarone pulmonary toxicity if they are symptomatic. Because pulmonary function test results vary considerably, their routine use is not recommended in asymptomatic patients. Higher mean desethylamiodarone levels, but not amiodarone levels, are observed in patients who

Table 6.11.
Amiodarone: Potential Interactions

Antihypertensive agents
Drugs that are negatively inotropic verapamil, diltiazem, β -blockers
Agents that inhibit SA and AV node conduction: diltiazem, verapamil
Agents that \uparrow the QT interval
Class IA agents: quinidine, disopyramide, procainamide
Sotalol
Tricyclic antidepressants
Phenothiazines
Erythromycin (other macrolides)
Pentamidine
Zidovudine
Agents that decrease serum K^+ (diuretics)
Agents that are renal eliminated: digoxin, flecainide, procainamide
Anticoagulants
Cimetidine

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develop pulmonary toxicity. However, hepatic and neuromuscular adverse effects are related to high desethylamiodarone and amiodarone plasma levels.

- Holter monitoring early in the course of therapy confirms arrhythmia suppression and is useful to screen for intermittent bradycardia.

SOTALOL (BETAPACE, SOTACOR)

Sotalol is a useful antiarrhythmic. Studies that support this view include the following:

- After DC cardioversion of AF, sotalol is as effective as quinidine in maintaining sinus rhythm and is better tolerated. In 98 patients post-DC, cardioversion of AF, 160–320 mg of sotalol daily caused maintenance of sinus rhythm in 52%, and in 85 quinidine-treated patients, sinus rhythm was maintained in 48%. Some 26% of the quinidine group and 11% of the sotalol group withdrew because of adverse effects. Sotalol is useful for the management of paroxysmal AF. The drug is not recommended for slowing the ventricular rate in patients with chronic AF because other β -blockers have similar beneficial effects but they do not carry the risk of torsades de pointes.
- In small, nonrandomized studies with up to 18-month follow-up, sotalol therapy has caused reduction in the recurrence of sustained VT and VF. In a study of 16 patients with recurrent sustained VT refractory to an average of 4.8 antiarrhythmic agents, sotalol was effective at high dosage, 320–960 mg daily, in suppressing inducible sustained VT. Arrhythmias refractory to other antiarrhythmic agents, including amiodarone, have shown a beneficial response to sotalol administration. Patients evaluated with noninvasive or invasive means exhibit similar efficacy with sotalol compared with those empirically treated. Thus, both sotalol and amiodarone can be used as empiric therapy in patients with life-threatening ventricular arrhythmias.
- A head-to-head comparison of sotalol and amiodarone was carried out in the Amiodarone versus Sotalol Study Group. This multicenter trial studied 59 patients with documented VT who had failed a class I agent. Patients were randomized to amiodarone and sotalol. At 1-year follow-up, there was no significant difference between the groups. Treatment

failures (death, recurrent ventricular arrhythmias, and side effects) were similar: 13 of 29 on sotalol and 14 of 30 on amiodarone.

- In the EP Study versus Electrocardiographical Monitoring study, sotalol was superior to six sodium channel-blocking antiarrhythmic agents. The actuarial probability of a recurrence of ventricular arrhythmia, risks of death from any cause, from a cardiac cause, and from arrhythmia were significantly lower in patients treated with sotalol. The incidence of torsades de pointes is approximately 2% and is similar to that observed with quinidine. In a total of 1288 patients treated with sotalol in controlled trials, 27 patients experienced torsades de pointes (2%).

Dosage. 160–320 mg daily, in two divided doses; maximum 480 mg daily under close supervision (*see* Fig. 6.16 for use in AF).

Other Antiarrhythmic Agents

AZIMILIDE

Singer et al. studied a total of 172 patients randomized to daily treatment with placebo, 35 mg, 75 mg, or 125 mg of oral azimilide; a study of patients with old MI and HF managed with implantable cardioverter–defibrillators (ICDs).

The frequency of appropriate shocks and were significantly decreased among treated patients compared with placebo patients. $p = 0.0001$). Azimilide dihydrochloride was well tolerated and did not alter EF or energy requirements for defibrillation or pacing. Azimilide dihydrochloride appears to be a safe and effective drug for reducing the frequency of VT and VF in patients with ICDs.

BIBLIOGRAPHY

- Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the “Pill-in-the-Pocket” approach. *N Engl J Med* 2004;351:2384–2391.
- Alboni P, Tomasi C, Menozzi C, et al. Efficacy and safety of out-of-hospital self-administered single-dose oral drug treatment in the management of infrequent, well-tolerated paroxysmal supraventricular tachycardia. *J Am Coll Cardiol* 2001;37:548–553.
- Allen BJ, Brodsky MA, Capparelli EV. Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. *Am J Cardiol* 1989;64:1202.
- Amiodarone vs. Sotalol Study Group. Multi-centre randomized trial of sotalol vs amiodarone for chronic malignant ventricular tachyarrhythmias. *Eur Heart J* 1989;10:685.
- Anderson JL, Jolivet DM, Fredell PA. Summary of efficacy and safety of flecainide for supraventricular arrhythmias. *Am J Cardiol* 1988;62:62.
- Anderson JL, Platt ML, Guarnieri T, et al. Flecainide acetate for paroxysmal supraventricular tachyarrhythmias. *Am J Cardiol* 1994;74:578.
- Atié J, Bragada P, Bragada J, et al. Clinical and electrophysiologic characteristics of patients with antidromic circus movement tachycardia in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1990;66:1082.
- Beckman KJ, Parker RB, Hariman RJ, et al. Hemodynamic and electrophysiological actions of cocaine. Effects of sodium bicarbonate as an antidote in dogs. *Circulation* 1991;83:1799.
- Ben-David J, Zipes DP. Torsades de pointes and proarrhythmia. *Lancet* 1993;341:1578.
- Benditt DG, Williams JH, Jin J, et al., for the D, L-Sotalol Atrial Fibrillation/Flutter Study Group. Maintenance of sinus rhythm with oral D, L-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. *Am J Cardiol* 1999;84:270–277.
- Bisnov E, Mitchell JH, January CT. Potassium and long QT syndrome: a new look at an old therapy. *J Am Coll Cardiol* 2003;42:1783–1784.
- Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. American College of Cardiology; American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines. Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias. ACC/AHA/ESC guidelines for the management of patients with supraventricular

- tricular arrhythmias—executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation* 2003;108:1871–1909.
- Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy. A solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation* 2004;110:1885–1889.
- The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;22:1505.
- Bragada P, Bragada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 1991;83:1649.
- Breithardt G. Amiodarone in patients with heart failure. *N Engl J Med* 1995;333:121.
- Brodsky M, Doria R, Allen B, et al. New-onset ventricular tachycardia during pregnancy. *Am Heart J* 1991;123:933.
- Burkart F, Pfisterer M, Kiowski W, et al. Effect of antiarrhythmic therapy on mortality in survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias: basel antiarrhythmic study of infarct survival (BASIS). *J Am Coll Cardiol* 1990;16:1711.
- Calkins H, Niklason L, Sousa J, et al. Radiation exposure during radiofrequency catheter ablation of accessory atrioventricular connections. *Circulation* 1991;84:2376.
- Calkins H, Sousa J, el Atassi R, et al. Diagnosis and cure of the Wolff-Parkinson-White syndrome or paroxysmal supraventricular tachycardias during a single electrophysiologic test. *N Engl J Med* 1991;324:1612–1618.
- Calkins H, Yong P, Miller JM, et al., for the Atakr Multicenter Investigators Group. Catheter ablation of accessory pathways, atrioventricular nodal re-entrant tachycardia, and the atrioventricular junction: final results of a prospective, multicenter clinical trial. *Circulation* 1999;99:262–270.
- CAST Investigators (Cardiac Arrhythmia Suppression Trial). Preliminary report. Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406.
- Ceremuzynski L. Secondary prevention after myocardial infarction with class 3 antiarrhythmic drugs. *Am J Cardiol* 1993;72:82F.
- Clague JR, Dagues N, Kottkamp H, et al. Targeting the slow pathway for atrioventricular nodal re-entrant tachycardia: initial results and long-term follow-up in 379 consecutive patients. *Eur Heart J* 2001;22: 82–88.
- DiMarco JP, Miles WH, Akhtar M, et al. Adenosine for paroxysmal supraventricular tachycardia: dose ranging and comparison with verapamil: assessment in placebo-controlled, multicenter trials. The Adenosine for PSVT Study Group. *Ann Intern Med* 1990;113:104–110.
- DiMarco JP. Adenosine and digoxin. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside*. Third edition, Philadelphia, PA: WB Saunders; 2000: 933–938.
- Dougherty AH, Jackman WM, Naccarelli GV, et al. Acute conversion of paroxysmal supraventricular tachycardia with intravenous diltiazem. IV Diltiazem Study Group. *Am J Cardiol* 1992;70:587–592.
- Duff HF, Mitchell LB, Kavanagh KM, et al. Amiloride. Antiarrhythmic and electrophysiologic actions in patients with inducible sustained ventricular tachycardia. *Circulation* 1989;79:1257.
- Dusman RE, Stanton MS, Miles WM, et al. Clinical features of amiodarone-induced pulmonary toxicity. *Circulation* 1990;82:51.
- Ferguson JD, DiMarco JP. Contemporary management of paroxysmal supraventricular tachycardia. *Circulation* 2003;107:1096–1099.
- Friday KJ, Jackman WM, Lee IK, et al. Sotalol-induced torsades de pointes successfully treated with hemodialysis after failure of conventional therapy. *Am Heart J* 1991;121:601.
- Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 2004;110:2287–2292.
- Garratt C, Linker N, Griffith M, et al. Comparison of adenosine and verapamil for termination of paroxysmal junctional tachycardia. *Am J Cardiol* 1989;64:1310.
- Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003;290:2685–2692.
- Goldenberg IF, Lewis WR, Dias VC, et al. Intravenous diltiazem for the treatment of patients with atrial fibrillation or flutter and moderate to severe congestive heart failure. *Am J Cardiol* 1994;74:884–889.
- Gonzales A, Sager PT, Akil B, et al. Pentamidine-induced torsades de pointes. *Am Heart J* 1991;122:1489.

- Green HL, for the CASCADE Investigators. The CASCADE study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. *Am J Cardiol* 1993;72:70F.
- Greene HL, Roden DM, Katz RJ, et al. The cardiac arrhythmia suppression trial: First CAST...then CAST-II. *J Am Coll Cardiol* 1991;19:894.
- Griffith MJ, Garratt CJ, Mounsey P, et al. Ventricular tachycardia as default diagnosis in broad complex tachycardia. *Lancet* 1994;343:386.
- Halperin JL. Efficacy and safety study of oral direct thrombin inhibitor ximelagatran compared with dose-adjusted warfarin in the prevention of stroke and systemic embolic events in patients with atrial fibrillation: SPORTIF V. American Heart Association Scientific Sessions, Orlando, FL, November, 2003.
- Halperin JL. Ximelagatran: Oral direct thrombin inhibition as anticoagulant therapy in atrial fibrillation. *J Am Coll Cardiol* 2005;45:1–9.
- Hanna IR, Langberg JJ. The shocking story of azimilide. [Editorial] *Circulation* 2004;110:3624–3626.
- Herré JM, Sauve MJ, Malone P, et al. Long-term results of amiodarone therapy in patients with recurrent sustained ventricular tachycardia or ventricular fibrillation. *J Am Coll Cardiol* 1989;13:442.
- Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol* 2003;41:1633–1652.
- Hohnloser SH, Klingenhoben T, Singh BN, et al. Amiodarone-associated proarrhythmic effects. *Ann Intern Med* 1994;121:529.
- Hohnloser SH, Meinertz T, Dambacher T, et al. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: results of a prospective, placebo-controlled study. *Am Heart J* 1991;121:89.
- Hohnloser SH, van de Loo A, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. *J Am Coll Cardiol* 1995;26:852.
- Hohnloser SH, Woosley RL, Wood AJ. Drug therapy, sotalol. *N Engl J Med* 1994;331:31.
- Hood MA, Smith WM. Adenosine versus verapamil in the treatment of supraventricular tachycardia: a randomized double-crossover trial. *Am Heart J* 1992;123:1543.
- Hsu Li-Fern, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004;351:2373–2383.
- Joglar JA, Page RL. Treatment of cardiac arrhythmias during pregnancy: safety considerations. *Drug Saf* 1999;20:85–94.
- Juul-Møller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol vs. quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. *Circulation* 1990;82:1932.
- Kennedy HL, Brooks MM, Barker AH, et al. Beta blocker therapy in the cardiac arrhythmia suppression trial. *Am J Cardiol* 1994;74:674.
- Khan MG. Arrhythmias. In Khan MG. Heart disease, diagnosis, and therapy. Baltimore, MD, Williams & Wilkins, 1996.
- Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;42:1944–1951.
- Kottkamp H, Hindricks G, Autschbach R, et al. Specific linear left atrial lesions in atrial fibrillation. *J Am Coll Cardiol* 2002;40:475–480.
- Kowey PR, Levine JH, Herré JM, et al. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. *Circulation* 1995;92:3255.
- Kubac G, Klinke WP, Grace M. Randomized double blind trial ring sotalol and propranolol in chronic ventricular arrhythmia. *Can J Cardiol* 1988;4:355.
- Kunze KP, Schluter M, Kuck KH. Sotalol in patients with Wolff-Parkinson-White syndrome. *Circulation* 1987;75:1050–1057.
- Lauer MR. Dofetilide: Is the treatment worse than the disease? *J Am Coll Cardiol* 2001;37:1106–1110.
- Lazzara R. Amiodarone and torsade de pointes. *Ann Intern Med* 1989;111:549.
- Leenhardt A, Glasser E, Burguera M, et al. Short-coupled variant of variant of torsade de pointes: a new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. *Circulation* 1994;89:206.
- Lip GY, Kamath S. Thromboprophylaxis for atrial flutter. *Eur Heart J* 2001;22:984–987.
- Lydkis C, Lip GY, Beevers M, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999;12:541–547.

- Man KC, Williamson BD, Niebauer M, et al. Electrophysiologic effects of sotalol and amiodarone in patients with sustained monomorphic ventricular tachycardia. *Am J Cardiol* 1994;74:1119.
- Marcus FI. The hazards of using type IC antiarrhythmic drugs for the treatment of paroxysmal atrial fibrillation. *Am J Cardiol* 1990;66:366.
- Marza I, James S, and Holt P. Bialtrial pacing for paroxysmal atrial fibrillation. *J Am Coll Cardiol* 2002;40:457–463.
- Mason JW. On behalf of the ESVEM investigators. A comparison of 7 anti-arrhythmic drugs in patients with ventricular tachy-arrhythmia. *N Engl J Med* 1993;329:452.
- Mattioni TA, Zheutlin TA, Sarmiento JJ, et al. Amiodarone in patients with previous drug-mediated torsades de pointes. *Ann Intern Med* 1989;111:574.
- Mehta A-V, Chidambaram B. Efficacy and safety of intravenous and oral nadolol for supraventricular tachycardia in children. *J Am Coll Cardiol* 1992;19:630.
- Meissner MD, Akhtar M, Lehmann MH, et al. Nonischemic sudden tachyarrhythmic death in atherosclerotic heart disease. *Circulation* 1991;84:905.
- Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol* 1996;27:76.
- Moss AJ, Robinson J. Clinical features of the idiopathic long QT syndrome. *Circulation* 1991;85(Suppl I):1–140.
- Myers M, Peter T, Weiss D, et al. Benefit and risks of long-term amiodarone therapy for sustained ventricular tachycardia/fibrillation: minimum of three-year follow-up in 145 patients. *Am Heart J* 1990;119:8.
- Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;43:2044–2053.
- Nalos PC, Ismail Y, Pappas JM. Intravenous amiodarone for short-term treatment of refractory ventricular tachycardia or fibrillation. *Am Heart J* 1991;122:1629.
- Nora M, Zipes DP. Empiric use of amiodarone and sotalol. *Am J Cardiol* 1993;72:62F.
- Ochi RP, Goldenberg IF, Almquist A, et al. Intravenous amiodarone for the rapid treatment of life-threatening ventricular arrhythmias in critically ill patients with coronary artery disease. *Am J Cardiol* 1989;64:599.
- Olsson SB. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362:1691–1698.
- Orejarena LA, Vidaillet H Jr, DeStefano F, et al. Paroxysmal supraventricular tachycardia in the general population. *J Am Coll Cardiol* 1998;31:150–157.
- Ozcan C, Jahangir A, Friedman PA, et al. Sudden death after radiofrequency ablation of the atrioventricular node in patients with atrial fibrillation. *J Am Coll Cardiol* 2002;40:105–110.
- Page RL. Newly diagnosed atrial fibrillation. *N Engl J Med* 2004;351:2408–2416.
- Pappone C, Rosanio S, Augello G, et al. morbidity and mortality and quality of life after circumferential pulmonary vein ablation for atrial fibrillation. *J Am Coll Cardiol* 2003;42:185–197.
- Pappone C, Santinelli V, Rosanio S, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. *J Am Coll Cardiol* 2003;41:239–244.
- Peters NS, Schilling RJ, Kanagaratnam P, et al. Atrial fibrillation: Strategies to control, combat, and cure. *Lancet* 2002;359:593–603.
- Pitt B. The role of β -adrenergic blocking agents in preventing sudden cardiac death. *Circulation* 1992;85(Suppl I):1–107.
- Rankin AC, Pringle SD, Cobbe SM. Acute treatment of torsades de pointes with amiodarone proarrhythmic and antiarrhythmic association of QT prolongation. *Am Heart J* 1990;119:185.
- Rankin AC, Pringle SD, Cobbe SM, et al. Amiodarone and torsades de pointes. *Am Heart J* 1990;120:1482.
- Saksena S. For the PCD investigator group: clinical outcome of patient with malignant ventricular tachyarrhythmias and a multi-programmable implantable cardioverter-defibrillator implanted with or without thoracotomy: an international multi-centre study. *J Am Coll Cardiol* 1994;23:1521.
- Saksena, S., Prakash, A., Ziegler, P. et al. Improved suppression of recurrent atrial fibrillation with dual site right atrial pacing and antiarrhythmic drug therapy. *J Am Coll Cardiol* 2002;40:1140–1150.
- Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. *Pacing Clin Electrophysiol* 2000;23:1020–1028.
- Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med* 1997;29:135–140.
- Schwartz PJ, Locati EH, Moss AJ, et al. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. *Circulation* 1991;84:503.

- Seidl K, Hauer B, Schwick NG, et al. Risk of thromboembolic events in patients with atrial flutter. *Am J Cardiol* 1998;82:580–583.
- Shettigar UR, Toole JG, O’Came Appunn D. Combined use of esmolol and digoxin in the acute treatment of atrial fibrillation or flutter. *Am Heart J* 1993;126:368.
- Siebel J, Cappato R, Ruppel R, et al. for the CASH Study. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). *Am J Cardiol* 1993;72:109F.
- Singer I, Al-Khalidi H, Niazi I, et al. Related Articles, Links Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2004;43:39–43.
- Singh BN. When is QT prolongation antiarrhythmic and when is it proarrhythmic? *Am J Cardiol* 1989;63:867.
- Singh SN, Cohen A, Chen Y, et al. Sotalol for refractory sustained ventricular tachycardia and nonfatal cardiac arrest. *Am J Cardiol* 1988;62:399.
- Singh SN, Fletcher RD, Gross Fisher S, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Eng J Med* 1995;333:77.
- Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation* 2000;102:2385–2390.
- Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;330:1852.
- SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation: A Randomized Trial. *JAMA* 2005;293:690–698.
- Stambler BS, Wood MA, Ellenbogen KA, et al., for the Ibutilide Repeat Dose Study Investigators. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;94:1613–1621.
- Steurer G, Gursoi S, Frey B, et al. Differential diagnosis on the electrocardiogram between ventricular tachycardia and preexcited tachycardia. *Clin Cardiol* 1994;17:306.
- Stratmann HG, Kennedy HL. Torsades de pointes associated with drugs and toxins: recognition and management. *Am Heart J* 1987;13:1470.
- Tendera M, Wnuk-Wojnar AM, Kulakowski P, et al. Efficacy and safety of dofetilide in the prevention of symptomatic episodes of paroxysmal supraventricular tachycardia: a 6-month double-blind comparison with propafenone and placebo. *Am Heart J* 2001;142:93–98.
- Tobé TJ, de Langen Lees DJ, Bink-Boelkens ME, et al. Late potentials in a bradycardia-dependent long QT syndrome associated with sudden death during sleep. *J Am Coll Cardiol* 1992;19:541.
- Tzivoni D, Banai S, Schuger C, et al. Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. *Circulation* 1988;77:392.
- van der Hoof CS, Heeringa J, van Herpen G, et al. Drug-induced atrial fibrillation. *J Am Coll Cardiol* 2004;44:2117–2124.
- Verheugt FW. Can we pull the plug on warfarin in atrial fibrillation? *Lancet* 2003 22;362:1686–1687.
- Volgman AS, Carberry PA, Stambler B, et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. *J Am Coll Cardiol* 1998;31:1414–1419.
- Wanless RS, Anderson K, Joy M, et al. Multicenter comparative study of the efficacy and safety of sotalol in the prophylactic treatment of patients with paroxysmal supraventricular tachyarrhythmias. *Am Heart J* 1997;133:441–446.
- Wilson JS, Podrid PJ. Side effects from amiodarone. *Am Heart J* 1991;121:158.
- Winniford MD, Fulton KL, Hillis LD. Long-term therapy of paroxysmal supraventricular tachycardia: a randomized, double-blind comparison of digoxin, propranolol and verapamil. *Am J Cardiol* 1984;54:1138–1139.
- Wyse DG, Gersh BJ. Atrial fibrillation: a perspective: thinking inside and outside the box. *Circulation* 2004;109:3089–3095.
- Yeh SJ, Lin FC, Chou YY, et al. Termination of paroxysmal supraventricular tachycardia with a single oral dose of diltiazem and propranolol. *Circulation* 1985;71:104–109.
- Yellin NL, Drew BJ, Scheinman MM. Safety and efficacy of central intravenous bolus administration of adenosine for termination of supraventricular tachycardia. *J Am Coll Cardiol* 1993;22:741.
- Zehender M, Hohnloser S, Müller B, et al. Effects of amiodarone versus quinidine and verapamil in patients with chronic atrial fibrillation: results of a comparative study and a 2-year follow-up. *J Am Coll Cardiol* 1992; 19:1054.
- Zimetbaum P, Josephson ME. Current concepts: evaluation of patients with palpitations. *N Engl J Med* 1998;338:1369–1373.

Cardiac Arrest

CONTENTS

DEFINITION AND CAUSES
CARDIOPULMONARY RESUSCITATION
MANAGEMENT OF VF
DRUG THERAPY OF CARDIAC ARREST
BRADYARRHYTHMIAS: ASYSTOLE OR EMD
BIBLIOGRAPHY

DEFINITION AND CAUSES

Sudden cardiac death is defined as a sudden natural death caused by cardiac disease that is associated with the following:

- An abrupt loss of consciousness within 1 hour of onset of acute symptoms.
- Known or unknown pre-existing heart disease.
- Unexpected time and mode of death.

Hinkle and Thaler classified cardiac death as follows:

- Class I: An arrhythmic death if circulatory failure follows the disappearance of the pulse. In these situations, the nature of the terminal illness is an acute cardiac event in more than 98% of victims, and ventricular fibrillation (VF) or asystole has been observed to be the terminal event in approximately 83% and 17% of patients, respectively.
- Each day in the United States, approximately 1000 sudden deaths occur, and it is estimated that about 30% result from asystolic cardiac arrest.
- Class II: Circulatory failure death if the disappearance of the pulse is preceded by circulatory failure. This scenario is common in patients with terminal illnesses and usually is associated with a terminal bradyarrhythmia; asystole and VF have been observed in 67 and 33% of these patients, respectively.

Cardiac arrest is defined as the abrupt cessation of cardiac pump function that results in death, which may be averted if prompt intervention is instituted. A number of cardiac disorders cause lethal tachyarrhythmias or failure of formation or transmission of the cardiac impulse that results in cardiac arrest, but the mechanisms that initiate these fatal arrhythmias are mostly unknown and are diverse.

The basic cardiac causes of cardiac arrest include the following:

- VF or pulseless ventricular tachycardia (VT): in at least 80%; VF is defined as a pulseless, chaotic, disorganized rhythm with an undulating irregular pattern that varies in size and shape and a ventricular waveform greater than 150 minutes.
- Asystole: 10%.
- Electromechanical dissociation (EMD): 5%.
- Myocardial rupture, cardiac tamponade, acute disruption of a major blood vessel, and acute mechanical obstruction to blood flow that includes the pulmonary embolism.

The American College of Cardiology/American Heart Association (AHA) advise that there are only two cardiac arrest rhythms:

- VF/pulseless VT.
- Non-VF/VT: asystole and pulseless electrical activity (PEA).

Always assume VF or pulseless VT because patients who can be saved from cardiac arrest usually have these cardiac arrest rhythms. The single most effective intervention that can save victims of sudden cardiac arrest is the earliest delivery of defibrillation and widespread distribution of automatic external defibrillators will assist to accomplish early defibrillation programs.

Approximately 75% of all cases of cardiac arrest involve an unstable atheromatous plaque with overlying thrombus, causing occlusion or distal embolization of a major coronary artery. Cardiac arrest in coronary disease may occur with little or no warning (plaque emboli), during the acute phase of myocardial infarction (occlusion) or, later, caused by an arrhythmia circuit that may respond to trigger factors (catecholamines, ischemia, hypokalemia, critically timed ventricular premature beats) to precipitate VF. A history of ischemic heart disease (IHD) is present in up to 50% of patients; in a significant number of these patients, atheromatous coronary disease is silent until the time of the event. Most sudden cardiac deaths are the result of coronary atherosclerosis. In these individuals, VF usually occurs either because of a new acute ischemic event or because of myocardial scarring and/or hypertrophy, which predisposes the myocardium to re-entrant tachycardia that triggers VF. In a study by Davies, of 168 consecutive cases of sudden coronary death within 6 hours of symptoms, the proportion of deaths owing to IHD at time intervals of less than 1 hour and less than 6 hours did not differ. In this study, 73.3% showed thrombosis on an unstable plaque ([Fig. 7.1.](#)). No acute change in the coronary artery was observed in 19%. Adopting this principle, it is determined that cardiac sudden death is associated with no acute coronary lesion in approximately 20% of individuals who succumb to unexpected cardiac arrest.

Other underlying diseases or disturbances that may result in cardiac arrest include:

- Aortic stenosis.
- Hypertrophic cardiomyopathy.
- Dilated cardiomyopathy.
- Complete heart block or sinoatrial disease.
- Wolff-Parkinson-White syndrome in patients with very short refractory period of the bypass tract.
- Torsades de pointes in patients taking antiarrhythmic drugs or in those with prolonged QT syndromes (congenital or acquired).
- Structural abnormalities, such as pulmonary embolism or aortic dissection.

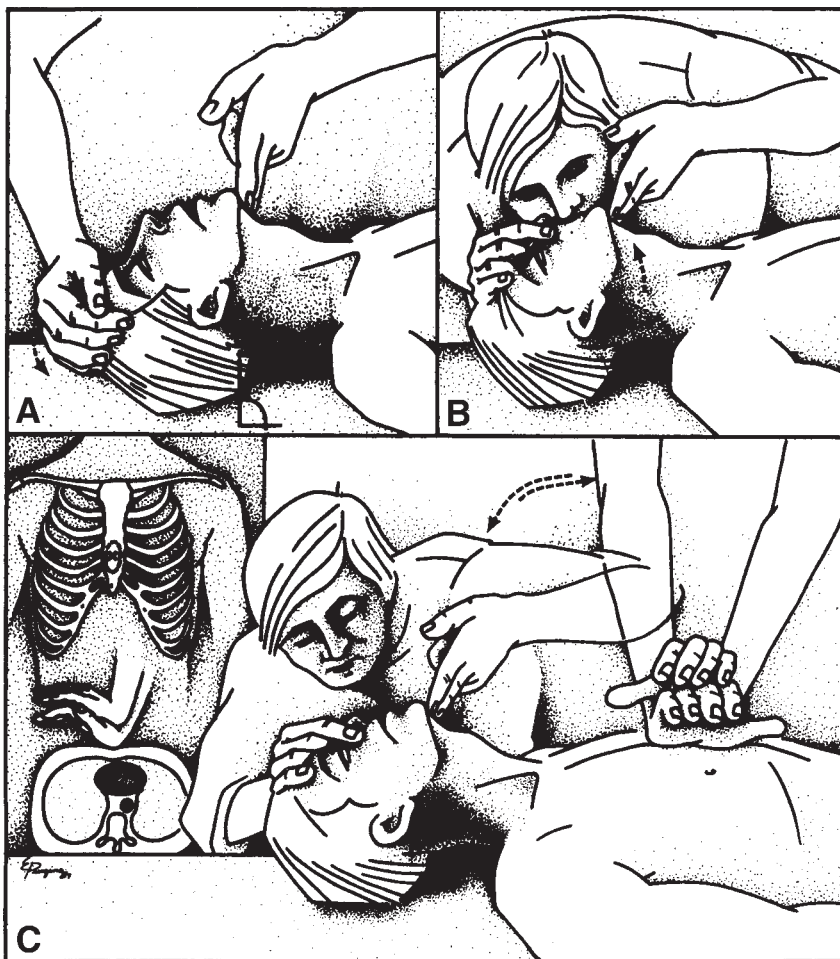


Fig. 7.1. The ABCs of cardiopulmonary resuscitation. (A) The airway is opened using the head tilt/chin lift technique. (B) Breathing: the victim's nostrils are pinched closed and the rescuer breathes twice into the victim's mouth. (C) Circulation: if no pulse is present, external chest compression is instituted at 90–100/minute. Two rescuers: five compressions to one ventilation. One or two rescuers: 15 compressions to 2 ventilations. Modified from Khan M. Gabriel. *Cardiac Drug Therapy*. Sixth Edition. London: WB Saunders, 2003, with permission from Elsevier.

Rarely, a sudden cardiac death resulting from electrical dysfunction occurs without discernible cardiac pathology (primary electrical disease). Current information strongly indicates that coronary artery spasm, latent pre-excitation, and prolonged QT syndromes do not play a role in patients with idiopathic VF. Physical and mental stress appears to be implicated in fewer than 33% of cases of idiopathic VF.

Pathogenesis of the syndrome of sudden death during sleep in young apparently healthy southeast Asian males is undetermined and appears to be unrelated to idiopathic VF in “normal” hearts. Wellens et al. suggest that because of the rarity of sudden arrhythmic death and the unexplained mechanisms in the absence of heart disease, a worldwide registry of these patients should be maintained.

Although an emergency coronary care system designed to get the defibrillator promptly to the patient via emergency vehicles was devised and put into practice by Pantridge and Geddes in Belfast as long ago as 1966 (and was quickly accepted in the US), the concept has only gradually gained acceptance in a number of countries. The AHA state-of-the-art review, *Improving Survival from Cardiac Arrest: The Chain of Survival Concept* is a timely one:

- Early access.
- Early cardiopulmonary resuscitation (CPR).
- Early defibrillation.
- Early advanced care.

Because prompt defibrillation is the single-most effective lifesaving intervention for most victims of cardiac arrest, the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee of the AHA have approved the widespread distribution of automated external defibrillators, which are now required items in all ambulances or emergency vehicles engaged in the transit of cardiac patients. It is a logical approach to have these lifesaving devices in housing complexes, stadiums, and at all large public gatherings, shopping centers, and so on. The AHA has endorsed the position that all first-responding hospital and nonhospital personnel (e.g., doctors, nurses, medical technicians, paramedics, firefighters, volunteer emergency personnel, and several other categories in the population) be trained in the use of and be permitted to operate a defibrillator. Zipes indicates that the time to defibrillation and/or pacing may be shortened by developing external devices that incorporate the automatic approaches to arrhythmia recognition and therapy available in the multiprogrammable, implantable pacemaker-cardioverter-defibrillator. These devices should become as accessible as fire extinguishers. A similar call for the widespread distribution of defibrillators was made by Dr. Pantridge and the late Dr. Grace in the early 1970s.

CARDIOPULMONARY RESUSCITATION

Unless immediate defibrillation is possible (e.g., in the cardiac care unit), early CPR is essential. Late CPR and/or late advance support must be avoided. Although in Seattle up to 20% of prehospital VF patients survive, in other areas of the United States, fewer than 10% of all cardiac arrest patients in or out of the hospital survive and, unfortunately, up to 50% of these patients have been observed to have a neurological deficit. Thus, unless the arrest is witnessed and CPR can be instituted within 4 minutes or with a defibrillator available within 8 minutes, caution is necessary. In the elderly or in patients with noncardiac underlying disease, such as stroke, terminal renal failure, cancer, or other chronic disease, the final arrhythmia is not unexpected and does not constitute true cardiac arrest. When appropriate in these situations, families and patients should be aware of the possibilities in advance.

CPR Technique

Basic life support (BLS) algorithm directs the rescuers to start the 6 basic steps of the international BLS algorithm:

1. Check responsiveness. Rapidly establish that the patient is unconscious and unresponsive.
2. Open the airway. Use the head tilt/chin lift maneuver to open the airway (see Fig. 7.1.).

3. Determine breathlessness. Promptly verify that the patient is not breathing; take a deep breath, seal your lips around the mouth.
4. Give two full breaths, 1–1.5 seconds/breath, and allow the chest to deflate fully between each breath.
5. Assess circulation. Determine that the pulses are absent in the large arteries.
6. Start chest compression if no circulation detected:
 - One or two rescuers: 15 compressions to two ventilations.
 - The compression rate should be about 90 to 100/minute.
 - At the end of compressions two full breaths are given.
 - When the airway is secured with a cuffed endotracheal tube, use five compressions to one ventilation.

MANAGEMENT OF VF

Immediate defibrillation within 2–4 minutes of witnessed cardiac arrest is the most important single therapy that may rescue patients in cardiac arrest, without producing tragic iatrogenic brain damage from attempting full CPR and the unavoidable hesitations that occur in many settings of cardiac arrest:

- Turn the monitor power on.
- Apply conductive medium to defibrillator paddles and evaluate rhythm with the “quick look” paddles.
- If VF is present, turn defibrillator power on. Be certain that the defibrillator is not in synchronous mode.
- Select energy and charge the defibrillator.
- Defibrillate using 200 J (Table 7.1.). While recharging of the defibrillator or administration of intravenous (IV) bolus drugs, CPR must be continued. Immediate de-fibrillation for the patient with VF is the key to success; intubation, establishment of IV lines, and administration of medications should commence only if the first series of direct current shocks fails to restore a spontaneous circulation.

If a defibrillator is immediately available and defibrillation is achieved within 4 minutes of a cardiac arrest, long-term survival rates of 20–30% are possible. However, without prompt defibrillation, the survival rate ranges from 1 to 5% and is not acceptable.

Eisenberg and Mengert have listed common errors that occur during CPR:

- Defibrillation errors: synchronized mode accidentally selected before defibrillation is attempted, thus no shock is delivered.
- The operator believes that lead I, II, or III is being displayed when, in fact, the selection is set to paddles and asystole is falsely displayed.
- Considerable chest hair should be shaved off where the paddles are to be placed, and smeared gel across the chest should be towed off.

Paramedic systems have been shown to achieve defibrillation in an average of 12 minutes, which is considered to be late defibrillation, resulting in about a 10% survival rate. Several countries and many communities in the United States have approved the use of semiautomated defibrillators by emergency medical technicians trained as first responders, after completion of a 40-hour training program. It is feasible to train ambulance personnel, firefighters, police officers, emergency volunteers, security guards, airline crews, designated attendants at stadiums, and so on.

Table 7.1.
Management of VF or Pulseless VT

Apply quick look paddles or press analyze ^a :	VF confirmed switch to DF
Nonsynchronized	Immediate
1st shock 200 J	Check pulse, rhythm VF: CPR; recharge DF
2nd shock 300 J	VF persists: recharge DF
3rd shock 360 J	CPR
	1 mg epinephrine IV bolus
	Repeat every 3–5 minutes
	40 U vasopressin IV, single dose, 1 time only
	IV line, intubate
4th shock 360 J	VF: CPR, for 1 minute (allow drug action)
	100 mg lidocaine IV
5th shock 360 J	VF
	1 mg epinephrine ^b IV VF persists, assess pH
6th shock 360 J	VF: CPR
	50 mg lidocaine IV allow 2 min
7th shock 360 J	VF: arrest > 10 min pH < 7.1
	50 mEq NaHCO ₃ IV bolus
8th shock 360 J	VF: CPR

^aSemiautomated external defibrillator.

^bRepeat every 5 minutes.

The operation of semiautomatic devices does not demand complex learning skills in rhythm analysis, and operation of the device can be mastered within hours. A single control activates the defibrillator to quickly analyze the cardiac rhythm, indicates that a shock is required, and, on command, charges and delivers the shock.

In four communities in the United States, survival rates for patients in VF increased from an average of 4–18% with the use of emergency defibrillators by medical technicians.

DRUG THERAPY FOR CARDIAC ARREST

Epinephrine

Epinephrine and other cardiac arrest drugs and their dosages are listed in [Table 7.2](#). Salutary effects of epinephrine are:

- Increased myocardial contractility.
- Elevated perfusion pressure.
- Possible conversion of EMD to electromechanical coupling.
- Improved chances for defibrillation.
- Improved blood flow to the heart and brain when sinus rhythm is restored.

Epinephrine is an α - and β -adrenergic agonist and is the drug of first choice, administered as an initial 1-mg IV bolus after the third shock fails to defibrillate. Intracardiac epinephrine is not recommended, except when IV or intratracheal routes are not possible.

A high dose of epinephrine is necessary to maintain adequate diastolic blood pressure to produce adequate coronary and cerebral perfusion. The drug produces peripheral arteriolar constriction and an increase in systemic vascular resistance, thus increasing aortic and coronary diastolic perfusion pressure. Also, coronary artery dilatation occurs.

Table 7.2.
Cardiac Arrest Drugs

<i>Drug</i>	<i>Dosage</i>	<i>Supplied</i>	<i>Comment</i>
Epinephrine	1 mg IV bolus repeated q 3–5 min 10 mL tracheobronchial (1:10,000)	10 mL (1 mg in 1:10,000 dilution)	Do not give with NaHCO ₃ in same IV
Sodium bicarbonate	1 mEq IV bolus (mmol)/kg, usually 50 mEq (mmol) initially; 1 amp = 44 mEq then 0.5 initial dose q 10–15 min	50 mL of 8.4% = 50.0 mEq (mmol)	Used for hyperkalemic arrest Recommended for trial after 7th shock, pH < 7.1, or 10 min in asystole
Atropine	1 mg In asystole q 2–5 min (max of 3 mg) 0.5 mg bradycardia q 5 min–2 mg	10 mL = 1 mg 5 mL = 0.5 mg (UK, 1-mL amp = 0.6 mg or 1 mg)	
Lidocaine (lignocaine)	75–100 mg IV bolus simultaneous infusion 2–3 mg/min 100 mg in 5 mL (2%)	50 mg in 5 mL (1%) 100 mg in 10 mL (1%)	
Propranolol for VF	USA: 1 mg over 2–5 min (q 2–5 min to max 5 mg) UK: 1 mg over 2 min (q 2 min to max 5 mg)		Useful in recurrent VF if lidocaine fails; also for VF following electrocution
Metoprolol	5 mg IV over 5 min		
Calcium chloride	2.5–5 mL 10%, (5–7 mg/kg 250–500 mg) IV bolus	10 mL 10% CaCl ₂	Not recommended in cardiac arrest, except with hyperkalemia or postverapamil Do not give with NaHCO ₃

Modified from Khan M. Gabriel. Cardiac drug therapy. Sixth Edition. London: WB Saunders, 2003, with permission from Elsevier.

INDICATIONS

- Fine VF is made coarse and more susceptible to removal by electrical counter-shock.
- VF that fails to respond to countershock may respond after epinephrine.
- Asystole and pulseless idioventricular rhythms.
- EMD.

Vasopressin

Vasopressin has recently been shown to be effective for both VF and asystole. Vasopressin is recommended by the ACC/AHA only for VF/pulseless VT. The recommended dosage of vasopressin is a single 40-U IV dose, one time only. There is no evidence to support the value of repeat vasopressin doses. If there is no response 5–10 minutes after a single dose of vasopressin, it is advisable to resume epinephrine.

The guidelines indicate that there is no evidence to support its use in asystole or pulseless electrical activity.

Most importantly, Wenzel et al. showed the success of vasopressin alone and vasopressin followed by epinephrine in refractory asystolic cardiac arrest; this represents a major breakthrough and guidelines will change. In this randomized study, out-of-hospital cardiac arrest patients were assigned to receive two injections of either vasopressin 40 IU or 1 mg of epinephrine followed by additional treatment epinephrine if needed. 589 patients received avasopressin; 597 received epinephrine. The effects of vasopressin were similar to those of epinephrine in the management of VF and PEA.

Vasopressin was however, superior, to epinephrine in patients with asystole. The authors concluded that vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.

Lidocaine (Lignocaine)

Lidocaine is given, after a fourth shock fails to defibrillate, as a 100-mg IV bolus, followed, after about 1 minute of CPR, by a 360-J shock. If defibrillation is successful, give a 50-mg bolus of lidocaine and an infusion at 2–3 mg/minute immediately. The lower dose is used for the elderly or those with heart failure (*see Figs. 1.10. and 1.11.*). An additional bolus is given 10 minutes later to maintain therapeutic lidocaine levels. Lidocaine is preferred to bretylium because trials have not shown bretylium to be superior and lidocaine does not produce severe hypotension, which is often seen with bretylium.

Sodium Bicarbonate

This agent is no longer recommended for routine use during cardiac arrest of brief duration except in patients with preexisting hyperkalemia. However, after about 10 minutes of CPR and if a seventh shock fails to result in defibrillation, an IV bolus of sodium bicarbonate (50 mEq) is advisable. The drug should not be used simultaneously with calcium chloride or epinephrine.

Calcium Chloride

Calcium chloride is no longer recommended. The drug may be useful if asystole is caused by verapamil or in the management of hyperkalemia causing arrest. The drug is, however, of no value in EMD.

DOSAGE

Give 2.5–5 mL 10% calcium chloride or (UK), calcium gluconate IV bolus; 10 mL of a 10% solution.

Amiodarone

The role of bretylium has dwindled appropriately with the availability of amiodarone, and manufacturing has been halted because of lack of supplies. Amiodarone is useful in the management of cardiac arrest. Amiodarone is superior to bretylium and is advisable if it is necessary to continue resuscitative measures (*see* Chapter 6 for discussion on amiodarone).

For VF/pulseless VT, give 300 mg IV push and for recurrence 150–500 mg bolus over 5–10 minutes, followed by 10 mg/kg/24 hours (0.5 mg/mL) continuous infusion; maximum 2.2 g over 24 hours.

Magnesium Sulfate

One to 2 g IV in polymorphic VT (TdP) may expedite ventricular defibrillation and is advisable for suspected hypomagnesemia.

BRADYARRHYTHMIAS: ASYSTOLE OR EMD

Severe symptomatic bradycardia is usually treated with 0.5–0.6 mg atropine repeated every 2 minutes to a maximum of 2.4 mg. When atropine is used to treat asystole before pacing, a dose of 1 mg is given immediately, followed by an additional 1 mg after 2 minutes. In severe bradycardia or atrioventricular block without a QRS complex, atropine is worth a trial. No harm can ensue, as if VF is precipitated by atropine; defibrillation may produce a stable rhythm to allow coronary perfusion before pacing. Be aware that VF may masquerade as asystole. Thus, rotate the monitoring electrodes and check the monitor to ensure that VF is not present. Give epinephrine with the hope that fibrillation may ensue and then countershock.

Asystole in a heart that was beating forcefully minutes before the occurrence of asystole may complicate anterior infarction, and pacing may be lifesaving. Asystole in the atonic heart (agonal) and EMD are usually caused by irreversible myocardial damage and prognosis is very poor.

Management of EMD

- Commence CPR.
- IV line.
- Epinephrine (1-mg IV bolus).
- Intubate.
- Assess for cardiac rupture and tamponade.

Search for Extracardiac Causes of EMD

- Inadequate ventilation, including intubation of right main stem bronchus and tension pneumothorax.
- Poor perfusion: hypovolemia (jugular venous pressure [JVP] decreased), give fluid challenge. If the JVP is markedly elevated, suspect cardiac tamponade or massive pulmonary embolism.
- Severe acidosis or hyperkalemia.

CPR should be continued with the hope that one of these factors may be correctable. Mobitz Type 2 block and complete heart block must be managed with ventricular pacing. If there is asystole or severe bradycardia unresponsive to atropine continue CPR, give 1 mg epinephrine IV or endotracheal. If there is no response, consider pacing. For severe hypotension with mild bradycardia, dopamine is advisable (*see* Infusion Pump Chart, Table 3.6.).

BIBLIOGRAPHY

- LA, Eliastam M, Kerber, RE, et al. Report of the American Heart Association Task Force on the future of cardiopulmonary resuscitation. *Circulation* 1992;85:2346.
- Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: the "Chain of Survival" concept. *Circulation* 1991;83:1832.
- Davies MJ. Anatomic features in victims of sudden coronary death. *Circulation* 1992;85 (suppl 1):1–19.
- Dimarco JP. Management of sudden cardiac death survivors: role of surgical and catheter ablation. *Circulation* 1992;5(Suppl I):1–125.
- Echt DS, Cato EL, Cox DR. pH-Dependent effects of lidocaine on defibrillation energy requirements in dogs. *Circulation* 1989;80:1003.
- Forgoros RN, Elson JJ, Bonnet CA. Long-term outcome of survivors of cardiac arrest whose therapy is guided by electrophysiologic testing. *J Am Coll Cardiol* 1992;19:780.
- Gray WA, Capone RJ, Most AS. Unsuccessful emergency medical resuscitation—are continued efforts in the emergency department justified? *N Eng J Med* 1991;325:1393.
- Hinkle LE, Thaler JH. Clinical classification of cardiac deaths. *Circulation* 1982;65:457.
- Hurwitz JL, Josephson ME. Sudden cardiac death in patients with chronic coronary heart disease. *Circulation* 1992;85(Suppl I):1–143.
- Kerber RE. Statement on early defibrillation. From The Emergency Cardiac Care Committee, American Heart Association. *Circulation* 1991;83:2233.
- Lars W, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA* 2005;293:299–304.
- Lazzam C, McCans JL. Predictors of survival of in-hospital cardiac arrest. *Can J Cardiol* 1991;7:113.
- Pantridge JF, Geddes JS. Cardiac arrest after myocardial infarction. *Lancet* 1966;1:807.
- Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. *Lancet* 1967;2:271.
- The Public Access Defibrillation Trial Investigators. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med* 2004;351:637–646.
- Ruskin JN. Role of invasive electrophysiological testing in the evaluation and treatment of patients at high risk for sudden cardiac death. *Circulation* 1992;85(Suppl I):1–152.
- Sanders AB, Ewy GA. Cardiopulmonary resuscitation in the real world: when will the guidelines get the message? *JAMA* 2005;293:363–365.
- Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992;85(Suppl I):1–77.
- Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;330:1852.
- Viskin S, Belhassen B. Idiopathic ventricular fibrillation. *Am Heart J* 1990;120:661.
- Weaver WD. Resuscitation outside the hospital—what's lacking? *N Eng J Med* 1991;325:1437.
- Wellens HJJ, Lemery R, Smeets JL, et al. Sudden arrhythmic death without overt heart disease. *Circulation* 1991;85(Suppl I):1–92.
- Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med*. 2004;350:105–113.
- Zipes DP. Sudden cardiac death. Future approaches. *Circulation* 1992;85(Suppl I):1–160.

8

Hypertension

CONTENTS

RELEVANT KEY ISSUES
DIAGNOSIS
PRIMARY (ESSENTIAL) HYPERTENSION
NONDRUG THERAPY
DRUG THERAPY
WHICH β -BLOCKER TO CHOOSE
ACCELERATED AND MALIGNANT HYPERTENSION
HYPERTENSIVE CRISIS
DRUG THERAPY
HYPERTENSION IN PREGNANCY
SECONDARY HYPERTENSION
BIBLIOGRAPHY

RELEVANT KEY ISSUES

There are as many as 1 billion individuals with hypertension worldwide and physicians have only four recommended antihypertensive drugs to treat this varied population of patients. More than 50 million Americans have hypertension, and at ages 65–75 more than 60% of individuals have hypertension. The incidence is higher in African Americans.

This silent killer provokes much harm to the body; it is the leading cause of:

- Cerebrovascular and cardiovascular morbidity and mortality, and is thus responsible for many fatal and nonfatal strokes.
- Fatal and nonfatal myocardial infarctions (MIs).
- More than 50% of patients with heart failure (HF) have a background of hypertension. Effective control of hypertension is the single greatest means to prevent systolic or diastolic HF. Diastolic HF has no effective therapy and prevention is the key.
- Hypertension is the most common cause of atrial fibrillation (AF), the most common sustained arrhythmia encountered in practice. There is an epidemic of AF worldwide.
- It is a leading cause of renal failure.
- It predisposes to rupture of aortic aneurysms and berry aneurysms.

From: *Contemporary Cardiology: Heart Disease Diagnosis and Therapy:
A Practical Approach, Second Edition*

Edited by: M. Gabriel Khan © Humana Press Inc., Totowa, NJ

Unfortunately, although there are more than 1 billion, hypertensives who require treatment we only have four groups of drugs to treat them:

- Diuretics.
- β -blockers
- Angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs).
- Calcium antagonists.
- Importantly, the use of α -blockers is restricted because they may cause HF in patients with left ventricular (LV) dysfunction and a predisposition to rupture of aneurysms.

The author has made the following statement in *Cardiac Drug Therapy*:

“This situation will change only if pharmaceutical companies and experts who formulate hypertension therapeutic guidelines will admit that after more than 50 years of research and many randomized clinical trials (RCTs) and blatant advertisements that we only have four antihypertensive agents” and that new agents are urgently required.”

Most important, several RCTs have been done comparing the β -blocking drug atenolol with a calcium antagonist or ACE inhibitor. *Experts are not aware that this commonly used β -blocker does not have the same cardioprotective value as does carvedilol, metoprolol or bisoprolol.* It is important for clinical trial organizers to recognize that β -blockers are not all alike; they have subtle clinical differences and only some of these agents cause a significant improvement in survival (see the discussion under subtle differences amongst the β -blocking drugs.)

DIAGNOSIS

The following is a classification of blood pressure (BP) provided by the Seventh Joint National Committee (JNC) on the Detection and Evaluation of Hypertension:

- The levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) differentiate high BP into SBP or DBP. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's BP status.
- Normal = SBP less than 120 mmHg or DBP less than 80.
- Prehypertension = SBP 120–139 or DBP 80–89 mmHg; antihypertensive agents are used only for compelling indications: kidney disease, diabetes, HF.
- Stage 1 hypertension = SBP 140–159 or DBP 90–99 mmHg; lifestyle modification and drug treatment necessary.
- Stage 2 hypertension = SBP greater than 160 or DBP 100 mmHg; drug combination is recommended.
- The JNC has little grounds, however, in ascribing less than 120 mmHg as normal. The less than 120 mmHg level advised by the JNC is not in keeping with clinical practice worldwide; the JNC has exaggerated the case.

It is more logical to adopt the following:

- A normal SBP range is 100–135 mmHg; DBP less than 85 mmHg. Patients with comorbid disorders should be kept in this range.
- Optimal SBP is less than 120 mmHg; DBP less than 80 mmHg.

The individual is classified as stage 1 or 2, based on the average of two or more readings taken at each of two or more visits after an initial screening. The World Health Organization and International Society of Hypertension definition emphasizes the concept of

repeated measurements at 4 weeks and at 3 months in patients with borderline levels. If the DBP is 90–99 and/or SBP is 140–160, measurements should be repeated on at least 2 further days over 4 weeks prior to drug therapy, because life time therapy is required once the diagnosis is established. In addition, home BP readings are advisable in patients with borderline hypertension prior to therapy and later to assess drug treatment goals. Although ambulatory monitoring is most useful, it is advisable only in selected individuals because of cost considerations.

The techniques for BP measurement must be assiduously followed:

- The patient should be seated comfortably with the back supported by a backrest and arms bared. Both feet must be on the floor.
- The sphygmomanometer should be at the heart level.
- Use an appropriate cuff size: a larger cuff is necessary for larger arms.
- Palpate the brachial artery and ensure the cuff bladder arrow is over this point. The stethoscope must be placed over the brachial artery.
- The disappearance of sound should be used for the DBP reading.

PRIMARY (ESSENTIAL) HYPERTENSION

In about 95% of hypertensive adults aged 20–65 years, no identifiable cause can be determined. Their hypertension should be defined as primary, idiopathic, or essential. In approximately 5% of cases, a secondary cause for hypertension is present. Secondary hypertension will be considered after a discussion of primary hypertension.

Evaluation

Information obtained from the patient's history, physical examination, response to previous drug therapy, complete blood count, urinalysis, serum creatinine, glucose, electrolytes, total cholesterol high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, echocardiogram (ECG), and chest X-ray should give clues that might initiate further investigation to identify the presence of secondary hypertension. In patients with primary hypertension, data obtained from the evaluation serve as a baseline and may influence the selection of an appropriate antihypertensive drug.

NONDRUG THERAPY

Nondrug therapy should be rigorously tried in all patients with mild hypertension before drug therapy. Examples of nondrug therapy are as follows:

- Weight reduction.
- Lowered sodium diet, and increased potassium and calcium intake.
- Cessation of smoking.
- Reduction in alcohol intake.
- Lifestyle change: removal of stress and/or learning to deal with stress.
- Relaxation and exercise.

These measures may result in adequate control of hypertension in up to 40% of patients with borderline or stage 1 hypertension and should be rigorously tried.

Weight Reduction

Weight loss nearly always results in a lowering of BP. In overweight hypertensive individuals, each kilogram of weight loss is expected to result in a decrease in BP of

2/1 mmHg, and a regression of LV hypertrophy (LVH) may be achieved. More than 40% of North Americans are overweight, and the incidence is much higher in black women. Physician dietary advice is necessary, but weight reduction is seldom achieved. Small group sessions organized by weight loss clinics have the greatest success.

Low-Sodium Diet

There is little doubt that increased salt intake causes mild but significant elevations of BP in “salt-sensitive” individuals, and dietary restriction is worth a trial before drug therapy. A 2-g sodium diet is sufficient, and compliance is feasible. In salt-sensitive individuals, a reduction in BP of about 5 mmHg diastolic and 15 mmHg systolic is expected. Patients often fail to achieve a 2-g daily sodium diet because they relate salt intake mainly to the amount used from the salt shaker. [Table 8.1](#), indicates that three pieces of fried chicken or a large hamburger from a fast food restaurant contains much more than the daily requirement. The patient should understand that 250 mL of canned soup or products, such as meat tenderizer, garlic salt, and similar additives, contain much more than 0.5 teaspoons of salt.

If needed, compliance can be assessed; an overnight urine collection should show more than a 30% reduction in urinary sodium content. If the patient is compliant, the urine shows more than 30% reduction in sodium. If there is no appreciable fall in BP over a 3-month period, salt restriction should not be enforced.

Potassium-rich foods are required particularly in patients treated with thiazide diuretics that cause significant potassium depletion in more than 30 % of patients.

Potassium-rich foods include:

- Avocado: half/medium = 600 mg.
- Watermelon: one 6-inch slice = 600 mg.
- Prunes: 6 large dried = 600 mg.
- Banana: one medium = 600 mg.
- Potato: one large = 600 mg.
- Tomato: one large = 300 mg.
- Orange: one medium = 300 mg.
- Apricots: five halves dried = 300 mg.

Alcohol Intake Reduction

Consumption of one to a maximum of two alcoholic drinks daily appears to produce a mild increase in HDL cholesterol. This salutary effect is lost, however, if three or more alcoholic drinks are consumed daily, because this quantity of alcohol may cause a significant increase in BP in sensitive individuals; also, hepatic dysfunction may ensue. Alcohol intake is an important cause of secondary hypertension. Reduction of alcohol consumption in patients with hypertension usually causes a significant lowering of BP.

Smoking Cessation

In addition to causing pulmonary complications, cigarette smoking is implicated in the pathogenesis of atherosclerosis, coronary artery vasoconstriction, and sudden cardiac death. Cigarette smoking inhibits the salutary effects of antihypertensive drugs, such as propranolol and calcium antagonists. The cardioprotective effects of hepatic-metabolized β -blockers are blunted by cigarette smoking.

Table 8.1.
List of Foods With Comparative Sodium (Na) Content

<i>Food</i>	<i>Portion</i>	<i>Mg of sodium</i>
Bouillon	1 cube	900
Bacon back	1 slice	500
Bacon side (fried crisp)	1 slice	75
Beef (lean, cooked)	3 oz (90 g)	60
Garlic salt	1 teaspoon (15 mL)	2000
Garlic powder	1 teaspoon	2
Ham (cured)	3 oz (90 g)	1000
Ham (fresh cooked)	3 oz	100
Ketchup	1 tablespoon	150
Milk pudding (instant, whole)	1 cup (250 mL)	1000
Meat tenderized (regular)	1 teaspoon	2000
Meat tenderized (low Na)	1 teaspoon	2
Olive green	1	100
Pickle dill	Large (10 × 4 1/2 cm)	1900
Peanuts, dry roasted	1 cup	1000
Peanuts, dry roasted (unsalted)	1 cup	10
Wieners	1 (50 g)	500
Canned foods		
Carrots	4 oz	400
(Carrots raw)	4 oz	40
Corn whole kernel	1 cup	400
(Corn frozen)	1 cup	10
Corn beef (cooked)	4 oz	1000
Crab	3 oz	900
Peas (cooked, green)	1 cup	5
Shrimp	3 oz	2,000
Salmon (salt added)	3 oz	500
Salmon (no salt added)	3 oz	50
Soups (majority)	1 cup (250 mL)	1000
Sauerkraut	1 cup (250 mL)	1800
Salad dressing		
Blue cheese	15 mL	160
French (regular)	15 mL	200
Italian	15 mL	110
Oil and Vinegar	15 mL	1
Thousand Island	15 mL	90
Fast food		
Chopped steak	One portion	1000
Fried chicken	3-piece dinner	2000
Fish & chips	One portion	1000
Hamburger	Double	1000
Roast beef sandwich	One	1000
Pizza	One medium	1000

Normal diet contains 1000–3000 mg sodium.

DRUG THERAPY

For several years the JNC has recommended β -blockers and diuretics as the initial agents of choice based on:

- Their proven value.
- Low long-term adverse effect profile.
- Low cost.

This advice has not been altered by the results of the large ALLHAT study.

ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) showed diuretics to be as effective as calcium antagonists and ACE inhibitors in reducing the risk of stroke in hypertensive individuals; unfortunately the comparison did not include β -blockers. Diuretics and β -blocker (carvedilol, metoprolol, or bisoprolol, not atenolol) therapy are equally effective in reducing BP to goal and have the same beneficial effects on outcomes (fatal and nonfatal MI and fatal and nonfatal strokes); both these agents are inexpensive.

Importantly, patients younger than 55 years were excluded; the mean age of the 24,335 subjects was 67 years. Thus, this trial studied mainly elderly hypertensives and the results cannot be generalized to patients younger than 60 years of age.

One objective of the trial was to compare diuretic (13.5–25 mg daily chlorthalidone) therapy with the α -blocker, doxazosin, as part of a study of four types of antihypertensive drugs: chlorthalidone, doxazosin, amlodipine, and lisinopril in hypertensives with at least one other coronary artery disease (CAD) risk factor. After a median follow-up of 3.3 years the doxazosin arm, compared with the chlorthalidone arm, had a higher risk of stroke and combined cardiovascular disease (CVD) (4-year rates, 25.45% vs 21.76%; $p < 0.001$).

- The HF risk was doubled by doxazosin therapy (4-year rates, 8.13% vs 4.45%; $p < 0.001$).
- At 5-year follow-up the primary outcome (fatal or nonfatal MI), revealed no significant difference between diuretic therapy or amlodipine or ACE inhibitor.
- The secondary outcomes—all-cause mortality, stroke, and combined coronary heart disease (CHD) were similar, except for a higher 6-year rate of HF with amlodipine therapy.

Systolic Hypertension in the Elderly Program (SHEP): Guidelines for the management of isolated systolic hypertension in patients aged 65–85 years have been previously clarified by the results of the SHEP.

- SHEP indicates a threefold and twofold increase in the risk of stroke and ischemic heart disease (IHD) in elderly hypertensive patients with SBPs greater than 180 mmHg.
- Treated patients in the SHEP showed a 36% reduction in the risk of stroke ($p = 0.0003$) and a 27% decrease in IHD event rates. A 54% decrease in the risk of LV failure was observed. These beneficial results of antihypertensive therapy should provoke urgent application, which should result in a considerable decrease in mortality, morbidity, and financial burden to patients and to society. SHEP results indicate that it is advisable to treat all patients aged 65–85 who have isolated systolic hypertension constantly greater than 180 mmHg. In patients with SBP from 180–240 mmHg, a 20% to maximum 25% reduction in SBP is recommended, based on the results of SHEP.

Objections to diuretic and β -blocker include:

- The only objection to the use of a β -blocker or diuretic as initial therapy are the controversial effects on blood glucose and lipid profile.

Table 8.2.
Choice of Drug for the Treatment of Isolated Systolic Hypertension

White patients (younger than age 65)

1. β -blocker: carvedilol, bisoprolol or metoprolol (Toprol XL) preferred over other β -blockers.
2. ACE inhibitor or ARB: often requires combination with diuretic to achieve goal BP.
3. DIURETIC
4. Choice one or two +3

Black patients (younger than age 65)

1. β -blocker
2. Calcium antagonist
3. Choice 1 \pm 2

White patients (older than 65)

1. β -blocker or diuretic
2. ACE inhibitor or ARB
3. Choice 1 + 2 (not complementary but both cardioprotective: patients over age 65 at risk)
4. Calcium antagonist

Black patients (older than 65)

1. Diuretic
 2. Calcium antagonist
 3. Choice 1 + 2
-

From Khan M. Gabriel. Cardiac Drug Therapy. Sixth edition. Philadelphia: WB Saunders, 2003, with permission from Elsevier.

- Diuretics may cause a variable and modest increase in blood glucose and total serum cholesterol, but long-term studies are inconsistent and diuretics have proven to cause significant reduction in cardiovascular mortality and morbidity when compared with other agents.
- β -Blockers, depending on the type used, may cause a 1–7% decrease in HDL cholesterol but do not affect total cholesterol; a variable increase in triglycerides occurs in some individuals. The evidence linking triglycerides with CAD is weak. The cardioprotective effects of β -blockers, particularly carvedilol, metoprolol, and bisoprolol far outweigh the minor changes in HDL cholesterol.

Initial Monotherapy

Strive for monotherapy in the treatment of stage 1 systolic or diastolic hypertension whenever possible. The ideal choice is a drug that is effective for 24 hours when given once daily and that produces few or no adverse effects.

Both diuretics and β -blockers recommended for initial therapy, and second line agents (ACE inhibitors, ARBs, and calcium antagonists) have unique pharmacological properties that can be tailored to the hemodynamic, neurohormonal, volume-related factors and concomitant diseases that may exist in certain subsets of hypertensive patients; further selection is based on age and ethnicity as indicated in RCTs (*see Table 8.2.*).

- White patients of all age and black patients less than age 70 respond well to beta blockers (*Fig. 8.1.*). The agents have the advantage of providing some cardioprotection depending on the β -blocker used and the presence or absence of smoking (*see later discussion for which β -blockers are recommended.*
- Diuretics have been shown in many studies to be effective in white and black patients older than age 60. Materson et al., the SHEP and ALLHAT, confirmed this beneficial

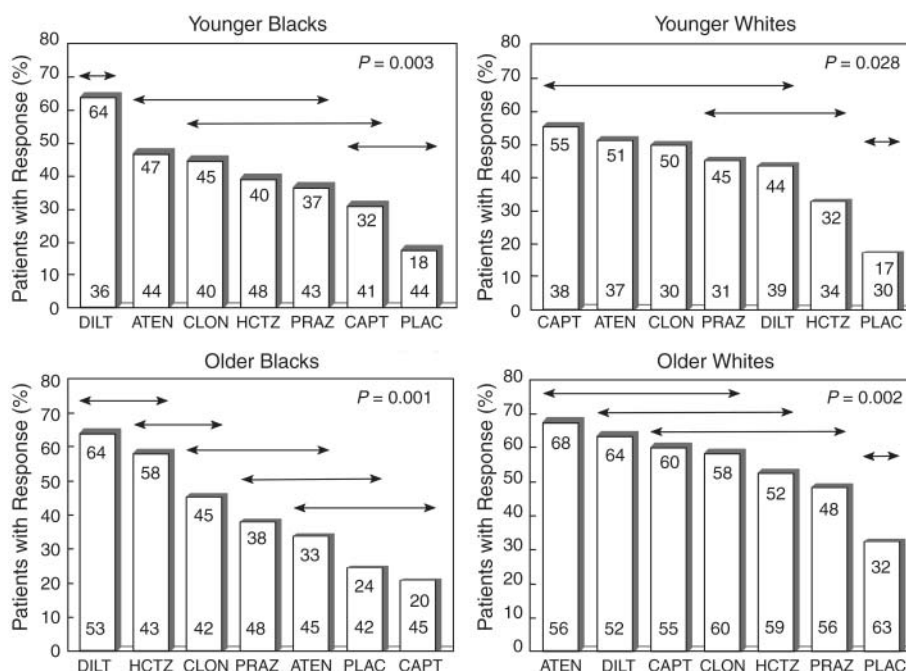


Fig. 8.1. Younger black patients, younger white patients, older black patients, and older white patients with responses in each of the study groups. From Materson et al. N Engl J Med 1993;328:919. ©1993 Massachusetts Medical Society. All rights reserved.

effect (Fig. 8.1.); If hypokalemia is observed, the thiazide should be switched to a potassium-sparing diuretic, preferably thiazide plus half tablet amiloride daily (Moduretic; Moduret); spironolactone should be avoided for long-term use because it causes gynecomastia.

- The spironolactone analog eplerenone is an effective antihypertensive agent and has a role; the drug reduces cardiac fibrosis and the occurrence of diastolic dysfunction.
- Calcium antagonists are effective in blacks of all ages and older whites but are not superior to β -blockers in the latter group.
- ACE inhibitors are effective in young whites, moderately effective in older whites, but are not predictably effective in blacks at any age (Fig. 8.1.). They often require the addition of small dose diuretic to attain goal BP.
- In females with a high risk for osteoporosis, diuretics are the first choice because they are the only antihypertensive agents that increase bone mass.
- Diabetics are at high risk for cardiac events and are recommended an ACE inhibitor and in those not prone to hypoglycemia, a β -blocker provides cardioprotection. Table 8.3. gives a logical assessment of initial choice depending on patient characteristics.
- Suggested dosages of antihypertensive drugs are given in Table 8.4. and adverse effects in Table 8.5.
- Patients with hyperlipidemia diabetes are at high risk for cardiac events and are recommended a β -blocker and an ACE inhibitor or ARB along with a statin to attain lipid goals.

β -Blockers

INDICATIONS

- In white patients older than 60, these agents are effective in more than 65%, and in younger blacks, atenolol was shown by Materson et al. to be effective in 47% of patients.

Table 8.3.
Which Drug to Choose as Initial Monotherapy for Grade I Hypertension
Based on Patient Characteristics

<i>Patient type</i>	β -blocker	Diuretic	ACE-I	CA	α -blocker
White Age >60	1	1		3	4
Age <60	1	3	2	3	4
Blacks <60	3	1	3	2	4
Blacks <60	1	3	4	1	4
Any age group					
Ischemic heart disease	1	2	2	2	RCI
LVH	1	2	2	3	RCI
Aneurysms	1	2	2	2	CI
Cerebral ischemia	1	2	2	2	4
Heart failure (compensated)	1	1	1	3	CI
Diabetes					
Insulin-dependent	2	2	1	2	3
Prone to hypoglycemia	CI	2	1	2	3
Hyperlipidemia	1	2	1	2	3
Smokers: won't quit	1 ^a	1	2	3	4
Osteoporosis women >50	1	1 ^b	2	3	4
Women < age 40	1	2	CI ^c	4 ^c	4
Chronic lung/asthma	CI	1	1	2	4

^aUse metoprolol, carvedilol not propranolol as ineffective.

^bIncreases bone mineral density.

^cRisk during pregnancy.

ACE-I, Angiotensin-converting enzyme inhibitor; CA, calcium antagonist; CI, contraindicated; RCI, relative contraindication; ARB angiotensin-receptor blocker; LVH, left ventricular hypertrophy. 1, first choice; 4, poor choice. Rationale for choice, see Fig. 8.1.

- β -Blockers are first choice in patients with IHD manifested by angina or silent ischemia, after MI, and in individuals at high risk for IHD events (males > 45, females > 55).
- First choice in patients with supraventricular or ventricular arrhythmias.
- Aneurysms: They are first choice in patients with all forms of aneurysms and are crucial for the acute management of dissection. They are the only category of antihypertensive agent that decreases the rate and force of myocardial contraction and ejection velocity. This effect has been shown to decrease the rate of aneurysmal dilatation in patients with Marfan syndrome. β -Blockers are an essential part of the treatment of patients with dissecting aneurysm. The beneficial effects of β -blockers in arteries prone to rupture logically dictates that these agents may be useful in decreasing the risk of cerebral hemorrhage and other complications of CVD. It is important to recognize that α -blockers are contraindicated in patients with aneurysms because they may accelerate dilatation and rupture.
- Patients with LVH are at high risk for sudden death; β -blockers are the only antihypertensive agents that have the potential to prevent sudden death in this subset of patients. ACE inhibitors prevent LVH but have not been shown to prevent sudden death.
- They are of particular value in patients with increased adrenergic activity, including the younger age group, who often have high plasma norepinephrine levels, and in patients with hyperkinetic heart syndrome, alcohol withdrawal hypertension, or the hyperdynamic β -adrenergic circulatory state, with labile or elevated BP and palpitations.

Table 8.4.
Daily Dosage of Antihypertensive Drugs

	<i>Dose (mg)</i>		
	<i>Initial</i>	<i>Usual maintenance</i>	<i>Maximum^a</i>
ACE inhibitors ^b			
Captopril (Capoten)	12.5–25	50–100	150
Cilazapril (Inhibace)	1	1–2.5	5
Enalapril (Vasotec)	2.5–5	10–30	40
Lisinopril (Prinivil, Zestril)	2.5–5	10–30	40
Benazepril (Lotensin)	5	5–30	40
Fosinopril (Monopril)	5–10	10–30	40
Perindopril Aceon (Coversyl)	1–2	2–6	8
Quinapril (Accupril)	2.5–5	5–30	40
Ramipril (Altace)	1.25–2.5	5–10	15
ARBs			
Candesartan (Atacand, Amias)	4–8	8–16	32
Eprosartan (Teveten)	300–400	300–600	800
Irbesartan (Avapro, Aprovel)	75–150	150–300	300
Losartan (Cozaar)	50	100	100
Telmisartan (Micardis)	20	20–80	80
Valsartan (Diovan)	40	80–160	320
Calcium antagonists			
Diltiazem			
Cardizem CD 120, 180, 240, 300	180	180–240	300
Adizem SR (UK) 120 mg	120	120–360	360
Amlodipine (Norvasc)	2.5–5	5–10	10

(continued)

- Patients with migraine and hypertension.
- Patients prone to postural hypotension may benefit because these agents, unlike all other antihypertensives, do not usually decrease systemic vascular resistance.
- In females over age 55, β -blockers are a rational choice because the incidence of myocardial rupture is high in hypertensive women who sustain a first infarction. β -Blockers protect sufficiently from myocardial rupture to warrant their use in patients considered at risk.

There is still no clear consensus regarding the mechanisms by which beta-blocking drugs cause a reduction in BP. An interplay of mechanisms appears to be responsible. Negative chronotropic and inotropic effects lead to a reduction in cardiac output and some reduction in BP. Antagonism of sympathetically mediated renin release and reduction in plasma renin and aldosterone have a role. Added mechanisms include central nervous system effects, reduction in norepinephrine release, reduction in plasma volume and venomotor tone, resetting of baroreceptor levels, and inhibition of the catecholamine pressor response to stress.

DOSAGE OF β -BLOCKERS

It is advisable to use a small dose initially and then titrate to a moderate dose that is within the “cardioprotective” range. If BP is not adequately controlled, it is advisable to

Table 8.4. (Continued)

	<i>Dose (mg)</i>		
	<i>Initial</i>	<i>Usual maintenance</i>	<i>Maximum^a</i>
Nifedipine Extended Release:			
Procardia XL, Adalat XL(C) 30, 60, 90 mg	30	30–60	60
Adalat Retard 20 mg (UK)	20–40	60–80	80
Verapamil			
Calan SR1 20, 180, 240 mg	120	120–240	240
Isoptin SR 120, 180, 240 mg	120	120–240	
Covera HS, (Chronovera)	180	180–240	240
Nicardipine 20, 30 mg	40	40–60	90
Cardene			
Nitrendipine Baypress	5	5–20	40
Felodipine Plendil 5, 10 mg	5	5–10	15
Central acting			
Clonidine (Catapres)	0.1	0.2–0.8	1
Guanabenz (Wytensin)	4	8	16
Guanfacine (Tenex)	1	1	3
Methyldopa (Aldomet)	250–500	500–1000	1500
β-Blockers			
Acebutolol (Sectral, Monitan)	100–400	400–800	800
Atenolol (Tenormin)	25–50	50–100	100
Bisoprolol (Zebeta, Monacor)	5–10	10–15	20
Carvedilol (Coreg, Eucardic)	12.5	25–50	100
Labetalol (Trandate, Normodyne)	100–400	400–800	800
Metoprolol (Toprol XL, Lopressor, Betaloc)	50	50–200	300
Nadolol (Corgard)	40–80	40–160	160
Penbutolol (Levatol)	20	20–40	80
Propranolol (Inderal)	40–120	160–240	240
Inderal LA	80	80–240	240
Timolol (Blocadren)	5–10	10–20	30
Diuretics			
Bendroflumethiazide	2.5	2.5	5
Bendrofluazide (UK)	2.5	2.5–5	5
Benzthiazide	12.5	2.5	50
Chlorothiazide	125	250	500
Chlorthalidone	12.5	25	50
Hydrochlorothiazide	12.5	12.5–25	50
Hydroflumethiazide	12.5	12.5–25	50
Indapamide	1.2	2.5	2.5
Polythiazide	2	2	4
Bumetanide	0.5	1–5	10
Furosemide (Frusemide, UK)	40	40–160	240

^aIn clinical practice, a dose less than the manufacturer's maximum is advised and reduces the incidence of adverse effects.

^bIncrease dosing interval with renal failure or in the elderly.

C, Canada; UK, United Kingdom.

Note: All drugs are available in the United States, except where labeled "C" or "UK."

add another agent rather than using the manufacturer's suggested maximum dose of β -blocker. At very high doses of a β -blocking drug, cardioprotective properties are lost. A 20-mg daily dose of timolol produced significant reduction in mortality in the Norwegian Post Myocardial Infarction Trial. In the β -blocker heart attack trial (BHAT), 160–240 mg propranolol achieved a reduction in mortality. The effect on mortality at lower doses is unknown, and animal experiments using larger doses indicate increased mortality.

Advantages

β -Blockers decrease cardiac mortality in post-MI patients. Sudden deaths were decreased some 67% by timolol in the Norwegian Post Myocardial Infarction Trial. β -Blockers are the only agents that have been proven to prevent sudden death. Hypertensives with concomitant ischemic heart disease are at risk for ischemic heart disease events and deserve therapy with β -blockers even though the protection afforded has been judged by some to be modest. The Carvedilol Postinfarction Survival Control in DV Dysfunction (CAPRICORN) study showed that β -blockers improved survival significantly in post-MI treated for several years. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study showed conclusively that the β -blocker, carvedilol, improved survival in patients with moderate-to-severe HF. Long term RCTs in hypertensive patients are required to assess if carvedilol or metoprolol controlled release are superior to diuretic therapy in preventing fatal and nonfatal MI.

β -Blockers reduce the rate-pressure product that determines cardiac workload and myocardial oxygen consumption. Reduction in pulsatile force and decrease in peak velocity, multiplied by the heart rate, decreases hemodynamic stress on the arterial tree, especially at areas just beyond the branching of arteries. β -Blockers protect from the development of aneurysms. It is not surprising that β -blockers play a vital and protective role in the management of dissecting aneurysms in patients, even when BPs are in the low normal range (*see* Chapter 10). β -Blockers are first-line hypertensive therapy with ventricular ectopy and other arrhythmias. Salutary effects observed in hypertensive patients treated with β -blockers are not obtained with vasodilators which include hydralazine, prazosin, or centrally acting drugs. β -Blockers prevent LVH and cause regression. This finding is not consistently observed with diuretics, some calcium antagonists, or vasodilators that increase sympathetic activity and produce an increase in heart rate.

Unlike most other antihypertensive agents, β -blockers do not usually cause orthostatic hypotension and are a reasonable choice for patients with strokes or cerebral circulatory insufficiency. Labetalol, which has α -blocking properties, can cause orthostatic hypotension and should not be classified as a β -blocker.

Disadvantages

HDL: β -Blockers may cause a decrease in HDL cholesterol of approximately 1–6%; this finding is variable and appears to occur only in susceptible individuals. Several studies have shown no significant fall in HDL with long-term use of β -blockers. A minimal lowering of HDL, 6% in the BHAT, was coincident with an increased survival in patients' postinfarction. Recent RCTs confirm a significant reduction in mortality and morbidity despite this exaggerated postulate of HDL reduction.

Triglycerides: An increase in serum triglycerides from 5 to 24% may be observed but occurs in only a few individuals treated over 1 year. Triglycerides are a weak and unproven link in the pathogenesis and manifestations of IHD. The variable and modest decrease in HDL cholesterol and increases in triglycerides in a very small percentage of patients

Table 8.5.
Adverse Effects of Antihypertensive Drugs

<i>Drug type</i>	<i>Adverse effects</i>
β -blockers	Bronchospasm, exacerbation heart failure, bradycardia, fatigue, dizziness, masking and worsening of hypoglycemia; rarely Raynauds, impotence, nightmares, depression
Thiazide diuretics	Hypokalemia, hyponatremia, dehydration, postural hypotension, gout, glucose intolerance, impotence, muscle cramps
Nifedipine extended release, other dihydropyridines Verapamil and diltiazem	Headache, flushing, edema, dizziness, jitteriness, heartburn Above, plus bradycardia; rarely sinus arrest, heart block, precipitation of heart failure, constipation, hepatic dysfunction
ACE inhibitors	First-dose syncope, hypotension, angioneurotic edema, pruritic rash, cough, wheeze, hyperkalemia, worsening of renal failure, loss of taste, mouth ulcers, cerebral circulatory insufficiency; rarely neutropenia, agranulocytosis, proteinuria, membranous glomerulopathy, impotence, pemphigus, hepatitis, positive ANA.
Centrally acting (methyldopa, clonidine, guanfacine, guanabenz)	Postural hypotension, drowsiness, dry mouth, parotitis, depression, lethargy, impotence, rebound hypertension
α_1 -blockers	First-dose syncope, postural hypotension, palpitations, precipitation of heart failure or angina; impotence, retrograde ejaculation, progression of aneurysmal dilatation
Labetalol	No first-dose syncope, otherwise similar to effects given under α_1 -blockers and β -blockers plus positive ANA, rare lupus-like syndrome; caution hepatic necrosis

treated with β -blockers for prolonged periods should not be regarded as sufficient evidence to disqualify these agents as the mainstay of therapy, considering their aforementioned protective advantages. It must be reemphasized that acebutolol causes no significant lipid derangements during long-term administration.

Some antihypertensives, including atenolol, have been shown to decrease BP throughout 24 hours but with less activity between 7 and 9 AM. It is important to cover these hours of peak activity. *The use of atenolol in RCTs should be curtailed.*

Contraindications

- Decompensated class IV HF patients, but beneficial in class II and III, and compensated some class IV patients (*see* Chapter 5).
- Asthma, severe chronic obstructive pulmonary disease (COPD), and allergic rhinitis.
- Severe peripheral vascular disease.
- Heart block, sick sinus syndrome.
- Diabetes in patients prone to hypoglycemia.

WHICH β -BLOCKER TO CHOOSE

The pharmacological features of β -blockers are given in [Table 8.6](#). There are important subtle differences. The usual classification into cardioselective and nonselective is

Table 8.6.
Pharmacologic Features of β -Blockers

	<i>Atenolol</i>	<i>Acebutolol</i>	<i>Carvedilol*</i>	<i>Metoprolol</i>	<i>Bisoprolol</i>
Cardioselectivity β_1	+++	+	+	+++	++++
Intrinsic Sympathomimetic activity (ISA) (partial agonist)	—	+		—	—
Hydrophilic	++++	+		—	+
Lipophilic ^a	—	+++	++	+++	+++
Hepatic metabolized	—	+++	+	++++	+++
Renal excretion	Yes	Partial		None	+
α_1 -blocker	—	—		—	—

(continued)

an oversimplification. Atenolol, bisoprolol, and metoprolol are cardioselective β -adrenergic blockers. At high doses, however, these agents can produce bronchospasm, because a small quantity of β_1 -receptors is present in the lungs. A classification of β -adrenergic blocking agents is given in Fig. 8.2.

The lipophilic agents are metabolized in the liver and obtain high brain concentration, which may confer some adverse effects. It is possible, however, that increased brain concentration and elevation of central vagal tone may confer greater cardiac protection provided that salutary effects are not nullified by cigarette smoking.

Abald et al., in a rabbit model, showed that although both metoprolol (lipophilic) and atenolol (hydrophilic) caused equal β -blockade, only metoprolol caused a reduction in sudden cardiac death. Metoprolol, but not atenolol, caused a significant increase in RR interval variation, which indicates an increase in parasympathetic tone. Only the β -blockers with lipophilic properties (acebutolol, metoprolol, propranolol, and timolol) have been shown in clinical trials to prevent sudden cardiac death. It is now important for the physician to select an appropriate β -blocker with the understanding that all β -blockers are not alike.

Statements in editorials, such as “ β -blockers do not reduce cardiac mortality in hypertensives,” must be considered erroneous because β -blockers possess subtle differences that are clinically important. It is not surprising that cardiac mortality was not reduced by propranolol in smokers in the large hypertension clinical trials of the 1980s. The protective cardiovascular effects of hepatic metabolized β -blockers, such as propranolol, oxprenolol, and penbutolol are blunted by cigarette smoking. Thus, in smokers, totally hepatic-metabolized β -blockers and diuretics have about equal beneficial effects in the prevention of cardiovascular events. In hypertensive patients, decrease in cardiac mortality may be significant with the use of partially metabolized β -blockers that attain high brain concentration, such as metoprolol, propranolol, carvedilol, bisoprolol, timolol, and acebutolol, but studies have not adequately tested this hypothesis.

Cominacini et al. studied the vasodilator mechanisms of nebivolol, a high selective α_1 -receptor antagonist with antioxidant properties. Their findings indicate that nebivolol increases nitric oxide (NO) also by decreasing its oxidative inactivation.

- Carvedilol is a unique β -blocker and provides maximum cardioprotection.

Table 8.6.
(Continued)

<i>Penbutolol</i>	<i>Propranolol</i>	<i>Pindolol</i>	<i>Timolol</i>	<i>Sotalol</i>	<i>Labetalol</i>
None	None	None	None	None	None
+	—	+++		Sotalol not recommended for hypertension	+
	—	+	+	++++	+++
++++	++++	++	+++	—	
+++	++++	++	++	—	++
Partial	None	Partial	Partial	Yes	No
—	—	—	—	—	+

^aIncrease concentration in brain.

+, Mild; +++++, maximum.

*, Added weak α_1 -blocker, antioxidant properties.

IS, intrinsic sympathomimetic activity.

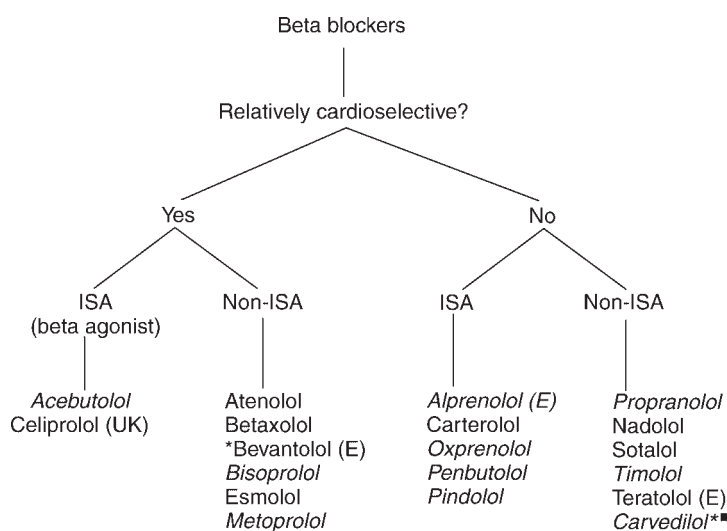


Fig. 8.2. Classification of β -blockers. All available in the United States except when labeled “(UK)” or “(E).” *Added weak α -blocker. ISA, intrinsic sympathomimetic activity; *Italic*, lipid soluble; ■ = blocks oxidation of LDL, plus antioxidant properties. From Khan M. Gabriel. Cardiac drug therapy. Sixth edition. Philadelphia: Elsevier, 2003, with permission from Elsevier.

The β -blocking drugs have important subtle differences in pharmacological and adverse effect profile that may dictate which β -blocker is best for a given clinical situation. Also, switching from one β -blocking agent to another may result in the disappearance of adverse effects and/or improvement of salutary effects.

The following guidelines are recommended *regarding which β -blocker to choose*:

- *Carvedilol is a unique β -blocker with mild α_1 -blocking properties that causes modest arteriolar vasodilation; this agent blocks oxidation of LDL cholesterol and has antioxidant properties. The drug without doubt improves survival in patient with CHD and in those with LV dysfunction (see CAPRICORN and COPENICUS trials).*

- Depression with propranolol: switch to bisoprolol then, if needed, try metoprolol or carvedilol.
- Mild memory impairment on propranolol: switch to bisoprolol, metoprolol, or carvedilol.
- Insomnia with propranolol or pindolol: switch to bisoprolol.
- Refractory smoker: switch from propranolol to bisoprolol or metoprolol to ensure salutary effects, including prolongation of life.
- Vivid dreams with highly lipophilic β -blocker: switch to bisoprolol or timolol.
- Decreased performance for complex tasks with atenolol: switch to bisoprolol or metoprolol: Toprol XL has a 24-hour duration of action.
- Marked fatigue with atenolol or sotalol: switch to bisoprolol, acebutolol, metoprolol, or timolol.
- Sedation with atenolol: change to bisoprolol, metoprolol or timolol.
- Symptomatic sinus bradycardia with propranolol or other but β -blocker necessary: switch to acebutolol.
- Renal failure, serum creatinine greater than 2.3 mg/dL (203 μ mol/L): extend the dosing interval of hydrophilic renal excreted agents, atenolol, nadolol, sotalol to alternate day or change to, carvedilol, metoprolol, bisoprolol, or hepatic metabolized agents.
- Bronchospasm in a patient with mild COPD: switch from β_1 , β_2 agent to β_1 -selective bisoprolol or metoprolol.
- Type II diabetes: choose bisoprolol or carvedilol. *Carvedilol has advantages over metoprolol and should be tried if there is no occurrence of hypoglycemia.* A recent RCT by Bakris et al.: Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension, reveals the following: the mean (SD) HbA_{1c} increased with metoprolol (0.15% [0.04%]; $p < 0.001$) but not carvedilol (0.02% [0.04%]; $p = 0.65$). Insulin sensitivity improved with carvedilol (-9.1% ; $p = 0.004$) but not metoprolol (-2.0% ; $p = 0.48$); the between-group difference was -7.2% (95% CI, -13.8% to -0.2% ; $p = 0.004$). Blood pressure was similar between groups. Progression to microalbuminuria was less frequent with carvedilol than with metoprolol ($p = 0.04$). Both β -blockers were tolerated; use of carvedilol in the presence of rennin–angiotensin system blockade did not affect glycemic control and improved some components of the metabolic syndrome relative to metoprolol in participants with diabetes and hypertension.

The aforementioned points indicate that the use of carvedilol, bisoprolol, and metoprolol, carries major advantages over other β -blocking agents.

- *The choice of the poorly cardioprotective atenolol in several in RCTs may have produced incorrect assumptions: several editorials by experts including Messerli et al., who state that β -blockers should not be first-line therapy for elderly hypertensives; these authors quote the MRC trial in the elderly in which diuretics reduced mortality from CHD but β -blockers did not. The investigators for the Medical Research Council (MRC) trial state that over the 5.5-year follow-up, 25% of people were lost to follow-up. Approximately 63% of the β -blocker group were either withdrawn or lost to follow-up. This type of incorrect information has been used by the World Health Organization (WHO) and by the JNC VII to proclaim that diuretics should be first choice and β -blockers second line. These two beneficial agents should be tailored to suit individual characteristics as described in Tables 8.2. and 8.3.*

Diuretics

Diuretics are economical one-a-day drugs that are highly recommended as the initial choice of antihypertensive drug for the management of stage 1 hypertension, particularly in patients older than 60 years of age. Tables 8.2. and 8.3. indicate the rationale for the

choice of diuretics in many subsets of hypertensives. SHEP and ALLHAT confirm the salutary effects of low-dose diuretic therapy in patients over age 60.

The exact mechanism of action by which diuretics produce a reduction in BP is unknown. A decrease in vascular volume, negative sodium balance, and long-term arteriolar dilatation occurs. They decrease the risk of hip fractures in both women and men.

Hypertensive patients treated with diuretics and followed for over 14 years showed a significant increase in the incidence of glucose intolerance; this was also observed in ALLHAT. Discontinuation of diuretics promptly reversed the hyperglycemic response. The mechanism for the development of diuretic-induced glucose intolerance appears to be the result of a suppressive effect of hypokalemia on insulin secretion. If hyperglycemia develops during diuretic use, the drug should be discontinued and the patient should be assessed for glucose intolerance.

Short-term studies have indicated that diuretics cause minor elevations in serum cholesterol and decreases in HDL. Long-term trials, however, with large numbers of patients, such as the Medical Research Council Hypertension Trial, showed no significant difference in total serum cholesterol before and after 3 years of treatment with diuretics. Total and HDL cholesterol levels did not change after 4–5 years of therapy with chlorthalidone in SHEP. Lipid derangements are not significant with long-term diuretic therapy (*see Table 8.4* for dosages).

ADVERSE EFFECTS

These include impotence, weakness, and fatigue. The incidence of impotence is higher than that observed with the use of β -blockers. Although rare, hyponatremia may develop over a period of weeks or years in some susceptible individuals. Electrolyte imbalance and hypomagnesemia are well-recognized complications. Gout occurs, and the prevalence is increased in patients with combined hyperlipidemia. Rarely, thrombocytopenia, agranulocytosis, and pancreatitis occur. Thiazide appears in breast milk, crosses the placental barrier, and can cause decreased placental perfusion, fetal or neonatal thrombocytopenia, jaundice, and acute pancreatitis. Avoid during pregnancy and lactation.

INTERACTIONS

- Oral anticoagulants.
- Steroids.
- An increase in serum lithium levels may occur.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, interfere with the diuretic effect of furosemide.

BENDROFLUAZIDE (APRINOX, BERKOZIDE, CENTYL, NEO-NACLEX, URIZIDE)

This drug is supplied in 2.5- and 5-mg tablets. The dosage used is 2.5 to 5 mg daily.

HYDROCHLOROTHIAZIDE (HYDRO-DIURIL, ESIDREX, ORETIC, HYDROSALURIC, DIREMA)

This is supplied as 25-, 50-, and 100-mg tablets. Commence with a dosage of 12.5 mg and then, if needed, go to the usual maintenance dose of 25 mg, with a maximum of 50 mg, once daily. Alternate day therapy may suffice in some patients with mild hypertension.

POTASSIUM-SPARING DIURETICS

These agents are very useful in the management of hypertension; they also conserve magnesium. They usually are used in combination with other diuretics.

Dyazide (25 mg Hydrochlorothiazide and 50 mg Triamterene, a Potassium-Sparing Diuretic). A dosage of one tablet each morning is used.

Moduretic; Moduret (UK and Canada) (50 mg Hydrochlorothiazide and 5 mg Amiloride, a Potassium-Sparing Diuretic). Moduret 25 or mini-Moduretic (25 mg hydrochlorothiazide and 2.5 mg amiloride, UK and Europe) is a useful combination.

Contraindications to the use of potassium-sparing diuretics include:

- Renal failure.
- Concomitant use of ACE inhibitors and/or K supplements.
- Renal calculi, avoid triamterene.

OTHER DIURETICS

Indapamide (Lozol; Lozide, Canada; Natrilix, UK, Europe). Indapamide is a thiazide-like diuretic with a different indoline structure. Indapamide is chemically related to chlorthalidone but has an added mild vasodilator effect that is not related to diuretic action. The incidence of hypokalemia and hyperuricemia is similar to that of thiazides, but indapamide claims not to produce disturbances in blood lipid, blood glucose, or insulin levels in hypertensive patients administered 2.5 mg daily for 1 year. Caution: the usual contraindications and cautions to the use of thiazides apply, including avoidance in patients with hypersensitivity to sulfonamides. Because approximately 60% of indapamide is excreted by the kidney, the drug should not be administered to patients with moderate or severe renal failure. Indapamide can be used in patients with mild renal dysfunction; dosing interval does not require adjustment, but periodic evaluation of serum potassium and creatinine is advised.

Eplerenone (Inspar). Eplerenone, a selective aldosterone blocker added to optimal therapy has been shown to reduce mortality and morbidity among patients with HF caused by acute MI and LV dysfunction; eplerenone is as effective as spironolactone in this setting. Most important, the drug does not cause gynecomastia and should replace spironolactone. *This agent is a good addition to our antihypertensive armamentarium and can be safely added to β -blocker therapy.*

Pitt et al. have shown that 200 mg eplerenone daily was as effective as enalapril in controlling BP and in obtaining LVH regression. The combination of eplerenone and enalapril was more effective in reducing LV mass and SBP than eplerenone alone.

Dosage. 50–200 mg once daily. Hyperkalemia may occur when used concomitantly with ACE inhibitors, ARBs, or potassium-retaining agents.

ACE Inhibitors and ARBs

ACE inhibitors have provided a major advance in the management of hypertension. They are useful agents for initial therapy in some subsets of hypertensive patients ([Tables 8.2. and 8.3.](#) and [Fig. 8.1.](#)). These inhibitors of ACE prevent the conversion of angiotensin I to the potent vasoconstrictor, angiotensin II. This action causes arteriolar dilatation and a fall in total systemic vascular resistance.

Diminished sympathetic activity causes vasodilatation (but heart rate does not increase as with other vasodilators), reduction in aldosterone secretion promoting sodium excretion, and potassium retention.

The pharmacological profile of ACE inhibitors is given in [Table 8.7.](#) (for dosages see [Table 8.4.](#)).

INDICATIONS

- ACE inhibitors are most effective in patients with high renin hypertension and especially in white patients under age 65. Materson et al. showed a 55% antihypertensive response in younger and older whites, but a poor effect in young or old black patients (Fig. 8.1.).
- Hypertensives with LVD or HF.
- Diabetics with hypertension of all grades. Mild hypertension (SBP 140–160 mmHg, DBP 90–95 mmHg) in diabetics must be aggressively treated, preferably with an ACE inhibitor and a β -blocker combination because both agents are cardioprotective.

ADVANTAGES

ACE inhibitors have been shown to cause regression and prevention of LVH. Other vasodilators may not prevent the development of hypertrophy, presumably because they cause sympathetic stimulation, which results in an increase in heart rate and increased myocardial oxygen requirement.

Unlike ACE inhibitors, other vasodilators, particularly α_1 -blockers, hydralazine, and minoxidil, cause sodium and water retention, and diuretics are usually required to achieve successful antihypertensive effects. The BP-lowering response to various doses of captopril flattens after about 75 mg or equivalent ACE inhibitor dosages. A captopril dose higher than 100 mg produces little further reduction in BP. Addition of a diuretic stimulates the renin angiotensin system and enhances the BP-lowering effect of ACE inhibitors. These agents have been shown to reduce mortality in patients with New York Heart Association class II, III, and IV HF, and they are first choice, along with diuretics, in the management of hypertensive patients who HF or LV systolic dysfunction. In addition, they blunt diuretic-induced hypokalemia and hypomagnesemia.

ACE inhibitors do not alter lipid levels or cause glucose intolerance. Thus, they are advisable in patients with hyperlipidemia and/or diabetes mellitus. They decrease diabetic proteinuria and appear to preserve nephron life in diabetics with diabetic nephrosclerosis. Hyperkalemia may occur in patients with renal failure and in diabetic patients with hyporeninemic hypoaldosteronism; however, caution is necessary. ACE inhibitors increase uric acid excretion and may have a salutary effect in some hypertensive patients with gout. Impotence, weakness, and lethargy observed with methyl-dopa and diuretics are rarely observed with the use of ACE inhibitors or ARBs. Thus, quality of life is preserved.

DISADVANTAGES

ACE inhibitors are generally well-tolerated by patients with mild hypertension. In this group, renovascular hypertension is rare. Caution is necessary in patients with renovascular hypertension who may have tight renal artery stenosis or stenosis in a solitary kidney because acute renal failure may be precipitated. In patients with severe bilateral renal artery stenosis or stenosis of a solitary kidney, renal circulation depends critically on high levels of angiotensin II. ACE inhibitors markedly decrease angiotensin II and renal blood flow. Renal failure with a sudden elevation in serum creatinine signals this dangerous situation, which should be anticipated and avoided. Patients receiving ACE inhibitors may develop severe hyperkalemia if they have renal failure or diabetes with hyporeninemic hypoaldosteronism or if they are given potassium-sparing diuretics, potassium supplements, or salt substitutes.

ACE inhibitors cause rare but life-threatening angioedema; deaths have been reported albeit rarely; thus, ARBs can replace ACE inhibitors when costs are not a concern.

Table 8.7.
Pharmacologic Profile and Dosages of ACE Inhibitors

	<i>Benazepril</i>	<i>Captopril</i>	<i>Cilazapril</i>	<i>Enalapril</i>	<i>Fosinopril</i>	<i>Lisinopril</i>	<i>Perindopril</i>	<i>Quinapril</i>	<i>Ramipril</i>	<i>Trandolapril</i>
US and Canada	Lotensin	Capoten	Inhibace	Vasotec	Monopril	Prinivil, Zestril	Coversyl	Accupril	Altace	—
UK	—	Capoten	Vasace	Innovace	Staril	Carace, Zestril	Coversyl	Accuprin	Tritace	Gopten/Odrik
Europe	Cibace	Lopril, Lopirin	Inhibace	Xanef, Renitec	Carace,	Zestril	Acertil	Accupro	Tritace	Gopten
Prodrug action	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Partial	Yes
Apparent (h)	1	0.5		2–4		2–4		3–6		
Peak effect (h)	2	1–2		4		4–8		3–6		
Duration (h)	12–24	8–12	>24	12–24		24–30		24–48		
Half life (h)	10–11	2–3	>40	11	>24	13	>24	>24	14–30	24
Metabolism	—	Partly hepatic		Hepatic		None		Partial		
Elimination	Renal	Renal	Renal	Renal	Renal and hepatic	Renal	Renal	Renal	Renal	Renal
SH group	No	Yes	No	No	No	No	No	No	No	No
Tissue specificity	No	No	Yes	No	Yes	No	Yes	—	Yes	Yes
Approved use US hypertension	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—
Approved use US heart failure	No	Yes	Yes(c)	Yes	—	Yes	—	Yes	Yes	—
Equivalent dose	10 mg	100 mg	2.5	20 mg	10	20 mg	3	15	10 mg	2
Initial dose	5–10 mg	6.25 mg	1.5	2.5 mg	5	2.5 mg	2	2.5–5	0.5	
Total daily dose										
Hypertension	10–20 mg	25–150 mg	1–5 mg	5–40 mg	5–40 mg	5–40 mg	2–8 mg	5–40 mg	2.5–10 mg	1–4 mg
Heart failure	—	25–150	1–2.5	5–20 mg	—					
Dose frequency ^a	1 daily	2–3 daily	1 daily	1–2 daily	1 daily	1 daily	1 daily	1 daily	1 daily	1 daily
Supplied, tabs	5, 10, 20, 40 mg	12.5, 25, 50, 100 mg	1, 2.5, 5 mg	2.5, 5, 10, 20–30 mg	10, 20 mg	2.5, 5, 10, 20, 40 mg	2, 4 mg	5, 10, 20, 40 mg	1.25, 2.5, 5, 10 mg	0.5, 1.2 mg

US, United States; UK, United Kingdom; h, hour; SH, sulphhydre.

^aIncrease dosing interval with renal failure or in the elderly.

Modified from Khan M. Gabriel. Cardiac Drug Therapy. Sixth edition. Philadelphia, PA: WB Saunders, 2003, with permission from Elsevier.

CONTRAINDICATIONS

- Renal artery stenosis of a solitary kidney or severe bilateral renal artery stenosis.
- Severe anemia.
- Aortic stenosis.
- Hypertrophic and restrictive cardiomyopathy.
- Hypertensive, hypertrophic “cardiomyopathy” of the elderly with impaired ventricular relaxation.
- Severe carotid artery stenosis.
- Hypertensive patients with concomitant angina.
- Uric acid renal calculi.
- Pregnancy and breastfeeding.
- Porphyria.
- Relative contraindications include patients with collagen, vascular diseases, or concomitant use of immunosuppressives, because neutropenia and rare agranulocytosis observed with ACE inhibitors appear to occur mainly in this subset of patients.

ADVERSE EFFECTS

These include hyperkalemia in patients with renal failure, pruritus, and rash in about 10% of patients and loss of taste in approximately 7% of patients. A rare but important adverse effect is angioedema of the face, mouth, or larynx, which may occur in approximately 0.2% of treated patients and can be fatal. Rarely, mouth ulcers, neurological dysfunction, gastrointestinal disturbances, and proteinuria occur in about 1% of patients with preexisting renal disease; neutropenia and agranulocytosis are rare and occur mainly in patients with serious intercurrent illness, particularly immunological disturbances, altered immune response, or collagen vascular disease. Cough occurs in about 20% of treated patients; wheezing, myalgia, muscle cramps, hair loss, impotence or decreased libido, hepatitis or occurrence of antinuclear antibodies, and pemphigus occasionally occur.

INTERACTIONS

- Allopurinol.
- Acebutolol.
- Hydralazine.
- NSAIDs.
- Procainamide.
- Pindolol.
- Steroids.
- Tocanide.
- Immunosuppressives and other drugs that alter immune response.
- Drugs that increase serum potassium levels have been emphasized.

CAPTOPRIL (CAPOTEN)

This is supplied in 12.5-, 25-, 50-, and 100-mg tablets. Commence with a dosage of 12.5 mg twice daily, one-half hour before meals, increase gradually to 50–100 mg daily, which is the dose required by most patients. The maximum suggested dose is 150 mg daily in severe hypertension. Serious side effects are more common in patients given a daily dose of 200 mg or more. Increase the dose interval in renal failure. Decrease the initial dose to 6.25 mg in the elderly or if a diuretic is used concomitantly. One hundred milligrams of Captopril equals approximately 20 mg of enalapril, 20 mg of lisinopril, 15 mg of ramipril.

ENALAPRIL (VASOTEC; INNOVACE, UK)

This is supplied in 2.5-, 5-, 10-, and 20-mg tablets. A dosage of 2.5–5 mg daily is used and increased over days to months to 10–30 mg daily in one or two divided doses with or without food. A maximum of 40 mg daily is used or less often in renal failure. In elderly patients or in those receiving a diuretic, begin with a dose of 5 mg daily.

LISINAPRIL (PRINIVIL, ZESTRIL)

This is supplied in 2.5-mg tablets (UK) and 5-, 10-, 20-, and 40-mg tablets. A dosage of 2.5 mg once daily is used; increase to 10–30 mg, with a maximum of 40 mg daily or less often in renal failure. Discontinue diuretic for 2 days before commencing lisinopril and resume later if required.

BENAZEPRIL (LOTENSIN)

This is supplied in 5, 10, 20, and 40 mg. A dosage of 5 mg is used and increase as needed to usual maintenance of 5–30 mg, with a maximum suggested of 40 mg. Commence with 2.5 mg in the elderly or if a diuretic is given concomitantly.

CILAZAPRIL (INHIBACE)

This is supplied in 1-, 2.5-, and 5-mg tablets, given in a dosage of 1–2.5 mg daily, with a maximum of 5 mg for hypertension, and 0.5–2.5 mg for HF. Cilizapril has been shown to improve vascular structure and functional abnormalities in resistance arteries in patients with mild essential hypertension. The incidence of cough is reportedly less than 5%. The drug causes a significant decrease in proteinuria in patients with renal dysfunction.

FOSINOPRIL (MONOPRIL)

This is supplied in 10- and 20-mg tablets. A dosage of 5–10 mg once daily is used, increased slowly, if required, to 20 mg and with assessment of renal function; maximum 40 mg daily with or without food. An initial dose of 2.5 mg is used in the elderly patients or those receiving a diuretic.

PERINDOPRIL ACEON (COVERSYL, C, UK)

This is supplied in 2- and 4-mg tablets. A dosage of 2 mg daily is used and increased, if required, after monitoring of BP to 4–8 mg daily. Discontinue diuretic 3 days before and resume later if needed.

QUINAPRIL (ACCUPRIL; ACCUPRO, UK)

This is supplied as 5-, 10-, 20-, and 40-mg tablets. A dosage of 5 mg once daily is used, with a usual maintenance dose of 10–40 mg daily. Reduce the initial dose to 2.5 mg daily in elderly patients, renal dysfunction, or with diuretic use.

RAMIPRIL (ALTACE; TRITACE, UK)

This is supplied in 1.25-, 2.5-, 5-, and 10-mg capsules. A dosage of 5 mg once daily is used and increased, if needed, to 10–15 mg.

Angiotensin Receptor Blockers (ARBs)

There are two main types of angiotensin II two receptor: AT1 and AT2, with most actions of angiotensin II being mediated by the AT1 receptor that is specifically blocked by ARBs. The risk of life-threatening angioedema and bothersome cough are advantages over ACE inhibitors. The Candesartan in HF—Assessment of Mortality and Morbidity

(CHARM) and Valsartan in Acute MI Trial (VALIANT) studies indicate safety and benefits equivalent to ACE inhibitors.

LOSARTAN (COZAAR)

Supplied 50 mg tablets: Dosage; 50 mg once daily or 25 mg twice daily, with a maximum of 100 mg daily, with or without food. For patients with intravascular volume depletion or hepatic impairment, the initial dose is 25 mg daily. Adverse effects include, rarely, muscle cramps, leg pain, dizziness, and insomnia, but these appear not to be significantly different from placebo. Two cases of angioedema have been reported. Contraindications include pregnancy and lactation.

HYZAAR

Is supplied in tablets of 50 mg losartan and 12.5 mg hydrochlorothiazide. A dosage of one tablet daily is given, with a maximum of two tablets. Contraindications and precautions include pregnancy and lactation, hepatic dysfunction, intravascular depletion, and sensitivity to sulfurs and thiazides.

CANDESARTAN (ATACAND)

Dosage is 8 mg daily increasing to 16; maximum dosage is 32 mg once daily. For Irbesartan, Eprosartan, and Telmisartan dosages, *see* [Table 8.4](#).

Calcium Antagonists

The BP-lowering effects of calcium antagonists are owing to peripheral arteriolar dilatation. Normally, calcium enters the cells through slow calcium channels and binds to the regulatory protein troponin, removing the inhibitory action of tropomyosin, which, in the presence of adenosine triphosphate (ATP), allows interaction between myosin and actin, resulting in contraction of the muscle cell. Calcium antagonists inhibit calcium entry into cells by blocking voltage-dependent calcium channels, thereby inhibiting contractility of vascular smooth muscle and thus producing vasodilatation.

[Table 8.8](#) gives the pharmacological and clinical effects of calcium antagonists. The dihydropyridine calcium antagonists (amlodipine nifedipine, felodipine, nicardipine, and nitrendipine) are more potent vasodilators and more effective antihypertensive agents than verapamil; diltiazem has modest vasodilator properties, and high doses are usually required to achieve adequate lowering of BP. In addition, verapamil and diltiazem have added electrophysiological effects on the sinoatrial (SA) and atrioventricular (AV) nodes and can produce bradycardia, sinus arrest, and AV block in susceptible individuals with disease of the sinus and AV nodes.

ADVANTAGES

Fortunately, calcium antagonists do not usually lower the BP of normotensive individuals. They can be used without a diuretic because they have a mild natriuretic effect; their effectiveness may or may not be enhanced by adding a diuretic. Calcium antagonists are useful in hypertensive patients with coexisting angina and peripheral vascular disease or when β -blockers produce adverse effects or are contraindicated. They do not cause abnormalities of lipid or glucose metabolism nor influence potassium and uric acid excretion and have advantages over diuretics in this subset of patients.

Calcium antagonists, particularly amlodipine, cause no serious adverse effects, and their use requires virtually no laboratory monitoring when compared with diuretics. Individual calcium antagonists have advantages that are important in terms of their

Table 8.8.
Pharmacological and Clinical Effects of Calcium Antagonists

	<i>Nifedipine^a</i>	<i>Diltiazem</i>	<i>Verapamil</i>	<i>Amlodipine</i>
Decrease systemic vascular resistance	Marked	Mild	Moderate	Moderate
BP	Marked reduction	Mild reduction	Moderate reduction; moderate	
Coronary dilation	Mild	Mild	Mild	Mild
Cardiac output	Mild increase	No change	No change or mild; no change decrease	
Heart rate	Mild increase	No change	Mild decrease; mild increase	
Negative inotropic	Very mild	Mild	Moderate; mild	
Sinus node depression	None	Moderate	Moderate	Mild
AV conduction	No change	Mild reduction	Moderate reduction; nil	
Antihypertensive effect	Good	Mild	Good	Good
Antianginal effect	Mild	Mild	Excellent	Mild
Precipitates heart failure	Yes, if EF <35% ^b	Yes, if EF <35%	Yes, if EF <40% ^c	
Combination with β -blocker	Relatively safe ^e	Bradycardia may occur	Relative contraindication ^d ; yes, if EF <35%	Safe ^e

^aAnd other dihydropyridines.

^bIn patients with left ventricular dysfunction.

^cContraindicated in all patients with left ventricular dysfunction.

^dMay cause severe bradycardia, sinus arrest.

^eIf EF >35%.

adverse effects. Nifedipine and amlodipine have virtually no electrophysiological effects and, although uncommon, verapamil and diltiazem can produce bradycardia, sinus arrest, and AV block in susceptible individuals. Verapamil has significant negative inotropic activity and can precipitate HF. Diltiazem has mild negative inotropic activity. In addition, it is relatively safe to combine amlodipine or nifedipine extended release with a β -blocker in the management of hypertension and when associated with angina. Verapamil should not be added to a β -blocker, and diltiazem must be used with caution. Nifedipine does not alter digoxin levels; however, verapamil and diltiazem cause about a 47% increase in digoxin level and may rarely precipitate bradycardia and AV block.

ADVERSE EFFECTS

Nifedipine extended release (Procardia XL, Adalat XL, PA, Adalat Retard) and other dihydropyridines produce pedal edema, mild facial flushing, dizziness, headaches, leg cramps, gastroesophageal reflux, and, rarely, sexual dysfunction in much the same frequency. Minor side effects include gingival hypertrophy, blurring of vision, muscle cramps, and burning in the gums.

Diltiazem may cause mild elevation in liver function tests and, rarely, acute hepatic injury. Care is required in patients with severe hepatic dysfunction, and dosage, especially of diltiazem and verapamil, must be reduced to avoid toxicity. Constipation is a bothersome side effect of verapamil.

Calcium antagonists should be avoided in pregnancy and by lactating mothers. Nifedipine has been used during the last trimester of pregnancy as short-term therapy for the control of accelerated hypertension of preeclampsia with salutary effects. Studies that are not methodologically sound suggest that the rapid, short-acting formulations may increase the risk of death. This possibility cannot be excluded. Further studies are required to document safety of long-term therapy with the currently used long-acting preparations.

CONTRAINDICATIONS

- Moderate or severe aortic stenosis.
- Diltiazem and verapamil are contraindicated with sick sinus syndrome, arrhythmia, bradycardia, heart block, LV dysfunction, or EF less than 40%.

Diltiazem and verapamil may interact with digoxin, amiodarone, quinidine, β -blockers, tranquilizers, oral anticoagulants, and disopyramide (Table 8.9.).

AMLOPIDINE (NORVASC, ISTIN UK)

This is supplied as 5- and 10-mg tablets. A dosage maintenance 5–7.5 mg, maximum 10 mg once daily, is used). The drug is relatively safe in patients with mild LV dysfunction but can precipitate pulmonary edema and HF in patients with severe LV dysfunction, EF less than 35%. Edema occurs in approximately 10–15%, similar to other dihydropyridines necessitating discontinuation of the drug.

DILTIAZEM (CARDIZEM CD, TIAZAC; ADIZEM-SR, BRITIAZIM [UK, ADIZEM SR 120 MG], CALCICARD, HERBESSER, TILDIEM, TILAZEM)

Supplied Cardizem CD, as 180-, 240-, and 300-mg capsules. A dosage of Cardizem CD 120 mg daily is used and increased as needed to 180–240 mg; maximum dosage of 300 mg or equivalent.

Table 8.9.
Calcium Antagonists–Drug Interactions

	<i>Digoxin Level</i>	<i>Quinidine</i>	<i>Amiodarone</i>	<i>β-Blocker</i>
Nifedipine	No change	No change or ↓	No change	Safe
Diltiazem	40% ↑	↑↑	Sinus arrest	Caution ^a
Verapamil	50–75% ↑		Contraindicated	Contraindicated ^a

^aSee text.

NIFEDIPINE EXTENDED RELEASE (PROCARDIA XL; IN CANADA ADALAT XL 30, 60, AND 90 MG; UK, ADALAT RETARD 10 AND 20 MG)

A dosage of Procardia XL or Adalat XL 30 mg once daily is used and increased, if needed, to 60 mg once daily.

Nifedipine extended release or amlodipine combined with a β-blocker is effective in severe hypertension. Nifedipine has virtually replaced hydralazine in triple therapy. The combination of a β-blocker, diuretic, and nifedipine or amlodipine is widely used for severe hypertension. Ten milligram capsules of Nifedipine capsules have a rapid onset of action and are not recommended.

NITRENDIPINE (BAYPRESS)

This is supplied as 10-mg tablets. A dosage of 5–10 mg once or twice daily is used and increased as needed.

FELODIPINE (PLENDIL; RENEDIL, CANADA)

This is supplied as 5- and 10-mg tablets. A dosage of 5 mg once daily is used to a maximum of 15 mg. In the elderly patients or those with liver dysfunction, BP should be carefully monitored because high plasma concentrations of felodipine may occur and caution is needed in dosing. The 5-mg dose should suffice in the elderly or in patients with impaired liver function; the maximum dose in these patients should not exceed 10 mg daily. Felodipine causes a mild increase in digoxin levels.

VERAPAMIL (ISOPTIN, CALAN, CORDILOX)

This is supplied as tablets (SR 120, 180, and 240 mg). The recommended dosage of verapamil SR is 120 to 240 mg daily; constipation may limit the dosage. Cautions: combination with a β-blocker may cause severe bradycardia or sinus arrest because of similar electrophysiological effects. Verapamil may produce bothersome constipation, especially in the elderly. Serum digoxin levels may be increased 50–75% by verapamil and about 45% by diltiazem; nifedipine has little or no effect on digoxin levels (Table 8.9). Verapamil increases quinidine plasma levels, as well as anticoagulant effects, and an interaction occurs with amiodarone.

α-Blockers

α-Blockers have a small role in the management of hypertension not controlled by more appropriate agents. Combination with a diuretic is often required because of sodium and water retention; also increase in heart rate may necessitate the addition of a β-blocker that improves safety of α-blockers.

The author condemned the use of α -blockers in the second edition of Cardiac Drug Therapy (1988). The ALLHAT study (2002) showed conclusively that α -blockers significantly increases the risk of HF and a warning has been issued. The doxazosin arm of the study was halted because the rate of HF was double that of the diuretic chlorthalidone.

α -Blockers cause an increase in heart rate and in peak velocity multiplied by heart rate. Thus, these agents increase cardiac work and are contraindicated in patients with IHD; also, they may increase the propensity to develop aneurysms. They cause an increase in circulating norepinephrine and activate the renin angiotensin system, causing sodium and water retention; thus, diuretics are often required to potentiate their BP-lowering action. Because of these disadvantages, an α -blocking agent is considered a poor choice for initial or second-line therapy for mild or moderate hypertension and is so indicated in [Table 8.3](#). The use of α_1 -blockers should dwindle because ACE inhibitors, β -blockers, and calcium antagonists are more effective, have less detrimental effects on the cardiovascular system, and do not usually require added diuretics to prevent salt and water retention, which always occurs with the use of α_1 -blockers.

CONTRAINDICATIONS

- Patients with aneurysms. Undoubtedly, aneurysms may remain occult for several years.
- Severe anemia.
- Moderate or severe aortic stenosis.
- Hypertrophic cardiomyopathy.
- Angina, including silent ischemia.

ADVERSE EFFECTS

These include orthostatic hypotension, first-dose syncope, dizziness, impotence, retrograde ejaculation, confusion, and, rarely, paranoid behavior and psychosis.

DOXAZOSIN (CADURA)

The recommended dosage is 1–2 mg daily. In patients in whom ACE inhibitors or calcium antagonist are not tolerated or contraindicated; advisable only in patients without LV dysfunction or CHD; use in combination with a diuretic and β -blocker particularly for resistant hypertension. Doses larger than 4 mg are not advisable.

PRazosin (MINIPRESS)

Withhold diuretics 1–2 days. Give 0.5–1 mg test dose at bedtime and then 1–2 mg twice daily; increase if needed to 5 mg two times daily.

TERazosin (HYTRIN)

A dosage of 1 mg at bedtime is given and increased slowly if needed to 5 mg once daily; occasionally twice daily dosing is necessary. A maintenance dose of 2–5 mg is used, with a maximum of 10 mg daily. The drug has action and effects similar to prazosin, with a 12- to 24-hour duration of action and better bioavailability. Five milligrams of terazosin equals approximately 10 mg prazosin.

Flomax is α_1 -blocker more specific for the urethral receptors and is mainly a urologic agent not recommended for hypertension.

HYDRALAZINE (APRESOLINE)

Hydralazine is a direct arteriolar dilator. Its use is now confined to pre-eclampsia.

This is supplied as 10-, 25-, and 50-mg tablets. A dosage of 25–50 mg three times daily is used, with a maximum of 200 mg daily. Intravenous (IV) doses are 10–20 mg/hour, with a maintenance of 5–10 mg/hour.

Adverse effects and contraindications are similar to that of α -blockers.

Centrally Acting Agents

Centrally acting agents include methyldopa, guanabenz, guanfacine, and clonidine.

INDICATIONS

Combination with diuretics and with vasodilators, including calcium antagonists and ACE inhibitors, especially in patients with severe and/or resistant hypertension.

Methyldopa is now mainly used for hypertension in pregnancy.

DISADVANTAGES

These drugs cause postural hypotension, rebound hypertension, and some sedation. Dry mouth is typical for clonidine, guanabenz, and guanfacine. Impotence and depression are not uncommon. Methyldopa is contraindicated in active liver disease; hepatitis, fatal necrosis, and a rare myocarditis have been reported. Coombs' positive hemolytic anemia may occur with this agent. Contraindicated with active liver disease, depressive states, and pheochromocytoma.

ACCELERATED AND MALIGNANT HYPERTENSION

In patients with moderate or severe essential or secondary hypertension treated with antihypertensive agents, acceleration and refractoriness of hypertension may occur because of:

- Poor compliance.
- Increased salt intake in salt-sensitive individuals.
- Rebound from discontinuation of centrally acting drugs, clonidine, guanfacine, methyldopa, and, rarely, β -blockers or calcium antagonists.
- Drug interactions: phenylpropanolamine combined with β -blockers. NSAIDs decrease the natriuretic action of diuretics and the BP-lowering effect of ACE inhibitors and β -blockers; acetylsalicylic acid or other NSAIDs may interfere with the diuretic effect of loop diuretics.
- Renal failure: in this situation, thiazides are rendered ineffective and BP may increase.

Treated or untreated patients may present with severe hypertension that is difficult to control, including the rare presentation with malignant hypertension and DBPs greater than 140 mmHg with or without end-organ damage. The presence of papilledema is not essential for the diagnosis of malignant hypertension.

In about 15% of cases with severe resistant hypertension, a secondary cause is present. Renal artery stenosis is an important cause in both young and older patients. Atherosclerotic occlusion of the renal artery may suddenly become worse, thus causing accelerated hypertension.

Pheochromocytoma and other causes of secondary hypertension must be excluded. See discussion of secondary hypertension.

Therapy

In most cases of severe hypertension with DBPs greater than 115 mmHg, combination drug therapy is necessary. Renal failure causes resistance to thiazide diuretics, and high

doses of furosemide combined with other agents may be required. Provided that HF or another contraindication to β -blockade is absent, β -blockers are useful in most patients who have severe hypertension regardless of the underlying cause. All antihypertensive agents, with the exception of β -blockers, cause a decrease in systemic vascular resistance and fortunately have different sites of action. Therefore, they may be combined in these difficult scenarios.

Additional drug therapy is selected to affect each regulatory system:

- Loop diuretics to control renal and other volume-dependent hypertension.
- ACE inhibitors or calcium antagonists to reduce peripheral vascular resistance.
- Centrally and peripherally acting drugs that interfere with α -mediated vasoconstriction, for example, methyldopa, clonidine, or guanfacine and an α -blocker.

If edema or severe renal failure is present, 160–320 mg of furosemide may be required. If the diuretic and BP-lowering effects are inadequate, metolazone, 5–10 mg, added to furosemide or bumetanide often produces a salutary response; however, hypokalemia may ensue with this potent but useful diuretic combination.

HYPERTENSIVE CRISIS

Hypertensive crisis is usually subclassified into either hypertensive emergency or urgency.

Hypertensive emergency is defined as a severe sudden elevation in BP: DBP greater than 120 mmHg and/or SBP greater than 220 mmHg. A sudden rise from the range 160–170 to more than 220 systolic signifies a likely crisis. The rate of rise of BP in relation to previous is more important than the absolute BP reading and should be associated with acute organ damage or dysfunction which confers an immediate threat to life.

- Hypertensive emergencies require reduction in BP within minutes by IV therapy.
- Hypertensive urgencies refer to other situations in which markedly elevated BP is not associated with immediate threat to life or organ damage and it is advisable to reduce elevated BP within a day or two with oral drugs.

DBP consistently in excess of 140 mmHg with evidence of target organ damage (e.g., retinal hemorrhages, papilledema, acute pulmonary edema, decreased renal function, cerebrovascular accident, or hypertensive encephalopathy) requires immediate but carefully monitored modest reduction of BP. A 20–25% reduction from baseline DBP and/or SBP avoids relative hypotension and is sufficient to produce salutary effects.

Hypertensive emergencies are often associated with a malignant phase of essential hypertension, renal failure, cerebrovascular accidents, hypertensive encephalopathy, and, rarely, pheochromocytoma. In dissecting aneurysm, BP may be markedly elevated or remain modestly elevated in the range of SBP 160–190 mmHg, DBP 90–100 mmHg, and is considered a special hypertensive emergency, as BP must be promptly lowered within minutes. This is usually achieved by using nitroprusside; also, a β -blocker is necessary to decrease the rate of rise of aortic pressure, to prevent further dissection (*see* Chapter 10).

DRUG THERAPY

Table 8.10. gives guidelines and choices of drug therapy for the management of hypertensive emergencies associated with various conditions and complications.

Table 8.10.
Hypertensive Emergencies and IV Drug of Choice as Listed

<i>Emergency</i>	<i>Drug choice</i>	<i>Caution or comment</i>
Accelerated malignant hypertension	Labetalol Fenoldopam Enalaprilat Urapidil (Europe)	Asthma Asthma, glaucoma, IHD Renal artery stenosis
Acute coronary syndrome	Nitroglycerin+ morphine+ metoprolol	
Aortic dissection	Nitroprusside+ β -blocker Labetalol	Hepatic and renal failure May not be effective if on α - or β -blocker
Catecholamine crisis	Nitroprusside+ β -blocker Labetalol +nitroglycerin if cocaine	
Eclampsia	Hydralazine Labetalol, Urapidil	+MgSO ₄ for seizures
LVF with acute pulmonary edema	Nitroglycerin+ furosemide+ morphine Urapidil Enalaprilat	Renal artery stenosis; crash hypotension
Perioperative or post-operative	Labetalol or nitroprusside Fenoldopam Nitroglycerin	Clipping aneurysms, neurosurgical or ear surgery
Renal dysfunction	Fenoldopam Labetalol, calcium antagonist	Coronary bypass surgery

LVF, left ventricular failure; IHD, ischemic heart disease. Khan M. Gabriel. Cardiac Drug Therapy. Sixth edition. Philadelphia, PA: Elsevier, 2003, with permission from Elsevier.

In patients with cerebrovascular accident, caution is required because elevations in BP may fluctuate, being triggered by cerebral irritation, and it is essential to carefully monitor the BP for a few hours to confirm that the DBP is constantly elevated. The need for lowering the BP should be carefully considered, and if deemed necessary, the slow controlled titrated lowering of BP with the use of either nitroprusside or labetalol is used, depending on the cause of hypertension, underlying disease process, and complications. There is some evidence that nitroprusside increases intracranial pressure, but clinically the drug is effective. Labetalol is a reasonable alternative, provided that precautions for the use of a β -blocking drug are enforced. Labetalol causes postural hypotension, and the patient must remain in bed. Also, the BP-lowering effect may occasionally last from 1 to 12 hours, whereas the hypotensive effect of nitroprusside dissipates within minutes of cessation of the infusion.

Pulmonary edema resulting from severe hypertension can be controlled with IV furosemide and nitroglycerin (IV infusion). The combination of IV nitroglycerin and furosemide should suffice, but if the BP remains markedly elevated, nitroprusside is indicated. Labetalol is contraindicated with HF but captopril could be used in this situation.

Renal failure is usually associated with volume overload, and 80–160 mg of furosemide IV should be administered. Fenoldapam or labetalol are the recommended IV agents.

Oral nifedipine also has a role, and in this subset, sublingual nifedipine has been used widely and successfully. The oral preparation, however, lowers BP as quickly as sublingual administration and is the preferred route (sublingual route is not approved by the US Food and Drug Administration). Failure of nifedipine therapy should prompt the use of labetalol IV infusion, as well as continuation of oral agents to wean the patient off labetalol as quickly as possible.

The following drugs are selected for IV administration:

- Labetalol for aortic dissection, hypertensive encephalopathy, eclampsia, renal dysfunction, perioperative hypertension.
- Fenoldapam for: renal dysfunction, hypertensive encephalopathy.
- Nitroprusside mainly for aortic dissection; other agents have displaced nitroprusside because of the need for arterial line, fear of cyanide and thiocyanate intoxication, coronary steal and tachycardia that may precipitate ischemia, and metabolic acidosis that may occur within hours of use; also, light occlusive bags are necessary.
- Urapadil for LV failure, encephalopathy, and eclampsia.
- Nimodipine for subarachnoid hemorrhage.
- Esmolol along with nitroprusside for dissection aneurysm.

Nitroprusside

Labetalol, fenoldopam, and urapadil should replace nitroprusside for most emergencies.

Nitroprusside infusion reduces BP to any desired level in almost 100% of patients and is the treatment of choice for most hypertensive emergencies that require the lowering of BP, except when nitroprusside is contraindicated. Caution is needed in patients with inadequate cerebral circulation.

A dosage of 50 mg sodium nitroprusside in 100 mL 5% dextrose water is a convenient solution for use with a nitroprusside infusion pump. See [Table 8.11](#) for the appropriate rate of infusion based on the weight of the patient. Wrap the infusion bottle in aluminum foil or other opaque material to protect it from light. The solution must be used within 4 hours. Start the infusion at 0.5 µg/kg/minute and increase by 0.2 µg/kg/minute every 5 minutes until the desired BP is obtained. Dosage range is 0.5–6 µg/kg/minute. It is important to begin oral antihypertensive agents as soon as possible so that the patient can be weaned off nitroprusside.

CONTRAINDICATIONS

- Pregnancy.
- Severe anemia.
- Severe hepatic dysfunction because cyanide poisoning may occur; if renal disease is present and the use of nitroprusside is extended for more than 2 days, thiocyanate may accumulate.

Table 8.11.
Nitroprusside Infusion Pump Chart
(50 mg of Nitroprusside [1 vial] in 100 mL [500 mg/L])

Dosage ($\mu\text{g/kg/min}$)	Weight						
	40 kg	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg
	Rate (mL/h)						
0.2	1	1	1	2	2	2	2
0.5	2	3	4	4	5	5	6
0.8	4	5	6	7	8	9	10
1.0	5	6	7	8	10	11	12
1.2	6	7	9	10	12	13	14
1.5	7	9	11	13	14	16	18
1.8	9	11	13	15	17	19	22
2.0	10	12	14	17	19	22	24
2.2	11	13	16	18	21	24	26
2.5	12	15	18	21	24	27	30
2.8	13	17	20	23	27	30	34
3.0	14	18	22	25	29	32	36
3.2	15	19	23	27	31	35	38
3.5	17	21	25	29	34	38	42
3.8	18	23	27	32	36	41	46
4.0	19	24	29	34	38	43	48
4.5	22	27	32	38	43	49	54
5.0	24	30	36	42	48	54	60
6.0	29	36	43	50	58	65	72

The above rates apply only for a 500 mg/L concentration of nitroprusside. If a different concentration must be used, appropriate adjustments in rates should be made. Start at 0.2 $\mu\text{g/kg/min}$. Increase slowly. Average dose 3 $\mu\text{g/kg/min}$. Usual dose range 0.5–5.0 $\mu\text{g/kg/min}$. From Khan M. Gabriel. Hypertension. In Cardiac Drug Therapy. Sixth edition, Philadelphia, Elsevier, 2003, with permission from Elsevier.

Fenoldopam Corlopam

Fenoldopam is a peripherally acting selective D1-receptor antagonist. Unlike dopamine, fenoldopam does not have α - or β -adrenergic agonist activity. The drug causes peripheral arterial dilatation and significant renal mesenteric and coronary vasodilatation.

Onset of action is within 5 minutes and duration of action is 30 minutes.

Advantages over nitroprusside include the absence of significant rebound hypertension and an increase in renal blood flow, lack of coronary steal and absence of thiocyanate and cyanide intoxication, and metabolic acidosis. The drug is as effective as nitroprusside.

- Unlike other adrenergic agonists, the drug does not cross the blood–brain barrier.
- Fenoldopam, however, contains sodium metabisulfite and may cause allergic-type reactions, particularly asthmatic episodes.
- The drug should be avoided in patients with glaucoma because it increases intraocular pressure.
- It should be avoided in patients with IHD because it may precipitate tachycardia and ischemia; importantly, the tachycardia must not be treated with a β -blocker.

Dosage: IV infusion; initial 0.1 $\mu\text{g/kg/minute}$, titrate 0.05–0.1 $\mu\text{g/kg/minute}$ at intervals of 15 minutes to 1–1.6 $\mu\text{g/kg/minute}$.

Nifedipine

Nifedipine administered as capsules is a useful agent in the management of hypertensive emergencies and is of special value in patients with hypertensive encephalopathy and renal failure when nitroprusside is relatively contraindicated. Nifedipine is contraindicated in the management of cerebrovascular accidents, including hemorrhage, and in patients with IHD, because in these situations, slow careful titration is needed to avoid a rapid fall in BP, which may precipitate cerebral or myocardial ischemia. A dosage of 10-mg capsules orally every 2–4 hours is used for four to eight doses, along with furosemide, if volume hypertension or renal failure is present. The use of rapid-acting nifedipine capsules is limited to hypertensive emergencies and should not be used sublingually. Thereafter, nifedipine dosage is structured four times daily. When BP is under control, a long-acting preparation, 60 mg of extended-release nifedipine (Procardia XL or Adalat XL) once daily, for example, is advisable for maintenance therapy.

CONTRAINDICATIONS

Myocardial ischemia or cerebral circulatory insufficiency; abrupt uncontrolled fall in BP may lead to ischemia and MI or stroke.

Labetalol

This α - and β -blocker is indicated for the management of hypertensive emergencies caused by renal failure, clonidine withdrawal, and dissecting aneurysm, although in the latter situation, a combination of nitroprusside and a β -blocker is preferable.

IV infusion of 2 mg/minute 20–160 mg/hour under close and continuous supervision is used. The patient must be recumbent during and for 4 hours after the infusion. Hypotensive effects may last from 1 to 12 hours after cessation of the infusion. Alternatively, bolus injections of 20 mg over 1 minute are used, repeated after 5 minutes, if necessary to a maximum of 80 mg. Excessive bradycardia can be controlled with 0.6–2 mg IV atropine in divided doses.

Diazoxide

Diazoxide has been virtually replaced by nitroprusside, labetalol, fenoldopam, and nifedipine. The drug is used when other medications are not available or when renal failure is present and there is concern for nitroprusside toxicity. The drug is of value in malignant hypertension and is used in hypertensive emergencies associated with renal failure and hypertensive encephalopathy. A dosage of a 150-mg IV bolus injected undiluted and within 30 seconds directly into a peripheral vein is used. The 300-mg dose is not recommended because it causes too great a reduction in BP, is often unpredictable, and has caused cerebral and MIs. Diazoxide has sodium-retaining effects and must not be used in patients with HF. Forty to 80 mg of Furosemide IV should be given after a bolus of diazoxide. Alternative dosage regimen: a slow infusion of 5 mg/kg of diazoxide, given at the rate of 15 mg/minute over 20–30 minutes to a total dose of 300–450 mg is safer than bolus therapy.

CONTRAINDICATIONS

- Cerebral hemorrhage.
- Cerebrovascular accidents.

Hydralazine

This vasodilator has a role when nitroprusside, nifedipine, and labetalol are not available. The drug is particularly useful for hypertensive emergencies associated with renal failure and in pregnancy. A recommended dosage is a 10-mg test dose followed in 30 minutes by IV infusion of 10–20 mg/hour; the maintenance dose is 5–10 mg/hour. The addition of furosemide and a β -blocker to hydralazine greatly enhances antihypertensive effects, and the latter agent prevents hydralazine-induced tachycardia.

Urapadil

Dosage: 12.5-mg bolus then infusion 5–40 mg/hour.

Urapadil is an α -blocker with serotonin agonist activity. The onset of action is 3–5 minutes with duration of action 4–6 hours. The drug may be used for hypertensive crisis particularly in patients with hypertensive encephalopathy and eclampsia. Unlike nitroprusside, it does not cause tachycardia or coronary steal and thus may be useful in patients with LV dysfunction and HF.

Methyldopa

Methyldopa is useful in hypertensive encephalopathy and renal failure. It is not the drug of choice in cerebrovascular accidents because of its sedative properties and slow onset of action but is considered useful if other agents are not available and reduction of BP is not required within the hour. A dosage of 250–500 mg IV is given every 4–6 hours.

Nitroglycerin

Nitroglycerin is useful in hypertensive states associated with myocardial ischemia, HF, MI, and after coronary artery bypass or other vascular reconstructive surgery and during cardiac catheterization. For dosage, *see* Infusion Pump Chart, Table 4.9.

HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is present if the BP taken at least 6 hours apart exceeds 140/90 mmHg or if there is an increase above the baseline of 30 mmHg systolic or 15 mmHg diastolic. A mean arterial pressure greater than 90 mmHg (SBP plus twice the DBP divided by 3) causes a twofold increase in perinatal mortality.

BP should be estimated with the patient sitting or semireclined, because the BP may be lower in the recumbent position.

β -Blockers, methyldopa, and hydralazine have all been used successfully in the management of hypertension from the 16th week to delivery and for hypertensive complications during pregnancy. Reduced birth weight, neonatal bradycardia, and hypoglycemia have been reported with β -blockers. However, recent results using β -blockers have shown better control of BP and less effect on the fetus than observed with methyldopa or hydralazine. A combination of pindolol and hydralazine has been used successfully in randomized studies. Twenty-five to 75 mg of atenolol daily has had favorable short- and long-term comparison with methyldopa. Combination therapy lowers the dose of individual drugs and reduces adverse effects.

Caution is necessary to avoid using antihypertensive agents during the first and early half of the second trimester of pregnancy to prevent the rare possibility of inducing congenital malformations. Early pregnancy is fortunately associated with vasodilation,

which protects against hypertension. Antihypertensive agents considered relatively safe for chronic use from the 16th week to delivery are β -blockers, methyldopa, and hydralazine.

Agents suitable for short-term use during the third trimester if no alternative exists include:

- Thiazide diuretics at low dosages.
- Nifedipine (10–20 mg) twice daily for hypertensive emergencies during the last trimester, if other agents are not effective, are contraindicated, or cause serious adverse effects. Nifedipine should be avoided during labor because calcium antagonists may cause cessation of uterine contractions. Diltiazem and verapamil are contraindicated in pregnancy and during lactation. These agents should not be used concomitantly with magnesium sulfate because severe hypotension may occur.

Atenolol

A dosage of 25 mg once daily is used and increased to 50 mg daily only after several determinations of BP, preferably made during two office or clinic visits. Maintenance of up to 50 mg in the morning, 25 mg at night; maximum of 50 mg twice daily. Long-term results are similar to those observed with methyldopa. Atenolol should not be used during lactation because the concentration in breast milk is high and adverse effects to infants have been reported.

Propranolol

A dosage of 20–40 mg three times daily is used and increased if needed to a maximum of 80 mg twice daily. The drug is well-tried, but atenolol is the preferred agent. Propranolol is the only β -blocker advised during lactation, however, because concentration in breast milk is lower than that of other β -blockers.

Labetalol

A dosage of 100–200 mg twice daily is used; a maximum of 800 mg daily is effective but may be implicated in causing retroplacental hemorrhage. Postural hypotension, perioral numbness, itching of the scalp, positive antinuclear antibody, and Lupus-like syndrome have been observed. Acute hepatic necrosis is a rare but life-threatening complication. Thus, labetalol must not be considered as just another β -blocking drug. The use of the drug during pregnancy is not justifiable, except for crises.

A dosage of 125–250 mg twice daily is used; increase the dose only after several reassessments over two or three visits; maximum suggested 500 mg twice daily. In a study of 117 methyldopa-treated women, one (0.9%) fetal death occurred; nine (7.2%) fetal deaths occurred in the control group of 125 women. No significant differences were noted at 7-year follow-up of children born to these mothers in both groups. If BP control is urgently needed before delivery, methyldopa is preferred to β -adrenergic blockers. The addition of hydralazine may be required if methyldopa is not sufficiently effective.

Hydralazine

An IV 5-mg bolus over 1–2 minutes is given, repeated in 20 minutes. If needed, infusion of 5 mg to maximum of 15 mg/hour, with constant fetal monitoring of heart rate and maternal BP. An oral dose of 25 mg three times daily for a few weeks is also used. This pure arterial vasodilator may be used during the last trimester if BP is not adequately

controlled with atenolol, pindolol, labetalol, or methyldopa. The drug is teratogenic in animals.

Sodium and water retention may occur, requiring the unwarranted use of a thiazide, and sinus tachycardia may be troublesome, necessitating β -blockade. Fetal thrombocytopenia has been reported. Thus, this agent is best reserved for a short period of therapy (i.e., 1–2 weeks) in the last trimester, along with a small dose of methyldopa or atenolol.

Thiazides

Thiazide diuretics are relatively contraindicated because they decrease placental blood flow, causing low birth weight. Thrombocytopenia, neonatal jaundice, and, occasionally, pancreatitis may occur.

Pre-eclampsia is associated with reduced plasma volume, and thiazides are not recommended. Although several studies have indicated freedom from serious adverse effects, the results are questioned and the use of thiazides is restricted. Low-dose thiazide therapy may be considered in the third trimester if other agents are contraindicated or unavailable, particularly in the following category of patients.

- Those whose hypertension predated conception or manifested before midpregnancy;
- Hypertension causing heart failure associated with volume overload.

A dosage of hydrochlorothiazide 12.5 mg daily (maximum 25 mg) or bendrofluazide 1.25–2.5 mg daily for a period of 1–6 weeks is used. After 6 weeks, alternative therapy should be considered.

Drugs that are contraindicated include:

- Nitroprusside. There is a risk of cyanide toxicity and fetal death.
- ACE inhibitors. These agents may cause skull defects and oligohydramnios or may disturb fetal and neonatal renal function and BP control.

Hypertensive Crisis in Pregnancy

Severe hypertension in pregnancy, especially near term or during labor, associated with DBPs greater than 105 mmHg may require urgent treatment with the following agents and/or combinations.

Hydralazine

A dosage of 5 mg IV over 10–20 minutes is used, and then 5–10 mg every 20–30 minutes; or, after the first bolus, give by IV infusion 5 mg/hour, increase to 10 mg (maximum 15 mg/hour) with continuous evaluation of heart rate and BP and fetal monitoring. Fetal distress may occur. In the United Kingdom, the drug is given by the above method or by IV infusion initially (200–300 μ g/minute; maintenance 50–150 μ g/minute).

Methyldopa

A dosage of 500 mg orally causes BP reduction within 6 hours. IV 250 mg in 100 mL 5% dextrose in water, over 30 minutes to 1 hour, repeated every 6 hours.

Labetalol

An IV bolus of 10–60 mg given every 20 minutes is effective and appears to cause less fetal distress than hydralazine. Clinical trials are necessary to compare efficacy and safety over hydralazine, the preferred drug. Practitioners should ascertain if labetalol is

approved for IV use in their areas of practice before use. The IV use in pregnancy is not FDA-approved.

Magnesium Sulfate

This drug is useful in women admitted for delivery with severe pre-eclampsia and DBP greater than 110 mmHg. The drug causes mild transient lowering of BP. The drug has proven more effective than phenytoin for the prevention of eclamptic convulsions.

A dosage of 4 g diluted in 100–200 mL IV solution infused over 20 minutes is given, and then 2 g/hour with careful monitoring of BP and urinary output. The drug is continued during labor and for at least 24 hours postpartum. Combination therapy using the vasodilator action of hydralazine, the central action of methyldopa, and enhancement by magnesium sulfate usually produces salutary effects with fewer adverse effects than observed with high doses of a single agent. Magnesium sulfate has only mild antihypertensive effects and is not considered an antihypertensive agent, and the major benefit of this drug is to prevent seizures associated with eclampsia.

CAUTION

Magnesium sulfate must not be used concomitantly with nifedipine because severe hypotension may be precipitated; magnesium sulfate should be avoided in patients with renal failure.

SECONDARY HYPERTENSION

In approximately 7% of hypertension cases, a secondary cause can be identified.

Causes of secondary hypertension and their approximate incidence include the following:

- Renal parenchymal disease (2%).
- Renovascular disease (2%).
- Cushing's syndrome (0.1%).
- Pheochromocytoma (0.1%).
- Primary hyperaldosteronism (0.1%).
- Coarctation of the aorta (0.1%).
- Estrogens (0.4%).
- Alcohol (0.2% or more).

Others (2%):

- Cocaine abuse.
- Carcinoid syndrome.
- Central nervous system tumors.
- Acromegaly.
- Thyrotoxicosis.
- Hypercalcemia.

Renal Parenchymal Disease

The history, physical, and laboratory screenings give clues to the type and duration of the underlying disease.

Screening includes assessment for the presence and type of urinary casts and the degree of proteinuria and anemia. The level of serum creatinine, urea or blood urea nitrogen, serum calcium, phosphate, and albumin.

The most common underlying diseases are:

- Chronic glomerulonephritis.
- Diabetic nephropathy.
- Collagen vascular disease.
- Polycystic kidney.
- Chronic pyelonephritis.
- Interstitial renal disease.

An increase in total peripheral resistance, hypervolemia, increased total body sodium stores, and a high cardiac output are prominent features that give rise to the hypertension of renal failure.

Therapy

FUROSEMIDE

As emphasized under the section on diuretics, thiazides lose their natriuretic effect in patients with glomerular filtration rates less than 25 mL/hour or serum creatinine greater than 2.3 mg/dL (203 μ mol/L). A dosage of 80–240 mg of furosemide daily or 5–10 mg daily of bumetanide may be expected to produce sufficient natriuresis, which is best reflected in the degree of weight loss. Rarely, up to 500 mg furosemide or 240 mg plus 5 mg metolazone may be required.

β -BLOCKERS

β -Blockers combined with diuretics are effective in reducing BP in patients with chronic renal failure. Atenolol, nadolol, and sotalol are excreted by the kidney; their dosing interval should be increased, and the total daily dose may have to be reduced in chronic renal failure if exaggerated β -blockade is manifest. Propranolol and metoprolol are actively metabolized, do not require dose adjustment, and are preferred for the management of hypertension with severe renal failure. Timolol and pindolol are partially excreted by the kidney but usually require little or no adjustment in dosage (*see Table 8.4*, for dosages of antihypertensive agents).

CALCIUM ANTAGONISTS

Calcium antagonists, particularly nifedipine, have had extensive trials and have proven effective in reducing total peripheral resistance, which is usually markedly increased in patients with chronic renal failure. Nifedipine and diltiazem are metabolized, and dosages may not require alteration. A few patients with renal failure reportedly showed deterioration with nifedipine and diltiazem. Recovery of function occurs upon discontinuing the calcium antagonist. Verapamil may accumulate with renal failure and is not advisable. Nifedipine has replaced hydralazine in the combination β -blocker plus diuretic plus vasodilator, but hydralazine may be added to the combination because the mechanism of vasodilation is different and the effect is additive.

HYDRALAZINE

When calcium antagonists are contraindicated or produce adverse effects, hydralazine has a role in lowering total peripheral resistance and BP and has proven effective in patients with severe hypertension associated with renal failure. A dosage of 25–100 mg twice daily is given. The dosage interval for hydralazine should be increased with chronic renal failure, with creatinine clearance less than 25 mL/minute.

CENTRALLY ACTING AGENTS

Centrally acting drugs, such as methyl dopa, clonidine, and guanfacine, are useful in combination with furosemide and nifedipine or appropriate agents in managing resistant renal hypertension, including patients on dialysis. Dosing should be reduced to once daily, preferably at bedtime.

Renovascular Hypertension

Renovascular hypertension is a rennin-dependent elevation of BP caused by decreased renal perfusion and ischemia. Intense activation of the renin angiotensin II system is responsible for the accelerated hypertension. A stenotic lesion of the renal artery or its branches is the culprit lesion usually responsible.

Diagnostic considerations in renovascular hypertension include:

- Abrupt onset of severe (stage II) hypertension before age 30, particularly in women suggests fibromuscular dysplasia (mainly medial fibroplasia) that accounts for approximately 17% of cases of renovascular hypertension. Medial fibroplasia is responsible for greater than 65% of all fibromuscular dysplasia and is most commonly observed in women 25–45 years of age; the occlusive lesion with poststenotic dilatation is located most often in the distal two-thirds of the main renal artery and has a typical “string of beads” appearance.
- Abrupt onset after age 55 suggests obstruction by atheroma. True ostial lesions may be difficult to differentiate from overgrowth of atheromatous plaques within the aorta. Such ostial plaques are often nonamenable to stenting.
- The sudden onset of malignant, accelerated, or resistant hypertension.
- A sharp rise in serum creatinine after the use of an ACE inhibitor is indicative of significant renal artery stenosis.
- Refractory hypertension not responsive to therapy with more than three drugs.
- Any of the above accompanied by a renal bruit.

DIAGNOSTIC EVALUATION

Confirmation by the gold standard intra-arterial angiography is necessary mainly in patients in whom interventional therapy is deemed essential. Iodinated contrast material are contraindicated in patients with renal insufficiency; the reported mortality is 0–2%. Complications include contrast induced renal failure, atheroemboli, pseudoaneurysm, and hematoma formation.

Doppler Ultrasonography. Duplex ultrasound scanning is highly operative dependent and there is a steep learning curve for this technique; technical failure may be caused by obesity and the presence of the bowel gas. The technique is claimed by some to have a sensitivity and specificity of 85–90% for skilled operators. Hartman et al. claim that, in their hands, the technique has a sensitivity and specificity of 85%.

Diagnosis of hemodynamically significant stenosis depends on the finding of an increased peak systolic velocity of blood flow through the stenotic segment. A peak systolic velocity greater than 200 cm/second and a ratio of the peak systolic velocity in the renal artery to the peak systolic velocity in the aorta of greater than 3.5 (renal aortic ratio). *It is necessary to image the entire lengths of the main renal artery to use this criteria, and Hartman et al. point out that this, unfortunately, is not as easy as it might seem.*

Captopril-stimulated Duplex scanning does not appear to increase sensitivity and specificity and is unreliable.

ACE Inhibition Renal Scintigraphy. This technique images the kidneys with tubular agents, such as Tc 99m, mercapto-acetyltriglycine, and I 131. The test is performed after ACE inhibitor therapy has been discontinued. The test reportedly has a sensitivity and specificity of 80% and 93%, respectively. Importantly, there is a good correlation between findings on scintigraphy and results of therapy. It is important to recognize that not all observed renal artery occlusion indicates renovascular hypertension and it is well-recognized that some patients with renal artery stenosis do not receive any benefit from revascularization. The sensitivity of the test decreases markedly; however, in patients with bilateral renal artery stenosis and in patients with renal dysfunction serum creatinine greater than 2.4 mg/dL.

Magnetic Resonance Angiogram (MRA). A major disadvantage is overgrading of stenoses. In patients with severe degrees of stenosis, the test may give a false impression that the artery is more stenotic than it is or indicate that it is occluded when it is not. Often only the proximal renal arteries can be imaged. Excellent images are obtained when the renal arteries are normal or only mildly diseased. The test application is limited in claustrophobic patients and there is a lack of capable scanners. Gadolinium-enhanced three-dimensional imaging during a single breath-hold is widely used. The test reportedly has a sensitivity and specificity of 97 and 92%, respectively.

Computed Tomography Angiography. Multidetector helical computed tomography (CT) scanners have greater spatial resolution than MR angiography and reportedly has a sensitivity and specificity of 93 and 87%, respectively. The technique does not overestimate the degree of stenosis. A major drawback is the requirement for iodinated contrast material and ionizing radiation. The test is unfortunately contraindicated in patients with renal dysfunction because of the iodinated product; many patients with renal artery stenosis have renal dysfunction. Also, allergic reactions are not uncommon with iodinated contrast material.

Therapy. Drug therapy includes the judicious use of combination therapy, β -blocker, thiazide (furosemide if renal failure is present), and amiloride to conserve potassium. Calcium antagonists are often add-ons.

The BP goal is SBP 140–150 mmHg, DBP 70–95 mmHg. The BP should not be drastically reduced.

ACE inhibitors are contraindicated in patients with severe bilateral renal artery stenosis or stenosis of a solitary kidney because in these patients, renal circulation is dependent on high levels of angiotensin II. Thus, a sharp fall in renal blood flow may occur and renal failure may ensue with the loss of a solitary kidney.

Angioplasty with stent and surgery are equally effective and superior to drug therapy in patients in whom renal artery stenosis is caused by fibrous dysplasia and hypertension is present for less than 3 years with normal renal function. Angioplasty has a role in patients who are poor surgical candidates. Restenosis postangioplasty frequently occurs, but a second dilatation may be rewarding. In patients with unilateral renal artery stenosis, elevation of serum creatinine indicates that nephrosclerosis is present in the contralateral kidney, and a salutary effect of angioplasty or revascularization is unlikely.

Surgery appears to be somewhat more effective than angioplasty for atherosclerotic renovascular disease. But the advent of drug-eluting stents will change the rationale for surgery. Either therapy is advisable for atherosclerotic occlusion in younger patients with unilateral renal artery disease, especially when hypertension is difficult to control with antihypertensive agents. A serum creatinine level greater than 1.4 mg/dL (124 μ mol/L) and the presence of IHD increase the surgical mortality rate. Ostial lesions require surgical expertise as they are difficult to stent.

Pheochromocytoma

Fewer than 0.1% of patients with moderate to severe diastolic hypertension are expected to have a pheochromocytoma:

- Approximately 10% of these tumors of the adrenal medulla are bilateral.
- 10% are malignant.
- 10% are outside the adrenals.
- 10% are familial.

Patients with familial or bilateral pheochromocytomas may be part of the Type II Multiple Endocrine Neoplasia syndrome and should be screened for medullary carcinoma of the thyroid and hyperparathyroidism.

CLINICAL HALLMARKS

These include:

- Severe headaches and profuse sweating.
- Palpitations and tremor.
- Pallor owing to vasoconstriction.
- Paroxysmal or diastolic hypertension; severe increase of BP with induction of anesthesia; surgery; or use of histamine, phenothiazines, or tricyclic antidepressants.
- Postural hypotension.
- Weightless.

Diagnostic Evaluation

The following investigations are usually diagnostic:

- Elevated 24-hour urine total metanephrine is the most reliable urinary screening test (see Fig. 8.3.).
- Free catecholamines and vanillylmandelic acid (VMA) are often elevated, but interference with urinary screening occurs with phenothiazines, chloral hydrate, and other drugs. β -Blockers, thiazides, calcium antagonists, and ACE inhibitors, however, cause no interference. A special diet and avoidance of several drugs for at least 3 days are necessary for accurate VMA results.
- An increase in plasma catecholamines: an assessment is carried out with a heparin lock in an arm vein; the patient is sedated with 1 mg of sublingual lorazepam (Ativan) and is allowed to lie quietly for 20 minutes. Blood is then drawn for epinephrine and norepinephrine levels.
- Elevated dopamine serum level is estimated on the same blood sample taken for epinephrine because dopamine may be the only chemical produced by some malignant pheochromocytomas. Plasma catecholamines may be mildly elevated with stress and essential hypertension, diuretics, prazosin, and other α_1 -blockers, hydralazine, labetalol, and calcium antagonists. CT or magnetic resonance imaging (MRI) may reveal a tumor. I^{131} meta-iodo-benzyl-guanidine (MIBG) enters chromaffin tissue and an MIBG scan helps identify extra-adrenal tumors.

Therapy

PHENTOLAMINE (REGITINE; ROGITINE, CANADA AND UK)

Hypertensive crisis may require the use of phentolamine before the administration of phenoxybenzamine. A dosage of 2–5 mg IV bolus given over 5 minutes, every 5 minutes, or an infusion of 10–20 $\mu\text{g/kg/minute}$ or 5–60 mg over 10–30 minutes at a rate of 0.1–2 mg/minute. The drug has a rapid onset of action and lasts only 10–20 minutes.

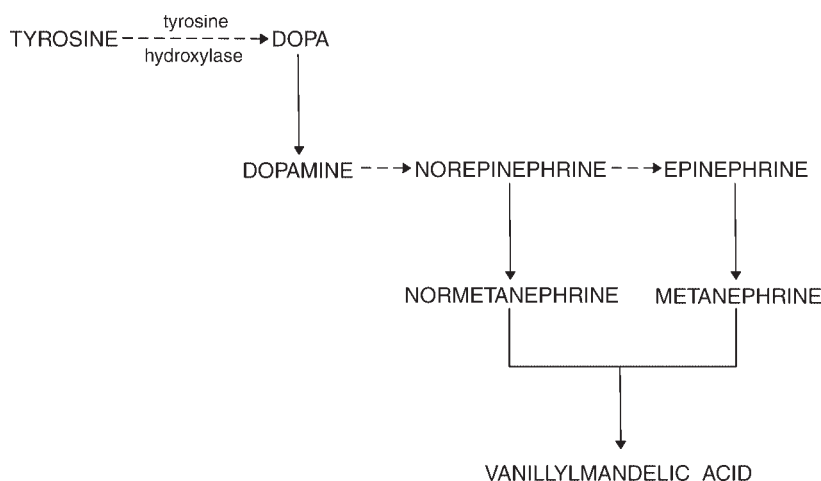


Fig. 8.3. Catecholamine metabolic pathway.

Caution: deaths owing to arrhythmia and acute MI have been reported, and β -blockade may be required. If β -blockers are used, care is required in patients who are considered at high risk for precipitation of HF.

NITROPRUSSIDE

Nitroprusside should be used to lower BP during a crisis and is effective, but complicating tachyarrhythmias may cause problems with management, and β -blockade should not be used without adequate α -blockade (*see* infusion pump chart, [Table 8.11](#)).

PHENOXYBENZAMINE (DIBENZYLINE)

Oral therapy with this nonselective α -blocker is commenced once the BP is under control or if the BP is not severely elevated after control with phentolamine or other agent. A dosage of 1–2 mg/kg daily in two or three divided doses is given, usually 10 mg every 8–12 hours, increase every 3 or 4 days by 10 mg to a maximum 50 mg three times daily. Phenoxybenzamine therapy is usually required for control of BP over a period of 1–2 weeks before surgery. The drug is contraindicated in HF.

Patients with pheochromocytoma are hypovolemic and α -blockade causes vasodilation. Thus, a marked fall in BP may occur, causing severe postural hypotension. Increase in salt intake and vigorous saline infusion are usually required during the 1–2 weeks before surgery to prevent severe postural hypotension, but careful monitoring is required to prevent the precipitation of HF. Postoperative hypotension may be avoided by discontinuing phenoxybenzamine several days before surgery. Because the presynaptic α_2 -receptor is blocked by this agent, the release of norepinephrine from adrenergic neurons increase, causing tachycardia that may require control with a β -blocker.

NIFEDIPINE

This agent, used universally for the management of all grades of hypertension, may be used in the emergency setting with temporary beneficial results expected in some patients and may occasionally avoid the use of nitroprusside (*see* [Table 8.10](#)).

β -BLOCKERS

β -Blockers must not be used before adequate α -blockade because unopposed stimulation of α -receptors can cause a severe increase in BP. β -Blockade may be required after 1 week of oral α -blockade if catecholamine-induced arrhythmias require control. A β -selective drug, such as atenolol is preferable to propranolol.

Metyrosine (Metirosine, UK)

(α -Methyl-L-Tyrosine) (Demser). This agent is an inhibitor of tyrosine hydroxylase and, hence, the synthesis of catecholamines. Metyrosine reduces catecholamine production by about 70% and has a role in the preoperative management of pheochromocytomas as an alternative to phenoxybenzamine. The drug is particularly useful for the management of inoperable tumors in combination with an α -blocker. A dosage of 250 mg four times daily is used and increased daily by 250 mg to reach a maximum of 4 g daily. Adverse effects, such as severe diarrhea, sedation, extrapyramidal symptoms, and hypersensitive reactions, may occur.

SURGERY

CT and MRI are invaluable for locating tumors. A transabdominal incision is advisable to allow a search of all abdominal chromaffin tissue. Enflurane is considered the safest anesthetic agent, as it does not stimulate catecholamine release or sensitize the myocardium to catecholamines. Management of fluid blood volumes necessitates the use of a Swan–Ganz catheter. If the shrunken blood volume caused by excess catecholamine and blood loss is replenished, marked fluctuations in BP can be prevented. Elevated BP is controlled with nitroprusside or nitroglycerin, especially in patients where the occurrence of HF is predictable. Postoperative hypotension and HF present a greater hazard with the use of α -blockers and β -blockade than with the use of nitroprusside or nitroglycerin. Removal of the tumor may cause a precipitous fall in BP because of a shrunken blood volume and the release of the intense vasoconstriction that was produced by the pheo.

A surgical cure is expected in 80% of patients. Approximately 10% of patients have a recurrence, and patients should be screened annually for 5 years. The 5-year survival is about 95% for patients with benign tumors and 45% for patients with malignant tumors.

Coarctation of the Aorta

Hypertension in the arms with weak, absent, or delayed femoral pulses is a hallmark. After the age of 10, chest X-ray shows notching of the fourth to eighth ribs bilaterally or unilaterally and right sided if the coarctation is proximal to the left subclavian.

THERAPY

Drug therapy is often required in the adult before surgical correction. Coarctation of the aorta causes activation of the renin angiotensin aldosterone system; thus, ACE inhibitors are first-line agents. All patients should be screened for septal defects, polycystic kidneys, and berry aneurysms; the latter not uncommonly causes the patient's demise.

Surgical repair may not be curative. Postoperative hypertension may be a problem requiring antihypertensive therapy. Aortic dissection may occur distal or proximal to the site of surgical repair. Also, restenosis may require balloon angioplasty, and close follow-up is essential.

Two risk factors have been identified for premature death after surgery:

- Age at the time of surgical correction: the younger the patient, the better the outcome.
- Hypertension, both preoperative and postoperative, carries a guarded prognosis.

BIBLIOGRAPHY

- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
- Aram V, Chobanian MD, Bakris GL, et al. and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and the Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2571.
- Bakris GL, Fonseca V, Katholi RE, et al. for the GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; 292:2227–2236.
- Bennet NE. Hypertension in the elderly. *Lancet* 1994;344:447.
- Black HR, Elliott WJ, Grandits G, et al., CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA* 2003;289:2073–2082.
- Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004;364:1684–1689.
- Cominacini L, Fratta Pasini A, Garbin U, et al. Nebivolol and its 4-keto derivative increase nitric oxide in endothelial cells by reducing its oxidative inactivation. *J Am Coll Cardiol* 2003;42:1838–1844.
- Committee on Detection, Evaluation and Treatment of High Blood Pressure. The seventh report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNCV). *Arch Intern Med* 2003.
- Crow RS, Prineas RJ, Routaharju P, et al. Relation between electrocardiography and echocardiography for left ventricular mass in mild systemic hypertension (Results from Treatment of Mild Hypertension Study). *Am J Cardiol* 1995;75:1233.
- Cunningham FG, Lindheimer MD. Current concepts: hypertension in pregnancy. *N Engl J Med* 1992;326:927.
- Dabaghi S. ACE inhibitors and pancreatitis. *Ann Intern Med* 1991;115:331.
- Edelson JF, Weinstein MC, Tosteson ANA, et al. Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. *JAMA* 1990;263:408.
- Felson DT, Sloutsis D, Anderson JJ, et al. Thiazide diuretics and the risk of hip fracture. Results from the Framingham Study. *JAMA* 1991;265:370.
- Franco V, Oparil S, Carretero OA. Hypertensive therapy: part II. *Circulation* 2004;109:3081–3088.
- Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326.
- Giannoccaro PJ, Wallace GJ, Higginson LAJ, et al. Fatal angioedema associated with enalapril. *Can J Cardiol* 1989;5:335.
- Hanson MW, Feldman JM, Beam CA, et al. Iodine 131-labeled metaiodobenzylguanidine scintigraphy and biochemical analyses in suspected pheochromocytoma. *Arch Intern Med* 1991;151:1397.
- Hartman RP, Kawashima A, King F. Evaluation of renal causes of hypertension. *Radiol Clin N Am* 2003;41:909.
- Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003;107:1401–1406.
- Khan MGabriel. Hypertension. In: *Cardiac Drug Therapy*. Sixth edition. Philadelphia: WB Saunders, 2003.
- Lakshman MR, Reda DJ, Materson BJ, et al, for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. *Arch Intern Med* 1999;159:551–558.
- Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995;333:201.
- Lunde H, Hedner T, Samuelsson O, et al. Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1994;308:18.

- Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000;283:1967–1975.
- Materson BJ, Reda DJ, Cushman WC. Single drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993;328:914.
- Mattioli AV, Zennaro M, Bonatti S, et al. Regression of left ventricular hypertrophy and improvement of diastolic function in hypertensive patients treated with telmisartan. *Int J Cardiol* 2004;97(3):383–388.
- Nissen SE, Tuzcu EM, Libby P, et al. for the CAMELOT Investigators. Effect of Antihypertensive Agents on Cardiovascular Events in Patients with Coronary Disease and Normal Blood Pressure: The CAMELOT Study: a randomized controlled trial. *JAMA* 2004;292:2217–2225.
- Panacek EA, Bednarzyk EM, Dunbar LM, et al. Randomized prospective trial of fenoldopam versus sodium nitroprusside in the treatment of acute severe hypertension. *Acad Emerg Med* 1995;2:959.
- Parks WJ, Thang DM, Plauth WH, et al. Incidence of aneurysm formation after dacron patch aortoplasty repair for coarctation of the aorta: long-term results and assessment utilizing magnetic resonance angiography with three-dimensional surface rendering. *J Am Coll Cardiol* 1995;26:266.
- Pearson AC, Pasierski T, Labovitz AJ. Left ventricular hypertrophy: diagnosis, prognosis and management. *Am Heart J* 1991;121:148.
- Pepine CJ. What is the optimal blood pressure and drug therapy for patients with coronary artery disease? *JAMA* 2004;292:2271–2273.
- Pitt B, Reichek N, Willenbrock R, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation*. 2003;108:1831–1838.
- Salathe M, Weiss P, Ritz R. Rapid reversal of heart failure in a patient with pheochromocytoma and catecholamine-induced cardiomyopathy who was treated with captopril. *Br Heart J* 1992;68:527.
- SHEP Cooperative Study Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Programs (SHEP). *JAMA* 1991;265:3255.
- Slater EE, Merrill DD, Guess HA, et al. Clinical profile of angioedema associated with angiotensin converting enzyme inhibition. *JAMA* 1988;260:967.
- Szlachcic J, Tubau JF, O'Kelly B, et al. What is the role of silent coronary artery disease and left ventricular hypertrophy in the genesis of ventricular arrhythmias in men with essential hypertension? *J Am Coll Cardiol* 1992;19:803.
- The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study. A randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med* 1991;151:1413.
- UK prospective Diabetes study group. Efficacy of atenolol and captopril in reducing risk of microvascular and macrovascular complications in Type II diabetes: UKPDS. *BMJ* 1998;317:713.
- Wassertheil-Smoller S, Blafox D, Oberman A, et al. Effect of anti-hypertensives on sexual function and quality of life: the TAIM Study. *Ann Intern Med* 1991;114:613.
- Wilkstrand J, Warnold I, Tuomilhto J, et al. Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY Study. *Hypertension* 1991; 17:579.
- Wood SM, Mann RD, Rawlins MD. Angioedema and urticaria associated with angiotensin converting enzyme inhibitors. *Br Med J* 1987;294:91.
- Yusuf S. Calcium antagonists in coronary artery disease and hypertension: time for reevaluation? *Circulation* 1995;92:1079.
- Yusuf S, Gerstein H, Hoogwerf B, et al, for the HOPE Study Investigators. Ramipril and the development of diabetes. *JAMA* 2001;286:1882–1885.

9

Dyslipidemias

CONTENTS

SECONDARY DYSLIPIDEMIAS
PRIMARY DYSLIPIDEMIAS
DIAGNOSTIC BLOOD LEVELS
NATIONAL EDUCATION PROGRAM MODIFIED GUIDELINES
DIETARY MANAGEMENT
DRUG THERAPY
NEW DRUG CLASS AND NEW THERAPIES
BIBLIOGRAPHY

Dyslipidemias should be considered as being a result of primary and secondary causes.

SECONDARY DYSLIPIDEMIAS

Secondary causes should always be excluded.

Secondary causes of dyslipidemia include:

- Polygenic hypercholesterolemia: manifested in susceptible individuals on a diet rich in saturated fats. There is no clear-cut pattern of inheritance; a combination of more than one genetic variant appears to be necessary (polygenic inheritance) for this form of dyslipidemia. Genetic factors appear to be important as individuals in the general population vary in their cholesterol response to a high saturated fat diet. Total serum cholesterol and low-density lipoprotein-C (LDL-C) increase in response to a high saturated fat intake. Polygenic hypercholesterolemia is the most common cause of increased total cholesterol and LDL-C observed in the general population. It is not a defined inherited genetic defect and is believed to be a hepatic overproduction of very low-density lipoprotein (VLDL) that is converted rapidly to LDL that VLDL triglyceride concentrations remain within the normal range. The estimates prevalence among adults of European descent is 20–80%.

Causes of secondary dyslipidemias include:

- Diabetes mellitus.
- Hypothyroidism.
- Nephrotic syndrome.
- Chronic liver disease.
- Obesity.

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- Dysgammaglobulinemia (monoclonal gammopathy).
- Obstructive jaundice.
- Biliary cirrhosis.
- Pancreatitis.
- Excess alcohol consumption.
- Estrogens/progesterone.
- Glycogen storage disorders.
- Lipodystrophy.
- Medications

Medications

Corticosteroids, immunosuppressive agents, retinoids, and antiretroviral therapy cause an increase in triglycerides, total cholesterol, and a decrease in high-density lipoprotein (HDL) cholesterol levels. Diuretics (thiazides) may cause a mild elevation in total cholesterol (1–4%) and a slight lowering of HDL (approximately 1–10%). This effect is minimal, however, and occurs in fewer than 10% of individuals. Chronic treatment for more than 2 years usually produces no significant elevation in total cholesterol or decrease in HDL, and modest changes have been exaggerated. The long-term effects of β -blockers on HDL-C have been poorly studied and an increase of 0–7 % has been reported in small studies.

It is clear that LDL cholesterol is not increased by β -blockers. Metoprolol has shown no effect on HDL in one well-run study, and a decrease of 6% in another. The effect on HDL-C levels is considered clinically insignificant by the author. These agents are proven to improve survival and decrease unfavorable outcomes in all types of patients with coronary artery disease (CAD). Frishman points out that alteration in HDL-C levels is of minimal clinical concern because the effect is so small, if it occurs at all. There is a documented significant increase in triglycerides however, but the evidence linking triglycerides to an increased risk of coronary heart disease (CHD) is extremely weak and is considered unproven.

PRIMARY DYSLIPIDEMIAS

Primary dyslipidemias are a rare cause of dyslipidemia encountered in clinical practice. Fewer than 0.1% of the population appears to have a genetic abnormality characterized by cellular LDL receptor deficiency. Individuals with a marked increase in serum levels of cholesterol greater than 350 mg/dL (9 mmol/L), or severe hypertriglyceridemia represent a small group of patients seen in clinical practice. These individuals often show evidence of xanthomas and diffuse vascular disease and are at very high risk for developing premature atherosclerotic CAD. If the situation is suspected, screen first-degree relatives, parents, siblings, and children.

The gene for the LDL receptor is located on chromosome 19 and its diminished expression in familial hypercholesterolemia was discovered by Goldstein and Brown in 1974. These workers indicated that mutations of this receptor prevent it from efficient cellular uptake of LDL from tissue fluid because it cannot be transported to the cell surface, cannot bind properly to LDL, cannot be internalized, or is not released from the endosome.

Causes of primary dyslipidemia include the genetic hyperlipoproteinemias. Observation of the standing plasma after storage overnight at 4°C. reveals characteristic findings that most often obviate the need for expensive electrophoretic analysis.

These have been classified by Fredrickson as:

- Type I: elevated chylomicrons normal to mildly elevated total cholesterol; markedly elevated plasma triglycerides; creamy supernatant, clear infranant; fortunately type one is very rare (<1%).
- Type IIa: elevated LDL lipoproteins; plasma total cholesterol and LDL are elevated but with normal triglycerides and with a clear plasma on standing overnight (frequency ~10%).
- Type IIb; elevated LDL and VLDL lipoproteins: the total cholesterol is elevated, as well as triglycerides: this is the most common hyperlipoproteinemia (~40%).
- Type III: elevated intermediate-density lipoprotein with a mildly elevated serum cholesterol, markedly elevated triglyceride; the overnight standing plasma is turbid and usually has a separate creamy chylomicron supernatant (<1%).
- Type IV: elevated VLDL and chylomicrons; serum cholesterol is normal triglycerides are markedly elevated and the overnight plasma is turbid (~45%).
- Type V: elevated VLDL and chylomicrons; plasma cholesterol is mildly elevated with markedly elevated triglycerides: a turbid plasma and usually a separate creamy chylomicron supernatant (5%).

It is not necessary to use the Fredrickson classification in clinical practice, except for rare cases of familial hyperlipidemia associated with xanthomatoses; fortunately these are rarely seen in clinical practice. Fredrickson phenotypes do not represent diagnoses and the classification does not address whether the dyslipidemia is primary or secondary; also, it does not take into account HDL cholesterol levels. Most importantly this classification describes only rare genetic dyslipidemias; electrophoretic determination is costly and genetic hypolipoproteinemias are observed in less than 0.1% of patients with dyslipidemias seen in cardiology or in general practice.

Selected causes of hyperlipoproteinemia include:

- Heterozygous familial hypercholesterolemia: an autosomal dominant trait with complete phenotypic expression in childhood. The genetic mutations reduce the number of high affinity LDL receptors by about 50%. Frequency is reportedly 1 in 500 patients in the Western world. There is a two- to fourfold increase in LDL cholesterol. Tendon xanthomas are commonly present; corneal arcus before age 25; atherosclerotic vascular disease, particularly premature obstructive CHD, causes early demise if not aggressively treated. In these patients, a thorough physical examination should record the presence or absence of xanthoma tendinosum, tuberosum, and planum. These lesions are mainly observed in patients with familial genetic severe hyperlipidemias; xanthelasma of the eyelids is not closely associated and is a variable finding.
- Primary combined hyperlipidemia; familial combined hyperlipidemia. The frequency is reportedly 1 in every 300 patients (this is an exaggeration and may relate to findings in referrals seen in lipid clinics). There is overproduction of LDL and VLDL or both. This disorder is associated with increased risk for CAD but about 10 years later than in heterozygous familial hypercholesterolemia.
- Primary hypertriglyceridemia: familial hypertriglyceridemia type IV; triglycerides usually in the range 200–500 mg/dL; and the very rare Type V in which triglyceride levels of more than 1000 mg/dL are observed and demands immediate treatment because of the risk for pancreatitis. Early CAD occurs in some families.

DIAGNOSTIC BLOOD LEVELS

Determination of total cholesterol LDL-C, HDL-C and triglyceride is recommended every 5 years in all adults.

Classification of Blood Lipid Levels

TOTAL CHOLESTEROL

- Less than 180 mg/dL (4.6 mmol/L) is desirable.
- 200–239 mg/dL is borderline.
- Greater than 240 is highly abnormal, and importantly, the majority of patients with acute myocardial infarction (MI) have levels in the range 210–260 mg/dL.

LDL-C

- LDL-C less than 100 mg/dL (2.6 mmol/L) for high-risk patients, with a goal of about 80 mg/dL (2.0 mmol/L) or less; in very high-risk patients a level less than 70 mg/dL (1.8 mmol/L) is optimal.
- 100–129 is near or above optimal.
- 130–159 is borderline.
- Greater than 160 (4 mmol/L) is high.

HDL-C

- Less than 40 mg/dL (1 mmol/L) is low.
- More than 60 is high because <10% of individuals age 30–70 have such high levels, a level >50 mg/dL should be considered optimal).

Triglycerides

- Less than 150 mg/dL is normal.
- More than 200 is high.

A total blood cholesterol level less than 180 mg/dL (4.5 mmol/L) is considered desirable. Individuals with cholesterol levels greater than 350 mg/dL (9 mmol/L) are at high risk for the development of premature atheromatous occlusion of the coronary arteries and early manifestations of ischemic heart disease (IHD); fortunately, this scenario is uncommon, and the attention given to familial hypercholesterolemia in the 1960s to early 1980s is now being focused on mild and moderate elevations of blood cholesterol.

Recommendations concerning the management of borderline high blood cholesterol varies in different countries. The Canadian guidelines are not as aggressive as those of the United States, and the guidelines of the United Kingdom are even more conservative.

NATIONAL EDUCATION PROGRAM MODIFIED GUIDELINES

LDL Cholesterol

Presence of CAD or risk equivalent and diabetes mellitus

LDL-C greater than 80 mg/dL (2.0 mmol/L):

- Advise drug therapy preferably with a powerful statin, such as 10 mg of rosuvastatin, 20 mg of atorvastatin, or 40 mg of simvastatin to achieve the goal levels less than 80 mg/dL (2 mmol/L).

If several major risk factors are present in the absence of coronary, carotid, or peripheral vascular disease, drug therapy is considered if the LDL-C is greater than 130 mg/dL (3.5 mmol/L), with a goal of less than 100. In patients considered to have average risk for atheromatous disease, drug therapy is considered if the LDL-C is greater than 160 mg/dL (> 4 mmol/L) with a goal of less than 120 mg/dL (3 mmol/L), *see* [Fig. 9.1.](#) and [Table 9.1.](#)

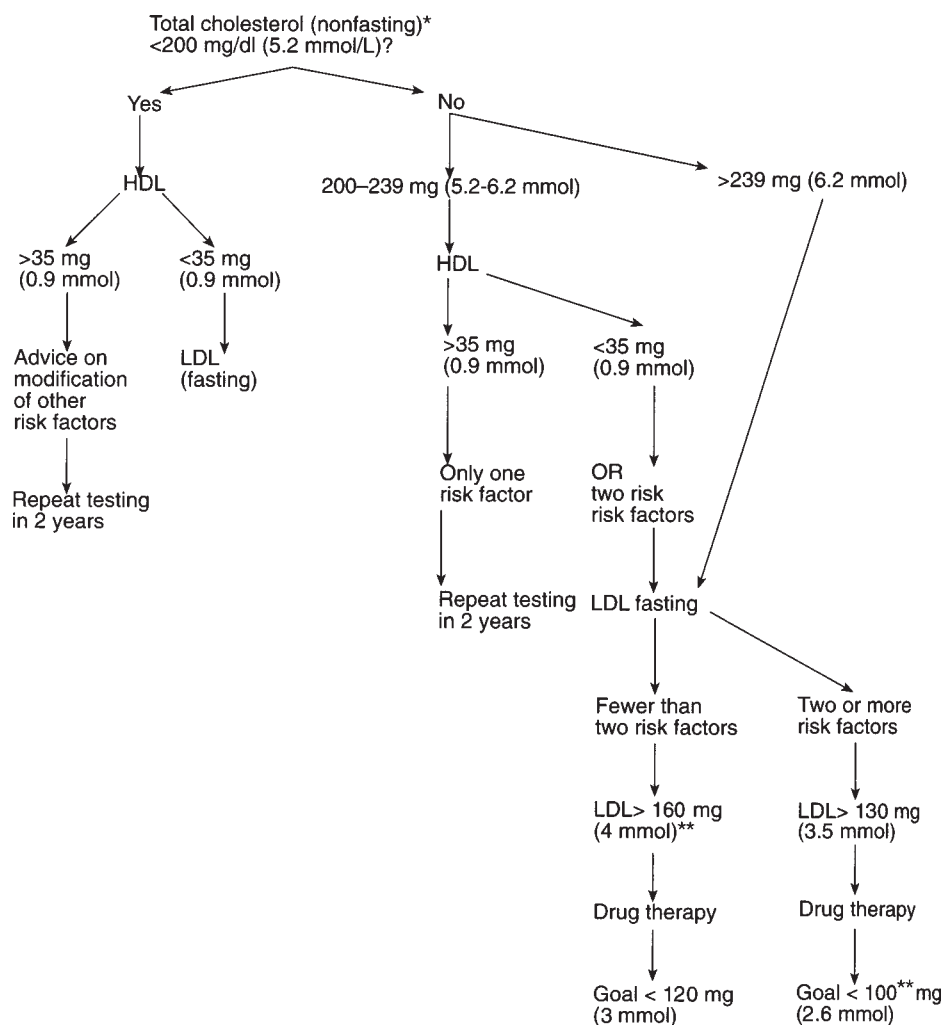


Fig. 9.1. Guidelines for the management of elevated low-density lipoproteins cholesterol: when to use drug therapy. *Total cholesterol and HDL levels are preferably done nonfasting to save time and cost to patients, the LDL cholesterol is always requested in the fasting state. LDL, low-density lipoprotein. **very high risk <70 mg/dL (1.8 mmol/L) is optimal.

Risk factors apart from diabetes and elevated LDL-C include:

- Current cigarette smoking.
- Hypertension
- Low HDL cholesterol less than 39 mg/dL; 1 mmol/L.
- Family history of premature CAD: male first-degree relative, less than 55; or in female first-degree relative, less than 65.
- Age at least 45 years in men; 55 years less than women.
- Peripheral vascular disease.
- Obesity/metabolic syndrome.
- Total cholesterol and HDL levels are not influenced by food and can be tested in the nonfasting state at the initial visit if convenient. This strategy saves time and cost for the patient, because it prevents a return visit to a laboratory for blood work.

Table 9.1.
Coronary Artery Disease or Diabetes

<i>YES*</i>	<i>NO**</i>		
	<i>Several risk factors</i>	<i>Average risk (one or two risk factors)</i>	<i>Low risk</i>
LDL-C >100mg/dL (2.5 mmol/L)	LDL-C >130 mg/dL (3.5 mmol/L)	LDL-C >160 mg/dL (4 mmol/L)	LDL-C 190 mg/dL (5 mmol/L)
Drug therapy	Drug therapy	Consider drug therapy	Consider drug
Goal <70 mg/dL (<1.8 mmol/L)	Goal <100 mg/dL (<2.6 mmol/L)	Goal <120 mg/dL (<3.0 mmol/L)	Goal <160 mg/dL (<4 mmol/L)

LCL-C, low-density lipoprotein-C.

*CAD or diabetes.

**No CAD or diabetes.

- If total cholesterol is less than 180 mg/dL (4.5 mmol/L), follow-up depends on the levels of HDL cholesterol. If the HDL cholesterol is greater than 35 mg/dL (0.9 mmol/L), general advice on diet and risk factor modification is given and levels are repeated, depending on presence of atheromatous disease and assessment of risks.

Most heart attacks occur in individuals with total cholesterol levels between 210 and 240 mg/dL (5.5 and 6.2 mmol/L), and approximately 50% of adult Americans have cholesterol levels in this range. The average cholesterol level for North Americans is about 212 mg/dL (5.5 mmol/L). In these individuals with borderline high blood cholesterol, a low level of HDL cholesterol further increases the risk for CHD. The emphasis, therefore, must be placed on the general population, in which mild-to-moderate elevation of total cholesterol associated with a low HDL cholesterol is a common health problem. Indeed, mild hypertension is a parallel marker and the conditions often coexist, thus increasing CHD risk, which is compounded by cigarette smoking.

Although total cholesterol can be measured in the nonfasting state, the measurement of LDL cholesterol requires a 12- to 14-hour fasting specimen for accurate determination of the triglyceride level, which is required for the estimation of the LDL cholesterol. It must be re-emphasized that a greater than 12-hour fasting specimen is necessary because triglyceride estimation must be performed in the fasting state.

- LDL cholesterol is derived as follows: $\text{LDL (mg/dL)} = \text{total cholesterol} - \text{HDL} - (\text{triglyceride} \div 5)$; or $\text{LDL (mmol/L)} = \text{total cholesterol (mmol/L)} - \text{HDL} - (\text{triglyceride} \div 2.2)$. If the triglyceride value is above 200 mg/dL (2.2 mmol/L), the estimation is invalid (conversion for triglyceride from: $\text{mmol/L} \times 88 = \text{mg/dL}$; for cholesterol $\text{mmol/L} \times 39 = \text{mg/dL}$).

When a patient has documented high-risk LDL cholesterol levels or premature CHD and familial genetic disease is confirmed, all available first-degree relatives should be tested.

An HDL cholesterol level is vital in decision-making concerning the management of hyperlipidemia. Data from the Framingham Study indicate that the mortality risk from CHD increases as HDL cholesterol levels decrease. The average risk of mortality from CHD is at a level of 39 mg/dL (1 mmol/L). Every 1% increase in HDL cholesterol decreases CHD risk by about 2%, and each 1% reduction in total cholesterol should produce a 2% reduction in CHD risk. The HDL cholesterol shows a strong inverse

association with incidence of CHD at all levels of total cholesterol, including levels under 200 mg/dL (5.2 mmol/L). A 12-year follow-up indicates that the relationship does not diminish appreciably with time. The study confirms that nonfasting HDL cholesterol and total cholesterol are related to development of CHD in both men and women over age 49.

HDL cholesterol above 60 mg/dL (1.6 mmol/L) is a protective negative risk factor. HDL acts hypothetically to export nonoxidized LDL from foam cells; LDL cholesterol that is not oxidized can potentially be re-exported.

HDL cholesterol, as well as total cholesterol, is not affected by food eaten within prior hours; thus, a nonfasting specimen is not required. A nonfasting specimen allows the sample to be taken immediately after the physician consultation and saves the time and cost of a return visit to a laboratory.

C-reactive protein: Ridker et al. indicate that CRP monitoring should be used to assess risk, regardless of LDL goal achieved by statin therapy. High-risk patients with acute coronary syndrome who have low CRP levels after statin therapy appear to have better clinical outcomes than those with higher CPR levels.

Triglycerides

Triglyceride-rich VLDLs are secreted by the liver. The VLDL surface coat contains apolipoprotein B and other lipoproteins. VLDL triglycerides undergo hydrolysis by lipoprotein lipase.

VLDL remnants have one or two fates. Direct removal by the liver or degradation into LDL by lipolytic removal of remaining triglycerides.

Triglyceride levels of 200–400 mg/dL (2–4 mmol/L) are considered borderline and 400–1000 mg/dL (4–10 mmol/L) is high. Levels more than 900 mg/dL carries a high risk for acute pancreatitis and requires immediate dietary and drug therapy. A positive role for high triglyceride levels in CHD still remains controversial as shown in large clinical studies. Because increased triglyceride and low levels of HDL cholesterol are closely associated, the independent contribution of triglyceride may disappear, particularly in men, once the risk of HDL has been taken into account. In a meta-analysis of 17 studies, triglyceride was shown to be an independent risk factor, particularly in women, after controlling for HDL cholesterol but the association is modest and unproven. Fortunately, elevations of triglycerides are most often controlled by restriction of carbohydrates and alcohol, weight reduction, and exercise an appropriate management of diabetes.

DIETARY MANAGEMENT

Dietary modification is expected to decrease an elevated blood cholesterol by 7–15%, depending on the degree of adherence to a low-saturated fat, low-cholesterol diet, and the previous intake of these substances. Some individuals have a marked increase in total cholesterol in response to dietary cholesterol, whereas in others, an increase in saturated fat or cholesterol intake has little or no effect. Of interest is the report of an 88-year-old man who consumed 25 eggs daily for over 50 years with maintenance of a normal serum cholesterol level. This is a common story relayed by many elderly individuals who may have sustained a very high intake of cholesterol and saturated fats over prolonged periods. In some individuals, a decrease in cholesterol absorption, an increased transformation, and excretion of bile acid serve to maintain total cholesterol in the desired range. Also, conversion of cholesterol to bile acid activates an upregulation of LDL receptor activity, permitting further clearance of blood cholesterol. Thus, genetic differences in response

to the amount of dietary saturated fat appear to be important, and hypercholesterolemic individuals appear to be more sensitive to its presence.

Dietary change brings about a salutary effect in only some individuals, but a consistent effort must be made to enforce the change, especially because drug therapy entails costs and risks of adverse effects, and because compliance is poor. Several clinical trials have documented the effect of the dietary approach in significantly reducing total cholesterol. Approximately 28% of Americans with elevated total cholesterol appear to respond to dietary cholesterol and saturated fat restrictions with a 10–15% decrease in cholesterol. In London, the incidence of hypercholesterolemia and response to diet appear to be similar to that observed in Americans. The number of civil servants in London with cholesterol levels less than 200 mg/dL (5.2 mmol/L) rose from 5 to 29% with a simple cholesterol-lowering diet. The average level of cholesterol while following the diet was approximately 220 mg, with an approximately 10% salutary response to diet.

Step 1: Therapeutic Diet

The expert panel recommends the following:

- An average of 30% or less of total calories from total fat.
- Saturated fatty acids should not exceed 10% of total calories.
- 20% of total calories should be derived from the combination of polyunsaturated fatty acids and monounsaturated fatty acids. Polyunsaturated fatty acids should not exceed 10% of total calories. Because the average diet of an adult male living in North America contains approximately 36% calories from fat, a reduction of 6–7% is feasible and allows dietary calorie levels adequate to maintain a desirable body weight.
- Fewer than 300 mg cholesterol daily.
- Carbohydrates 50–60% of total calories.
- Protein 10 to maximum 15% of calories.
- Avoid organ meats, such as liver, kidney, sweetbreads, heart, or brain; heavily marbled steaks, salt pork, or duck; whole milk or whole-milk products, cream, lard, and nonvegetable margarine; coconut oil or products containing coconut oil (such as non-dairy creamers), palm oil, peanut oil, grapeseed oil, or peanut butter ([Table 9.2.](#)).
- Use luncheon meat, sausage, bacon, hamburger, spare ribs, butter, cheese made from whole milk or cream, pie, chocolate pudding, ice cream, or whole milk pudding sparingly. One egg yolk contains about 225–250 mg cholesterol, depending on the size of the egg. Thus, four to five eggs per week should suffice for adequate nutrition, as well as enjoyment. Lobster should be used without abundant butter. Nuts to avoid include peanuts and Brazil nuts.
- Recommended foods include fruits, whole grain products, beans, peas, vegetables, cereals; low-fat dairy products, including skim or low-fat milk, skim or low-fat butter (skim milk is a good source of calcium); fish, such as salmon, mackerel, tuna, or cod, which contain an abundance of ω 3 fatty acids; moderate amounts of chicken without skin and lean red meat (up to 6 oz) two or three times weekly. Shrimp contain a fair amount of cholesterol but no saturated fatty acids, provided that they are not fried in a batter. Vegetable oils, such as safflower, sunflower, soybean, corn, and olive oil, are recommended, but coconut, palm, and peanut oils are not. Oat bran has little specific cholesterol-lowering effect and is not superior to low-fiber dietary grain supplements; a high-fiber diet offers some cardioprotection and is advisable. Walnuts contain a high amount of polyunsaturated fatty acid but are low in saturated fat; walnuts contain linolenic acid which is cardioprotective. *The best nuts are walnuts and hazelnuts.*

Table 9.2A.
Saturated Fat and Cholesterol Content of Foods

<i>Item^a</i>	<i>Cholesterol (mg)</i>	<i>Total fat (g)</i>	<i>Saturated fat recommended (g)</i>	<i>Not recommended</i>	<i>Recom.^b</i>	<i>Use sparingly</i>
Meats						
Beef liver	395	10	3	X		
Kidney	725	11	4	X		
Sweetbread	420	21	—	X		
Lean beef	82	5	2		••	
Roast beef						
e.g., rib	85	33	14	X		•
rump	85	21	9	X		
stewing	82	27	11	X		•
lean cut	82	9	4		••	
ground	85	18	8	X		•
Steak						
sirloin	85	25	10	X		•
lean cut	85	5	2		••	•
Veal	90	12	5		••	•
Lamb, lean	90	7	4			•
chop and fat	110	33	18	X		
Ham						
fat roasted	80	28	7	X		
boiled						
sliced	80	18	5			•
Pork chop	80	30	12	X		
Chicken						
breast and skin	72	6	1		••	
drumstick (fried)	80	9	2		••	
Turkey	80	5	2		••	
Fish						
sole	45	1	Trace		••	
trout	50	13	3		••	

(continued)

Table 9.2A. (Continued)

<i>Item^a</i>	<i>Cholesterol (mg)</i>	<i>Total fat (g)</i>	<i>Saturated fat recommended^a (g)</i>	<i>Not recommended</i>	<i>Recom.^b</i>	<i>Use sparingly</i>
tuna	60	7	2		••	
salmon						
Fresh	42	7	1		••	
Canned	32	11	2		••	
mackerel	85	10	2		••	
halibut	54	6	Trace		••	
crabmeat	91	1	Trace			•
shrimp	130	1	Trace			•
lobster (450 g)	80	1	Trace			•
Dairy products						
30 mL butter	460	25	16	X		
egg (50 g)	275	6	2		••	
substitute	0	0	0		••	
buttermilk*	10	2	1			
yogurt (250 mL)	16	3	2		••	

Table 9.2B.
Saturated Fat and Cholesterol Content of Foods

<i>Item^a</i>	<i>Cholesterol (mg)</i>	<i>Total fat (g)</i>	<i>Saturated fat recommended (g)</i>	<i>Polyunsaturated fat</i>	<i>Not recommended</i>	<i>Recom.^b</i>	<i>Use sparingly</i>
Whole milk 250 mL	35	9	5				•
2% Skim milk	20	5	3			••	
Ice cream	Trace	Trace	Trace			••	
Vanilla reg (125 mL)	32	8	5				•
Rich(125mL)	46	12	8		X		
butter	30	11	1	Trace			•
lard	12	13	5	1	X		
Cheese (1 oz)							
brick	27	8	6	Trace			•
blue	24			Trace		••	
cheddar	30	10	6	Trace			•
cottage ^b	2	0.6	0.5	Trace		••	
Skim milk, processed, 1 oz (30 g)	0	Trace	Trace	Trace		••	
Oils							
corn oil	0	14	1	7		••	
rapeseed	0	14	1	3	X		
safflower	0	13	1	10		••	
sunflower	0	14	1	9		••	
soyabean	0	14	2	7		••	
coconut	0	14	12	0.2	X		
palm	0		7	0.2	X		
olive	0	14	2	1		••	
peanut		14	2	4	X		
Nuts							
almonds	0	16	1	3		••	
brazil nuts	0	22	5	8	X		
cashews	0	13	3	2	X		
coconut	0	13	11	Trace	X		
peanuts	0	17	3	4	X		
peanut butter	0	7.5	1.5	2	X		
pecans	0	21	2	5			•
walnuts	0	19	2	11		••	

^aQuantity is 3 oz (90 g) unless specified; 15 mL = 1 tablespoonful.

^bFoods recommended contain less than 5 g saturated fat per 3 oz.

From Khan M Gabriel: In Heart trouble encyclopedia. Toronto, Stoddart, 1996.

A prospective, randomized, single-blind, secondary prevention trial using a Mediterranean linolenic acid-rich diet has proven that linolenic acid is useful in preventing cardiac deaths and nonfatal infarctions. In a study of 605 patients randomized within 6 months of MI, a total of 302 patients were given a diet containing an increased amount of α -linolenic and oleic acids. This diet was modeled on the Cretan Mediterranean diet that includes a high intake of α -linolenic acid, which has a beneficial effect on platelet reactivity. Oleic acid is derived mainly from olive oil. A canola oil-based margarine with a high content of α -linolenic acid was used daily, and the study was based on the hypothesis that the Cretans and Japanese have the lowest CAD mortality in the world and have a high intake of α -linolenic acid. The Japanese have a high consumption of canola and soybean oils; the Cretans derive their consumption of linolenic acid mainly from walnuts and purslane. At a mean follow-up of 27 months, there were 16 cardiac deaths and 17 nonfatal infarctions in the control versus 3 deaths and 5 nonfatal infarctions in the experimental groups ($p = 0.001$). [Figure 9.2.](#) shows the survival curves for combined cardiac death and nonfatal acute MI. The serum lipids were similar in both groups throughout the study period. In this study, no sudden death occurred in the experimental group versus eight in the control group. It is possible that α -linolenic acid may protect from lethal arrhythmias. The author is not surprised by the results of this study because in 1966, I mounted a small study in postinfarct patients using capsules containing linolenic acid provided by Parke Davis. The assumption at that time was that linolenic acid had antiplatelet activity, which may prevent coronary thrombosis.

Trans fatty acids are at high levels in several frequently used foods that include: hard margarines, cookies, commercially baked products, and fast foods. Most important, trans fatty acids are now reduced in some products but are being replaced by saturated fatty acids that maintain the increased coronary risk caused by trans fatty acids.

Step 2: Therapeutic Diet

- An average of 25% of total calories (or less) from total fat.
- Less than 7% of total calories from saturated fat.
- Cholesterol 200–250 mg daily.

The step 2 diet is recommended for patients with cholesterol elevated to 275–310 mg/dL (7.1–8 mmol/L) after a 6-month to 1-year trial of the step 1 diet. The step 2 diet is, therefore, mainly required for patients with severe familial hyperlipidemia in conjunction with drug therapy.

DRUG THERAPY

Except in patients with atheromatous disease and patients at high risk for CHD, drugs are used after an adequate trial of dietary therapy, a concerted effort by the patient and physician, and/or the assistance of a dietician or lipid clinic fail to adequately lower total or LDL cholesterol to the desired level.

When drugs are prescribed, dietary restrictions must be continued. Dietary therapy can achieve only about a 10% lowering of total cholesterol but can reduce triglyceride levels in most individuals from 25 to 50%. Guidelines for drug therapy are directed by high-risk elevations of LDL cholesterol and the presence or absence of CHD or other atheromatous vascular disease ([Fig. 9.1.](#)).

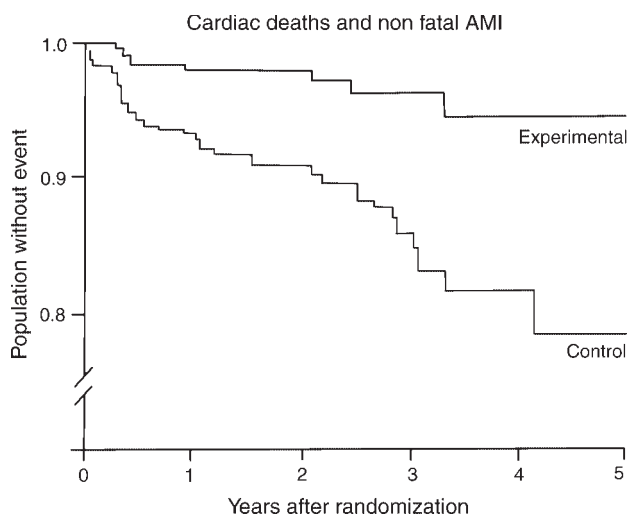


Fig. 9.2. Survival curves combined cardiac death and nonfatal acute myocardial infarction. Log rank test, using only the first event. AMI, acute myocardial infarction. From Lancet 1994;343:1454, with permission from Elsevier.

STATINS (3-Hydroxy-Methylglutaryl Coenzyme A Reductase Inhibitors)

The statins constitute a major advance in the management of patients with dyslipidemia. Their proven value in reducing mortality from CAD and their ability to cause modest regression and significantly prevent progression of atheroma give a ray of hope that the epidemic of atheromatous disease can be halted. There were approximately 12 million deaths caused by cardiovascular disease in 1998; the death toll is expected to be more than 25 million in 2025.

Available agents include atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and the recent addition of rosuvastatin, a drug even more powerful than atorvastatin. A 10-mg dose is as effective as 40-mg dose of atorvastatin. The statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in the biosynthesis of cholesterol, conversion of HMG-CoA to mevalonate.

A modest reduction in intracellular cholesterol occurs, resulting in an increase in the number of hepatic LDL receptors that bring about clearance of circulating LDL cholesterol. In a well-designed, randomized study of 2845 individuals, lovastatin caused a 24–40% decrease in LDL cholesterol, a 17–29% decrease in serum cholesterol, a 10–19% decrease in triglyceride level, and an increase of 6.6–9.5% in HDL level at dosages of 20 and 80 mg daily over a 48-week period. The LDL cholesterol goal of 160 mg/dL (4 mmol/L) was achieved in 80 and 96% of those treated with 20 and 80 mg, respectively. These agents cause no significant changes in triglyceride levels; a modest decrease (if any) may be observed. In the 48-week Expanded Clinical Evaluation of Lovastatin Study of 8245 patients with total cholesterol levels of 240–300 mg/dL (6.2–7.8 mmol/L) and LDL cholesterol greater than 160 mg/dL (4.1 mmol/L), the average changes from baseline for lovastatin (20, 40, and 80 mg daily) were –24%, –32%, and –40% for LDL cholesterol and 6.6, 7.9, and 9.5% for HDL cholesterol. The 20-mg twice-daily dose produced a more favorable trend than 40 mg each evening for both LDL and HDL cholesterol. An increase

in the frequency of muscle symptoms with creatine kinase elevations was seen only in the 80-mg-daily group.

At the end of 2 years, the LDL cholesterol-lowering effect was maintained in the 1000 patients followed. Myopathy occurred in one patient and was not related to combination with other agents known to cause myopathy. No effect on the lens was observed.

The Multicenter Antiatheroma Study demonstrated that 20 mg simvastatin administered daily for 4 years reduced hyperlipidemia and slowed progression of focal and diffuse coronary atherosclerosis.

The Pravastatin Limitations of Atherosclerosis in the Coronary Arteries trial showed that pravastatin therapy reduced the progression of CHD by 40% and caused a 54% reduction in nonfatal and fatal infarctions. A total of 408 patients with a less-than 50% angiographic coronary stenosis was randomized to pravastatin or placebo. At 3-year follow-up, repeat angiograms showed 15 new lesions in the pravastatin patients versus 33 new lesions in the placebo group.

The Monitored Atherosclerosis Regression Study and the Canadian Coronary Atherosclerosis Intervention Trial indicate that the statins decrease angiographic coronary artery atheromatous lesions; they have been shown to slow the progression of coronary disease and to inhibit the development of new lesions. The Scandinavian Simvastatin Survival Study (4S) reported a remarkable reduction in total mortality of 30%, and revascularization rates fell by 37% (*see* discussion under Simvastatin).

In the Scotland Prevention study, pravastatin administered to men 45–64 years of age with average cholesterol 272 mg/dL (7 mmol/L), significantly reduced the incidence of heart attack and death. The Cholesterol and Recurrent Events (CARE) trial indicates that in survivors of MI, the benefit of cholesterol-lowering therapy extends to levels of less than 240 mg/dL (6.2 mmol/L).

WHICH STATIN TO CHOOSE

- Hydrophilic agents excreted by the kidney include the pravastatin and rosuvastatin; thus, interactions with hepatic metabolized agents do not occur.
- Lipophilic agents include atorvastatin, lovastatin, fluvastatin, and simvastatin; these are hepatic metabolized. Interactions may occur with cimetidine and other agents that use the cytochrome P450 pathway. It appears that atorvastatin increases fibrinogen levels.
- Rosuvastatin must not be used in conjunction with cyclosporin; cyclosporin levels are increased.

Contraindications include Porphyria; concomitant use of cyclosporin nicotinic acid or fibrates, cyclosporin, other cytotoxic drugs; erythromycin and similar antibiotics; also contraindicated in women of childbearing age and during lactation. Hepatic metabolized agents must be avoided in individuals with hepatic dysfunction. Caution in elderly over age 75 and in patients with hypothyroidism.

Atorvastatin (Lipitor). This statin is more effective than pravastatin, fluvastatin, and simvastatin.

Dosage: 10–40 mg daily. Maximum dose is 60 mg; (80 mg may be used with close monitoring) the author advises a maximum of 40 mg and if the LDL-C goal is not achieved, the addition of ezetimibe is preferred.

Atorvastatin (10 and 40 mg) has been shown to cause a 38 and 46% decrease in LDL cholesterol. The drug causes a 12–20 % decrease in triglyceride levels and may be used in mixed dyslipidemia. In the atorvastatin versus revascularization treatments (AVERT) study, treatment with 80 mg of this agent caused a 36% reduction in nonfatal MI,

revascularization, and increasing angina as compared to patients receiving coronary angioplasty plus usual care. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study, 16 weeks of immediate atorvastatin therapy was associated with a significant reduction in the composite endpoint of death, non-fatal MI, or urgent readmission for angina compared with placebo in 3086 patients with unstable angina or non-Q-wave myocardial infarction (14.8% vs 17.4%, $p = 0.048$). Although there was significantly lower rates of readmission, reductions in mortality were not significant (4.4% vs 4.2%).

The REVERSAL investigators randomized 2163 patients to moderate lipid-lowering (40 mg of pravastatin) or intensive treatment (80 mg of atorvastatin) for 18 months. Intravascular ultrasound (IVUS) was performed during baseline coronary arteriography and repeated at study completion.

LDL-C (mean: 150.2 mg/dL) was reduced to 110 mg/dL in the pravastatin arm versus 79 mg/dL in the atorvastatin group ($p < 0.0001$). The primary end-point (percent change in atheroma volume) showed progression in the pravastatin cohort; +2.7%, $p = 0.001$, and showed no progression in the atorvastatin arm (−0.4%, $p = 0.98$). The progression rate was significantly lower in the atorvastatin arm ($p = 0.02$). In addition, pravastatin caused a 5.2% decrease in C-reactive protein (CRP) versus 36.4% for atorvastatin ($p < 0.0001$). In this subset of patients, LDL-C levels should be maintained less than 80 mg/dL (2 mmol/L).

Simvastatin (Zocor). The hallmark 4S study indicates that long-term treatment with simvastatin is safe and improves survival in patients with CAD. A total of 4444 patients with angina or previous infarction and total cholesterol of 5.5–8 mmol/L were randomized to double-blind treatment with simvastatin or placebo. All patients followed a lipid-lowering diet. Over the 5.4 years median follow-up, there were 189 cardiac deaths in the placebo group and 111 in the simvastatin arm (relative risk 0.58). The number of noncardiovascular deaths was similar in both groups. The treatment group had a 37% reduction in the risk of undergoing revascularization ($p < 0.0001$). Long-term simvastatin therapy was associated with a 25% decrease in cholesterol, 35% reduction in LDL cholesterol, and an 8% increase in HDL cholesterol. In the study, 79% of patients had a history of previous MI.

Dosage of 5–10 mg is given with the evening meal; increase if needed in 8–12 weeks to 20 mg daily to a maximum of 40 mg once daily. The author does not recommend the top dose of 80 mg; it is safer to combine 40 mg simvastatin with 10 mg ezetimibe (Vytarin). Twice-daily dosing provides no added benefit. In the 4S study, simvastatin was administered just before the evening meal and produced salutary effects.

The Medical Research Council (MRC)/British Heart Foundation (BHF) Heart Protection study showed that in vascular high-risk patients, 40 mg of simvastatin reduces the risk of MI, stroke, and revascularization by approximately 33%. Importantly, cholesterol lowering proved to be beneficial in reducing major outcomes, irrespective of cholesterol levels, sex, or age. A significant reduction in major events was observed among the 4000 patients with cholesterol levels less than 200 mg/dL (5 mmol/L).

Pravastatin (Pravachol; Lipostat, UK). This is supplied as 10-20- and 40-mg tablets. A dosage of 10 mg is given with the evening meal; increase over 2–4 months to a maximum of 40 mg once daily or 20 mg twice daily. Contraindications are the same as those outlined for lovastatin. Adverse effects are similar, but hyperuricemia and thrombocytopenia have been observed, albeit rarely.

Pravastatin is a hydrophilic compound and primarily has a hepatic site of action with little influence on cholesterol synthesis in other tissues. The fact that it does not cause cataracts in dogs at 100 mg/kg is probably related to its hydrophilic property.

Fluvastatin (Lescol). This is supplied in 20- and 40-mg capsules. A dosage of 20 mg is given in the evening, to a maximum of 40 mg daily. Fluvastatin is a fully synthetic HMG-CoA reductase inhibitor. Fluvastatin is rapidly and completely absorbed from the gastrointestinal (GI) tract.

Rosuvastatin (Crestor). This is supplied as 5-, 10-, 20-, and 40-mg tablets. A dosage of 10 to 20 mg daily is recommended. If goal is not achieved at 30 mg, add 10 mg of ezetimibe. The 30 mg with ezetimibe may be required in genetic familial hyperlipidemia. *The author does not recommend the 40-mg dose.*

Rosuvastatin is a potent agent that causes a 40–65% reduction in LDL cholesterol. Importantly, the drug causes a modest but significant increase in HDL cholesterol beyond that of atorvastatin and simvastatin. The drug is hydrophilic and avoids the cytochrome 450 pathway, resulting in no interactions with drugs that use the pathway. An increase in HDL cholesterol levels of 12% has been noted after 18 months of therapy. In addition, there is no interaction with clopidogrel, as opposed to an interaction noted with atorvastatin.

Clinical Studies. Measures Effective Reductions in Cholesterol using Rosuvastatin Therapy I: this multinational trial in 3161 adults randomized to 10 mg of rosuvastatin, 10 mg of atorvastatin, 20 mg of simvastatin, and 40 mg of pravastatin, indicated that switching from atorvastatin to equivalent doses of rosuvastatin brought more patients within the international LDL-C treatment guidelines. A 10-mg dose of rosuvastatin versus 10 mg of atorvastatin resulted in 88% versus 76 % of patients achieving a European LDL-C goal, and 80% versus 63% met the goal set in the US ($p < 0.001$). Ten milligrams of rosuvastatin caused a consistent, repeatable 9.2% increase in HDL-C versus 20 mg of atorvastatin causing a 5.7% increase ($p < 0.001$).

A similar RCT of 2431 patients (the Statin Therapies for Elevated Lipid Levels compared A cross-doses to Rosuvastatin Study) confirms the above beneficial effects; most important, HDL cholesterol levels increased 9.5% and 9.6% with 20- and 40-mg of rosuvastatin, versus 4.8% and 4.4% with 20- and 40-mg doses of atorvastatin.

Adverse Effects of Statins. Headaches occur in about 10%, stomach pain, flatulence, diarrhea, constipation, nausea, hepatic dysfunction with increased hepatic transaminases occur in 2%, chest pain owing to stomach disturbance or muscular aches may occur. A flu-like illness with myalgia, elevation of creatine kinase, myopathy occurred in 0.5%, and rhabdomyolysis has been observed in patients receiving concomitant niacin, gemfibrozil, cyclosporin, and other immunosuppressive drugs. MedWatch Reporting System listed 3339 cases of statin-associated rhabdomyolysis over a 12-year period. Myopathy and deaths occurred most commonly with cerivastatin (Baycol), which was withdrawn in 2000.

The risk of rhabdomyolysis is increased in the elderly over age 75 and in patients with hepatic and renal dysfunction, hypothyroidism, and diabetes.

Rabdomyolysis occurs rarely and is usually the result of the following:

- too high a dose of statin: atorvastatin 60 mg or greater, simvastatin > 60 mg or greater, rosuvastatin > 20 mg.
- combination with interacting drug, particularly: cyclosporin, fibrates, niacin, antifungal agents, antibiotics such as erythromycin, azithromycin and clarithromycin.

- with rosuvastatin and pravastatin if the creatinine clearance is <60 mL/min, serum creatinine >1.5 mg/dL (133 μ mol/L).
- Patients with hypothyroidism.

The mechanism for statin-induced myopathy is unclear; statins appear to reduce the production of small regulatory proteins that are important for myocyte maintenance. Minor muscle pain and weakness was reported in 1–5% of patients.

Lens opacity observed in animals given high doses has not been a clinical problem, although minor lens opacification occurs. Rash is uncommon. Baseline transaminase and creatine kinase are advisable. If more than a threefold increase in transaminases occurs, the drug should be discontinued. Pancreatitis occurs rarely. Caution: avoid in renal transplant patients on cyclosporin or immunosuppressives. In patients receiving oral anticoagulants, reduction in the dose of warfarin is usually required with atorvastatin. Severe myositis may cause hyperkalemia in patients with renal insufficiency, particularly including long-standing diabetics who are also on angiotensin-converting enzyme (ACE) inhibitors. *Do not combine with fibrates or niacin.* Although it is rare for the combination to cause rhabdomyolysis and kidney damage, *the combination of statins with a fibrate or nicotonic acid is not recommended by the author.*

Bile Acid-Binding Resins

Bile acid-binding resins have been available for the past 35 years. Their disagreeable taste, however, causes poor patient compliance. The use of bile acid-binding resins declined with the advent of HMG-CoA reductase inhibitors and will become obsolete with the advent of ezetimibe.

Bile acid-binding resins are not absorbed from the GI tract and act by binding bile salts in the gut; they are, therefore, bile-acid sequestrants. This action causes cholesterol catabolism to bile acids and a decrease in serum LDL cholesterol. A decreased concentration of intrahepatic cholesterol stimulates the activity of LDL receptors that increase hepatic uptake of circulating LDL cholesterol.

CHOLESTYRAMINE (QUESTRAN LIGHT)

A dosage of 4 g (one packet) twice daily with meals for 1–2 weeks and then 8 g two or three times daily is used. Medications, especially digoxin, oral anticoagulants, diuretics, β -blockers, thyroid hormone, and HMG-CoA reductase inhibitors must be administered 1 hour before or 4 hours after the resin to prevent interference with absorption. Adverse effects include constipation, abdominal cramps, and, rarely, mild malabsorption of fat-soluble vitamins; hypoprothrombinemia is rare, and a mild increase in triglycerides may occur. Thus, the drug should not be used in patients with triglyceride levels < 500 mg/dL (5 mmol/L). Contraindications are complete biliary obstruction.

COLESTIPOL (COLESTID)

A dosage of 5 g one to two times daily in liquid is used. Increase if necessary at intervals of about 2 months to 25 g daily. The adverse effects and contraindications are similar to that of cholestyramine.

Fibrates

These agents are activators of the enzyme plasma lipoprotein lipase. Fibrates cause a modest decrease in total or LDL cholesterol. A 10–20% reduction in serum cholesterol, a 30–50% reduction in triglycerides, and a 10–15% increase in HDL cholesterol have been observed in most studies.

In patients with high triglyceride levels (>400 mg/dL) resistant to concerted weight reduction and control of diabetes, fibrate therapy is required. In the majority of this subset of patients, LDL-C levels are increased to greater than 130 mg/dL, and some endocrinologists and lipid clinics advocate addition of statins; now, the use of ezetimibe added to fibrate is preferable to prevent the rare but disastrous problem of myopathy.

GEMFIBROZIL

This is supplied as 300-mg capsules. A dosage of 300–600 mg 30 minutes before morning and evening meals is given. Gemfibrozil is a chemical homolog of clofibrate. The drug decreases hepatic production of VLDL triglyceride. Gemfibrozil causes a 30–40% reduction in triglycerides, but only 2–10% reduction in serum cholesterol and a 5–12% increase in HDL cholesterol. Gemfibrozil has a small role in the management of severe hypercholesterolemia.

Indications include the following:

- Severe hypertriglyceridemia, greater than 1000 mg/dL (10 mmol/L), that is unresponsive to dietary measures, exercise, and cessation of alcohol. In these patients, treatment is necessary to prevent pancreatitis.
- Type III hyperlipoproteinemia that is associated with marked elevation of triglycerides.

The use of gemfibrozil in patients with moderate hypercholesterolemia has gained support because of the results of the Helsinki Heart Study, which enrolled 4081 men (40–50 years of age) who were free of coronary symptoms. A 10% increase in HDL occurred from a baseline of 47 mg/dL and an 11% decrease from baseline of total cholesterol (290 mg/dL). At the end of 5 years, there was no reduction in cardiac or total mortality; there were 61 nonfatal myocardial infarcts and 7 fatal infarcts in the placebo group, with 40 nonfatal and 3 fatal infarcts in the gemfibrozil-treated group (a 1.4% absolute difference). Thus, gemfibrozil therapy over 5 years is expected to improve the individual's chance of not having a cardiac event from approximately 96% to a little more than 97%, which is a 34% decrease in cardiac event rates, but without causing significant improvement in survival.

Adverse effects include bloating, cramps, diarrhea, muscle aching, eczema, increase in liver function tests, and, rarely, mild increases in blood sugar and impotence. The lithogenic activity appears to be less than that of clofibrate, but gallstone formation is increased, and costly monitoring is necessary. In the Helsinki Study, there were 10 violent or accidental deaths in patients treated with gemfibrozil versus four in controls. Also, 81 GI operations were required in the treated patients, versus 53 in the placebo group ($p < 0.02$). The association with intracerebral bleed, as well as hepatobiliary cancers, is not established but is a concern.

The physician must persist with dietary advice for a prolonged period and should justify the use of fibric-acid derivatives, taking into account the adverse effects, the necessity for careful monitoring of hepatobiliary complications, and the cost-effectiveness in terms of prevention of some nonfatal infarcts without the prolongation of life.

Caution: reduce oral anticoagulant dose. Do not combine with HMG-CoA reductase inhibitors because of the risk of severe myositis and rhabdomyolysis. The drug is renally excreted. Reduce dose to 300 mg daily with renal failure.

Contraindications include hepatic impairment, alcoholism, gallstones, and pregnancy.

FENOFIBRATE

The recommended dosage is 160–200 mg daily with the main meal. The drug decreases LDL-C levels 10–15% increases in HDL-C approximately 20%, and triglycerides decrease

more than 30%. Fenofibrate has been shown to decrease small dense LDL, Lipoprotein (Lp) (a) and fibrinogen levels. High levels of Lp (a) small dense LDL and fibrinogen are risk factors for CAD. Lipidil Micro should find a role in patients with elevated total cholesterol, LDL cholesterol, triglycerides, Lp (a) and fibrinogen, particularly in those with HDL levels less than 35 mg/dL (0.9 mmol/L). Fibrates have been shown to decrease circulating levels of small dense LDL and reduce platelet aggregability and reactivity in response to epinephrine.

Gastrointestinal disturbances occur in fewer than 7% of patients. If cholelithiasis is suspected during treatment therapy, ultrasound of the gallbladder is indicated. If gallstones are present, fenofibrate should be discontinued. Thus, it is wise to perform this procedure before commencing therapy. Abnormal liver function tests with an elevation of transaminases and an increase in alkaline phosphatase have been observed but normalized upon discontinuation of the drug. Test liver function monthly and then annually or if there are symptoms that suggest hepatic dysfunction. Rash, pruritus, urticaria or erythema, weight loss, impotence, alopecia, pancreatitis, hepatitis, and creatine kinase elevations may occur but subside on discontinuation of the drug.

Contraindications include the following:

- Severe renal or hepatic impairment. Fibrates are excreted by the kidney and should be used with caution in patients with renal dysfunction.
- Gallbladder disease.
- Pregnancy, women of childbearing potential, and during lactation.
- Primary biliary cirrhosis.

Fibrates may potentiate the effects of oral anticoagulants. Myositis has been reported with the combination of other fibrates and statins, thus careful monitoring is essential.

BEZAFIBRATE

This is supplied as 200- to 400-mg tablets. A dosage of 200 mg twice daily with or after food is used. The drug can be taken once daily. Contraindications include severe renal or hepatic impairment, hypoalbuminemia, primary biliary cirrhosis, gallbladder disease, nephrotic syndrome, and pregnancy.

Adverse effects include nausea, abdominal pain, myositis, urticaria, headache, and impotence. Bezafibrate causes a fall in glucose levels; also, an increase in serum creatinine occurs and monitoring is necessary. Long-term trials are necessary to document efficacy in reducing mortality and to assess adverse effects. The drug may cause alopecia.

Interactions.

- Oral anticoagulants: the dosage of anticoagulants should be reduced with careful management of prothrombin time or international normalized ratio.
- HMG-CoA reductase inhibitors: severe myositis and rhabdomyolysis have been observed with the combination of fibrates and lovastatin, with marked elevation of serum potassium, which may be life-threatening.

NICOTINIC ACID

This is supplied in 50-, 100-, and 500-mg doses. Assess transaminases and glucose levels. A dosage of 50 mg with the evening meal for 1 week is given, with 325-mg coated aspirin taken 30 minutes before to prevent flushing. Increase to 100 mg twice daily and, over months, slowly increase from 100 to 500 mg three times daily, always after meals.

Adverse effects include flushing, pruritus, nausea, abdominal pain, diarrhea, hepatic dysfunction, jaundice, exacerbation of diabetes, gout, palpitations, arrhythmias, hypotension, and, rarely pigmentation and optic neuritis with blurred vision. Acute hepatitis is a

dangerous complication of niacin therapy, presenting with a flu-like illness with fatigue, malaise, anorexia, pruritis, and jaundice. The sustained-release preparations cause more frequent hepatic dysfunction than the short-acting tablet. A case has been reported of a patient who developed fulminant liver failure after switching from 1-year therapy with nicotinic acid to a sustained-release preparation. Niacin has caused myopathy in the absence of concomitant statin or fibrate therapy.

Caution: do not use in combination with HMG-CoA reductase inhibitors because severe myositis may occur. Avoid the drug in patients with acute MI, heart failure (HF), gallbladder disease, jaundice, liver disease, peptic ulcer, and diabetes. Treatment with aspirin decreases flushing. Aspirin can be discontinued when tolerance occurs and flushing abates, but the aspirin dose should be increased along with increases in nicotinic acid.

The drug has a small role in the management of familial combined hyperlipoproteinemia, where triglycerides remain greater than 900 mg/dL. The combination of nicotinic and ezetimibe has a role. Nicotinic acid is claimed to be one of the few lipid-lowering drugs that have been shown to prolong life. However, only an 11% reduction in all-cause mortality and a 12% decrease in CHD death were observed in the 15-year Coronary Drug Project. These results hardly justify the use of nicotinic acid, except in rare instances.

Management of Elevated Serum Triglycerides

A triglyceride level up to 200 mg/dL (2.0 mmol/L) is considered to be within normal limits. 200–400 mg/dL (2–4 mmol/L) is borderline high. 400–600 mg/dL (4–10 mmol/L) is high and more than 900 carries a risk for pancreatitis.

Treatment of hypertriglyceridemia becomes urgent if triglyceride levels are above 900 mg/dL (10 mmol/L) because of the risk of pancreatitis and avascular necrosis of the femoral head. Fortunately, control is nearly always achieved with a low-carbohydrate diet. Weight loss almost always reduces triglyceride levels. Alcohol abuse is one of the most common causes of high triglyceride levels, and cessation of alcohol consumption is necessary for control. Failure to reduce levels to less than 500 mg/dL (mmol/L) is an indication for a fibrate with weight reduction diet, increase in exercise, and cessation of alcohol.

The evidence linking triglycerides directly with an increased risk of CHD remains controversial.

To re-emphasize, elevated triglyceride levels virtually always decrease when significant weight loss is achieved, alcohol consumption is curtailed, and diabetes is brought under strict control; fibrates are overused in this setting. It is most important to do no harm.

If the LDL-C is also elevated, the author advises the addition of ezetimibe rather than the addition of a statin; this strategy should obviate the rare but life-threatening occurrence of rhabdomyolysis.

NEW DRUG CLASS AND NEW THERAPIES

Ezetimibe

Trade name: Zetia, Ezetrol (C)

Supplied as 10-mg tablets, with a recommended dosage of 10 mg once daily, with or without food.

Ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits cholesterol absorption. The drug is a potent and selective inhibitor of cholesterol

absorption and decreases delivery of cholesterol to the liver, thus promoting the synthesis of LDL receptors, with a subsequent 20% reduction in LDL-C. Importantly, this location of action appears to be largely unaffected by the pathophysiology of genetic familial hyperlipidemia, for which treatment is still most unsatisfactory.

Ezetimibe's half-life is approximately 22 hours and is not altered by renal or hepatic function. The drug does not use the cytochrome P450 or *N*-acetyltransferase and there is no significant interaction.

Ballantyne et al., for the Ezetimibe Study Group, randomized 628 patients with baseline LDL-C of 145–250 mg/dL and triglycerides of 350 mg/dL or lower to 12 weeks: ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo. Ezetimibe combination caused a significant additional 12% LDL-C reduction, 3% HDL-C increase, and 8% triglyceride reduction versus atorvastatin alone. The ezetimibe/atorvastatin combination caused a 50–60% reduction of LDL-C of 30–40% reduction in triglycerides; HDL-C increased 5–9%.

In patients with genetic familial hypercholesterolemia resistant to 80 mg of atorvastatin with LDL-C greater than 220 mg/dL, the addition of 10 mg of ezetimibe has led to a reduction to less than 180 mg/dL.

Sitosterolemia is a genetic defect that has been recently uncovered. This very rare, inherited disorder causes increased absorption and decreased excretion of plant sterols, particularly sitosterol, the blood levels of which increase and appear to cause premature growth of atheroma. In RCT, 10 mg of ezetimibe for 8 weeks caused a 21% decrease in sitosterol levels versus a 4% increase in placebo patients.

Ezetimibe is a valuable addition to our therapeutic armamentarium as it is effective and allows for the use of moderate doses of statins in resistant cases of hypercholesterolemia; this will avoid adverse effects of high-dose statin therapy (> 60 mg of atorvastatin, >40 mg of rosuvastatin). The administration of ezetimibe will render bile acid resins obsolete.

Torcetrapib

Torcetrapib is a potent inhibitor of cholesteryl ester transfer protein (CETP). Inhibition of CETP raises HDL cholesterol levels. Brousseau et al. have shown in a recent study of 19 patients with HDL cholesterol less than 40 mg/dL (1 mmol/L), that 120 mg of torcetrapib daily combined with atorvastatin increased HDL cholesterol by 61% ($p < 0.001$) and 46% ($p = 0.001$) in the atorvastatin and non-atorvastatin groups, respectively. Administration of 120 mg twice daily increased HDL cholesterol 106% ($p < 0.001$). Torcetrapib reduced LDL cholesterol by 17% in the atorvastatin group ($p = 0.02$). Our cardioprotective armamentarium will be strengthened by adequately tested CETP inhibitors.

Apo A-I Milano

A mutated gene *Apo A-I Milano* passed down from an 18th-century ancestor of a patient who was found to have excessively high serum cholesterol but with normal coronary arteries, has led to development of a drug, a gene that is cardioprotective. A variant of apolipoprotein, ApoA-I Milano has been identified in inhabitants of rural Italy who exhibit very low levels of HDL but are atheroma free. Nissen et al. have shown that the intravenous (IV) administration of a synthetic version of the agent into a small group of patients caused significant regression of atheroma in coronary arteries. Patients with coronary atheroma were given five weekly IV infusions of a recombinant Apo A-I Milano phospholipid complexes and were compared with controls. Intravascular ultrasonography

indicated a 4.2% decrease in volume of atheroma; the degree of regression in this short period was unexpected and long-term trials are required.

It appears that individuals with another cardioprotective isoform, ApoA-I Paris, also show an HDL pattern that consists primarily of HDL-3 particles. An epidemiological study observed that HDL-3, but not HDL-2, was associated with a reduced risk of progression of CHD. The prevention and/or release oxidative damage to LDL by HDL-3 offers a potentially important mechanism of cardioprotection; HDL-2 particles, however, show little cardioprotective activity.

BIBLIOGRAPHY

- Area M, Vega GL, Grundy SM. Hypercholesterolemia in postmenopausal women. Metabolic defects and response to low-dose lovastatin. *JAMA* 1994;271:453.
- Aro A, Kindinaal AFM, Salminen I, et al. Adipose tissue isomeric trans fatty acids and risk of myocardial infarction in nine countries: the EURAMIC study. *Lancet* 1995;345:273.
- Ascherio A, Rimm ENB, Stampfer MJ, et al. Dietary intake of marine ω -3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 1995;332:977.
- AVERT: Pitt B, Waters D, Brown WV, et al. for the atorvastatin versus revascularization treatment investigators: aggressive lipid lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med* 1999;341:70–76.
- Birjmohun RS, Hutten BA, Kastelein JP, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds. A meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:244–245.
- Boekholdt SM, Sacks FM, Jukema JW, et al. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: individual patient meta-analysis of 13,677 subjects. *Circulation* 2005;111:278–287.
- Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia. *Arch Intern Med* 1991;151:43.
- Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results: two-year efficacy and safety follow-up. *Am J Cardiol* 1994;74:667.
- Brewer Jr HB. Increasing HDL cholesterol levels. *N Engl J Med* 2004;350:1491–1494.
- Brousseau ME, Schaefer EJ, Wolfe ML, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *N Engl J Med* 2004;350:1505–1515.
- Brown WV, Bays HE, Hassman DR, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J* 2002;144:1036–1043.
- Brown MS, Goldstein JL. A receptor mediated pathway for cholesterol homeostasis. *Science* 1979;323:361.
- Byington RP, Worthy J, Craven T. Propranolol-induced lipid changes and their prognostic significance after a myocardial infarction: the beta-blocker heart attack trial experience. *Am J Cardiol* 1990;65:1287.
- Calhoun DA, Oparil S. Hypertensive crisis since FDR—a partial victory. *N Engl J Med* 1995;332:1029.
- Cannon CP, Braunwald E, McCabe CH, et al. for the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [PROVE IT—TIMI 22 trial]. *N Engl J Med* 2004;350:1495–504.
- CCAIT Study Group-The Canadian Coronary Atherosclerosis Intervention Trial. Walters D, Higginson L, Gladstone, P, et al., For the CCAIT Study Group. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. *Circulation* 1994;89:959.
- Criqui MH, Heiss G, Cohn R, et al. Plasma triglyceride level and mortality from coronary heart disease. *N Engl J Med* 1993;328:1220.
- Davidson M, Ma P, Stein EA, et al. Comparison of effects on low density lipoprotein cholesterol and high density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with Type IIa or IIb hypocholesterolemia. *Am J Cardiol* 2002;89:268–275.
- de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454.

- Deslypere JP. Clinical implications of the biopharmaceutical properties of the fluvastatin. *Am J Cardiol* 1994;73:12D.
- Durrington P. Dyslipidaemia. *Lancet* 2003;362:717–731.
- Expert Panel on detection evaluation and treatment of high blood cholesterol in Adults: executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486.
- The 4S Investigators. Randomised trial of cholesterol lowering 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;334:1383–1389.
- Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-Prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237.
- Gagne C, Caudet D, Bruckert E. Efficacy and safety of ezetimibe co-administered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105:2469–2475.
- Genest J, McNamara JR, Ordovas JM, et al. Lipoprotein cholesterol, apolipoprotein A-I and B and lipoprotein (a) abnormalities in men with premature coronary artery disease. *J Am Coll Cardiol* 1992;19:792.
- Gharavi AG, Diamond JA, Smith DA, et al. Niacin-induced myopathy. *Am J Cardiol* 1994;74:841.
- Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585–2590.
- Grundy SM. Atherosclerosis imaging and the future of lipid management. *Circulation* 2004;110:3509–3511.
- Grundy SM, Cleeman JJ, Noel Bairey Merz C, et al. and Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004;44:720–732.
- Guallar E, Hennekens CH, Sacks FM, et al. A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians. *J Am Coll Cardiol* 1995;25:387.
- Heart Protection Study Collaborative Group MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a Randomised placebo-controlled trial. *Lancet* 2002;360:7–22.
- Hu FB. The Mediterranean diet and mortality Olive oil and beyond. *N Engl J Med* 2003;348:2595–2596.
- Jacotot B, Benghozi R, Pfister P, et al. Comparison of fluvastatin versus pravastatin treatment of primary hypercholesterolemia. *Am J Cardiol* 1995;76:54A.
- Jones PH, Davidson MH, Stein EA. Et al for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin, versus atorvastatin, simvastatin, and, pravastatin across doses. (STELLAR Trial). *Am J Cardiol* 2003;93:152–160.
- Katan MB. Fish and heart disease. *N Engl J Med* 1995;332:1024.
- Keenan JM, Fontaine PL, Wenz JB, et al. A randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. *Arch Intern Med* 1991;151:1424.
- Knoops KTB, Lissette CP, deGroot GM, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE Project. *JAMA* 2004;292:1433–1439.
- Levine GN, Keaney JF, Vita JA. Cholesterol reduction in cardiovascular disease. *N Engl J Med* 1995;332:512.
- LIPID study group: prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–1357.
- MAAS Investigators. Effect of simvastatin on coronary atheroma: The Multi-Centre Anti Atheroma Study (MAAS). *Lancet* 1994;344:633.
- Mann GV. Metabolic consequences of dietary trans fatty acids. *Lancet* 1994;343:1268.
- MARS Study—The Monitored Atherosclerosis Regression Study, Lakenhorn DH, Azen SP, Krams DM, et al., and the MARS Research Group. Coronary angiographic changes with lovastatin therapy. *Ann Intern Med* 1993;119:969.
- MIRACL: Schwartz GG, Olsson AG, Ezcekwitz MD et al. effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. A randomized controlled trial. *JAMA* 2001;285:1711–1718.
- Mullin GE, Greenson JK, Mitchell MC. Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. *Ann Intern Med* 1989;111:253.
- National Cholesterol Education Program. Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). 2002.
- Nissen SE, for the REVERSAL Investigators. REVERSAL comparison of intensive versus moderate lipid lowering on the progression of coronary atherosclerosis measured by intravascular ultrasound: a randomized controlled trial. *Circulation* 2003;108:2723.

- Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of a recombinant ApoA -1 Milano on coronary atherosclerosis in patients with acute coronary syndromes. *JAMA* 2003;290: 2292–2300.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al. for the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005;352:29–38.
- Olsson AG, Istad H, Luurila O, et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J* 2002;144:1044–1051.
- Oomen C M, Ocke MC, Feskens EJM. Association between the transfer the acid intake and 10 year risk of coronary heart disease in the Zutphen elderly study: a prospective population base to study. *Lancet* 2001;357:746–751.
- Ridker PM, Cannon CP, Morrow D, et al. for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigator. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20–28.
- Roberts TL, Wood DA, Riemersma RA, et al. Trans isomers of oleic and linoleic acids in adipose tissue and sudden cardiac death. *Lancet* 1995;345:278.
- Rosenson RS, Fraueheim WA. Safety of combined pravastatin-gemfibrozil therapy. *Am J Cardiol* 1994;74:499.
- Rubins HB, Robins ST, Collins D, et al. Distribution of lipids in 8500 men with coronary artery disease. *Am J Cardiol* 1995;75:1196.
- Sacks FM for the Expert Group on HDL Cholesterol. The role of high-density lipoprotein (HDL) cholesterol in the prevention and treatment of coronary heart disease: expert group recommendations. *Am J Cardiol* 2002;90:139–143.
- Sacks FM, Pfeffer MA, Move LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.
- Schmieder RE, Schobel HP. Is endothelial dysfunction reversible. *Am J Cardiol* 1995;76:117A.
- Schwartz GG, Oliver MF, Ezekowitz MD, et al. Rationale and design of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study that evaluates atorvastatin in unstable angina pectoris and in non-Q-wave acute myocardial infarction. *Am J Cardiol* 1998;81:578–581.
- Shear CL, Franklin RA, Stinnett S, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. Effect of patient characteristics on lovastatin-induced changes in plasma concentrations of lipids and lipoproteins. *Circulation* 1992;85:1293.
- Shepherd J, Cobbe SM, Ford I, et al. For the West of Scotland Coronary Prevention Study Group: prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301.
- Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high-risk patients (Indo-Mediterranean diet heart study): a randomized double-blind trial. *Lancet* 2002;360:1455–1461.
- Thompson PD, Clarkson P, Karas RH, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J* 2002;144:1036–1043.
- Thompson PD, Clarkson P, Karas RH. Statin-Associated Myopathy. *JAMA* 2003;289:1681–1690.
- Topol EJ. Intensive statin therapy—a sea change in cardiovascular prevention. *N Engl J Med* 2004;350:1562–1564.
- Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995;332:481.
- Trichopoulou A, Costacou T, Bamia C, et al. Adherence to a Mediterranean diet and survival in a Greek population *N Engl J Med* 2003;348:2599–2608.
- Wald NJ, Law N, Watt HC, et al. Apolipoproteins and ischemic heart disease implications for screening. *Lancet* 1995;343:75.
- Wong ND, Wilson PWF, Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham Study. *Ann Intern Med* 1991;115:687.
- The Writing Group for the PEPI Trial. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial: effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA* 1995;273:199.

10

Aortic Dissection

CONTENTS

ETIOLOGICAL FACTORS AND ASSOCIATIONS
DIAGNOSTIC HALLMARKS
INVESTIGATIONS
MEDICAL THERAPY
SURGICAL TREATMENT
DISSECTION OF THE DESCENDING AORTA
BIBLIOGRAPHY

Dissection involving the ascending aorta has an extremely high mortality (up to 1% per minute, 60% in 60 minutes). Thus, time-consuming investigations that are not sufficiently sensitive or specific, such as computed tomography (CT), must be forsaken. Emergency surgery carries the only hope of survival for the unfortunate patient with dissection of the ascending aorta, and immediate accurate diagnosis is mandatory to guide interventional therapy. Presently, the quickest, most accurate diagnostic procedure is transesophageal echocardiography (TEE), which can be performed at the bedside, in the intensive care unit, or in the operating room.

Dissection involving the ascending aorta, type I of DeBakey, accounts for up to 66% of all aortic dissection. Usually, the intimal tear is located just above the aortic valve. It is very rare for the dissection to start or end in the transverse arch, so there is usually no need for arch repair, which requires hypothermic arrest and carries a high mortality rate. Also, it is important to know where the tear ends.

Type II of DeBakey may be regarded as a subgroup of type I, in which dissection is confined to the ascending aorta. Type III of DeBakey accounts for up to 25% of all aortic dissections, in which the tear usually ends just distal to the left subclavian artery; the dissection is confined to the descending aorta, and rupture may occur into the left pleural space, causing a left hemothorax.

The Stanford classification system divides aortic dissections into the following two types:

- Type A dissection, in which there is involvement of the ascending aorta regardless of the site of entry (DeBakey types I and II).
- Type B, distal dissections not involving the ascending aorta (DeBakey type III).

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ETIOLOGICAL FACTORS AND ASSOCIATIONS

Several pathological processes cause a weakening of the media via micro apoplexy of the vessel wall. This leads to higher wall stress, which induces aortic dilatation and aneurysm formation, eventually resulting in intramural hemorrhage or rupture; aortic dissection may occur prior to prominent aneurysm formation.

Three inherited connective tissue diseases cause extensive damage to the aortic medial wall:

- Marfan syndrome has an estimated incidence of 1 in 7000 and an autosomal dominant inheritance with variable penetrance. It is the most common hereditary connective disorder. Marfan syndrome is the leading cause of aortic dissection in patients under age 40. Patients with Marfan syndrome may develop aortic root dilatation, aortic regurgitation, and aneurysm of the ascending aorta. Patients may survive for several years. Management includes intensive control of blood pressure (BP). β -Adrenergic blockers must be given to all patients with aneurysms, even if the BP is in the normal range. In a study from Johns Hopkins Hospital and the University of Tennessee, β -blockers were shown to decrease the rate of aortic root dilatation. α -Blockers and hydralazine are contraindicated. Surgery is indicated if the aneurysm exceeds 5 cm. The outlook is bleak, however, even with surgery.
- Ehlers-Danlos syndrome is a group of hereditary connective tissue disorders characterized by articular hypermobility, skin hyperextensibility, and tissue fragility.
- Familial forms of thoracic aneurysm and dissection: other causes include giant cell arteritis, lupus erythematosus, relapsing polychondritis, and Turner's and Noonan's syndromes.

The non-Marfan patient with an asymptomatic, ascending aortic aneurysm should be submitted to surgery if the aneurysm is greater than 6 cm.

- Most patients with aortic dissection are hypertensive and over age 60. Hypertension coexists in up to 80% of patients and is more common in type B distal dissections. Hypertension accelerates the mild degree of aortic medial degeneration that occurs with normal aging.
- Normotensive younger patients usually have associated underlying disease of the aortic root.
- A congenital bicuspid valve appears to be present in up to 20% of patients with aortic dissection, versus 1.5% in the general adult population with a tricuspid aortic valve. The bicuspid valve is at least five times more common in patients with aortic dissection than in those individuals with a tricuspid aortic valve.
- Approximately 15% of patients with coarctation of the aorta succumb to aortic dissection.
- The male to female ratio is 3:1; up to 40% of dissections in women occur in the third trimester of pregnancy and in the subsequent few weeks, in conjunction with other factors that predispose dissection.

DIAGNOSTIC HALLMARKS

Diagnosis must be prompt. Clues include the following:

- Sudden onset of severe chest and/or interscapular pain, like a "gunshot," whereas in acute myocardial infarction (MI), pain builds up gradually over several minutes.
- Tearing, ripping pain.
- The diagnosis of acute aortic dissection must be considered in patients with unexplained syncope, chest pain, back pain, upper abdominal pain, atypical stroke with associated chest pain or pulse differentials, or malperfusion syndrome of extremities.

- Pain may spread to other areas as dissection advances.
- A shock-like state: cool, clammy, and vasoconstricted; impaired sensorium, yet the BP may be in the normal range. Occasionally, the BP is high.
- Hypotension, an ominous sign usually from external rupture.
- Syncope, usually indicates rupture into the pericardial space with cardiac tamponade; pericardial effusion heralds an extremely poor prognosis.
- A new, loud aortic diastolic murmur.
- An aortic thrill is a strong diagnostic point, if present.
- Sternoclavicular joint pulsation.
- Loss of one or more pulses or pulses that come and go.
- BP difference in arms if the left subclavian is affected.
- Ischemic neuropathy owing to ischemia of the limbs.
- Signs of stroke.
- Paraparesis or paraplegia may occur with marked decrease in blood supply to the cord.
- The scenario may mimic arterial embolism;
- May be associated with MI if the dissection extends to coronary vessels. In this clinical setting, thrombolytic agents are contraindicated.

When features are less typical in the presence of central chest pain, a diagnosis of MI is considered. The lack of developing Q-waves and the absence of ST-segment elevation in most cases, especially in association with an elevated BP in the presence of a shock-like state, should prompt the diagnosis of dissection. The early absence of an increase in creatine kinase (CK) and CK-MB does not exclude acute MI, and estimation is not relevant for the urgent diagnosis of dissection.

INVESTIGATIONS

Investigations are limited to estimation of the hemoglobin, serum creatinine and potassium, chest X-ray, and echocardiogram to exclude MI.

TEE, CT, or MRI

- TEE and contrast-enhanced CT (in spiral and multislice technique) give excellent accuracy.

Nienaber et al. showed both TEE and magnetic resonance imaging (MRI) to have a sensitivity of 100% and specificity of 68 and 100%, respectively. False-positive TEE occurred mainly in patients with ascending dissection and was caused by extensive plaque formation and reverberations in an ectatic vessel. Multiplanar echocardiographic imaging may overcome these deficiencies of TEE. Because retrograde angiography requires the injection of contrast that has a potential risk of aortic dissection.

The MRI was positive in 58 of 59 patients with positive findings. TEE was diagnostic in 43 of 44 patients. The sensitivities of MRI and TEE for type A dissection were 100% and 96%, respectively.

MEDICAL THERAPY

Short-term stabilization is attempted in the emergency room and in the operating room using intravenous (IV) β -blockade (esmolol, metoprolol, propranolol, or labetalol) and nitroprusside to target systolic blood pressure of 100 mmHg. Intravenous diltiazem may be required if β -blockers are contraindicated.

Nitroprusside

A dosage of IV 0.2–2 µg/kg/minute, that is, 12–120 µg/minute for a 60-kg patient (*see Table 8.11.*, Nitroprusside Pump Chart). Sodium nitroprusside at an initial dose of 0.3 µg/kg per minute is often effective if severe hypertension is present. α-Blockers, diazoxide, and hydralazine are contraindicated because they cause tachycardia and increase cardiac ejection velocity and rate of rise of aortic pressure that predispose rupture.

The aim is to reduce the BP to the lowest possible level yet preserve cardiac, cerebral, and renal perfusion. An intra-arterial cannula is advisable to accurately monitor BP.

Patients with profound hemodynamic instability often require intubation and mechanical ventilation. Presence of cardiac tamponade requires urgent sternotomy and surgical access to the ascending aorta; this strategy can prevent circulatory arrest, shock, and ischemic brain damage. Percutaneous pericardiocentesis is not advisable because it is often not beneficial and can accelerate bleeding and shock.

β-Adrenergic Blockers

β-Adrenergic blockade is of benefit because it decreases the velocity and force of myocardial contraction and reduces the rate of rise of aortic pressure, which is a major factor in determining extension of the dissection. Nitroprusside increases the velocity of ventricular contraction, the rate of pressure rise and, hence, the need for combination with a β-adrenergic blocker.

Esmolol

A dosage of an IV infusion, 3–6 mg over 1 minute (30–500 µg/kg/minute), is used and then maintenance (1–5 mg/minute, maximum 50 µg/kg/minute). If hypotension is present or develops, decrease the maintenance dose to 1–3 mg/minute.

Propranolol

A dosage of 0.5 mg/minute IV at 2- to 5-minute intervals is given to a maximum of 5 mg and then 0.05–0.15 mg/kg every 4–6 hours (*see Table 3.4.*).

Metoprolol

A dosage of 1 mg/minute at 5-minute intervals is given to a maximum of 15 mg repeated every 6–8 hours.

Atenolol

A dosage of an IV infusion of 150 µg/kg is given over 20 minutes and repeated every 12 hours if required.

SURGICAL TREATMENT

Surgical therapy is necessary in proximal type A (type I, II) dissection to prevent rupture or cardiac tamponade. The sudden onset of aortic regurgitation and coronary flow obstruction needs urgent surgery for resection of the region of intimal tear in dissection limited to the ascending aorta and replacement by a graft. The Stanford experience with methods of surgical interventions in type A dissection was recently reported. This report stresses that unrecognized intimal tears in the arch or descending thoracic aorta, occur in approximately 25% of patients and predisposes to later distal aortic reoperation.

For types A and B dissection, emergency surgery is a necessity if life is to be salvaged. Because it is extremely rare for the dissection to end or start in the transverse arch, there is usually no need for arch repair, which requires hypothermic arrest and results in an increase in surgical mortality. In the study by Nienaber et al., 27 of 32 patients with type A lesions had surgical correction. There were three preoperative and three postoperative deaths. Surgical intervention was carried out at a median interval of 13.5 hours from initial hospitalization. Surgery for type B aortic dissection is best performed between a few days and 6 months after hospitalization.

Contraindications to surgery include the following:

- Cancer or other underlying severe debilitating disease.
- Age over 80 unless in robust health.
- Neurologic complications of dissection.

DISSECTION OF THE DESCENDING AORTA

Some time is available here for diagnostic work-up with CT and aortic arteriography. In patients with dissection of the descending aorta, as opposed to those with ascending dissection, ischemic heart disease is often present and coronary arteriography is required.

BP is aggressively controlled with nitroprusside and β -blockers, and surgery should proceed in 12–48 hours. If spinal involvement is present, the patient and next of kin must thoroughly understand that spinal problems may not be helped. If the dissection extends to the aortic arch or the descending aorta, resection of the entire intimal flap may not be possible or the patient may require partial or total arch replacement.

Postsurgery Follow-Up

Aggressive control of BP is necessary. BP must be kept fairly low and the rate of rise of aortic pressure must be decreased with the use of β -adrenergic blockers. With all types of dissection, intensive postsurgery follow-up is essential. Patients with ascending dissection repair should be followed monthly with TEE for 3 months; descending aortic dissection necessitates CT or MRI to assess enlargement. A false lumen is invariably present with some flow and is not an indication for surgery, except when the false lumen widens considerably. Postoperative late deaths are usually a result of rupture; thus, close monitoring of both surgical and medical patients is necessary.

BIBLIOGRAPHY

- Ballal RS, Nanda NC, Gatewood R, et al. Usefulness of transesophageal echocardiography in assessment of aortic dissection. *Circulation* 1991;84:1903.
- Bortone AS, Schena S, D'Agostino D, et al. Immediate versus delayed endovascular treatment of post-traumatic aortic pseudoaneurysms and type B dissections: retrospective analysis and premises to the upcoming European trial. *Circulation* 2002;106(Suppl I):I-234–I-240.
- Bossone E, Rampoldi V, Nienaber CA, et al. Pulse deficits: a simple clinical sign as independent predictor of in-hospital complications and mortality in patients with type A aortic dissection. *Am J Cardiol* 2002;89:851–855.
- Cigarro JE, Isselbacher B, DeSanctis RW, et al. Diagnostic imaging in the evaluation of suspected aortic dissection. *N Engl J Med* 1993;28:35.
- Collins JS, Evangelista A, Nienaber CA, et al. on behalf of the International Registry of Acute Aortic Dissection. Differences in clinical presentation, management, and outcomes of acute type A aortic dissection in patients with and without previous cardiac surgery. *Circulation* 2004;110:II-237–II-242.
- Dake M, Kato N, Mitchell RS. Endovascular stent-graft placement for the treatment of acute aortic dissection. *N Engl J Med* 1999;340:1524–1531.
- DeBakey ME, Hendy WS, Cooley DA, et al. Surgical management of dissecting aneurysm of the aorta. *J Thorac Cardiovasc Surg* 1965;49:130.

- Devereux RB, Roman MJ. Aortic disease in Marfan's Syndrome. *N Engl J Med* 1999;340:1358–1359.
- Erbel R, Alfonso F, Boileau C, et al. Diagnosis and management of aortic dissection: task force report of the European Society of Cardiology. *Eur Heart J* 2001;22:1642–1681.
- Evangelista A, Garcia-del-Castillo H, Conzalez-Alujas T, et al. Diagnosis of ascending dissection by transesophageal echocardiography: utility of M-Mode in recognizing artifacts. *J Am Coll Cardiol* 1996;27:102.
- Fenoglio JJ Jr, McAllister HA Jr, DeCastro CM, et al. Congenital bicuspid aortic valve after age 20. *Am J Cardiol* 1977;39:164.
- Finkbohner R, Johnston D, Crawford ES, et al. Marfan syndrome: long-term survival and complications after aortic aneurysm repair. *Circulation* 1995;91:728–733.
- Gott VL, Greene PS, Alejo DE, et al. Replacement of the aortic root in patients with Marfan's syndrome. *N Engl J Med* 1999;340:1307–1317.
- Hagan PG, Nienaber CA, Isselbacher EM, et al. The international registry of acute aortic dissection (IRAD): new insights into an old disease. *JAMA* 2000;283:897–903.
- Hirata K, Triposkiadis F, Sparks E, et al. The Marfan syndrome: abnormal aortic elastic properties. *J Am Coll Cardiol* 1991;18:57.
- Ince H, Nienaber CA. The concept of interventional therapy in acute aortic syndrome. *J Card Surg* 2002;17:135–142.
- Isselbacher EM, Cigarroa JE, Eagle KA. Cardiac tamponade complicating proximal aortic dissection: is pericardiocentesis harmful? *Circulation* 1994;90:2375–2379.
- Januzzi JL, Isselbacher EM, Fattori R, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 2004;43:665–669.
- Kazui T, Washiyama N, Muhammad BA, et al. Extended total arch replacement for acute type A aortic dissection: experience with seventy patients. *J Thorac Cardiovasc Surg* 2000;119:558–565.
- Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med* 2000;160:2977–2982.
- Lai DT, Robbins RC, Mitchell SC, et al. Does profound hypothermic circulatory arrest improve survival in patients with acute type A aortic dissection? *Circulation* 2002;106(Suppl I):I-218–I-228.
- Mehta RH, O'Gara PT, Bossone E, et al. Acute type A aortic dissection in the elderly: clinical characteristics, management, and outcomes in the current era. *J Am Coll Cardiol* 2002;40:685–692.
- Nienaber CA, Eagle KA. Aortic Dissection: New Frontiers in Diagnosis and Management Part I: From Etiology to Diagnostic Strategies. *Circulation* 2003;108:628–635.
- Nienaber CA, Eagle KA. Aortic Dissection: New Frontiers in Diagnosis and Management Part II: Therapeutic Management and Follow-Up. *Circulation* 2003;108:772.
- Nienaber CA, Ince H, Petzsch M, et al. Endovascular treatment of thoracic aortic dissection and its variants. *Acta Chir Belg* 2002;102:292–298.
- Nienaber CA, Spielmann RP, von Kodolitsch Y, et al. Diagnosis of thoracic aortic dissection. Magnetic resonance imaging versus transesophageal echocardiography. *Circulation* 1992;85:434.
- Nienaber CA, von Kodolitsch Y. Therapeutic management of patients with Marfan syndrome: focus on cardiovascular involvement. *Cardiol Rev* 1999;7:332–341.
- Nienaber CA, von Kodolitsch Y, Nicholas V, et al. The diagnosis of thoracic aortic dissection by non-invasive imaging procedures. *N Engl J Med* 1993;328:1.
- Nguyen B, Muller M, Kipfer B, et al. Different techniques of distal aortic repair in acute type A dissection: impact on late aortic morphology and reoperation. *Eur J Cardiothorac Surg* 1999;15:496–500.
- O'Gara PT, DeSanctis RW. Acute aortic dissection and its variants. Towards a common diagnostic and therapeutic approach. *Circulation* 1995;92:1376.
- Palma JH, Marcondes de Souza JA, Alves CMR, et al. Self expandable aortic stent-graft for treatment of descending aortic dissections. *Ann Thorac Surg* 2002;73:1138–1142.
- Reed D, Reed C, Stemmerman G, et al. Are aortic aneurysms caused by atherosclerosis? *Circulation* 1992;85:205.
- Roberts CS, Roberts WC. Aortic dissection with the entrance tear in abdominal aorta. *Am Heart J* 1991;121:1834.
- Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *J Am Coll Cardiol* 1991;17:712.
- Salim MA, Alpert BS, Ward JC. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. *Am J Cardiol* 1994;74:629.
- Schor JS, Yerlioglu ME, Galla JD, et al. Selective management of acute type B aortic dissection: long-term follow-up. *Ann Thorac Surg* 1996;61:1339–1341.
- Yacoub MH, Gehle P, Candrasekaran V, et al. Late results of a valve preserving operation in patients with aneurysms of the ascending aorta and root. *J Thorac Cardiovasc Surg* 1998;115:1080–1090.

11

Valvular Heart Disease and Rheumatic Fever

CONTENTS

AORTIC STENOSIS
AORTIC REGURGITATION
MITRAL STENOSIS
MITRAL REGURGITATION
MITRAL VALVE PROLAPSE
RHEUMATIC FEVER
BIBLIOGRAPHY

AORTIC STENOSIS

Aortic stenosis is the most common valvular lesion in the United States. This lesion is common because approximately 2% of individuals are born with a bicuspid valve which is prone to stenosis, and the aging population is increasing, and calcific aortic stenosis progresses with advancing years.

Rheumatic aortic stenosis is now uncommon, except in Asia, Africa, the Middle East, and Latin America. The patient's age at the time of diagnosis usually gives a reasonable assessment of the underlying disease.

- Diagnosis before age 30 is typical of congenital aortic stenosis.
- In patients over age 70, calcific aortic sclerosis owing to degenerative calcification is common, and significant stenosis develops in up to 5% of these individuals. Aortic sclerosis is common in the elderly, and although the lesion is significant, it is hemodynamically not important. Stenosis develops particularly when there is associated hypercholesterolemia. Importantly, the progression of stenosis can be significantly retarded by statin therapy.
- A bicuspid valve occurs in approximately 2% of the population, with a male to female ratio of 4:1, and is predisposed to degenerative calcification and stenosis. Between ages 30 and 70, calcification of a bicuspid valve is the most common cause of aortic stenosis, and much less frequently, cases of rheumatic valvular disease are encountered.

The causes of aortic stenosis can be seen in [Table 11.1](#).

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Table 11.1
Causes of Aortic Valvular Stenosis

Bicuspid calcific	60% ^a
Degenerative calcific	15%
Rheumatic	20% ^a
Other	5%

^aReverse in Asia, Africa, Middle East, and Latin America.

Physical Signs of Significant Aortic Stenosis

Some physical signs of significant aortic stenosis include the following:

- A systolic crescendo–decrescendo murmur best heard at the left sternal border, the second right interspace, or occasionally at the apex, with radiation to the neck.
- The timing of the peak intensity of the murmur is a more reliable sign of severity of aortic stenosis than the intensity of the murmur. Severe stenosis is indicated by a murmur that peaks late in systole.
- The longer the murmur the greater the gradient.
- The intensity of the murmur, in the absence of significant aortic regurgitation, is usually grade 3 or greater, except if cardiac output (CO) is low, as with heart failure (HF); then, even a grade 2 murmur may be in keeping with severe stenosis. Aortic regurgitation (AR) increases flow across the aortic valve and may produce a loud systolic murmur without stenosis.
- An absent or very soft aortic component of the second sound (A_2). With increased calcification, mobility of the valve leaflets is reduced; thus, the closing sound of the aortic valve becomes soft or even lost; A_2 disappears when the valve does not open or closes well. The soft pulmonary second heart sound produces a soft single second heart sound. Paradoxical splitting of the second heart sound may occur, but is uncommon.
- An S_4 gallop is usually present and is highly significant in patients under age 50.
- A thrill is commonly present over the base of the heart or the carotid arteries; this indicates a murmur of grade 4 or louder and may relate to the severity of aortic stenosis if AR is absent.
- A thrusting, forceful apex beat of left ventricular hypertrophy (LVH); the apex beat is usually not displaced, except in patients with concomitant AR or with terminal left ventricular (LV) dilatation.
- The carotid or brachial pulse in patients under age 65 shows a typical delayed upstroke. In the elderly, loss of elasticity in arteries often masks this important sign. The decreased elasticity increases the rate of rise of the carotid upstroke, and this may mislead the clinician into thinking that the stenosis is mild when it is severe.

The average survival of patients are given in [Table 11.2](#).

- Approximately 50% of patients present with dyspnea and more than half are expected to die within 2 years.
- Approximately 33% of patients with aortic stenosis present with angina and half are expected to die within 5 years.
- Approximately 15% of patients present with syncope and half of these die within 3 years.

Table 11.2.
Average Survival in Patients With Moderate or Severe Aortic Stenosis

<i>Clinical parameters</i>	<i>Survival (years)</i>
Left ventricular failure	1–2
Severe shortness of breath	50% die within 2
Mild shortness of breath	3–5
Syncope	50% die within 3
Angina	50% die within 5

Investigations

ELECTROCARDIOGRAM

The electrocardiogram (ECG) in patients with moderate to severe stenosis often shows features of LVH:

- S-wave in V₁, plus R in V₅ or V₆ greater than 35 mmHg.
- S wave-V₃, plus R in aVL greater than 20 mmHg.
- Left atrial enlargement.
- ST-T change typical of LV strain: the ascending limb of the T-wave is steeper than the descending in leads V₅ and V₆, with a lesser change in V₄.
- Left bundle branch block.

Although some patients with LVH caused by aortic stenosis may not manifest ECG signs of LVH, the ECG remains an important test in those who do show LVH. The presence of LVH on ECG in the absence of significant hypertension is in keeping with severe aortic stenosis.

CHEST X-RAY

Concentric LVH occurs; thus, the chest X-ray usually shows a normal heart size, with some rounding of the left lower cardiac border and apex, and occasionally some posterior protrusion in the lateral view may suggest LVH. The heart size may be increased if cardiac failure supervenes or with concomitant AR. A common hallmark of valvular aortic stenosis is poststenotic dilatation of the ascending aorta.

ECHOCARDIOGRAPHY

The severity of aortic stenosis can be determined by continuous-wave Doppler echocardiography. This technique agrees with data obtained from catheterization in up to 85% of cases.

Mild aortic stenosis is indicated by a mean aortic valve pressure gradient equal to or less than 20 mmHg. Moderate stenosis is indicated by a mean pressure gradient 21–39 mmHg. A valve area greater than 1.5 cm² indicates mild aortic stenosis.

Moderate to severe aortic stenosis is indicated by the following:

- Valve mean pressure gradient greater than 40 (range in several clinical studies, 40–120 mmHg).
- Doppler peak systolic pressure gradient is usually greater than 50 mmHg in the presence of a normal CO but in more than 33% of patients the gradient is 40–50 mmHg.
- Maximal instantaneous Doppler gradient greater than 60 mmHg (range 55–165 mmHg).
- Peak systolic flow velocity greater than 4 m/s (range often observed, 4–7 m/s).

Table 11.3.
Hemodynamic Parameters for Severe Aortic Stenosis

	<i>Aortic valve area^a (cm²)</i>	<i>Aortic valve area index (cm²/m²)</i>	<i>Peak systolic gradient (mmHg)</i>	<i>Mean gradient (mmHg)</i>
Severe stenosis	<0.75	<0.4	>80	>70
Probable severe	0.75–0.9	0.4–0.6	50–79	40–69
Uncertain	>0.9–1.2	>0.6	<50	<40

^aIn an average-sized adult.

- Valve area less than about 0.75 cm² in an average-sized adult, 0.4 cm²/m² of body surface area, severe or critical stenosis (Table 11.3.).
- 0.8 to 1.4 cm² indicates moderate stenosis.

The aortic valve area (AVA) and expected mean gradient is as follows:

- 0.5 cm² mean gradient greater than 100 mmHg
- 0.7 cm² mean gradient greater than 50 mmHg
- 0.9 cm² mean gradient greater than 30 mmHg
- 1.0 cm² mean gradient greater than 25 mmHg
- 3 to 4 cm² is normal and gradient less than 3 mmHg

It must be emphasized that in cardiac catheterization studies, no aortic valve gradient (mean or peak) has been found to be both sensitive and specific for severe aortic stenosis. Eslami et al. points out that AVA should be measured at cardiac catheterization in all patients with suspicion of severe aortic stenosis even when the mean aortic valve gradient is less than 50 mmHg (0% of their study patients) and/or the peak gradient is less than 60 mmHg (present in up to 47% of their patients). These authors believe that the severity of aortic stenosis is best determined by measuring the AVA as follows:

- severe aortic stenosis AVA is less than 1.0 cm², AVA index less than 0.6 cm².
- Moderate stenosis AVA greater than 1.0–1.5².
- In patients with congenital aortic stenosis, the peak instantaneous valve pressure gradient is used for determining the severity of stenosis.

Therapy

Medical therapy plays a small role in management. Because the consequences of valve surgery may be life-threatening, the timing of valve replacement requires accurate knowledge of the natural history of significant aortic stenosis, as well as careful attention to details in the patient's history and the sound appraisal of information gathered from Doppler echocardiography correlated with catheterization data.

Sophisticated echo-Doppler techniques are available and can, in over 80% of patients, dispense with catheterization data. However, because valve surgery is a life-saving but hazardous procedure, it is vital to gather information from all sources, including catheterization, to allow for sound decision making when surgery is being contemplated. In certain patients, ancillary information about the state of the coronary arteries is of cardinal value in reaching a therapeutic decision. In a study comparing echo-Doppler with catheterization data to determine the timing for valve surgery, agreement varied from a 92% level for AR to 90% for mitral stenosis but only 83% and 69% for aortic stenosis and mitral regurgitation, respectively.

Natural History

Significant aortic stenosis has a variable natural history. An elderly patient with moderately severe degenerative calcific aortic stenosis may progress rapidly to a more severe status with life-threatening symptomatology. Some patients with rheumatic or bicuspid valve calcification with moderate to severe stenosis may remain asymptomatic for several years. Fewer than 5% of asymptomatic patients with moderate or severe acquired aortic stenosis die suddenly, but even in these patients, a careful history taken weeks before death often elicits some symptomatology, albeit minimal. Thus, minimally symptomatic patients with moderate or severe aortic stenosis must be followed closely with attention to careful history, physical examination, assessment of ECG, Doppler echocardiographical data, and Holter monitoring. The aortic valve index and a decrease in ejection fraction (EF) are important parameters.

When symptoms are manifest, the natural history can be anticipated. Patients with LV failure or severe breathlessness have a less than 2-year survival (Table 11.2.). Mild shortness of breath or syncope indicate a 3-year survival, and angina without other manifestations usually indicates a 4–5-year survival in the absence of significant ischemic heart disease (IHD). Angina may, of course, be a result of IHD in some patients with mild to moderate aortic stenosis. Thus, decision making in the management of symptomatic patients is straightforward.

PATIENTS WITH SYMPTOMATIC SEVERE AORTIC STENOSIS

A calculated valve area of less than 0.8 cm² adds little to the database for clinical decision-making if the patient is symptomatic and has a peak systolic pressure gradient greater than 50 mmHg, which indicates severe aortic stenosis. In these patients, surgical correction is required regardless of the calculated valve area. It is important, however, to ensure that symptoms are the result of severe aortic stenosis.

The echocardiographical findings usually indicate a valve area less than 0.75 cm² in an average-sized adult and Doppler peak systolic pressure gradient >50 mmHg, with a maximal instantaneous gradient in the range of 64–145 mmHg. If the CO is low or the valve gradient appears inadequate to account for symptomatology, the valve area index should be calculated (Table 11.3.).

Patients with LV failure or LV dysfunction require emergency surgery. Others require prompt surgery. During the waiting period, dental work under antibiotic coverage should be completed. The patient should be instructed concerning the risk and strictness of long-term anticoagulant regimen.

Diuretics are indicated if HF is present and digoxin is used if systolic dysfunction is documented. HF is not a contraindication to surgery. Coronary angiography is necessary in patients over age 35 or in those with chest pain.

PATIENTS WITH SYMPTOMATIC MODERATE AORTIC STENOSIS

Patients who have a valve area of 0.75–1.4 cm² are usually categorized as having moderate aortic stenosis. The situation in patients with valve area of 0.75–1 cm² is regarded by some as a “fool’s paradise” (Table 11.3.). Some determine severe stenosis by valve area of 0.9 cm² or less and/or valve area index 0.6 cm²/m² or less. Patients who have moderate aortic stenosis, if minimally symptomatic, should be regarded as being at high risk for development of complications during the next 1 or 2 years, especially if the EF is less than 50% or if there is hemodynamic evidence of LV decompensation. In a study of 66 patients who had moderate aortic stenosis, 31% with minimal symptoms

experienced serious complications within 4 years. Also, patients who have EF less than 50% at catheterization appear to have up to a 64% chance of complications owing to aortic stenosis over a 4-year period. The absence of severe symptoms does not ensure a favorable outcome. Mildly symptomatic patients with degenerative calcific aortic stenosis of a moderate degree are at high risk. Thus, if underlying diseases such as respiratory failure, stroke, renal failure, anemia, or cancer, are not present, surgery is recommended.

Medical therapy is required for the following:

- Careful supervision of asymptomatic patients with moderate or severe aortic stenosis.
- Follow-up of patients with mild aortic stenosis.
- Rheumatic fever and bacterial endocarditis prophylaxis.

ASYMPTOMATIC SEVERE AORTIC STENOSIS

Patients with truly asymptomatic severe aortic stenosis evaluated at valve area less than 0.75 cm² and having the other echocardiographical parameters listed earlier require close and careful follow-up. A careful history should be taken at each visit, supplemented by inquiry of a spouse, close relative, or friend. The patient may deny mild-to-moderate shortness of breath. Activities may be decreased by the patient to prevent significant breathlessness. The patient must be warned to report any change in breathlessness, dizziness, chest pressure, or discomfort on mild or moderate exertional activities, including walking up stairs. Any change in symptomatology or increase in ECG or echocardiographical features of LVH and increase in pressure gradient or decrease in valve area requires consideration of urgent surgical intervention.

A cardiologist or internist should assess the patient every 3 months with a thorough cardiac examination, ECG, and Holter monitor. Echocardiography is advisable at least every 4 months. Many truly asymptomatic patients can be followed for 1–4 years but with the assurance that rapid access to a known surgical team is available if the mildest symptom or distress is noted by the patient. The patient should be instructed to present immediately to the emergency room for admission if any of the following symptoms appear:

- Change in breathing pattern on usual or moderate activities.
- Chest discomfort or pain on moderate activities or at rest.
- Dizziness or presyncope.
- Sudden paroxysm of cough with frothy sputum.
- Fever, chills, or symptoms of chest infection.

Not all cardiologists agree with the concept of conservative therapy and watchful care in patients who have asymptomatic severe aortic stenosis. One option is to offer surgery, provided this can be performed at low risk; this decision must be based on sound knowledge of the expertise of the surgical team and their surgical mortality. Braunwald has severely criticized this approach and has cautioned that operative treatment is the most common cause of cardiac death in asymptomatic patients with aortic stenosis. In a study by Pellika et al., sudden death did not occur among 113 asymptomatic patients who had isolated aortic stenosis followed for 188 patient years, but two of 30 asymptomatic patients subjected to valve surgery died suddenly within 2 weeks of intervention. In this category of patient, timing for surgery may be individualized and surgery should be considered if any one of the following parameters is manifest:

- Peak transaortic blood flow velocity greater than 4 m/second, peak gradient greater than 64 mmHg. More than 70% of these patients become symptomatic and require surgery within 2 years.

- LV dysfunction at rest with EF less than 50%.
- The patient is very active and must continue strenuous physical work or must maintain professional athletic standards. It is likely, however, that this category of patients would be symptomatic.
- If painless ischemia, potentially lethal arrhythmias, or pulmonary hypertension is documented in the absence of other valve lesions. Of course, valve replacement should not be delayed until overt HF has supervened.

Exercise testing is dangerous in patients with symptomatic aortic stenosis but has been shown to be sufficiently safe in patients with asymptomatic severe aortic stenosis. Testing can identify some patients with latent symptoms, or exercise-induced hemodynamic instability during exercise, particularly hypotension or ventricular tachycardia (VT).

MILD AORTIC STENOSIS

The valve area in patients with mild aortic stenosis exceeds 1.5 cm^2 and the mean aortic valve pressure gradient is 20 mmHg or less. Individuals are usually asymptomatic. The patient is advised that aortic valve replacement may be required in 5–15 years. However, an operation may never be required. The patient should continue with normal activities, except for competitive sports.

In all categories of aortic stenosis, the prevention of rheumatic fever is necessary if the underlying disease is believed to be rheumatic in origin. Patients under age 40 suspected of having rheumatic heart disease are given prophylaxis 200,000 units of penicillin G orally twice daily or 1.2 million units of benzathine penicillin intramuscularly monthly. Prophylactic therapy is continued at least to age 40 and/or after 20 years from the previous episode of rheumatic fever.

SURGICAL THERAPY

Mechanical obstruction to the LV outflow owing to significant aortic stenosis is a pressure overload situation that leads to progressive LVH, LV strain, and finally HF or sudden death. Symptoms owing to obstruction of outflow are usually the main indications for valve replacement in patients with moderate or severe aortic stenosis (Table 11.4.). In most of these patients, the valve area is less than 1.0 cm^2 and the peak systolic gradient is greater than 60 mmHg. Fortunately, the hypertrophied myocardium often retains mechanical efficiency, and once the valve is replaced, significant improvement in ventricular systolic performance occurs in most patients. Thus, HF is not a contraindication to valve replacement. Patients with LV failure owing to severe aortic stenosis and followed for over 1 year because of intercurrent illness contraindicating surgery usually regain adequate LV function with later valve replacement, but there are exceptions to these findings. Because the 1-year mortality is over 50% in patients with HF, surgery should be done promptly.

Indications for valve replacement include the following:

- LV failure.
- Shortness of breath.
- Angina.
- Presyncope or syncope not owing to preload-reducing agents or other causes of syncope (see Chapter 15).

If valve replacement caused no mortality or morbidity, then there would be no problem with advising surgery for moderate or severe aortic stenosis in asymptomatic patients. In some institutions in the minimally symptomatic patient, in the absence of coronary artery

Table 11.4.
Indications for Aortic Prosthetic Valve Surgery

<i>Parameters</i>	<i>Intervention</i>
Severe aortic stenosis	
Aortic valve area $< 0.75 \text{ cm}^2$	
Valve area index $< 0.4 \text{ cm}^2/\text{m}^2$	
Symptomatic patients	
Heart failure or dyspnea	Emergency surgery
LV dysfunction or EF $< 50\%$	Urgent surgery
Angina	Urgent surgery
Syncope	Urgent surgery (within a few weeks)
Asymptomatic patients	
Valve area as above	No surgery
Hemodynamic deterioration	
LV dysfunction	Fairly urgent (within a few months)
Ejection fraction $< 50\%$	
Cardiomegaly or LVH on ECG or echocardiography	
Moderate aortic stenosis	
Valve area $0.75\text{--}1.4 \text{ cm}^2$	
Symptomatic	
Heart failure	Urgent surgery
Other symptoms or LV dysfunction or EF, $< 50\%$ (follow-up monthly)	Fairly urgent (within a few months)
Truly asymptomatic (follow-up at least every 3 months)	Surgery (1–5 years) (if becomes symptomatic)

LV, left ventricular; LVH, left ventricular hypertrophy; EF, ejection fraction.

disease (CAD) and other problems, mortality is 1–3%. The presence of IHD, peripheral vascular disease, cerebrovascular disease, pulmonary disease, or oral disease greatly increases the mortality and morbidity of surgery.

Patients with chest pain or those over age 35 require coronary angiography to assess the degree of atheromatous coronary stenosis and suitability for coronary artery bypass surgery. Young patients with left anterior descending disease should be offered left internal mammary artery to left anterior descending anastomosis or graft; in patients over age 65, vein graft is recommended by the American

College of Cardiology and the American Heart Association Task Force.

Contraindications to surgery include the following:

- Serious underlying disease, especially respiratory failure, cancer, severe renal failure, cerebrovascular accident with residual stroke and contraindication to anticoagulant therapy.
- Age over 80 is a relative contraindication, except in patients with robust health and excellent cerebral status. Severe intercurrent illness should weigh heavily against surgery, except in patients with HF owing only to severe aortic stenosis with a valve area less than 0.75 cm^2 . Because angina may require a combination of valve replacement and bypass surgery if there is coronary artery obstruction, care must be taken to individualize the selection. The patient and family must understand the risks. Many elderly patients, however, do extremely well with valve replacement.

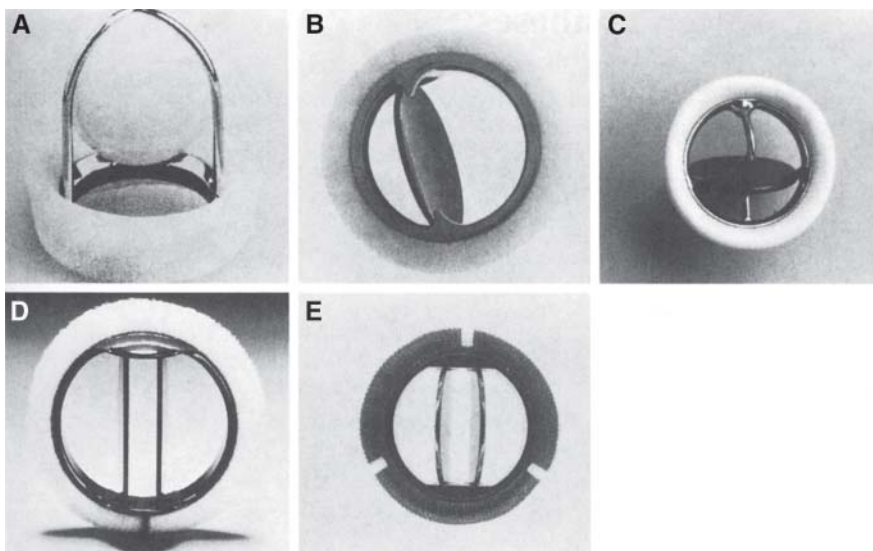


Fig. 11.1. (A) The Starr-Edwards ball and cage valve. (B) The omniscience valve. (C) The Medtronic-Hall valve. (D) The St. Jude valve. (E) The carbomedics bileaflet valve. From *Cardiol Rev* 1994;2:220.

PROSTHETIC VALVE CHOICE

Problems exist with all types of valve prostheses; none is ideal. The five types of mechanical aortic valves used in the United States since 1965 are shown in Fig. 11.1.

The St. Jude bileaflet design is the most widely used worldwide and accounts for approximately 60% of valve implants. It is the most popular mechanical prosthesis in the United States. More than half a million valves have been implanted worldwide. The low thromboembolic rate permits low anticoagulation, and an international normalized ratio (INR) of 2.5 is acceptable for prevention of thromboembolism.

The Medtronic Hall valve is very popular because the hemodynamics are excellent and similar to that of the St. Jude and it has a low thromboembolic rate; it is the dominant single-disc valve in the United States.

The Starr-Edwards valve requires an INR of 3.5–4 to prevent thromboembolism, is now hardly used because of poor flow characteristics, but has demonstrated excellent durability.

Bileaflet designs are easier to implant than single disk prostheses that are also somewhat noisier; thus, bileaflet designs have become increasingly popular among surgeons. Concerns about repetitive wear and thromboembolism owing to the hinge mechanism among bileaflet prosthesis have proven uncommon.

Mechanical prostheses actuarial estimates of freedom from all valve-related complications are as follows:

- Medtronic-Hall: 87% at 5 years, 72% at 10 years, and 60% at 15 years.
- St. Jude Medical: 70%, 58%, and 41.5% respectively.
- Star-Edwards Ball valve: 80%, 70%, and 51% respectively.

Scientific studies indicated a superiority of mechanical valves over bioprosthetic valves, especially in patients under age 60 or at all ages in the mitral position. Mechanical valves have maintained a dominant role in the aortic position and account for more than

Table 11.5.
Choice of Valve Prosthesis

<i>Clinical parameters</i>	<i>Mechanical valve</i>	<i>Bioprosthesis</i>
Age < 30	First choice	Not recommended
Anticoagulant necessary present in atrial fibrillation	Natural choice	Not recommended
Anticoagulant contraindicated	Not recommended	First choice
Aortic valve replacement		
Age 30–70	First choice	Second choice
Over age 70, sinus rhythm	Second choice	First choice
Mitral (all ages)	First choice	May be considered in patients over age 70 in sinus rhythm

^aHigher risk of bleeding with anticoagulants and average life span 10 years.

60% of aortic valve replacement. Atrial fibrillation (AF) occurs in more than 50% of patients who require mitral valve replacement. Mechanical valves are the obvious choice in patients with AF in whom anticoagulation is already necessary (Table 11.5.).

Collins points out that of 1117 isolated mitral valve replacements done at Brigham and Women's Hospital since 1971, 620 (54%) had AF and a need for anticoagulation. Bloomfield reiterates that 60% of mitral valves currently implanted in patients in the United States are mechanical; in 1988, the UK Registry reported that 68% of mitral valves implanted were mechanical. The surgeon's background and personal preferences, however, often dictate the choice of valve, taking into consideration the patient's age and the possible presence of contraindications to anticoagulant therapy. In underdeveloped countries, a mechanical valve is still considered first choice because it is preferable to monitor anticoagulation than to run the risk of two operations in 20 years, because reoperation carries a higher than 10% mortality and is costly. In the aortic position, it is expected that the durability of the mechanical valve is superior for use over a 20-year period because of a high reoperation rate with the use of bioprosthetic valves. The major disadvantage of mechanical valves is the small risk of bleeding because of anticoagulant therapy, and this must be weighed against possible reoperation over 7–15 years with a bioprosthetic valve.

It is well-established that reoperation is required much more frequently with bioprosthetic valves, but the complications of endocarditis and valve obstruction are similar. A bioprosthetic valve may be considered a reasonable choice in patients over age 70 whose life expectancy may be shorter than that of the bioprosthesis. In patients in whom anticoagulants are contraindicated or compliance is expected to be poor, a prosthetic valve is appropriate. In women who intend to become pregnant, a bioprosthetic valve or homograft is advisable, but a mechanical valve with the use of heparin subcutaneously for the first 4 months and during the last few weeks of pregnancy is an alternative. Accelerated calcification of glutaraldehydetreated bioprosthetic valves in patients under age 30 is of concern. Cryopreserved tissue valves are being tested and appear to maintain tissue flexibility with considerably less tendency to calcify.

Two studies compared the mechanical valve with the bioprosthesis. The Veterans' Administration (VA) study reported 10-year follow-up in 515 patients randomized between mechanical valve and bioprosthesis: reoperation for primary valve failure was necessary in 35 patients fitted with bioprostheses compared with 19 patients with mechanical valves; repeat surgery was performed for perivalvular regurgitation in only six bioprosthetic versus 13 mechanical valves. There was a significantly higher incidence of bleeding owing to anticoagulant therapy in patients with mechanical valves.

A 12-year comparison in Scotland of the Bjork-Shiley spherical disc valve with bioprosthesis in 261 mitral, 211 aortic, and 61 in both positions indicated no difference in reoperation or survival at 5 years. At 12 years, reoperation was necessary in 68 (37%) patients with bioprosthetic valve and 17 (8.5%) with mechanical valve. Porcine valve failure was usually owing to rupture of one or more cusps, causing severe regurgitation, with a much greater risk in the mitral position. Importantly, 16 patients died as a result of reoperation for porcine valve replacement. Also, valve failure may cause death before further surgical intervention. Using death and reoperation as endpoints for an actuarial assessment of survival with the original prosthesis intact, the survival rate in patients with Bjork-Shiley prostheses was 48%, versus a 30% survival rate in patients 12 years after porcine valve replacement. This effect was significant for mitral valves but inconclusive for the aortic position. As a result of the study, the Scottish group advises that a bioprosthesis appears to be contraindicated in the mitral position; replacement in young patients should be with a mechanical valve, but an aortic bioprosthesis has a role in patients over age 70 who are in sinus rhythm.

Homograft valves have a role in the young individual who does not want lifelong anticoagulation. In the aortic position, the homograft valve has shown improved hemodynamic function and absence of thromboembolic incidence. The surgical procedure is complicated and requires a very skilled surgical team. These valves are first choice in patients with endocarditis who require valve replacement. Shortage of homograft valves remains a major problem. A pulmonary autograft is used in the pulmonary switch operation. The operation is complex. Removal of the autograft requires inserting a pulmonary homograft in the right ventricular (RV) out flow tract. Patients in the young age group should benefit from this procedure with the improved experience of surgical teams. Transmission of communicable diseases, such as cytomegalovirus, hepatitis, and possible human immunodeficiency virus, is a potential problem with homograft valves; the US Food and Drug Administration is conducting a longitudinal study.

Complications of Valve Replacement

The major differences in complication rates in mechanical and bioprosthetic valves relate to the incidence of primary valve failure and major bleeding; primary valve failure is very high with bioprosthesis after 5 years and major bleeding is a drawback of the mechanical valve ([Table 11.6](#)).

Primary Valve Failure

Primary valve failure owing to central valvular regurgitation or nonthrombotic obstruction occurs in up to 12% of bioprosthetic valves and 6.6% of mechanical valves, as observed in the 10-year VA Study. The reoperation rate in the Scottish study was 37% and 8.5% for bioprosthetic and mechanical valves, respectively, followed for a mean of 12 years ([Table 11.6](#)).

Table 11.6.
Prosthetic Valve Complications

<i>Clinical Parameter</i>	<i>Mechanical Valve (%)</i>	<i>Bioprosthetic (%)</i>
Reoperation		
Veterans Administration ^a (10 year)	6.6	12
Scottish study ^b (12 year)	8.5	37
Major bleeding (12 year)	19	7
Perivalvular leak	4.5	2
Major embolism	8.8	9
Endocarditis	3.7	4.6
Survival rate (12 year)	51.5	44.4

Modified from: ^aJ Am Coll Cardiol 1991;176:41A. ^bN Engl J Med 1991;324–573.

Major Bleeding

Major bleeding was significantly greater in patients fitted with mechanical versus bioprosthetic valves in the 10-year VA Study, and this was also true (19 versus 7%) in the 12-year Scottish study. These figures are in agreement with other studies that indicate an incidence of major bleeding of 1–2% per year with fatal intracranial bleeding in 0.05–0.2% annually. Genitourinary, gastrointestinal, or retroperitoneal bleeding occurs at a rate of about 0.5% per patient year. Bleeding complications are related to inappropriate anticoagulant control.

Valve Obstruction Owing to Thrombosis and/or Pannus Formation

Thrombotic occlusion occurs more often with poor anticoagulation but may occur with apparently adequate control. The incidence of thrombosis with the Bjork-Shiley convexo-concave model was excessive, and in addition, this model, introduced in 1979, was withdrawn from the market owing to a high rate of strut fracture.

Valve obstruction resulting from thrombosis or pannus is very rare but is the most serious complication, occurring in 0.5–4.5% per patient year. In a reported study, inadequate anticoagulation appeared to be an important factor, present in up to 70% of the 100 patients with obstructed valves. In that series of 2100 St. Jude and 1892 Medtronic-Hall valves followed over a 10-year period, 100 patients underwent prosthetic valve declotting and excision of pannus resulting in a successful outcome.

Features of valve obstruction may appear in the following manners:

- Insidious with mild symptoms of breathlessness over 1–2 weeks.
- A subacute presentation with shortness of breath at rest for hours to a few days.
- Abrupt hemodynamic collapse often causing death.

Valve obstruction must be rapidly excluded in all patients with prosthetic heart valves who show new or worsening symptoms, especially shortness of breath on mild exertion or at rest. Valve obstruction is usually owing to thrombosis in up to 54%, chronic pannus associated with thrombosis in approximately 30%, and isolated pannus in only approximately 16% of patients.

The diagnosis should be straightforward in patients with shortness of breath at rest and a low output state. A change in prosthetic sounds, an absence of normal clicks on auscultation, or the development of a murmur should be followed by a prompt cinefluoroscopy or radiological screening if the occluder has a radio opaque marker. Echocardiography, particularly transesophageal echocardiography (TEE), is an alternative approach, and the delay associated with catheterization may prejudice prompt surgical intervention in this life-threatening situation. Thrombolytic agents have a role in some patients.

STREPTOKINASE

A dosage of intravenous (IV) 250,000–500,000 units over 30–60 minutes followed by infusion 100,000/hour for 24–72 hours has had salutary effects and may avoid surgery in some patients with a subacute presentation in the absence of hemodynamic collapse (*see* Chapter 1 for further advice on thrombolytic therapy).

UROKINASE

A dosage of 150,000 units over 30 minutes is given, and then 75,000–150,000 units/hour over 24–48 hours.

Caution: embolization of thrombotic material may occur, and the usual precautions with the use of thrombolytic therapy should be enforced (*see* Chapter 1).

Systemic Embolization

The incidence of systemic thromboembolism is less than 2% and about 4% annually for aortic and mitral valve prostheses, respectively, using mechanical or bioprosthetic valves. Small strokes, transient ischemic attacks (TIAs) with dysphasia, paraesthesia or mild weakness of the face or limb, visual disturbances, syncope, and, rarely, hemiplegia may occur. Small emboli to the kidneys or limbs may sometimes go unrecognized. Emergency embolectomy of a limb vessel is rewarding; thus, diagnosis must be prompt. An embolus to the kidney causes a sharp, marked rise in lactic dehydrogenase (LDH).

If embolization occurs, anticoagulants are commenced in patients with bioprosthetic valves, and with mechanical valves, dipyridamole (75–100 mg three times daily) is added to existing anticoagulant therapy.

Bacterial Endocarditis

Prosthetic valve endocarditis causes a high mortality of up to 62% with medical therapy and a somewhat lower fatality rate of less than 40% with valve replacement. The incidence is approximately the same for mechanical and bioprosthetic valves (0.7% per patient year). In the Scottish study over 12 years, endocarditis occurred in 3.7 and 4.6% of patients with mechanical and bioprosthetic valves, respectively. The organism involved and the therapy of prosthetic valve endocarditis are discussed in Chapter 12.

Hemolysis

Hemolysis is extremely rare with current mechanical prostheses. A small increase in LDH occurs but can increase dramatically when significant hemolysis occurs, as with paravalvular leak or strut fracture resulting in anemia, increased indirect bilirubin, reticulocytosis count, and hemosiderinuria. Hemolysis does not occur with tissue valves. The

occurrence of hemolysis points to a small periprosthetic leak, severe dysfunction when a valve cusp ruptures, or a dislodgement of a strut. Hemodynamic malfunction in a bioprosthesis with strut dislodgement or paravalvular leak may cause a 20–50-g/L fall in hemoglobin over a 1-week period with hemoglobinuria and myoglobinuria that can be mistaken for hematuria and prompt urological investigation. A marked rise in the LDH is seen without hemolysis in patients with renal infarction caused by embolism.

Prosthetic Valve Follow-Up

The follow-up of a patient with a prosthetic valve includes a careful history and physical examination. Auscultation for changes in heart sounds, alteration in valve clicks, and the appearance of regurgitant murmurs and gallops is important. Investigations include ECG, chest X-ray, complete blood count, and LDH. Two-dimensional Doppler echocardiography is done at least annually; a TEE is more reliable and is advisable if a valve complication is unresolved by the aforementioned investigations (*see* later discussion of TEE).

Anticoagulants

Anticoagulation control must be verified, and drugs that interact with oral anticoagulants should be discontinued or dosing should be modified. Anticoagulant therapy should achieve the following:

- The INR should be maintained (2–3, max 3.5) with added 80–100 mg of enteric coated aspirin in patients with tilting disk or bileaflet mechanical valves.
- The St. Jude valve has a low incidence of thromboembolism and an INR of 2–3 is acceptable with 80–100 mg aspirin.
- INR: maintain at 2.5–3.5 for caged ball or caged disc mechanical valves.
- An INR of 2–2.5 is advisable in the presence of a bioprosthetic valves for at least 3 months after surgery and to be continued if AF is present.

Aspirin added: Turpie et al. studied 370 patients, 75% of whom had mechanical heart valve prostheses and 25% bioprosthesis. The combination of warfarin and low-dose aspirin, 100 mg daily, showed a statistically significant decrease in major systemic embolism and vascular death. A meta-analysis of 10 studies by Masse et al. indicates that adding low-dose aspirin to warfarin decreases the risk of systemic embolism or death in patients with mechanical heart valves. Although the risk of major bleeding is slightly increased with antiplatelet therapy, bleeding is considerably diminished with use of 81–100 mg of low-dose aspirin daily and this has resulted in a favorable risk-to-benefit profile.

In patients undergoing noncardiac surgery, oral anticoagulants should be discontinued 5 days before surgery, and 300 mg of dipyridamole daily is advisable during the period that the patient is off warfarin. Heparin should be given IV to maintain the activated partial thromboplastin time at twice the control level. Heparin is infused up to 6 hours before surgery and recommenced 24–36 hours later until oral anticoagulant therapy achieves an INR of 2–3.

Transesophageal Echocardiography

TEE is superior to transthoracic assessment in many areas of clinical decision making and advisable for patients who have had valve replacements, especially in the following situations:

- Prosthetic valves, especially in the mitral position, are not well-visualized with the transthoracic procedure, because metal or plastic create artifacts and shadows. Thus, where problems are suspected with mitral valve prosthesis, TEE is superior.
- TEE is best to quantify the degree of mitral regurgitation, because the esophagus is immediately posterior to the left atrium.
- Vegetations of bacterial endocarditis: observed in 100% with TEE, compared with less than 60% with transthoracic two-dimensional (*see* Chapter 12).
- To detect abscess formation in aortic valve ring.
- To detect the source of cardiac emboli from prosthetic valve.
- Fatal cerebral event: 0.4%.
- Limb amputation: 0.6%.

Despite these complications, the procedure will undoubtedly undergo refinements because palliation is sometimes needed to prevent patient suffering.

Congenital Aortic Valvular Stenosis

INDICATIONS FOR AORTIC VALVE COMMISSURAL INCISION

Commissural incision is recommended in symptomatic and asymptomatic children and adolescents with severe congenital bicuspid aortic valve stenosis, valve area index less than $0.75 \text{ cm}^2/\text{m}^2$. This procedure has an acceptably low mortality rate of less than 1%. Progressive calcification of the incised valve may occur over the next 10–20 years. Nevertheless, it is best to defer valve replacement until severe aortic stenosis with symptoms occurs. Balloon aortic valvuloplasty at age 60–85 as discussed earlier has a very restricted application but appears to have a relatively good effect in childhood congenital noncalcified valvular aortic stenosis. A series involving 25 patients between 3 and 21 years of age showed a decrease in peak systolic gradient from 112 ± 35 to 44 ± 21 mmHg and valve area index increased from 0.3 ± 0.07 to $0.69 \pm 0.2 \text{ cm}^2/\text{m}^2$. There were three restenoses over 18 months.

Balloon aortic valvuloplasty may be rewarding as a temporary, palliative, cost-justifiable procedure in some countries in children and adolescents with severe congenital aortic valvular stenosis.

AORTIC REGURGITATION

Over the past 25 years, there has been a major change in the pattern of underlying conditions associated with diseases causing AR. Whereas rheumatic fever and syphilis comprised 70% and 20% of cases, respectively, they now account for less than 30% and 1%, respectively. With the fall in prevalence of these diseases, bicuspid valve, endocarditis, and diseases causing aortic root dilation have emerged as the common causes ([Table 11.7](#)).

Table 11.7.
Causes of Aortic Regurgitation

<i>Acute</i>	<i>Chronic</i>
Bacterial endocarditis	Rheumatic
Aortic dissection	Endocarditis
Prosthetic valve surgery	Congenital: bicuspid valve, ventricular septal defect, sinus of valsalva aneurysm
Aortic balloon valvuloplasty	Aortic root dilatation: connective tissue disorder: Marfan syndrome, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, lupus erythematosus
Trauma	Takayasu aortitis, cystic medionecrosis myxomatous degeneration, psoriatic arthritis, Behcet's syndrome, relapsing polychondritis, giant cell arteritis, osteogenesis imperfecta, ulcerative colitis
Rheumatic fever	Whipples disease
	Hypertension
	Arteriosclerosis
	Syphilis

Diagnostic Hallmarks

With chronic AR, the left ventricle tolerates regurgitant volume overload and compensates adequately; an asymptomatic period of from 10 to 30 years is not uncommon. Many patients with a moderate degree of AR deny shortness of breath on walking 3–5 miles and/or three flights of stairs. Complaints of shortness of breath on exertion, fatigue, palpitations, or dizziness are generally associated with moderate or severe regurgitation over a prolonged period or severe regurgitation of recent onset. Rarely, angina with diaphoresis occurs as the diastolic blood pressure (DBP) falls, frequently at night, causing a decrease in coronary perfusion. Symptoms and signs of HF at rest are late manifestations.

Physical Signs

Hallmarks on physical examination include the following:

- Typical collapsing pulse: water-hammer or Corrigan's pulse or a bounding pulse. The underlying mechanism is a rapid rise in upstroke followed by an abrupt collapse owing to a quick diastolic runoff from the arterial tree. Indeed, all conditions that cause a brisk runoff produce a collapsing or bounding pulse (Table 11.8.). The collapsing quality is detected by the examiner placing his or her fingers or palm closed firmly over the radial pulse with the entire limb extended to the ceiling. Pulsus bisferiens, a double peak to the pulse, may be observed with the combination of aortic regurgitation and significant aortic stenosis.
- The patient's head often bobs with each cardiac pulsation.
- The BP reveals a wide pulse pressure owing to an increase in SBP and a DBP that is often less than 50 mmHg. Occasionally, Korotkoff sounds persist to zero with diastolic arterial pressure still greater than 60 mmHg.
- Arterial neck pulsations are usually prominent.

Table 11.8.
Causes of a Collapsing Bounding Pulse

<i>Cardiac causes</i>	<i>Noncardiac causes</i>
Aortic regurgitation	Arteriovenous fistula
Patent ductus arteriosus	Paget’s disease
	Pregnancy
	Fevers
	Thyrotoxicosis
	Vasodilator drugs

- Quinke’s sign: exerting mild pressure on the nail beds brings out intermittent flushing.
- Finger pulsations: collapsing pulsations in the finger pulps or tips.
- Traube’s sign: pistol-shot sounds over the femorals.
- Duroziez’s sign: compression of the femoral artery proximal to the stethoscope produces a systolic murmur and a diastolic murmur with distal compression.

The apex beat is virtually always displaced downward and outward to the left, indicating LV enlargement in patients with moderate or severe AR. A diastolic thrill may be palpated in the second right interspace or third interspace at the left sternal border, where the murmur of AR is most prominent.

Hallmarks of auscultation include the following:

- Typical high-pitched blowing, early decrescendo murmur begins immediately after the A₂. The early decrescendo murmur beginning immediately after A₂ is unmistakable to the trained ear and is best heard with the diaphragm pressed firmly against the chest, with the patient leaning forward and the breath held in deep expiration. The listener should then listen to the murmur with the patient breathing normally and in the recumbent position in order to train the ear for detection of the softest diastolic murmur.
- The degree of AR correlates best with the duration of the murmur and may be pandiastolic with severe regurgitation.
- Perforation of an aortic cusp may change the quality of the murmur to one that resembles the cooing of a dove.
- A mid or late diastolic rumble at the apex, the Austin-Flint murmur, may be heard as the regurgitant jet hits the anterior mitral leaflet, as it opens and closes during diastole. The leaflet’s shuddering can be heard with the stethoscope or observed with the help of Doppler echocardiography.
- The A₂ may be increased, decreased, or normal, and the accompanying aortic systolic murmur and thrill may represent flow rather than stenosis.

ELECTROCARDIOGRAM

The ECG commonly shows nonspecific ST-T wave changes, and with LVH, the pattern of LVH with volume overload is often present.

CHEST X-RAY

In patients with moderate or severe AR, dilatation of the left ventricle with elongation of the apex inferoposteriorly is almost invariably visible. Progressive further enlargement occurs over years in patients with severe AR. Dilatation of the ascending aorta is

common in Marfan's syndrome and other causes of aortic root dilatation (Table 11.7.). The typical appearance of linear eggshell calcification of the ascending aorta is a hallmark of syphilitic aortitis, which is now rare.

ECHOCARDIOGRAPHIC FINDINGS

Echocardiographical findings include the following:

- Detection of the type of aortic valve abnormality and underlying disease, for example, AR owing to bicuspid valve or vegetations caused by endocarditis.
- LV chamber dimensions: estimates of LV volume and ventricular function measurements (LV end-systolic dimensions, LV end-diastolic dimensions, fractional shortening or EF; *see* discussion under unfavorable dimensions).
- Dilatation of the aortic root.
- Aortic dissection.
- Other valve disease.
- Other associated states, for example, perivalvular abscesses in infective endocarditis.

AR is observed in 0–3% of otherwise normal hearts. Thus, AR is usually associated with structural heart disease. In contrast, approximately 60% of healthy individuals under age 30 has tricuspid regurgitation and pulmonary regurgitation, and 40% has mitral regurgitation that is not significant. Fortunately, the stethoscope is not capable of detecting most of these minor degrees of regurgitation. Thus, less harm is done if the physician relies on the tested stethoscope. Nonetheless, echocardiographical evaluation is of indispensable value in following patients with moderate-to-severe regurgitation and has improved clinical decision making, particularly concerning the timing of surgical intervention.

Color flow Doppler provides accurate quantification of AR. The degree of AR can be assessed by measuring the width of the aortic regurgitant jet. The measurement is assessed just under the aortic valve in the LV outflow tract as a fraction of the LV outflow tract. Mild AR is indicated when the width of the jet is up to one-third of the LV outflow tract; severe AR is indicated when the width of the jet is greater than two-thirds of the LV outflow tract; and moderate AR is present when the width of the jet is between one-third and two-thirds.

The area or absolute length of the jet of AR are not accurate parameters for estimating the degree of AR.

Management of Acute AR

Acute AR causing hemodynamic instability requires immediate aortic valve replacement. TEE gives accurate, rapid diagnostic information if adequate data cannot be obtained from conventional echocardiogram. Some stability is attempted with the use of nitroprusside, and if aortic dissection is diagnosed, an IV β -blocking agent is given before TEE or on the way to the operating room (*see* Chapter 10). Patients with bacterial endocarditis who are hemodynamically stable should be managed with appropriate antibiotics, and surgery should be deferred for 2 weeks, provided the patients respond. The development of first-degree atrioventricular (AV) block on the ECG is an ominous sign and suggests perivalvular abscess formation, which demands early operation if the diagnosis is confirmed.

Management of Chronic AR

Medical therapy plays an important role, because the timing of valve surgery presents an ongoing challenge for both physician and patient. A review of the natural history of the condition indicates the following:

- More than 75% of patients with moderate AR survive for at least 5 years.
- More than 50% of patients are alive 10 years after diagnosis.
- More than 90% of patients with relatively mild AR survive over 20 years.
- As with aortic stenosis, the occurrence of HF carries about a 2-year survival, whereas for angina survival is about 5 years.

Valve replacement should be considered before irreversible myocardial deterioration. Because timing is often difficult, close follow-up of the patient with minimal or absent symptoms is essential.

The hemodynamic severity of AR can be graded as follows:

- Mild, if peripheral signs are absent or slight, and LV size is normal.
- Moderate, if peripheral signs are present with mild-to-moderate increases in LV, but normal systolic function.
- Severe, if there are prominent, peripheral signs with severe LV enlargement or if any degree of ventricular enlargement is associated with LV dysfunction.

Pharmacologic Agents of Controversial Value

NIFEDIPINE

The unloading effect of nifedipine appears to be capable of reversing LV dilatation and LVH, and this agent may delay the need for valve surgery. In a study of 72 patients followed for 12 months, LV end-diastolic volume index decreased from 136 ± 22 to 110 ± 19 mL/m² ($p < 0.01$), and LV mass decreased from 142 to 115 g/m² (Fig. 11.2.). A 25% reduction of the mean LV wall stress and an increase in EF from 60 to 72% were observed. A small randomized clinical trial (RCT) done by Rahimtoola et al. in 1994, confirmed the beneficial effects of nifedipine. In asymptomatic patients with isolated severe AR and normal LV systolic function, 20 mg of nifedipine (slow release) twice daily was administered to 69 patients; 0.25 mg of digoxin daily was administered to 74 patients. After 6 years, 34% of the patients in the digoxin group required valve replacement, versus 15% of those in the nifedipine group. Valve replacement was necessary because of the development of LV dysfunction in 75% of patients on digoxin.

Nifedipine is superior to hydralazine, which does not decrease LV mass or significantly decrease LV end-diastolic or systolic dimensions. It appears that afterload reduction with nifedipine in patients with moderate-to-severe AR and normal LV function can achieve a 5-year survival rate approaching 87%. The 5-year survival rate for aortic valve replacement is approximately 72%, and the surgical mortality is 5%.

Nifedipine is given as the extended release preparation: Procardia XL or Adalat XL, 30 mg once daily. The extended-release formulation is preferable because the nifedipine capsule causes an early and transient peak effect; also, adverse effects are more frequent than those observed with the sustained release preparation.

Nifedipine has a mild, negative inotropic effect that is somewhat offset by sympathetic stimulation. Verapamil and diltiazem are contraindicated because of their negative ino-

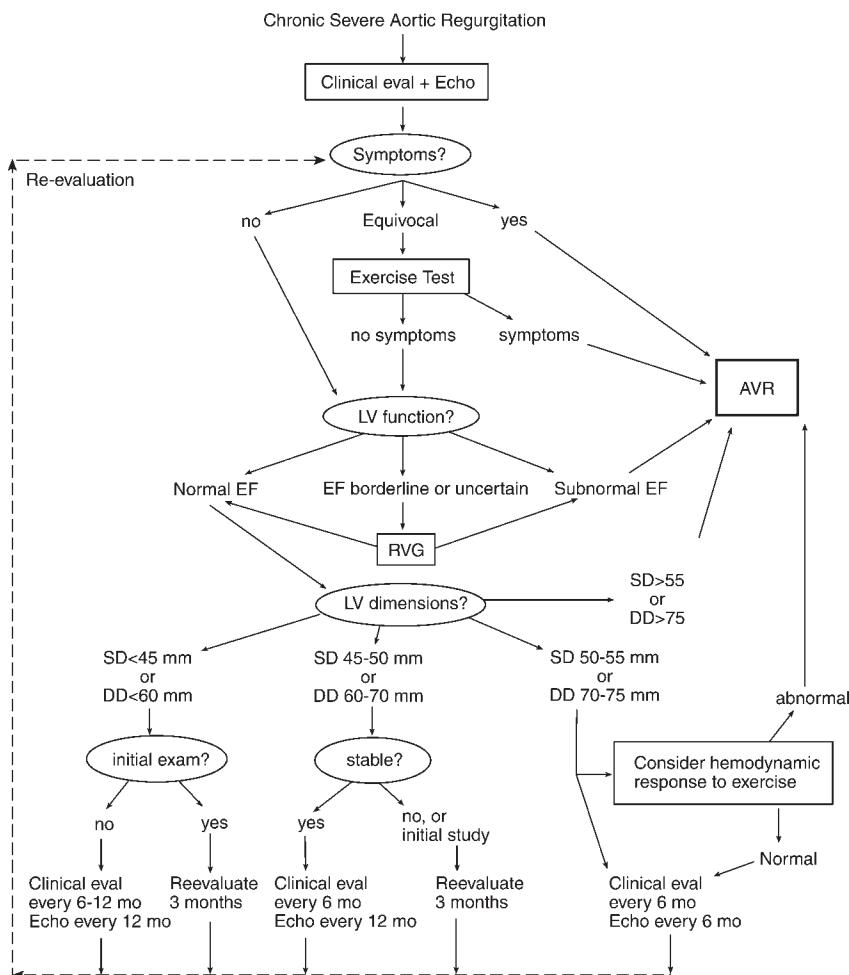


Fig. 11.2. Management strategy for patients with chronic severe aortic regurgitation. Preoperative coronary arteriography should be performed routinely as determined by age, symptoms and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. DD, end-diastolic dimension; RVG, radionuclide ventriculography; SD, end-systolic dimension. LV, left ventricular; AVR, atriocentric response. Reproduced from ACC/AHA Guidelines for Management of Patients with Valvular Heart Disease.

tropic effects and their propensity to cause bradycardia, which can worsen nocturnal angina or HF. Indeed, all vasodilators are not alike and hydralazine has not proven useful. Prazosin and other α_1 -blockers are contraindicated because postural hypotension and increased heart rate may occur; these agents do not decrease LV mass or favorably alter LV systolic or diastolic dimensions.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

In a study of 76 asymptomatic patients with mild-to-severe aortic regurgitation, randomized to enalapril or hydralazine, at 1 year, patients receiving enalapril had a significant reduction in LV and diastolic volume indexes. Hydralazine therapy showed no significant

changes. In a small study, quinapril therapy for 2 years caused a reduction in end-diastolic volume from a mean of 150–127 mL/m²; LV mass showed a reduction of 29%.

Nonetheless, Borer and Bonow indicate that in the single AR trial by Rahimtoola et al. that demonstrated an event-reducing benefit (of nifedipine compared with digoxin), the average SBP was greater than 150 mmHg, with many patients far exceeding this value. More recently, preliminary findings from retrospective analysis of 82 consecutive patients with AR entered prospectively into a Cornell natural history study associated nonrandomized drug treatment with increased mortality. Except for management of hypertensive patients, additional RCTs are needed to determine the value of afterload-reducing agents. The author advises the use of long acting nifedipine or amlodipine to patients with significant AR who fit the pattern of patients described in the 1994 study and SBP should be kept lower than 135 mmHg.

Angiotensin-converting enzyme (ACE) inhibitors have not been adequately tested. Caution is necessary because these agents have a marked lowering effect on DBP, which may worsen diastolic coronary perfusion in patients with AR, a situation that is prone to occur during sleep and can be deleterious in patients with significant, concomitant atheromatous coronary stenoses. These agents have been shown to be harmful in patients with angina and in patients with HF in the presence of AR; ACE inhibitors should be avoided in patients who manifest angina or silent ischemia. Calcium antagonists, unlike ACE inhibitors, do not usually cause a reduction in BP in normotensive individuals (*see* Chapter 8).

DIGOXIN

Digoxin should be given to all patients with moderate or severe AR, whether or not they are symptomatic. Digoxin increases resting EF. Peak exercise EF increases with both digoxin and nifedipine but not with hydralazine. The combination of digoxin and nifedipine improves chronic hemodynamics in symptomatic and asymptomatic patients with severe regurgitation. The combination requires testing in randomized trials in patients with severe AR with normal LV systolic function.

TIMING OF VALVE REPLACEMENT

Aortic-valve replacement in the United States carries a mortality of 4% when performed in isolation and 6.8% when performed with coronary bypass surgery.

There is a general agreement that symptomatic patients with severe chronic AR should have valve surgery in the absence of contraindications. Valve surgery is not indicated in asymptomatic patients with severe chronic AR who have good effort tolerance and normal LV function long-term vasodilator therapy with nifedipine reduces, and delays the need for aortic valve replacement in these patients.

Valve surgery is indicated in asymptomatic patients with severe AR and LV dysfunction: these individuals are expected to have LV end-diastolic volume index greater than 140 mL/m², EF 50% or less, end-diastolic volume greater than 70 mm, or end-systolic diameter greater than 50 mm.

Between these two extremes is a large group of patients for whom firm data comparing the effect of prognosis of medical with surgical management are lacking, and widely accepted criteria or a task force consensus that may guide the physician are absent.

Patients with moderate or severe AR should be followed at least every 6 months. A careful history is necessary, including questioning of a spouse or relative who may be able to describe symptoms that are denied by the patient. A cardiovascular examination and

ECG are done at each visit. Echocardiography is advisable every 6 months if LV end-diastolic volume index is greater than 90 mL/m² or LV end-systolic dimension is greater than 45 mm. A biannual exercise test is useful to assess functional capacity. If symptoms manifest (dyspnea on mild or moderate exertion, orthopnea, or chest discomfort), cardiac catheterization is necessary for verification of echocardiographical dimensions with a view to surgery.

Patients with prolonged severe LV dysfunction and marked LV dilatation are not expected to benefit from surgery. Although there are not fixed rules that would indicate clear contraindications, surgery generally is not advisable in patients who have EF less than 35% or prolonged severe LV dysfunction (18 months or more).

In these patients, symptoms, signs, and hemodynamic parameters of LV dysfunction may persist or worsen after successful valve replacement. Patients with EF greater than 45% and less than 1 year of LV dysfunction usually have a successful postoperative outcome, but those with EF less than 45% and prolonged LV dysfunction (more than 18 months) have a poor postoperative survival. Repeated radionuclide or echocardiographical assessment of EF and end systolic volume, especially at rest, is necessary for decision making. It must be emphasized that radionuclide EF is not accurate in patients with AF.

The role of the cardiologist is to consider interventional therapy before the occurrence of significant LV dysfunction. At this stage of careful follow-up, surgery is offered if LV function is impaired, if exercise capacity is reduced, or if LV dimensions are “highly abnormal” or show significant deterioration. Management of the asymptomatic patient with severe AR, depressed LV function, and abnormal dimensions, as indicated, should be individualized.

UNFAVORABLE LV DIMENSIONS

The following echocardiographical or catheter dimensions may be used to help serve in decision making regarding timing for valve surgery. No single estimation should be accepted for making decisions. Marked changes or rate of change at 3- or 6-month visits should guide the physician in the following:

- LV end-systolic dimension between 50 and 55 mm. A dimension greater than 50 mm usually indicates LV dysfunction and, as outlined earlier, one does not wait for such ominous signals.
- LV end-diastolic dimension greater than 70 mm.
- LV end-systolic volume index greater than 60 mL/m²; greater than 90 mL/m² indicates severe LV dysfunction.
- LV end-diastolic volume index 140–150 mL/m²; greater than 180 mL/m² indicates severe LV dysfunction.
- EF less than 50% or fractional shortening less than 35%: fractional shortening less than 25% indicates severe LV dysfunction. An EF less than 45% represents moderately severe LV dysfunction, and less than 35% indicates severe dysfunction.

The asymptomatic patient with severe AR should meet one or more of the above criteria and, in addition, should show a marked change 4–6 months before being regarded as a candidate for surgery. These patients should have cardiac enlargement on chest radiograph. Truly asymptomatic patients who do not have cardiac enlargement on chest radiograph usually do not require surgery. It must be re-emphasized that no single measurement is ideal and that most of them be obtained to enable the cardiologist to apply the

best clinical judgment, taking into account other variables, such as age, occupation, CAD, and intercurrent illness.

Aortic-valve replacement in the United States carries a mortality of 4% when performed in isolation and 6.8% when performed with coronary bypass surgery.

An algorithm for the management of patients with chronic severe AR is given in [Fig. 11.2](#).

Preparations for surgery include attention to dental work under antibiotic cover. Coronary angiography is necessary in patients over age 35 or in those with angina. The choice of prosthetic heart valve is discussed in this chapter under aortic stenosis. Elective valve surgery has a 3–6% operative mortality and emergency surgery over 10%. The 5-year survival for valve implant ranges from 60 to 85%.

MITRAL STENOSIS

Mitral stenosis is almost always a result of previous rheumatic fever. It takes 2 or more years after the rheumatic episode for sufficient fibrosis and thickening of the valve to produce the typical murmur. Most patients remain asymptomatic for 15–20 years after an episode of rheumatic fever, which is subclinical in over 50%.

Over the past 30 years, the problem of rheumatic valve disease has shown a marked decline in North America, the United Kingdom, and Europe. However, the disease is still endemic in much of Asia, Africa, the Middle East, Latin America, and the West Indies. Indeed, in these countries, significant mitral stenosis may emerge within a few years of the initial acute rheumatic fever and result in symptomatic disease in juveniles and young adults.

Symptoms

The patient with mild mitral stenosis, valve area 1.6–2.0 cm², may develop mild dyspnea on moderate-to-severe exertion but is usually able to do all normal chores and lifestyle is not altered. Symptoms progress slowly, if at all, over the next 5–10 years. However, infection, pregnancy, or tachycardias, including AF, may precipitate severe dyspnea.

Patients with moderately severe mitral stenosis, valve area 1–1.5 cm², usually have symptoms that affect or interfere with daily living. Dyspnea owing to progressive pulmonary venous hypertension becomes bothersome. Breathlessness is precipitated by moderate activity such as walking 100 yards briskly, walking up an incline, or even running slowly for 20 yards. Some patients with mild mitral stenosis may reduce activities and tolerate symptoms for several years. Pulmonary infection or AF often precipitates pulmonary congestion, emergency room visits, or hospitalization. Cough, shortness of breath, wheeze, and hemoptysis may mimic bronchitis for several months because the subtle signs of mitral stenosis can be missed by the untrained auscultator. Palpitations are usually a result of AF, and some patients may present with a very rapid tachycardia or systemic embolization.

Severe mitral stenosis, valve area less than 1 cm² and valve area index less than 1 cm²/m², usually causes symptoms on mild exertion. The patient presents with one or more of the following symptoms: progressive dyspnea, palpitations, marked fatigue, and occasionally cough, hemoptysis, hoarseness, or chest pain. Progression may be rapid with increasing edema, orthopnea, paroxysmal nocturnal dyspnea, and marked breathlessness. However, some patients tolerate dyspnea and are able to continue work that is not strenuous, at their own pace, for 3–12 months before interventional therapy. Fortunately,

with mitral stenosis, patients with the most bothersome symptoms benefit the most from mitral valvotomy.

Some patients present with progressive symptoms and signs of low CO and right HF with only mild pulmonary congestive features as a result of reactive hyperplasia of pulmonary arterioles and pulmonary arterial hypertension, a scenario appropriately termed “protected” mitral stenosis. At the other extreme, some patients present with florid pulmonary edema associated with only passive pulmonary arterial hypertension and mild or absent right HF, which is considered “unprotected” mitral stenosis. A mixture of protected and unprotected mitral stenosis is commonly observed.

Physical Signs

On inspection, a malar flush is common in the presence of long-standing, moderately severe mitral stenosis. A lower left parasternal lift of heave owing to right ventricular hypertrophy (RVH) may be present.

The apex beat is tapping in quality, usually not displaced. A diastolic thrill localized to the apex beat may be palpated. Auscultation reveals a loud, slapping first heart sound and is so typical that it warns the examiner to search for other signs of mitral stenosis. Immobility of the cusps reduces this valuable sign.

The pulmonary A_2 is intensified and this vibration associated with pulmonary valve closure is often palpable with significant pulmonary arterial hypertension.

An opening snap, a sharp high-pitched sound, is a hallmark of mitral stenosis. The opening snap is best heard with the diaphragm pressed firmly just internal to the apex beat and occurs from 0.04 to 0.14 seconds after the second heart sound. The opening snap may be heard over a wide area and, with severe mitral stenosis, usually occurs less than 0.08 seconds after the second heart sound, audible immediately rather than after a definite gap. The opening snap disappears if the valve becomes heavily calcified and nonpliable.

The loud, slapping first heart sound and opening snap produce a particular cadence that alerts the examiner.

The opening snap is followed by a low-pitched, mid-diastolic rumbling murmur that is associated, if there is sinus rhythm, with presystolic accentuation, best heard with the bell lightly applied over the apex beat. The murmur often is localized to an area the size of a coin and can easily be missed; it is brought out by exercising the patient and listening with the patient lying on the left side. Occasionally, critical mitral stenosis may cause a marked reduction in transmitral flow, and the murmur may be hardly audible. There is evidence that in these cases, the disease and contracted chordae increase the impedance to ventricular filling so that the reduced mitral valve area is no longer the limiting factor.

The severity of mitral stenosis correlates best with the length of the murmur rather than the intensity.

Investigations

CHEST X-RAY HALLMARKS

Chest X-ray hallmarks of mitral stenosis include the following:

- Straightening of the left heart border owing to left atrial enlargement.
- Larger than normal double density, seen through the right half of the cardiac silhouette, indicating left atrial enlargement.
- Elevation of the left main stem bronchus caused by distension of the left atrium with widening of the angle between the two main bronchi.

- Redistribution: restriction of lower lobe vessels and dilatation of the upper lobe vessels.
- If HF is present, signs of interstitial edema are present: Kerley B lines owing to lymphatic engorgement and fibrosis, perihilar haze, and eventually frank pulmonary edema are observed.
- Fluoroscopy is no longer commonly done but shows posterior displacement of the barium-filled esophagus.
- The heart size on posteroanterior X-ray is generally normal or near-normal, and the lateral film should be assessed for RV enlargement: “creeping up the sternum.”

ECG HALLMARKS

ECG hallmarks of mitral stenosis include the following:

- Signs of left atrial enlargement are common with moderate and severe mitral stenosis: broad bifid P-waves in lead 2 and, more specifically, an increase in the P-terminal force (PTF₁) 40 ms/mm or more, measured in V₁. Hazen et al. showed that when the PTF₁ is greater than 40 ms/mm, 95% of individuals had left atrial size greater than 4 cm; when the PTF₁ is 60 ms/mm or more, 75% had left atrial size greater than 6 cm.
- Right axis deviation of 90-150° reflects severe mitral stenosis.
- RVH may be present with severe stenosis but does not correlate well with the degree of pulmonary hypertension.
- AF is common with moderate longstanding rheumatic disease, with the left atrial size exceeding 4.5 cm, and is characteristically coarse in appearance.

ECG stress testing is of value in selected patients who are suspected of denying symptoms with the presence of a moderate degree of stenosis; functional capacity can be assessed.

ECHOCARDIOGRAPHICAL ASSESSMENT

Assessment of echocardiogram can reveal the following:

- The mitral diastolic gradient can be defined.
- Excellent quantification of mitral valve orifice area.
- Left atrial enlargement is uniformly present, and the size can be accurately determined.
- The degree of calcification of the mitral valve leaflets can be verified.
- Decreased posterior leaflet movement is often observed.
- The degree of RV enlargement can be documented.
- LV size is expected to be small;
- RV systolic pressures reflect the degree of pulmonary hypertension.
- The degree of concomitant mitral regurgitation can be assessed.

A flat E to F slope (or EF slope) less than 10 mm/second may indicate severe mitral stenosis, but this measurement is no longer used for quantitating the degree of obstruction. Marked alteration of the E to F slope may be observed in patients with aortic stenosis and regurgitation with no evidence of mitral stenosis and in patients with impaired LV filling caused by reduced LV compliance.

Medical Therapy for Mitral Stenosis

All patients should receive prophylaxis for the prevention of rheumatic fever for at least 25 years from the acute episode and up to age 45, whichever is the longest. Although pure mitral stenosis is rarely the site of endocarditis, trivial mitral regurgitation is often present and endocarditis prophylaxis should be strongly enforced (*see* Chapter 12).

MILD MITRAL STENOSIS

Patients are usually asymptomatic and should be followed annually. A chest X-ray and echocardiogram are done initially or if needed because of worsening symptomatology. Follow-ups about every 5 years should suffice. No treatment is indicated, except for advice on mild dietary salt restriction and avoidance of excessive weight gain and physically strenuous occupations.

MODERATE MITRAL STENOSIS

Moderate mitral stenosis, valve orifice area 1–1.5 cm², is usually mildly symptomatic. Salt restriction is advisable. Potassium-sparing diuretics, such as Moduretic (Moduret), ameliorate shortness of breath and prevent potassium and magnesium loss (*see* Chapter 5). If palpitations are bothersome or short runs of ST are documented, a small dose of a β -blocking drug is useful: 25–50 mg of metoprolol twice daily, 25 mg of atenolol daily, or an equivalent dose of another β -blocker should suffice. Digoxin is not indicated for patients with sinus rhythm or HF with pulmonary congestion, except as prophylaxis against fast ventricular rates and pulmonary edema if AF develops.

Chest infections must be vigorously treated because hypoxemia increases pulmonary hypertension and may precipitate right HF. Also, tachycardia may precipitate pulmonary edema. If the patient is managing daily chores and enjoying a near normal lifestyle, the interventional approach can await some progression of the disease or symptoms but is not delayed in very active patients who need to engage in strenuous work or sport. Marked limitation of lifestyle in such individuals may require early corrective measures. A patient with moderate mitral stenosis should be followed at least twice yearly, but annual echocardiography should suffice.

SEVERE MITRAL STENOSIS

Severe mitral stenosis, valve area corrected for body surface area (valve area index) less than 1 cm²/m², usually requires interventional therapy within 3–6 months to abolish symptoms or decrease complications and/or progressive increase in pulmonary vascular resistance.

ATRIAL FIBRILLATION

Digoxin: AF with a fast ventricular response decreases LV filling and may precipitate pulmonary congestion. Digoxin is indicated to control the ventricular response. Digoxin is discussed in detail in Chapter 5. If palpitations remain bothersome and the heart rate cannot be controlled with digoxin, as often occurs in very active individuals.

β -Blocker. The addition of a small dose of β -blocking drug is most helpful. The latter agents can also be used to decrease sinus tachycardia that is easily provoked in some patients without AF. Many physicians regard the development of AF as an indication for intervention when stenosis is of moderate severity, because the prospects for permanent restoration of sinus rhythm decreases rapidly with time from onset of arrhythmia.

Importantly, in pregnant patients with moderate-to-severe mitral stenosis in whom surgery must be deferred for a short while, the use of a small dose of a β -blocking agent can control sinus tachycardia which can precipitate life-threatening pulmonary edema.

ANTICOAGULANTS

The patient with AF must be anticoagulated, if no contraindication exists, because systemic embolization is common. Warfarin is given to maintain the INR 2–3. These tests

are done at least every 2 weeks until stabilized, and then once a month should be sufficient. If contraindications to anticoagulant therapy exist, enteric-coated aspirin (325 mg daily) is advisable.

Interventional Management

Balloon valvuloplasty or surgery to relieve valvular obstruction is indicated for most symptomatic patients who have moderate to severe mitral stenosis, valve orifice less than 1 cm², as determined by Doppler echocardiography. The results of this technique correlate sufficiently well with catheterization data. Cardiac catheterization is not required in patients under age 40, in whom IHD is not present or suspected and who have typical, clinical features of mitral stenosis that are confirmed by Doppler echocardiography.

Mild mitral stenosis, valve area 1.6–2.0 cm², often remains minimally symptomatic for 5–10 years or more. However, as explained earlier, in countries where rheumatic valve disease is endemic, tight mitral stenosis may emerge at a faster rate in the adolescent or young adult.

Moderately severe mitral stenosis, valve area 1–1.5 cm², usually does not require intervention, but decisions must be individualized. In these patients, intervention may be required the following situations:

- For symptomatic young patients engaged in strenuous activity.
- If AF supervenes.
- To allow a further pregnancy in a patient who manifested pulmonary edema in a previous pregnancy.

Elective procedures are sometimes performed in women who anticipate pregnancy, but relief of obstruction may be required during the second and third trimester of pregnancy, because the valve orifice is no longer large enough to permit the necessary increase in CO to occur without an unacceptable rise in left atrial and pulmonary venous pressures. Interventional therapy may take the form of the following:

- Surgical closed commissurotomy.
- Surgical open commissurotomy.
- Balloon valvuloplasty.
- Valve replacement.

SURGICAL OPEN VERSUS CLOSED COMMISSUROTOMY

Closed mitral commissurotomy was the technique of choice until the early 1970s for patients with severe mitral stenosis with noncalcified pliable valves. Open commissurotomy has largely replaced the closed technique, except in much of Asia, Africa, Latin America, and the West Indies, where closed valvotomy has remained the treatment of choice.

Undoubtedly, there will be a resurgence of closed commissurotomy in North America and Europe based on the survey entitled “Outcome probabilities and life history after surgical mitral commissurotomy.” In this study, Hickey et al. compared the outcome in 236 open and 103 closed commissurotomies performed between 1967 and 1988. The survival rate at 1 month, 1 year, 5 years, and 10 years was 99.7%, 99%, 95%, and 87%, respectively, with outcomes being similar after closed and open commissurotomy. Thus, both techniques provide excellent relief, although eventual restenosis is usual over the ensuing 10–20 years or more after mitral valvotomy. Mitral valve replacement was

required in 22% within 10 years of commissurotomy. In the entire study group, thromboembolism occurred in 33 (10% of 339 patients) and 9 (2.6%) patients had significant cerebral embolism.

Moderate-to-severe mitral stenosis accompanied by mild-to-moderate mitral regurgitation is not uncommon, and open repair with limited opening of the Tubbs dilator is considered an option for this category of patients.

TECHNIQUE FOR CLOSED SURGICAL COMMISSUROTOMY

The right index finger is inserted into the left atrium via an incision in the left atrial appendage. A Tubbs dilator, which has been introduced via a purse string stitch in the anterolateral LV freewall near the apex but not directly into the apex, is guided by the finger into the mitral valve. Four dilatations, commencing at 2.5 cm and terminating with 4 cm, are performed, followed by amputation or ligation of the left atrial appendage. The experienced surgeon is able to assess the degree of splitting and the degree of regurgitation (if any) after each dilatation.

MITRAL BALLOON VALVULOPLASTY

Percutaneous mitral balloon valvuloplasty appears to give hemodynamic results that are comparable with surgical closed commissurotomy, as shown by an 8-month follow-up study. The valve area is increased 100% from 1 to 2 cm² in up to 77% of cases. A mortality of up to 2.7% has been reported by the Valvuloplasty Registry. The National Heart, Lung, and Blood Institute 30-day follow-up report on 738 patients indicates an 83% overall clinical improvement and mortality of 3%; 4% of patients requires valve surgery. An iatrogenic atrial septal defect (ASD) has been reported to occur in 20–87% of patients depending on criteria used for defining the ASD, which takes up to 6 months to close. The defect, however, is usually small, the magnitude of the shunt being less than 2:1, and only few of these ASDs are clinically significant. Complication rates are relatively high (*see Table 11.9*).

The procedure should be done only by highly trained and experienced operators. In such hands, the procedure is first choice in appropriately selected patients for relief of severe mitral stenosis.

A multicenter study of 4832 patients in China and 600 patients in India indicated that mitral balloon valvuloplasty is an effective and safe procedure that can be performed worldwide. The reported restenosis rate of approximately 12% at 3 years is similar to that after closed surgical commissurotomy. Mitral balloon valvuloplasty must have a mortality less than 1 % to be considered an acceptable alternative to surgical commissurotomy. The proper selection of patients and technical aspects are changing such that morbidity and mortality from the procedure are expected to fall.

Patient Selection

The patient selection for mitral balloon valvuloplasty is crucial to obtaining a salutary effect with a minimum number of complications. The patients are usually selected based on two-dimensional echocardiographical results. Ideally, the patients should have the following:

- Very symptomatic severe mitral stenosis, mitral valve area less than 1 cm².
- Noncalcified, mobile valve with no subvalvular fibrosis (echo score <8): valve rigidity, valve calcification, thickening, and subvalvular fibrosis are graded from 0 to 4, and the

Table 11.9.
Complications of Mitral Balloon Valvuloplasty

<i>Clinical parameters</i>	<i>Complications, incidence (%)</i>
Mortality	2.7
Emergency surgery	6.7
Cardiac tamponade	6.7
Embolism	2.7
Significant mitral regurgitation	13
Emergency valve replacement	4
Restenosis	16
Latrogenic atrial septal defect	20–87

points are added together. The best candidates are patients who have an echo score of <8. Long-term results of mitral valvuloplasty are not as successful in patients with fluoroscopically visible mitral valve calcification, as in those without calcification.

Contraindications include the following:

- Bleeding disorder: abnormal prothrombin time, prolonged partial thromboplastin time, increased bleeding time (the patient must discontinue aspirin compounds for at least 1 week before the procedure).
- Left atrial or appendage thrombus.
- Recent embolization.
- Severe mitral valve calcification of subvalvular fibrosis.
- Moderate or severe mitral regurgitation.
- Cardiothoracic deformity.

TEE has a role in obtaining information needed for the selection of patients for balloon valvuloplasty, such as calcification, thickening, mobility, and subvalvular fibrosis. Atrial or appendage thrombus is best visualized with TEE. The technique is also of value in assessing the magnitude of the ASD after the procedure.

Mitral Valve Replacement

Mitral valve replacement using prosthetic valve implant may be required because of the presence of moderate-to-severe mitral regurgitation coexisting with mitral stenosis. Replacement may also be selected for management of heavily calcified and immobile valves, which are often conical in shape, when they are considered to be beyond repair at the time of surgery. In general, a mechanical valve is preferred in the mitral area (*see* earlier discussion of prosthetic valve choice and [Table 11.5.](#)). In up to 50% of patients, AF is present; a mechanical valve is a natural choice in this case because anticoagulants are necessary. In the young female who may wish to become pregnant, a bioprosthesis is sometimes recommended. However, a mechanical valve can be used in this situation with discontinuation of oral anticoagulants; heparin can be used subcutaneously for the first 4 months of pregnancy and again for the last 3 weeks. Importantly, in the young patient, accelerated calcification of a bioprosthesis may occur. Calcification, as well as pannus formation, may require a second operation.

Table 11.10.
Causes of Mitral Regurgitation

Acute
Myocardial infarction
Papillary muscle dysfunction
Rupture chordae tendineae
Rupture of papillary muscle
Mitral valve prolapse
Rupture chordae tendineae
Rapid progression of prolapse
Endocarditis
Acute
Rare subacute endocarditis
Chronic
Rheumatic
Mitral valve prolapse
Healed endocarditis
Ischemic heart disease
Functional dilatation

MITRAL REGURGITATION

Although mitral stenosis is nearly always a result of rheumatic disease, mitral regurgitation is a common valvular lesion that is caused by a number of conditions that alter the mitral valve apparatus: valve leaflets, annulus, chordae, and papillary muscles. Common causes of acute and chronic mitral regurgitation are given in [Table 11.10](#).

Acute Mitral Regurgitation

Acute mitral regurgitation commonly occurs during acute MI, which causes papillary muscle dysfunction, and less commonly, chordal or papillary muscle rupture (*see* Chapter 2). Other causes of acute mitral regurgitation are listed in [Table 11.10](#).

Chronic Mitral Regurgitation

Patients may tolerate a mild to moderate degree of mitral regurgitation for 5–20 or more years without the appearance of HF. Chronic volume overload, however, causes slow progressive dilatation and mild hypertrophy of the left ventricle.

Characteristically, a loud holosystolic murmur is heard maximal at the apex with radiation to the axilla, accompanied by a third heart sound gallop if regurgitation is moderate to severe. In patients with posterior papillary muscle dysfunction causing mitral regurgitation, however, the murmur radiates anteriorly and is best heard at the left sternal border without radiation to the axilla.

Mild-to-moderate shortness of breath indicates pulmonary congestion or LV dysfunction and should be managed with afterload-reducing agents, particularly ACE inhibitors to encourage forward flow at the expense of regurgitation; small doses are advisable: 6.25 mg of captopril twice daily for several days, increasing slowly to avoid hypotension to a maintenance of 37.5 mg twice daily (maximum 75 mg in two or three divided doses or equivalent doses of enalapril 10–30 mg).

A small dose of a β -blocking drug (25 mg of atenolol or 5 mg of bisoprolol) appears to ameliorate abnormal ventricular geometry and the author advises this therapy because it has caused lifestyle improvement in his practice. If concomitant IHD with angina is present and LV dysfunction is not severe, nifedipine is preferred to ACE inhibitors; in these patients, ACE inhibitors may increase angina. Also, digoxin and the judicious use of diuretics in combination with extended-release nifedipine may cause some beneficial effects before consideration of early valve repair or valve replacement. AF with a rapid ventricular response is managed with digoxin and anticoagulants to prevent embolization. Progressive dyspnea is a late-stage symptom and HF should be anticipated and prevented by timely surgical intervention.

Surgical Treatment

The timing of valve surgery, whether it is repair or valve replacement for chronic mitral regurgitation, remains a trial in decision making as with that of AR. An algorithm for the management of patients with chronic severe mitral regurgitation is given in [Fig. 11.3](#).

Patients with mitral valve prolapse and acute complications are often suitable for valve repair. There is an increasing tendency to attempt valve reconstruction. It is advisable to repair as many and as often as feasible, but success depends on the skill of the surgeon. For mitral stenosis and regurgitation, many valves are beyond repair and require replacement. Surgery should be considered in patients who have moderately severe mitral regurgitation before the development of severe pulmonary arterial hypertension and before a fall in EF to less than 60%. The interpretation of EF has to be adjusted downward to take into account the low impedance to retrograde flow resulting from mitral regurgitation. A patient with severe mitral regurgitation and an EF less than 30% will have a prohibitively high surgical mortality and will fare better with afterload reduction and digoxin. Because of the problems of assessing EF in the presence of mitral regurgitation. Other parameters of LV function have been used, including end-systolic volume index greater than 50 mL/m².

If surgery is done before the manifestations of the aforementioned parameters, survival, functional class, and LV systolic function should show significant improvement. If mitral regurgitation is moderately severe and LV dysfunction is present, it is hazardous to procrastinate. Early surgery is preferable. It is probably safe to wait until end systolic diameter reaches 40 mm but not greater than 50 mm. When the end systolic diameter is less than 40 mm in an asymptomatic patient deemed to have severe mitral regurgitation by other parameters, close observation without surgery and the use of long acting nifedipine or ACE inhibitor may be considered particularly to maintain SBP less than 135 mmHg. Clear answers will only become available in these difficult clinical situations, when the results of further large clinical trials are available.

In patients with predominant posterior leaflet prolapse, repair of the posterior leaflet followed by insertion of a nonflexible ring, as recommended by Carpentier, appears to be successful in preventing postoperative systolic anterior motion of the mitral valve.

In some patients with heavily calcified valves, the mitral valve annulus can be decalcified and valve repair, decalcification, and annuloplasty should be considered based on Doppler echocardiographical data. TEE gives a more accurate visualization of the mitral valve, however, and is advisable in potential candidates; the latter is justifiable and cost-effective, especially in view of the difficult decision as to timing of surgery. The tricuspid valve is also often severely incompetent; tricuspid annuloplasty is advisable in such cases.

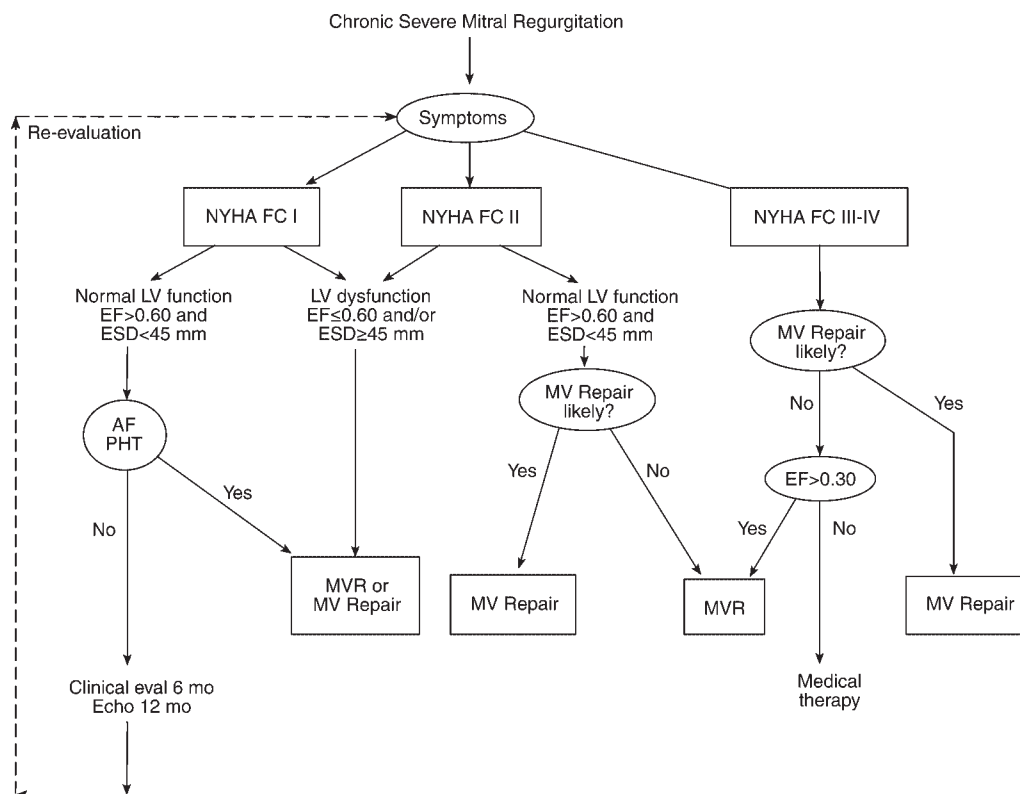


Fig. 11.3. Management strategy for patients with chronic severe mitral regurgitation. AF, atrial fibrillation; EF, ejection fraction; ESD, end-systolic dimension; FC, functional class; NYHA, New York Heart Association; PHT, pulmonary hypertension; MV, mitral valve; MVR, mitral valve replacement. Reproduced from ACC/AHA Guidelines for Management of Patients with Valvular Heart Disease.

Intraoperative TEE is of considerable value in assessing valve repair. The surgeon ensures excellent coapting edges and lines of closure; if the geometry is ideal, saline is pumped into the ventricle.

MITRAL VALVE PROLAPSE

Mitral valve prolapse is said to be a common condition affecting an estimated 5% of the US population. The incidence of mitral valve prolapse has been exaggerated

because of the inclusion of a large number of patients with a normal variant of mitral valve closure but with correct coaptation; leaflets may only billow slightly into the left atrium with normal coaptation. Also, the appearance may result from the normal saddle shape of the normal mitral ring.

The minor variant with a click, without a murmur and nondiagnostic echocardiographical features commonly labeled mitral valve prolapse, is subject to interpretation, and this “normal variant” disappears after age 40. Probably because of the inclusion of normal variants with billowing leaflets without true prolapse, the incidence of mitral valve prolapse is reported to be as high as 30% at age 10–20, 15% at age 30, 10% at age

50, 3% at age 70, and less than 1% at age 80. Under age 30, the female to male ratio is 3:1, but at age 70, both men and women are about equal. The incidence of significant mitral valve prolapse is about 6% in adult women and 3% in men. Genuine mitral valve prolapse has a familial incidence of about 33% as noted in first-degree relatives.

Causes of mitral valve prolapse include the following:

- In developed countries, the common underlying process is a degenerative nonrheumatic condition of unknown etiology described as a dyscollagenosis or myxomatous degeneration of the mitral valve. An increase in the spongiosa, myxomatous tissue, in the middle layer of the mitral valve leaflet, encroaches upon the fibrosa. The anterior and posterior leaflets become elongated, thickened, voluminous, and grossly redundant. The chordae become thin and elongated and have a propensity to rupture. Herniation of the posterior leaflet above the anterior leaflet may occur. A mural endocardial fibrous plaque is often observed beneath the posterior leaflet in patients who die suddenly from mitral valve prolapse. The mitral valve annulus is often dilated in patients with significant regurgitation, and in those patients who die suddenly, calcification and fibrosis of the annulus appears to be a common finding.
- Myxomatous changes and mitral valve prolapse are associated with Marfan and Ehlos-Danlos syndromes and osteogenesis imperfecta.
- Rheumatic heart disease, where this disease is still endemic. A dilated annulus allows elongation of chordae with, occasionally prolapse of the anterior leaflet, but marked billowing or redundancy of leaflets are unusual.
- Papillary muscle dysfunction because of IHD.

Symptoms

Most patients are asymptomatic. Dyspnea is rather vague, often occurs at rest, and is commonly out of proportion with the degree of mitral regurgitation that is usually asymptomatic in over 80% of patients. Extreme fatigue, dizziness, anxiety, panic disorders, palpitations, presyncope, syncope, and chest pain may occur without a satisfactory explanation. Psychogenical factors play a role in the varied symptomatology. Some symptoms relate to the presence of autonomic dysfunction with increased levels of circulating catecholamine, a hyperadrenergic state, and, in some patients,

Increased vagal activity is present. In this condition, there is a tendency for the sinus rate to increase steeply in the early part of exercise, and the high frequency of palpitations has been attributed to this pattern of response in these patients. It is not surprising, therefore, that Holter monitoring commonly shows sinus tachycardia when palpitations are a complaint.

Physical Signs

One or multiple mid- or late-systolic clicks of nonejection type may be constant or intermittent, changing with posture or maneuvers, but do not prove the existence of mitral valve prolapse. The timing of clicks may be misinterpreted as gallop sounds, but apart from their timing, clicks can be differentiated from a third heart sound by the high-pitched quality and by being most audible with a diaphragm. In some patients, the click is followed by a murmur; in others, only a murmur is present.

The murmur has typical features, such as the following:

- A typical late systolic murmur is unmistakable and confirms the diagnosis.

- The murmur is usually crescendo–decrescendo, and the auscultator gets the impression that the murmur is occurring synchronously with the second heart sound, and the murmur often extends through the aortic A₂.
- A whoop, a short honking sound, or a sound of other musical quality may highlight the murmur, which changes in intensity depending on LV volume and BP.
- The late systolic murmur or click is heard earlier and made louder by the following maneuvers that reduce LV volume: standing, tilting upright, valsalva, and tachycardia. Amylnitrite decreases ventricular volume and BP; therefore, the murmur is heard earlier but is made softer.
- The murmur or clicks are heard later and are softer with maneuvers that increase LV volume or decrease BP: squatting, bradycardia, β -blocking agents. Thus, the physician should listen to the patient lying, standing, and squatting because the murmur may be heard only on standing. With more severe mitral regurgitation, the duration of the murmur is longer and may become pansystolic.
- When chordal rupture occurs, the murmur changes in quality and radiation.
- The posterior mitral leaflet often has three scallops; rupture of the chorda to the middle scallop of the posterior leaflet is the most common chordal rupture. The resulting murmur radiates anteriorly and is maximal at the lower left sternal border and radiates toward the upper right sternal edge. The crescendo–decrescendo quality may simulate an aortic systolic murmur. However, the late timing of the murmur of mitral valve prolapse is a distinguishing feature that differentiates the murmur from the early timing of aortic valvular murmurs.
- Chordal rupture of the anterior leaflet causes the murmur to radiate to the posterior axilla.
- The flail mitral valve produces a loud murmur, the intensity of which is characteristically accentuated over the spine and may be heard from the occiput to the sacral spine.
- The mitral regurgitant jet can be identified by TEE; it moves in a counterclockwise direction with flail anterior leaflet and clockwise with posterior leaflet involvement.

Approximately 15% of patients with mitral valve prolapse has skeletal abnormalities: “straight back,” pectus excavatum or carinatum, scoliosis, or some features of Marfan syndrome.

Complications

SEVERE MITRAL REGURGITATION

Severe mitral regurgitation occurs in approximately 10% of patients with true mitral valve prolapse and is five times more common in men over age 45 than in women. Although mitral valve prolapse occurs most commonly in women, severe mitral regurgitation requiring surgery occurs in about 5% of men and less than 1.5% of women. Chordal rupture is a common occurrence in patients with severe mitral regurgitation.

ARRHYTHMIAS

Arrhythmias commonly occur and include ventricular premature complexes (VPCs), atrial ectopics, paroxysmal supraventricular tachycardia, and occasionally AF. Lethal arrhythmias have been reported (*see* Chapter 6).

SUDDEN DEATH

Sudden death, although rare, occurs in healthy, young, active individuals and is unexplained. [Table 11.11](#) lists clinical and morphological features in 15 patients who died suddenly secondary to mitral valve prolapse. These data and a review of previously

reported studies on 63 patients indicate that patients with mitral valve prolapse who die suddenly have the following clinical and morphological hallmarks:

- Women aged 21–51, without significant mitral regurgitation (70%).
- Dilated mitral valve annulus (80%).
- Elongated anterior mitral valve leaflet (over 80%).
- Abnormal elongated posterior mitral leaflet, and often there is herniation of the posterior leaflet above the anterior leaflet (approximately 80%).
- Fibrous endocardial plaque under the posterior mitral valve leaflet (up to 75%).
- Significant, moderate-to-severe prolapse of the mitral valve (53%).
- Ruptured chordae (33%).
- Significant, moderate or greater mitral regurgitation (10%).
- Mitral regurgitant murmur (50%).
- A click is present (only 25–37%).
- Arrhythmia (over 50%); VPCs (about 33%).

ENDOCARDITIS

The exact incidence of endocarditis in patients with true mitral valve prolapse is unknown but is estimated to be in the range of 1 in 6000 in all patients with mitral valve prolapse and about 1 in 2000 of those patients with mitral regurgitation (*see* Chapter 12).

SYSTEMIC EMBOLIZATION

TIAs, stroke, retinal arteriolar occlusions, and amaurosis fugax are rare complications of mitral valve prolapse owing to embolization of bland emboli; the exact incidence has not been accurately assessed.

Therapy

GENERAL ADVICE AND MANAGEMENT OF ARRHYTHMIAS

The physician must be careful in reassuring patients with mitral valve prolapse syndrome. Patients with billowing leaflets without genuine prolapse rarely get severe mitral regurgitation and should be reassured. Palpitations resulting from VPCs or occasionally runs of ST usually require no drug therapy. After reassurance, if episodes of VPCs or ST are bothersome and Holter monitoring demonstrates multiform VPCs, couplets or runs, or nonsustained VT or short bouts of ST, a very small dose of a β -blocking drug is appropriate and is the safest remedy. Metoprolol (25–50 mg twice daily) or atenolol (25–50 mg once daily) is advisable because they cause less fatigue than propranolol. Sotalol (80–160 mg once daily) is useful, but fatigue and the propensity to precipitate torsades de pointes (TdP), albeit rare, do not justify its use in this benign condition. Potentially lethal arrhythmias are rare with mitral valve prolapse and require higher doses of β -blockers (*see* Chapter 6). Chest pain requires reassurance or the use of enteric-coated aspirin (325 mg daily). If pain is bothersome or “angina-like,” a β -blocking drug should be administered with avoidance of nitrates, which reduce ventricular volume and thus increase the prolapse.

SYSTEMIC EMBOLIZATION

Small, bland emboli consisting of platelet and fibrin, which form in relation to the slightly abnormal valve apparatus, may cause TIAs or stroke. Management is with enteric-coated aspirin (160–325 mg daily) or one-quarter of a regular 325-mg aspirin daily.

Table 11.11.

Clinical and Morphological Features in 15 Patients Dying Suddenly Secondary to Mitral Valve Prolapse

Patient	Age (yr)	Race	Gender	MVP diagnosed clinically	The Marfan Syndrome	Location of death	Last activity	Auscultatory findings		
								SC	SM	SH
1	16	W	M	+	+	Basketball court	Sitting after playing	—	+	0
2	18	W	F	+	0	Home	Arguing	—	0	0
3	21	W	F	+	0	Work	Talking on phone	—	—	0
4	23	W	F	+	0	Work	Drinking water	+	+	0
5	26	W	F	+	0	Work	Talking	+	+	0
6	30	B	M	0	0	Work	Sitting alone	—	—	—
7	30	W	M	0	0	Golf course	Playing golf	—	—	0
8	40	W	F	0	+	Home	Playing with children	—	—	0
9	47	W	F	0	0	Home	Gardening	—	—	0
10	51	W	M	+	0	Restaurant	Sitting after fast dancing	+	+	0
11	53	W	F	+	0	Church	Sitting	—	—	0
12	53	W	F	0	0	Restaurant	Getting up to dance	—	—	—
13	55	W	F	+	0	Home	Standing	+	+	0
14	55	W	M	+	0	Home	Sleeping	—	+	0
15	69	W	F	0	0	Home	—	—	—	—

(continued)

If TIAs continue, it is advisable to add dipyridamole (75 mg three times a day); this agent is more effective when given on an empty stomach or 30 minutes before meals. The drug is expensive and of unproven value but appears to have a salutary effect when combined with aspirin. The drug is ineffective when used without aspirin.

MITRAL REGURGITATION

Severe mitral regurgitation resulting from mitral valve prolapse is managed with surgical reconstruction where possible, but in some cases, valve replacement is necessary. The same considerations apply as in other varieties of mitral regurgitation as discussed earlier in this chapter.

RHEUMATIC FEVER

Rheumatic fever is now rare in North America and the western world but is still prevalent in Asia, the Middle East, Africa, and Latin America, and is the most commonly acquired heart disease in childhood.

Clinical Features

The peak incidence is from age 5–15; rheumatic fever is uncommon under age 5 and virtually unknown under age 2. Symptoms are manifest 2–3 weeks after group A streptococcal pharyngitis, which causes a hyperimmune reaction in susceptible individuals.

Table 11.11.
(Continued)

VPCS CHF on ECG	HW (g)	MV Anulus (cm)	TV Anulus (cm)	AML Length (cm)	PML Length (cm)	Chords Missing	Grade of MVP (1–3+)	Plaque Under PML	MAC (0–4+)	VC PFO	Redundant of Membrane
+	325	12.5	12	3	2.5	+	2	0	0	—	—
+ ^a	220	9.6	11.5	2	1.5	0	1	+	0	0	0
—	360	14	—	3	1.5	+	2	0	1	—	—
—	280	10	9	2.5	2	0	3	+	0	+	+
0 ^b	265	12	11	3	3	0	3	+	0	+	+
—	570	15.5	13	3	2.5	0	3	+	0	0	0
—	475	10	11	3	2	0	1	+	0	0	0
—	355	13	12	—	—	+	2	0	2	—	+
+	445	12.5	12.5	2.5	2	0	3	+	0	0	0
0	500	10.5	12	2	1.5	0	1	0	0	0	0
+	325	12.6	10.5	2.5	3	0	2	+	3	0	0
—	390	13.6	11	3.5	3	0	3	+	1	+	+
+	390	13	13	3	2.5	+	3	+	0	0	0
+	670	>12	14	3.5	2	0	3	+	0	+	0
—	400	15.4	14.5	2.5	3	+	3	+	0	0	0

^aThis patient had survived a cardiac arrest 2 years earlier.^bThis patient had a history of paroxysmal atrial tachycardia.

AML, anterior mitral leaflet; B, black; CHF, congestive heart failure; F, female; FO, fossa ovale; HW, heart weight; M, male; MVP, mitral valve prolapse; MAC, mitral annular calcification; PFO, patent foramen ovale; PML, posterior mitral leaflet; SC, systolic click; SH, systemic hypertension; SM, systolic murmur; TV, tricuspid valve; VC, valvular competent; VPC, ventricular premature complex; W, white; +, present; 0, absent; —, no information available.

From J Am Coll Cardiol 1991;17:921.

Symptoms and signs include the following:

- Fever for 2–3 weeks.
- Anorexia.
- Weight loss.
- Arthritis occurs in over 80% of patients and is more pronounced in older patients. It takes the form of flitting or migratory polyarthritis. Pain, redness, and swelling usually occur in large joints, knees, elbows, wrists, and shoulders; notably, the latter joint is rarely involved in other arthritides. A single joint is inflamed for about 1 day–1 week only; the pain resolves completely and then moves on to the second joint. There is typically no deformity of joints.
- Sinus tachycardia.
- Subcutaneous nodules occur in up to 12% of cases.
- Erythema marginatum in up to 10% of individuals. This is an effervescent, nonpruritic rash with pink circumscribed circles with a pale center mainly involving the trunk.
- Sydenham's chorea (St. Vitus dance) may last for weeks to months and, rarely, for a few years.
- Pancarditis is more common in the young, who have minimal or no arthritis. When rheumatic fever "licks" the joints, the disease often spares the heart.
- New murmurs, friction rub, cardiomegaly, and HF indicate pancarditis.

- An apical pansystolic murmur grade I and II is common with valvular involvement and is usually accompanied by the Carey-Coombs murmur: a short, low-pitched rumbling, middiastolic apical murmur, and its presence serves to distinguish the systolic murmur of carditis from common innocent systolic murmurs that are typically early or midsystolic vibratory murmurs or a scratchy short-ejection systolic murmur located between the pulmonary area and the lower left sternal edge.
- First-degree AV block or, rarely, bundle branch block occurs.

Jones criteria: If supported by evidence of preceding group A streptococcal infection, the presence of two major manifestations or of one major and two minor manifestations indicates a high probability of acute rheumatic fever.

Major manifestations include the following:

- Carditis.
- Polyarthritis.
- Chorea.
- Erythema marginatum.
- Subcutaneous nodules.

Minor manifestations include the following:

- Arthralgia and fever.
- Elevated acute phase reactants, erythrocyte sedimentation rate, C-reactive protein (CRP) and prolonged PR interval.

Supporting evidence of antecedent group a streptococcal infection includes the following:

- Positive throat culture or rapid Streptococcal antigen test.
- Elevated or rising Streptococcal antibody titer.

Therapy

ACUTE PHARYNGITIS

Prophylaxis of rheumatic fever requires aggressive treatment of the initial attack of pharyngitis with 500 mg of oral penicillin G immediately and then 250 mg four times daily for 10 days, or intramuscular benzathine penicillin G 1.2 million units in patients over 60 lbs and 600,000 units for patients less than 60 lbs. A dose of 250–500 mg of clarithromycin twice daily for 7–14 days or clindamycin (150 mg every 8 hours) is administered to patients allergic to penicillin.

ARTHRITIS

This is controlled with enteric-coated aspirin (100 mg/kg daily) in four divided doses to achieve a blood level of 20–25 mg/dL. Corticosteroids should be avoided because they produce no better results than aspirin.

PANCARDITIS

Modified bed rest is necessary for several weeks until signs of carditis are improved or unchanging. The sedimentation rate should revert to normal, and the CRP should become negative.

Enteric-coated aspirin should be given if fever and carditis is present, as well as for arthritis. Corticosteroids are not usually indicated and are used only if carditis is progressive with manifestation of cardiomegaly and HF. When required, prednisone (60–80 mg/

d; 1.0–1.5 mg/kg/d) is administered in four doses for a period of 4–6 weeks. The dose is then reduced slowly with maintenance of aspirin. The possibility of steroid rebound may be reduced by using aspirin as overlapping therapy with steroids for 2–3 weeks, during which time the steroids are weaned off. Pericarditis should be managed with aspirin.

Secondary Rheumatic Fever Prevention

It is important to prevent recurrence because valvular damage is more intense with each recurrence of rheumatic fever. Management is with benzathine penicillin G (1.2 million units intramuscularly every 4 weeks), commonly used in North America and Europe, but in endemic areas, three weekly injections are advisable. Penicillin is continued for at least 20 years after the initial attack of rheumatic fever or to age 45, whichever occurs first. Patients allergic to penicillin are treated with sulfonamides: 1 g of oral sulfadiazine daily for patients over 60 lbs and 0.5 g once daily for patients under 60 lbs, with liberal fluid intake.

BIBLIOGRAPHY

- Alam M, Sun I. Superiority of transesophageal echocardiography in detecting ruptured mitral chordae tendineae. *Am Heart J* 1991;121:1819.
- American College of Cardiology /American Heart Association task force on practice guidelines: management of patients with valvular heart disease. Pocket guidelines July 2000.
- Arora R, Kalra GS, Murty GSR, et al. Percutaneous transatrial mitral commissurotomy: immediate and intermediate results. *J Am Coll Cardiol* 1994;23:1327.
- Biancianiello T. Innocent murmurs. *Circulation* 2005;111:e20–e22.
- Bisno AL. Group A streptococcal infections and acute rheumatic fever. *N Engl J Med* 1991;325:783.
- Bloomfield P, Wheatley DJ, Prescott RJ, et al. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *N Engl J Med* 1991;324:573.
- Bonow RD. Asymptomatic aortic and mitral regurgitation: how should I follow the patient in practice. ACC current journal review. March/April 2001, pp. 36–41.
- Borer JS, Bonow RO. Contemporary Approach to Aortic and Mitral Regurgitation. *Circulation*. 2003;108:2432.
- Braunwald E. On the natural history of severe aortic stenosis. *J Am Coll Cardiol* 1990;15:1018.
- Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333:11.
- Carrabello BA. aortic stenosis *New Engl J Med* 2002;346:677–682.
- Chen Chuan-rong, Cheng TO, for the Multicenter Study Group Gaungshou, China and Washington D.C. Percutaneous balloon mitral valvuloplasty by the Inoue technique: a multicenter study of 4,832 patients in China. *Am Heart J* 1995;129:1197.
- Chen CR, Hu SW, Chen JY, et al. Percutaneous mitral valvuloplasty with a single rubber-nylon balloon (Inoue balloon): long-term results in 71 patients. *Am Heart J* 1990;120:561.
- Dajani AS, Ayoub E, Bierman FZ, et al. Guidelines for the diagnosis of rheumatic fever: Jones criteria, updated 1992. *Circulation* 1993;87:302.
- Deviri E, Sareli P, Wisenbaugh T, et al. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. *J Am Coll Cardiol* 1991;17:646.
- Enriquez-Sarano M, Tajik AJ. Aortic regurgitation. *N Engl J Med* 2004;351:1539–1546.
- Eslami M, Rahimtoola SH. Decision to perform concomitant aortic valve replacement in patients undergoing coronary bypass surgery: current thinking. *J Am Coll Cardiol*; ACC current journal review. November/December 2001, pp. 84–87.
- Hammermeister KE, Sethi GK, Oprian C, et al. Comparison of outcome an average of 10 years after valve replacement with a mechanical versus a bioprosthetic valve results of the VA randomized trial. *J Am Coll Cardiol* 1991;17:41A.
- Hammermeister KE, Sethi GK, Oprian C, et al. Comparison of occurrence of bleeding, systemic embolism, endocarditis, valve thrombosis and reoperation between patients randomized between a mechanical prosthesis and a bioprosthesis. Results from the VA randomized trial. *J Am Coll Cardiol* 1991;17:362A.

- Hancock EW. When is the best time to operate for aortic regurgitation? *Cardiol Rev* 1993;1:301.
- Hazen MS, Marwick TH, Underwood DA. Diagnostic accuracy of the resting electrocardiogram in detection and estimation of left atrial enlargement: an echocardiographic correlation in 551 patients. *Am Heart J* 1991;122:823.
- Hirata K, Triposkiadis F, Sparks, et al. The Marfan syndrome. Cardiovascular physical findings and diagnostic correlates. *Am Heart J* 1992;123:743.
- Iung B, Cormier B, Ducimetiere P, et al. Functional results 5 years after successful percutaneous mitral commissurotomy in a series of 528 patients and analysis of predictive factors. *J Am Coll Cardiol* 1996;27:407.
- Kawanishi DT, Rahimtoola SH. Catheter balloon commissurotomy for mitral stenosis: complications and results. *J Am Coll Cardiol* 1992; 19:191.
- Klues HG, Statler LS, Wallace RB, et al. Massive calcification of a porcine bioprosthesis in the aortic valve position and the role of calcium supplements. *Am Heart J* 1991;121:1829.
- Lawrence H. Conn: aortic valve prosthesis. *Cardiol Rev* 1994;2:219.
- Lin S-L, et al. Vasodilator therapy in chronic asymptomatic aortic regurgitation: enalapril versus hydralazine therapy. *J Am Coll Cardiol* 1994;24:1046.
- Massel D, Little SH. The risks and benefits of adding antiplatelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. *J Am Coll Cardiol* 2001;37:569–578.
- NHLBI Balloon Valvuloplasty Registry. Complications and mortality of percutaneous balloon mitral commissurotomy. *Circulation* 1992;85:2014.
- NHLBI Balloon Valvuloplasty Registry Participants. Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI balloon valvuloplasty registry. *Circulation* 1991;84:2383.
- Novaro GM, Tiong IY, Pearce GL, et al. effect of hydroxymethylglutaryl coenzyme A reductase inhibitors and progression of calcific aortic stenosis. *Circulation* 2001;104:2205–2209.
- Otto CM. Evaluation and management of chronic mitral regurgitation. *N Engl J Med* 2001;345:740–744.
- Patel JJ, Shama D, Mitha AB, et al. Balloon Valvuloplasty versus closed commissurotomy for pliable mitral stenosis: A prospective hemodynamic study. *J Am Coll Cardiol* 1991;18:1318.
- Pellikka PA, Nishimura RA, Bailey KR, et al. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990;15:1021.
- Pollick C. What do echocardiographic reports of valvular regurgitation mean? *Cardiol Rev* 1994;2:324.
- Rahimtoola SH. Vasodilator therapy in chronic severe aortic regurgitation. *J Am Coll Cardiol* 1990;16:430.
- Rahimtoola SH. The year in valvular heart disease. *J Am Coll Cardiol* 2005;45:111–122.
- Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal LV function. *N Engl J Med* 1994;331:689.
- Sundt TM, current options for replacing the aortic valve in adults. *J Am Coll Cardiol*; ACC current journal review January February 2002, pp. 78–84.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429.
- Turpie AGG, Gent M, Laupagis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;329:524.
- Tuzcu EM, Block PC, Palacios IF. Comparison of early versus late experience with percutaneous mitral balloon Valvuloplasty. *J Am Coll Cardiol* 1991;17:1121.
- Tuzcu EM, Block PC, Griffin BP, et al. Immediate and long-term outcome of percutaneous mitral valvotomy in patients 65 years and older. *Circulation* 1992;85:963.
- Tuzcu EM, Block PC, Griffin B, et al. Percutaneous mitral balloon valvotomy in patients with calcific mitral stenosis: immediate and long-term outcome. *J Am Coll Cardiol* 1994;23:1604.
- Wisenbaugh T, Skudicky D, Sareli P. Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. *Circulation* 1994;89:191.

12

Infective Endocarditis

CONTENTS

DIAGNOSIS

THERAPY

BACTERIAL ENDOCARDITIS PROPHYLAXIS

BIBLIOGRAPHY

The diagnosis of infective endocarditis must be considered and excluded in all individuals with a heart murmur and fever of unknown origin. Infection of the heart valves is caused by bacteria and, rarely by *Coxiella*, or *Chlamydia*; fungi are causative in approximately 1%.

Only a few bacterial species cause the majority of cases of native valve endocarditis and these include:

- *Streptococci* approximately 33%.
- *Staphylococcus aureus* 40%.
- *Enterococci* 10%.
- Gram-negative *bacilli* 5%.
- Fastidious Gram-negative *cocobacilli* 3%.
- Culture negative endocarditis 5%.
- Miscellaneous organisms 6%: polymicrobial, pneumococcal.

As indicated above, only a few bacteria that gain entry to the bloodstream are capable of causing endocarditis. It appears that only those bacteria that are able to stick to the surface lining of the heart and to abnormal valves tend to cause endocarditis. The ability of these bacteria to stick to the surface lining is aided by pre-existing microscopic clot that often forms at damaged sites.

DIAGNOSIS

A few hours or days of fever, chills, and rigors are common with acute bacterial endocarditis (ABE). An insidious onset over weeks with fever, malaise, chills, and weight loss indicates subacute bacterial endocarditis (SBE). The division into ABE and SBE is helpful to clinicians.

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Predisposing Factors

In a patient with a murmur and a fever of undetermined origin, one of the following precipitating or predisposing factors, if present, should produce a high index of suspicion of infective endocarditis:

- Known valvular heart disease, especially rheumatic, bicuspid aortic valve or mitral valve prolapse, with significant regurgitation.
- Prosthetic valve.
- Marfan syndrome, floppy valve.
- Recent dental or oropharyngeal surgical procedure. Symptoms may appear within a few days, but the median is 1–2 weeks.
- Genitourinary instrumentation or surgery of the respiratory tract.
- Intravenous (IV) drug addict.
- Congenital heart disease: patent ductus, ventricular septal defect (VSD), Fallot's tetralogy, coarctation.
- Prolonged use of IV catheters and hyperalimentation.
- Patient with burns.
- Inflammatory and other bowel disease, suspect *Streptococcus bovis*. If this organism is isolated, exclude polyposis and carcinoma of the colon.
- Hemodialysis.

Infective endocarditis may occur, however, in the absence of previously known valvular disease or other precipitating factors, especially in elderly patients.

Classification

A logical classification that is useful for practicing clinician is as follows:

- Native valve endocarditis with acute or subacute presentation; the organisms in this setting are: *staphylococci*, 44%; *S. aureus* and coagulase, 38%; streptococcal, 31%; *enterococci*, 10%; negative blood cultures, 6%; *Haemophilus aphrophilus*, *H. paraphrophilus*, *H. parainfluenzae*, *Actinobacillus actinomycetemcomitans*, *cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species (HACEK) group, 4%; polymicrobial, 2%; other bacteria, 4%; and fungi 1%.
- Prosthetic valve endocarditis: early phase (< 60 days postsurgery) organisms include: *staphylococci*, 70% (coagulase negative *staphylococci* approximately 45%, *S. aureus* 25%); *enterococci*, 7%, negative culture, 23%. Late involvement (> 60 days postsurgery): *Staphylococcus*, 46%: (*S. aureus*, 21%; coagulase negative, 25%); *Streptococci*, 35%; *enterococci*, 7%; negative blood cultures, 7%; and others 5%.
- Right-sided endocarditis observed particularly in IV drug users. In this setting, the bacteria are: *S. aureus* approximately 70%; *streptococci*, 8%; *enterococci*, 2%; Gram-negative *bacilli*, 5%; polymicrobial, 8%; fungi, 2%, and negative culture others, 5%. In human immunodeficiency virus-1 (HIV-1) IV drug users the risk of and mortality from endocarditis increase inversely to the CD4 count; the risk appears to be unaffected in patients with CD4 count greater than 500 cells/ μ L and with counts less than 200/ μ L the risk increases fourfold.
- Nosocomial endocarditis associated with catheters, and medicosurgical procedures. Also observed with: hemodialysis as opposed to 0 with peritoneal; bone marrow transplant associated with central venous catheters. Organisms are predominantly *staphylococci* and *enterococci*. Nosocomial endocarditis has a fatality rate of more than 50% and less than 50% of patients have no predisposing cardiac factors.

- Culture negative endocarditis; organisms include: the usual organisms that are masked by previous antibiotic therapy; slow-growing penicillin sensitive to streptococcal with fastidious nutritional tastes; *Streptococcus mitis*, *Streptococcus anginosus*, and other strains. These organisms may be missed if blood cultures are not quickly subcultured to special media that support growth of nutritionally variant *viridans streptococci*. Others include: *Brucella*, *Chlamydia*, including *psittaci*; *coxiella burnetti* (Q fever), *Bartonella*, *Mycoplasma*, *Legionella* and *Trophetyma whipplei*.

PHYSICAL SIGNS

Physical signs of infective endocarditis include the following:

- A heart murmur is usually present with SBE, but absent in 1–5%.
- A murmur may be absent in up to 15% of patients with ABE and not heard in about 33% of individuals with right-sided endocarditis, especially if care is not taken to listen for the murmur of tricuspid regurgitation; holosystolic at the lower left sternal border and increased with inspiration or elicitation of the hepatojugular reflux.
- A change in the quality or grade of the murmur is an unreliable indicator.
- Intermittent medium- to high-grade fever is usually prominent, but in elderly or immunocompromised patients, fever may be mild or absent. Normal body temperature is lower in the elderly, 97°F (36°C) as opposed to 98°F (37°C) in individuals under age 70. However, these patients may feel chills.
- Finger clubbing takes about 6 weeks to appear, is seen only with SBE, and disappears a few weeks after successful treatment.
- Osier's nodes, although uncommon, are pathognomonic, manifest as exquisitely painful, yellowish, or erythematous subcutaneous papules, pea- to almond-sized on the palms and soles. Lesions disappear in 1–5 days and may be seen during adequate therapy.
- Petechiae with pale centers may be observed on evertting the upper eyelids. They may be seen in the oropharynx or on the trunk, hands, and feet as retinal cotton wool exudates, canoe-shaped hemorrhages with white spots in their center (Roth's spots).
- Splinter hemorrhages may be a result of trauma and occur in other conditions, but an increase in their numbers is relevant.
- Splenomegaly is observed in about 50% of patients with SBE and in about 15% of those with ABE. The enlarged spleen may be painful and tender and can rupture. An ultrasound is advisable in all cases of suspected infective endocarditis.
- Pigmentation: subtle changes in skin coloration; pasty, cafe au lait complexion is an important sign and reverts to normal after treatment.
- Janeway lesions are rarely observed: 1–4-mm painless, flat erythematous macules, nontender on the palms and soles, blanch on pressure.

Underlying Disease

The underlying disease in left-sided native valve endocarditis is rheumatic disease in over 50% of cases and mitral valve prolapse in up to 15%; endocarditis on a bicuspid aortic valve is not uncommon. The incidence of underlying rheumatic valvular disease is higher in Southeast Asia, Africa, the Middle East, and Latin America, where rheumatic disease is still common.

Complications of Endocarditis

Some complications of endocarditis include the following:

- Perivalvular extension of infection that occurs in approximately 50% of patients with prosthetic valve endocarditis and in about 10% of patients with native valve endocarditis.

- Neurological: embolism, intracranial hemorrhage, and mycotic aneurysm.
- Extracranial arterial embolism.
- Immune complex nephritis (10%).
- Splenic abscess (<5%).

Blood Cultures

When acute endocarditis is suspected, three separate sets of blood cultures are taken at separate venous sites over 24 hours. It is advisable to put 10 mL of blood in an aerobic culture bottle and 10 mL in an anaerobic bottle. The two subsequent cultures can be done at 20 minutes apart with 10 mL each in aerobic bottle, unless an anaerobic infection is strongly suspected. The increased volume of blood improves the bacteriological yield.

- Urinalysis often shows mild hematuria or increased red blood cells and few red blood cell casts.
- Increased creatinine, urea, or blood urea nitrogen is nonspecific.
- The erythrocyte sedimentation rate is virtually always elevated and can be 75–110 mm/hour (Westergren) with SBE.
- The rheumatoid factor is positive in approximately 50% of patients.
- Anemia is seen in more than 30% of patients with SBE.
- The white blood count may be slightly increased or remain normal. There is almost always a shift to the left, however, with an increase in band forms.
- It is advisable to check the Gram stain of the blood and buffy coat for organisms.

A sterile blood culture is observed in up to 25% of cases owing to the following:

- Prior antibiotic therapy.
- Fastidious organisms as with slow-growing *streptococci*.
- Fungal infection; request fungal precipitins.
- Q fever; serology should be requested.
- Chlamydia infection.

Bacteria Causing Endocarditis

- *S. aureus* is responsible for over 85% of cases of acute endocarditis. Of 113 patients with infective endocarditis observed at the University of Massachusetts Medical Center (1981 through 1988), 45 (40%) had *S. aureus* with a 28% mortality versus 9% in the non-*S. aureus* group. *S. aureus* causes up to 25% of cases of native valve endocarditis, and is the most common pathogen in IV drug users.
- *Streptococcus pneumoniae* causing acute fulminant endocarditis is now rare. *Gonococcus*, *pseudomonas*, and *Streptococcus marcescens* may cause right-sided acute endocarditis.
- *Streptococci* are implicated in 60–80% of cases. α -hemolytic *streptococcus*, excluding *S. pneumoniae* designated *S. viridans*, includes *Streptococcus milleri*, *Streptococcus mutans*, and *Streptococcus salivarius* originating in the upper respiratory tract and some in the upper gastrointestinal (GI) tract.
- Fecal *streptococci*, commonly termed “*enterococci*,” cause up to 10% of infective endocarditis, but with a higher incidence in the geriatric population. The organisms include varieties of *Streptococcus fecalis* and, rarely, *Streptococcus fecium* and *Streptococcus durans*, often penicillin resistant; *S. bovis* is an exception because it is often sensitive to penicillin.
- Nutritionally variant *streptococci*: *Streptococcus anginosus*, *S. mitis*, and similar organisms require special media for their growth.

Table 12.1.
Detection of Vegetations by Transesophageal vs Transthoracic Two-Dimensional Echocardiography

	Overall	>10 mm	6–10 mm	<5 mm
TEE	100%	100%	100%	100%
Transthoracic two-dimensional color Doppler	63%	70%	65%	25%

TEE, transesophageal echocardiography

- Other organisms include *Staphylococcus epidermidis*, proteus species, *H. influenzae*, *parainfluenzae*, *fusobacterium*, and *brucella*.
- *Escherichia coli* commonly cause bacteremia and septicemia but rarely cause endocarditis.

Echocardiography

Transthoracic two-dimensional echocardiography detects approximately 63% of vegetations (Table 12.1). *S. aureus* and some *streptococci* may produce small lesions of less than 5 mm, which are poorly detectable by transthoracic echocardiography.

Transesophageal echocardiography (TEE) is superior to the transthoracic technique and can be crucial to the management of endocarditis. Transthoracic two-dimensional Doppler echocardiography gives poor detection of prosthetic heart valves, especially in the mitral position, and of calcific sclerotic native valves. Vegetations that are less than 5 mm, 6–10 mm, or greater than 10 mm are observed in 25%, 65%, and 70%, respectively, by transthoracic technique. This is 100% for all lesions using TEE (Table 12.1).

A study of TEE in patients with acute endocarditis found no significant differences in the rates of systemic embolization between patients with vegetations of more than 10 mm, vegetations of less than 10 mm, or no detectable vegetations. The finding of large or small vegetations appear to bear no relation to complicated or uncomplicated endocarditis. TEE has a role in the following:

- Failure of transthoracic echocardiography to show vegetations in patients strongly suspected of having endocarditis.
- All prosthetic heart valves.
- Calcific sclerotic native valves.
- Valvular destruction secondary to infective endocarditis, especially perivalvular abscesses.

Complications of TEE include bronchospasm, arrhythmias, and, rarely, pharyngeal bleeding. Contraindications to TEE are given in Chapter 11.

THERAPY

It is important to have a personal discussion with the microbiologist, because some organisms require special culture medium and techniques.

Vegetations that are less than 1 cm are usually cured by 4–6 weeks of antibiotic therapy. Vegetations greater than 1 cm that do not respond to 3 weeks of antibiotic therapy often necessitate valve surgery. Therapy and prognosis are related to the underlying disease and sensitivity of the organism. Empiric therapy can be tailored based on the following.

Native Valve Endocarditis

When the presentation is subacute in patients with native valve endocarditis, particularly in patients under age 65, antibiotic therapy can be delayed for 24–48 hours until the organisms and sensitivities are determined. *S. viridans* is the causative organism in up to 70% of cases and fecal *streptococci* in up to 15%. Some clinicians therefore commence antibiotics after three sets of blood cultures from a separate venipuncture site are obtained over 24 hours.

Penicillin (2 million units every 4 hours IV) plus gentamicin (1–1.5 mg/kg every 8 hours IV) until the organism has been defined and sensitivities and the minimum inhibitory concentration (MIC) of the drug against the isolated organism are known.

In native valve endocarditis occurring in the elderly, fecal *streptococci* are commonly involved.

Therapy is as outlined above: fecal *streptococci* are more common and occur in up to 25% of patients; when the organism is identified it is advisable to use ampicillin/sulbactam (2 g every 4 hours) plus gentamicin (1.3–2 mg/kg every 8 hours). Penicillin is the second choice and an alternative to ampicillin/sulbactam, provided the SBE is present for less than 3 months (*see* further discussion of fecal streptococcal endocarditis). The dose interval of aminoglycosides must be increased in patients over age 65 or in individuals with renal impairment and titrated to blood levels to avoid renal and ototoxicity. A predose level (trough) greater than 2 µg/mL (2 mg/L) reflects decreased excretion rate and accumulation of the drug: extend the dosing interval. Keep predose level 1–2 µg/mL. Peak level 30 minutes postinfusion 6–10 µg/mL, depending on sensitivities and type of organism.

Acute Endocarditis

Antibiotics should be commenced immediately after collection of blood cultures in patients with rapidly progressive acute endocarditis or in those presenting with hemodynamic decompensation. Urgent IV antibiotic therapy may halt tissue damage and is necessary to prepare patients for surgical intervention.

Acute presentation obviously requires coverage for *S. aureus*, which causes more than 90% of ABE and up to 50% occurring on valves not known to be abnormal, especially bicuspid aortic valves: cloxacillin (2 g IV every 4 hours for 4–6 weeks), nafcillin (2 g IV every 4 hours for 4–6 weeks), or flucloxacillin (2 g IV every 4 hours).

ORGANISM ISOLATED AND SENSITIVITIES DETERMINED

When the micro-organism has been isolated and antibiotic sensitivities are available, an appropriate antibiotic combination is selected and changes are made, if needed, to the initial choice of antibiotic. Organisms that commonly cause endocarditis and appropriate antibiotic combinations include the following:

- *S. viridans* or *S. bovis*: if the MIC to penicillin is less than 0.1 µg/mL, give penicillin (IV 2–3 million U every 4 hours for 4 weeks), or 2 weeks IV followed by amoxicillin (500 mg orally every 6 hours for 2 weeks), or ampicillin/sulbactam (2 g every 6 hours for 2 weeks IV), and then amoxicillin (500 mg orally every 6 hours for 2 weeks), or penicillin and gentamicin IV for 2 weeks, or 2 g of ceftriazone once daily IV for 2 weeks. IV or intramuscular (IM) therapy administered once daily in the outpatient setting or in the home is cost-saving; however IM ceftriazone is painful.

- Partially sensitive *S. viridans* or *S. bovis*, MIC penicillin greater than 0.1 µg/mL: penicillin (3 million U every 4 hours IV) plus gentamicin (1–1.5 mg/kg every 8 hours IV for 2–4 weeks) or, from the third week, amoxicillin (500 mg orally every 6 hours for 2 weeks).
- *S. fecalis*, *S. fecium*, *S. durans*, or similar fecal *streptococci* are difficult to eradicate: if the length of illness is less than 3 months, it is advisable to give ampicillin/sulbactam (2–3 g IV every 6 hours for 4 weeks) plus gentamicin (1–1.5 mg/kg every 8 hours) and monitor levels and adjustment for renal function. Gentamicin is given for 4 weeks. Wells et al. showed that combinations of penicillin or ampicillin and the β-lactamase inhibitor sulbactam were significantly more active than a group of antibiotics tested against β-lactamase-producing gentamicin-resistant *Enterococcus fecalis*. In the management of fecal enterococcal endocarditis, a β-lactamase inhibitor combination is strongly recommended. Although vancomycin and imipenem-cilastatin may be β-lactamase stable, these agents are only bacteriostatic against *enterococci*. Only one apparent cure has been reported using vancomycin in a patient with *E. fecalis* (β-lactamase-producing aminoglycoside-resistant) endocarditis. If the duration of illness is greater than 3 months, give ampicillin and gentamicin IV for 4 weeks and then amoxicillin (500 mg) every 6 hours orally for at least 2 weeks, because relapse is common with less than 4 weeks of therapy. In patients with illness less than 3 months, success has been obtained with the combination of high-dose penicillin and gentamicin for 4 weeks, as observed in a study of 40 patients. However, if duration of symptoms is more than 3 months, penicillin is not advisable because in a series of 16 patients treated for 4 weeks with penicillin and gentamicin, there were seven relapses and four deaths. In the elderly, the dose of gentamicin combined with ampicillin or penicillin should be 1 mg/kg every 8 hours and adjusted further if renal function is impaired. Aim for peak levels of 6–8 µg/mL; if the peak is greater than 10 µg/mL, decrease the dose. If the range is too high (>2 µg/mL), extend the dosing interval. The combinations of ampicillin or penicillin and the β-lactamase inhibitor sulbactam have been shown to be the most active antimicrobials tested against gentamicin-resistant β-lactamase-producing *S. fecalis* and have proven useful in the treatment of *S. fecalis* endocarditis. β-Lactamase stable vancomycin and imipenem-cilastatin are mainly bacteriostatic against fecal *streptococci*. Daptomycin is an investigational antimicrobial that has shown activity against some gentamicin resistant *S. fecalis*.

Other less common organisms causing endocarditis are treated according to sensitivities; suggested combinations are given in [Table 12.2](#).

In the United Kingdom, *S. viridans* or *S. bovis* infection is managed with 2 weeks of penicillin and gentamicin IV and then oral amoxicillin (500 mg every 6 hours) for at least 2 weeks.

- *S. aureus*: Methicillin-sensitive strains constitute the most cases of *S. aureus* endocarditis and are treated with nafcillin or cloxacillin (at doses given above) or flucloxacillin (IV 2 g every 4 hours) plus optional addition of gentamicin (1 mg/kg every 8 hours IV) for 4–7 days; the dose to be monitored by levels. The dose is reduced in elderly patients and those with renal dysfunction, whereas the dosing interval is increased. Gentamicin is discontinued after 1 week, and nafcillin or flucloxacillin IV is continued for 5–6 weeks. The length of treatment is usually from 4–6 weeks. In the United Kingdom, *S. aureus* endocarditis is usually treated with IV flucloxacillin from 4–6 weeks and gentamicin IV for 14 days.
- *S. pneumoniae* is highly sensitive to penicillin and is managed with penicillin G (2 million units every 4 hours) for 2 or more weeks.

Table 12.2.
Organisms Causing Endocarditis and Suggested Antibiotic Therapy

Organisms	Antibiotic first choice	Alternatives
<i>S. viridans</i>	Penicillin-G	Penicillin + gentamicin, Penicillin + streptomycin
<i>S. faecalis</i>	Ampicillin/sulbactam + gentamicin	Penicillin + gentamicin, Penicillin + streptomycin
<i>S. bovis</i>	Penicillin	
<i>S. aureus</i>	Nafcillin or cloxacillin or flucloxacillin	Vancomycin or teicoplanin
<i>S. epidermidis</i>	Vancomycin	Teicoplanin, nafcillin
Gram-negative		
<i>Pseudomonas aeruginosa</i>	Tobramycin + imipenem ^a	Piperacillin or ceftazidime or aztreonam + tobramycin
<i>Xanthomonas maltophilia</i>	Ciprofloxacin	Trimethoprim + SMX
<i>Serratia marcescens</i>	Cefotaxime or imipenem + gentamicin	Aztreonam
<i>E. coli</i>	Ampicillin/sulbactam + gentamicin	Imipenem Aztreonam
Proteus	Ampicillin/sulbactam + gentamicin	
<i>Klebsiella pneumoniae</i>	Cefuroxime + gentamicin	Imipenem aztreonam
Bacteroides and fusobacterium	Imipenem or Cefotetan	High-dose penicillin + clindamycin High dose penicillin + ampicillin
Salmonella	Chloramphenicol	
Gonococcus	Penicillin	
Enterobacter	Cefotaxime or Imipenem or aztreonam + gentamicin	Surgery often necessary
<i>Coxiella burnetii</i>	Cotrimoxazole + rifampin	Tetracycline
Chlamydia	Erythromycin (trimethoprim + sulfamethoxazole)	
<i>Fungi</i>	Amphotericin B alone or + 5-fluorocytosine (if organism sensitive)	Surgery usually necessary

^aWith cilastatin.

In all cases of endocarditis, predisposing factors, such as genitourinary tract pathology and poor dental hygiene, must receive adequate therapy.

- For patients allergic to penicillin or methicillin-resistant *S. aureus*, give vancomycin (15 mg/kg IV every 12 hours given slowly over 6 hours) for 4–6 weeks. Monitor serum levels, peak 20–40 µg/mL 2 hours after completion of infusion, trough levels 5–10 µg/mL. Reduce dose and increase the dosing interval in renal failure.
- HACEK organisms: ceftriaxone 2 g IV once daily for 4 weeks IM for the last 2 weeks, but this is painful.

Prosthetic Valve Endocarditis

Infective endocarditis occurs in approximately 3% of patients within the first year of surgery and thereafter in about 1% per year. Depending on the region, prosthetic valve endocarditis accounts for 10–30% of all cases of endocarditis. The incidence is highest

in the first 2 months, and the most common organisms at that stage are *S. epidermidis* (in 45%) and *S. aureus* (in 20% of cases). *S. epidermidis* continues to be an important organism during the ensuing years but with a decreased incidence. Within the first 2 months, Gram-negative organisms, fungi, diphtheroids, and enterococci are infecting organisms. *S. epidermidis* is nearly always methicillin-resistant, and the use of vancomycin is necessary.

15 mg/kg of Vancomycin IV is given every 12 hours in combination with 1–1.2 mg/kg of gentamicin IV every 8 hours; the addition of 300 mg of rifampin orally every 8 hours may cause a modest improvement in the cure rate but increases the incidence of toxicity. If the organism is determined to be methicillin sensitive, a penicillinase-resistant penicillin should replace the vancomycin.

Late prosthetic valve endocarditis should be treated in a similar method, as outlined, pending results of culture and sensitivities because the offending organism is usually *S. viridans*, fecal *streptococci*, *S. aureus*, or *S. epidermidis*. Fungal infections, however, are uncommon with late cases.

As outlined earlier, TEE is superior to transthoracic echocardiography and plays an important role in the diagnosis of prosthetic valve endocarditis.

Right-Sided Endocarditis

Right-sided endocarditis is most common in IV drug addicts and may present with a pneumonic illness. Infecting organisms include the following:

- *S. aureus* in over 60%.
- *S. epidermidis* in 10%.
- *Pseudomonas* and *Serratia* in up to 10%.

Systemic emboli are not as threatening as with left-sided endocarditis, and the outcome of medical therapy for 4–6 weeks is generally good; therefore, there is less need for surgical intervention. Table 12.2. lists a selection of antibiotics for the management of pseudomonas and other organisms. Imipenem is partially inactivated in the kidney and is therefore administered with a specific enzyme inhibitor, cilastatin, which blocks its renal metabolism.

Risk Stratification

Hasbun et al. indicate that in patients with complicated left-sided native valve endocarditis, the following five factors are independently associated with 6-month mortality:

- Comorbidity.
- Moderate-to-severe congestive heart failure (CHF) primarily related to severe valve dysfunction; CHF has been reported as the most common cause of death in native valve endocarditis.
- Altered mental status (poor cerebral perfusion).
- Bacterial etiology other than *S. viridans*.
- *S. aureus* and *enterococcus*, associated with HF not treated surgically. It is well-recognized that *S. aureus*, enteric Gram-negative *bacilli*, and aminoglycoside-resistant *enterococci* are major risk factors for death.

Indications for Surgery

In patients with aggressive endocarditis valve replacement surgery has a mortality of approximately 12% and is performed in more than 20 % of patients with endocarditis. It is life-saving for some patients; but, deciding which patients should have surgery is always difficult, despite surgical or ID expert opinion and unvalidated scoring systems.

Indications include the following:

- Hemodynamic deterioration.
- Signs of prosthetic valve dysfunction assessed by TEE.
- Occurrence of HF.
- Uncontrolled infection.
- Conduction disturbances or suggestive ring abscesses.
- Large vegetation caused by fungal infection.
- Recurrent emboli.
- Relapse after adequate medical therapy.

BACTERIAL ENDOCARDITIS PROPHYLAXIS

Prevention is a priority because infective endocarditis, if untreated, is always fatal, and despite antibiotic therapy, considerable morbidity occurs. Dental procedures continue to be an important factor in the causation of endocarditis. A few studies indicate, however, that fewer than 20% of endocarditis cases are associated with dental procedures. Bacteremia commonly occurs soon after dental extractions. When *Serratia marcescens* was introduced into the oral cavity of patients just before tooth extractions as a sentinel organism, the organism was recovered from blood drawn soon after the extraction; in approximately 60% of cases the portal of entry cannot be identified.

The efficacy of prophylactic regimens has not been adequately tested in clinical trials. One study strengthens the hypothesis for prophylaxis. In 304 patients with prosthetic valves undergoing 390 procedures without prophylaxis, endocarditis occurred in 6%. No cases of endocarditis occurred in 229 patients undergoing 287 procedures with prior prophylaxis.

Recommendations from the American Heart Association (AHA) on the antibiotic prophylaxis of endocarditis are summarized below. Relevant changes include the following:

- Amoxicillin is used for dental procedures: 3 g of amoxicillin is given orally 1 hour before dental procedures, including professional cleaning, and then 1.5 g 6 hours later;
- Patients allergic to penicillin who can take oral medications are given the choice of erythromycin or clindamycin, 300 mg 1 hour before and 150 mg 6 hours after the procedure. This is a major improvement in prophylaxis, because erythromycin (at 800 mg as advised by the AHA or 1500 mg by the British group) causes severe nausea and/or abdominal discomfort. Also, the drug is not extremely effective for fecal streptococci. The author recommends the use of clindamycin because of adverse effects of erythromycin. Also, nine capsules of amoxicillin must be taken and many patients object to the large size and number of capsules. Consequently, three clindamycin capsules is more acceptable to most patients.
- Prophylaxis for mitral valve prolapse has caused confusion over the past 10 years. The AHA advises prophylaxis only for individuals with mitral regurgitation, that is, presence of a mid-to-late or holosystolic murmur. Men over age 45 tend to develop progressive mitral regurgitation more frequently than women (*see* Chapter 11). Mild-to-moderate mitral regurgitation is observed as frequently in women as in men, however, and requires antibiotic prophylaxis. Echocardiographic documentation is thus not necessary. If doubt exists in patients with a click, the echocardiographic findings of billowing leaflets are not an indication for antibiotics, except where there is actual mitral valve prolapse, thickening, or redundancy of valve leaflets (*see* Chapter 11). The British group recommends prophylaxis for mitral valve prolapse only when it is associated with a murmur.
- Procedures not requiring prophylaxis include injection of local anesthetic into the gum, fiberoptic bronchoscopy, endotracheal intubation, and GI endoscopy with biopsy. Pro-

phylaxis is advised in patients with prosthetic heart valve for all procedures, including endoscopies. Cases of endocarditis have been reported rarely in patients with prosthetic heart valve undergoing gastroscopy or other GI endoscopic procedures with or without biopsy. Endocarditis in patients with prosthetic heart valve carries a 50% mortality and must be prevented at all costs. Endocarditis prophylaxis has been shown to be effective. In a study of 533 consecutive patients with prosthetic heart valves, 229 patients given prophylaxis before 287 procedures resulted in no cases of endocarditis, versus six cases of endocarditis in 304 patients undergoing 390 procedures without prophylaxis.

- Patients with prosthetic heart valves are at high risk and require IV antibiotics for most procedures, including low-risk procedures.

Endocarditis prophylaxis is recommended for patients with the following:

- Prosthetic cardiac valves, including bioprosthetic and homograft valves.
- Previous bacterial endocarditis, even in the absence of heart disease.
- Surgically constructed systemic-pulmonary shunts or conduits.
- Most congenital cardiac malformations.
- Rheumatic and other acquired valvular dysfunction, even after valvular surgery.
- Hypertrophic cardiomyopathy.
- Mitral valve prolapse with valvular regurgitation.
- Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning; tonsillectomy and/or adenoidectomy; surgical operations that involve intestinal or respiratory mucosa; bronchoscopy with a rigid bronchoscope; sclerotherapy for esophageal varices; esophageal dilatation; gallbladder surgery; cystoscopy; urethral dilatation; urethral catheterization if urinary tract infection is present; urinary tract surgery if urinary tract infection is present; prostatic surgery; incision and drainage of infected tissue; vaginal hysterectomy; vaginal delivery in the presence of infection.

Endocarditis prophylaxis is not recommended for the following:

- Isolated secundum atrial septal defect (ASD).
- Surgical repair without residua beyond 6 months of secundum ASD, VSD, or patent ductus arteriosus.
- Previous coronary artery bypass graft surgery.
- Mitral valve prolapse without valvular regurgitation.
- Physiological, functional, or innocent heart murmurs.
- Cardiac pacemakers and implanted defibrillators.
- Dental procedures not likely to induce gingival bleeding, such as simple adjustment of orthodontic appliances or fillings above the gum line; injection of local intraoral anesthetic (except intraligamentary injections).
- Shedding of primary teeth; tympanostomy tube insertion; endotracheal intubation.
- Bronchoscopy with a flexible bronchoscope, with or without biopsy; cardiac catheterization; endoscopy with or without gastrointestinal biopsy; cesarean section; in the absence of infection for urethral catheterization, dilatation and curettage, uncomplicated vaginal delivery, therapeutic abortion, sterilization procedures, or insertion or removal of intrauterine devices.

The prophylactic regimens for dental oral respiratory tract or esophageal procedures as recommended by the AHA 1997 guidelines are as follows:

- General prophylaxis: amoxicillin (adults): 2.0 g; children 50 mg/kg administered orally 1 hour before the procedure.
- For patients unable to take oral medications, give 2 g of ampicillin IM or IV; children, 50 mg/kg IM or IV within 30 minutes before the procedure.

- For patients allergic to penicillin: 600 mg of clindamycin is recommended for adults; 20 mg/kg IV for children within 30 minutes before procedure; 500 mg of orazithromycin for adults, 15mg/kg orally for children 1 hour before procedure.

Prophylactic regimens for genitourinary, GI procedures are follows:

- High-risk patients should be given 2 g of ampicillin IM or IV plus 1.5 mg/kg of gentamicin not to exceed 120 mg within 30 minutes of starting the procedure; 6 hours later, 1 g IM or IV of ampicillin or 1 g of amoxicillin orally.
- For high-risk patients and for patients allergic to penicillin or amoxicillin, give 1 g of vancomycin IV over 1–2 hours; complete the infusion within 30 minutes of starting the procedure.

BIBLIOGRAPHY

- Alexiou C, Langley SM, Stafford H, et al. Surgery for active culture-positive endocarditis: determinants of early and late outcome. *Ann Thorac Surg* 2000;69:1448–1451.
- Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936–2948.
- Bayer AS, Scheld WM. Endocarditis and intravascular infection. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, fifth edition. Philadelphia, PA: Churchill Livingstone; 2000, pp. 857–902.
- Cabell CH, Abrutyn E, Karchmer AW. Cardiology patient page. Bacterial endocarditis: the disease, treatment, and prevention. *Circulation* 2003;107:e185–e187.
- Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA* 1997;277:1794–1801.
- De Castro S, Magni G, Beni S, et al. Role of transthoracic and transesophageal echocardiography in predicting embolic events in patients with active infective endocarditis involving native cardiac valves. *Am J Cardiol* 1997;80:1030–1034.
- Devereux RB, Frary CJ, Kramer-Fox R, et al. Cost-effectiveness of infective endocarditis prophylaxis for mitral valve prolapse with or without a mitral regurgitant murmur. *Am J Cardiol* 1994;74:1024.
- Durack DT. Prevention of infective endocarditis. *N Engl J Med* 1995;332:38.
- Ferrieri P, Gewitz MH, Gerber MA, et al., from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association Council on Cardiovascular Disease in the Young. Unique features of infective endocarditis in childhood. *Circulation* 2002;105:2115–2126.
- Granowitz EV, Longworth DL. Stratification and bedside prognostication in infective endocarditis. *JAMA* 2003;289:1991–1993.
- Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. *JAMA* 2003;289:1933–1940.
- Hayek E, Gring CN, Griffin BP. Mitral valve prolapse. *Lancet* 2005;365:507–518.
- Jault F, Gandjbakhch I, Rama A, et al. Active native valve endocarditis: determinants of operative death and late mortality. *Ann Thorac Surg* 1997;63:1737–1741.
- Lavie CJ, Khandheria BK, Seward JB, Tajik AJ, Taylor CL, Ballard DJ. Factors associated with the recommendation for endocarditis prophylaxis in mitral value prolapse. *JAMA* 1989;262:3308–3312.
- Lewin MB, Otto CM. The bicuspid aortic valve: adverse outcomes from infancy to old age. *Circulation* 2005;111:832–834.
- Moreillon P, Que YA. Infective endocarditis. *Lancet* 2004;363:139–149.
- Spirito P, Rapezzi C, Bellone P, et al. Infective endocarditis in hypertrophic cardiomyopathy: prevalence, incidence, and indications for antibiotic prophylaxis. *Circulation* 1999;99:2132–2137.
- Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. *Ann Intern Med* 1998;129:761–769.
- Strom BL, Abrutyn E, Berlin JA, et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. *Circulation* 2000;102:2842–2848.
- Tischler MD, Vaitkus PT. The ability of vegetation size on echocardiography to predict clinical complications. *J Am Soc Echocardiogr* 1997;10:562–568.
- Wilson WR, Karchmer AW, Bisno AL, et al. Antibiotic treatment of adults with infective endocarditis due to viridans streptococci, enterococci, other streptococci, staphylococci, and HACEK microorganisms. *JAMA* 1995;274:1706–1713.

13

Pericarditis and Myocarditis

CONTENTS

PERICARDITIS
CARDIAC TAMPONADE
CONSTRICTIVE PERICARDITIS
MYOCARDITIS
BIBLIOGRAPHY

PERICARDITIS

In more than 90% of patients with acute pericarditis the cause of the disease is unknown (idiopathic: viral). The common causes of pericarditis are listed in [Table 13.1](#). The classification into:

- causes based on the presence of an easily recognizable underlying disease.
- those caused by adverse reactions (easily excluded by history).
- and due to viral or unknown (idiopathic) causes, provides for easy recall.

Clinical Hallmarks

Chest pain is typically:

- Retrosternal or left precordial.
- Occasionally radiates to one or both trapezius ridges (a radiation that does not occur with angina); may radiate to the neck or left arm and may simulate angina or myocardial infarction (MI).
- At times localized to the epigastrium or left upper quadrant.
- Sharp, pleuritic, but may be described as an oppressive, dull, vague ache.
- Increased by deep inspiration, coughing, swallowing, recumbency.
- Relieved by sitting and leaning forward.

Genuine shortness of breath, forced shallow breathing owing to pain, and palpitations are common features. Underlying infection may cause fever and myalgia. A pericardial friction rub observed in about 85% of patients is characteristically:

- Heard between the lower left sternal edge and apex.
- Localized to any area or over most of the precordium.
- Heard with the diaphragm pressed firmly against the chest wall, with the patient leaning forward with the breath held at end expiration.
- Variable in intensity from minute to minute and can be missed (this calls for repeated auscultation).

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Table 13.1.
Causes of Pericarditis

1. Underlying diseases
Viral infections: Coxsackie B ₅ B ₆ , echovirus, HIV, Epstein-Barr, Influenza, mumps, varicella, rubella; mycoplasma
Post-MI: early, late
Aortic dissection
Cardiotomy, thoracic surgery
Renal failure
Neoplastic
Tuberculosis
Septicemia (purulent)
Endocarditis
Collagen disease: vasculitis, rheumatic fever, rheumatoid arthritis, lupus, scleroderma (>30 individual forms)
Myxedema
Trauma: iatrogenic: surgery, catheter, pacemaker
2. Adverse reactions easily excluded by history
Drugs: anticoagulants, cromolyn, daunorubicin, dantrolene, hydralazine, isoniazid, methysergide, minoxidil, procainamide, phenytoin; radiation
3. Idiopathic: probable viral (specific diagnosis unidentified)

- Triphasic in about half of patients, biphasic in one-third.
- High-pitched scratchy or squeaky.

Electrocardiogram Findings

The four stages of the electrocardiographic abnormalities are given in [Table 13.2](#). Because tachycardia is common, it may be the only electrocardiographic finding if supraventricular tachycardia (ST) elevation has resolved and the T-waves remain normal.

- The electrocardiogram (ECG) obtained at the earliest stage of acute pericarditis usually reveals (PR) segment depressions in most leads and PR segment elevation in aVR, occasionally in V₁ ([Fig. 13.1.](#), [Table 13.2.](#)). Typical ECG changes are observed in more than 80% of patients with pericarditis.
- Some patients manifest only PR segment depressions, which are misinterpreted as ST elevations, normal variant. Spodick points out that marked and widespread PR depressions are virtually never observed in early repolarization pattern, and sometimes only ST (J-point) deviations occur in acute pericarditis without PR deviations and these may resemble those observed in early repolarization; in such ECGs and in most patients with acute pericarditis, the J-point height in lead V₆ measures more than 25% of the height of the T-peak from the baseline.
- ST-segment elevation, when present, is a J-point ST elevation concave upward (anormal shape) with no T-wave inversion, whereas with MI, the ST segment is convex, often with emerging Q-waves present and the T-waves begin to invert before the ST segment normalizes. The ST segment is depressed in lead aVR and sometimes minimally in V₁.

TROPONIN LEVELS

Imazio et al. have shown that in viral or idiopathic acute pericarditis troponin elevation is frequently observed and is associated with male gender, magnitude of the ST-segment elevation, and pericardial effusion at presentation. The increase in troponin observed in

Table 13.2.
ECG Clues to Pericarditis

Stage I (hours to days)	Widespread ST-segment elevation 2–5 mm concave upward and PR depression in leads I, II, III, V ₂ –V ₅ ; reciprocal depression aVR, V ₁
Stage II (few days later)	ST and PR segments isoelectric, upright, or flattened T
Stage III	After normalization of ST segment, diffuse T-wave inversion occurs
Stage IV (days to weeks)	T-waves normalize, rarely remain inverted

more than 45% of patients is roughly related to the extent of myocardial inflammatory involvement; unlike acute coronary syndromes, elevated levels do not predict an adverse outcome. Elevated levels usually returned to normal within 1 to 2 weeks and myocarditis should be suspected if these persist beyond 2 weeks.

Echocardiography

The finding of a pericardial effusion helps to confirm the diagnosis. Echocardiography is necessary to detect and quantitate associated pericardial effusion and in assessing tamponade (Fig. 13.2.).

Idiopathic and Viral Pericarditis

Most cases of so-called idiopathic pericarditis are caused by viral infections (Table 13.1.). The patient should be hospitalized and observed for tamponade. The occurrence of tamponade is manifested by hemodynamic compromise, elevation of the jugular venous pressure (JVP), and pulsus paradoxus and hypotension; the latter may mask pulsus paradoxus.

Echocardiography is helpful to confirm the diagnosis or tamponade (Fig. 13.2.). Pericardiocentesis is not done routinely, even with moderate-sized effusions, if tamponade is not present. Pericardiocentesis may be necessary for diagnosis, for example, viral, bacterial, or molecular biological studies. If pain is bothersome, the patient should rest in bed and chair for a few days, followed by slow ambulation over 1–2 weeks.

After a few days to 1 week of acute pericarditis, the ST segments return to the isoelectric level, there is widespread T-wave inversion, typical of the second stage of acute pericarditis. Occasionally, the ST-segment elevation resolves and there is no progression to the second stage.

MANAGEMENT OF PAIN IN ACUTE PERICARDITIS

- Physical activity may worsen nonsignificant myocarditis reflected by ST segment and T-wave changes; thus, activities should be curtailed for the first week and monitored depending on symptomatology, ECG, and echocardiographical findings.
- Pain is usually relieved by the nonsteroidal anti-inflammatory drugs (NSAIDs): 400–800 mg of ibuprofen every 8 hours, the combination of ibuprofen and colchicine, have been shown to be rapidly effective, with symptomatic relief within 1–3 days if acute pericarditis is the correct diagnosis.
- 0.6 mg of colchicine twice daily has been shown to be effective, used alone or in combination. Most important colchicine has been shown to prevent recurrent pericarditis.
- Indomethacin usually controls pain but may reduce coronary flow and has more adverse effects compared with ibuprofen.
- All NSAIDs (selective and nonselective) are contraindicated with acute MI, however, because myocardial healing and scar formation appear to be impaired by these agents.

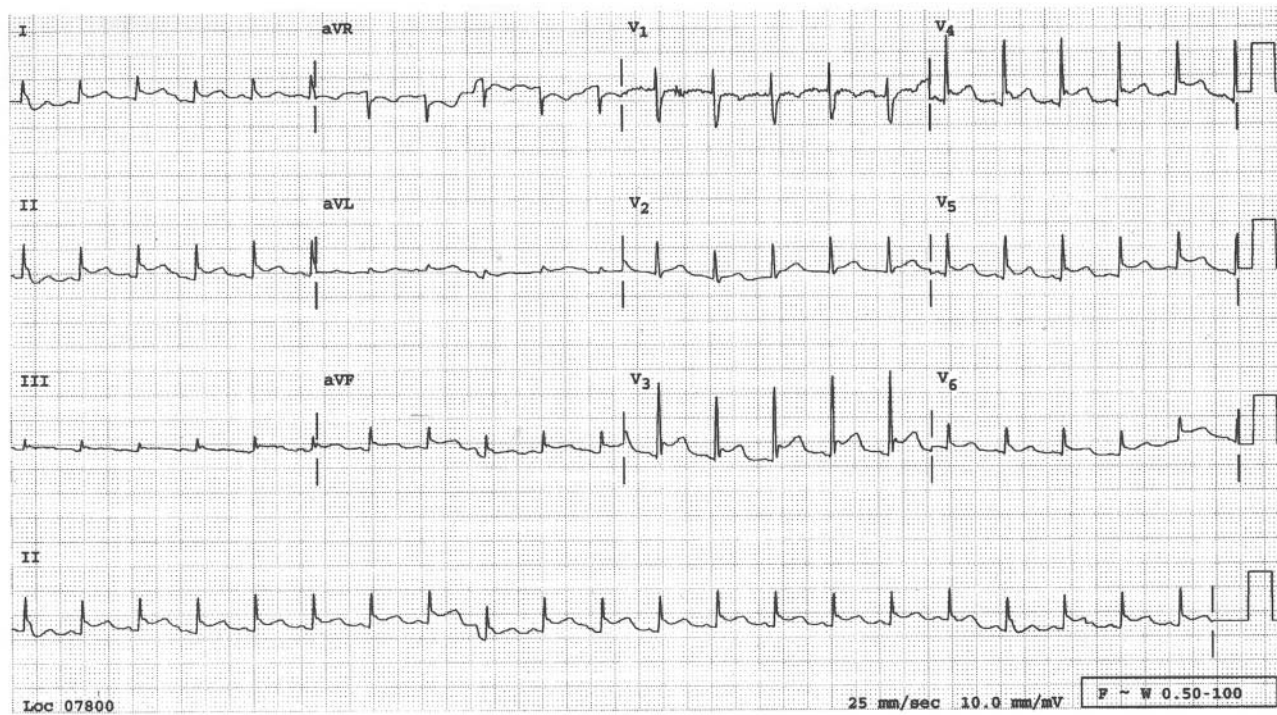


Fig. 13.1. Acute pericarditis (ST stage) widespread ST-segment elevation with upward concavity in leads I, II, aVF, V₂ to V₆, with ST-segment depression in aVR. Note the PR segment depression in many leads, and PR depression in aVR.

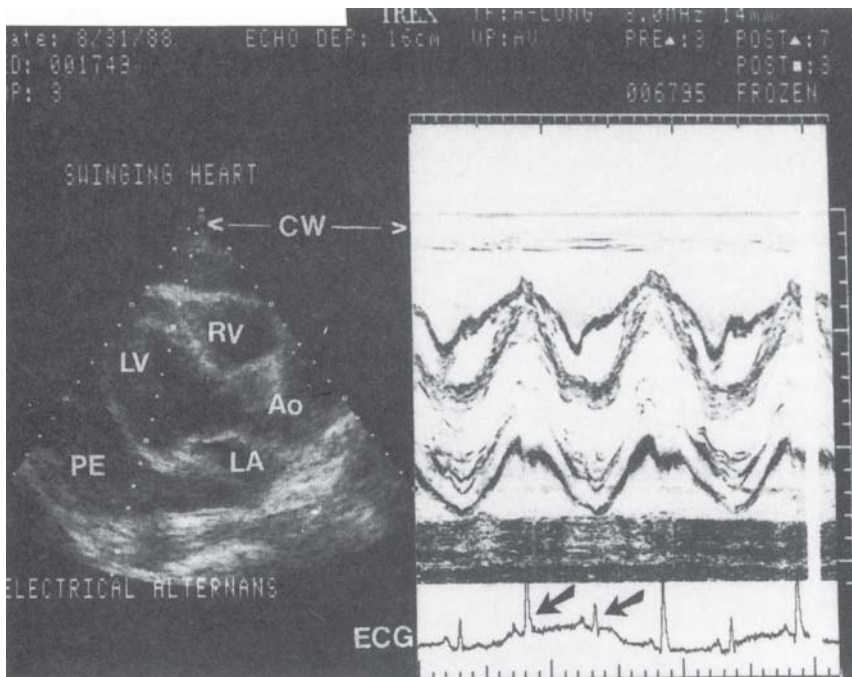


Fig. 13.2. Cardiac tamponade in a patient with carcinoma of the lung. M-mode and two-dimensional echocardiogram reveal a large pericardial effusion with a swinging heart motion, diastolic collapse of the right ventricle and left atrium and electrical alternans. Note in the M-mode tracing that when the cardiac wall swings anteriorly, the QRS voltage is high (arrow) and low (arrow) when it swings posteriorly. Ao, aorta; RV, right ventricle; LV, left ventricle; LA, left atrium; PE, pericardial effusion; CW, continuous wave. From Gazes PC. Clinical cardiology. Philadelphia: Lea & Febiger, 1990, p. 374. Reprinted with permission.

- Randomized clinical trials of NSAIDs are not available, but several reports indicate clearly that combined therapy is usually effective within 1–3 days. Combined therapy is advisable for 7–14 days then slow tapering of doses for 1 or 2 weeks to prevent early recurrence.

Corticosteroids. An oral corticosteroid should only be used if it is also indicated for an underlying disease or if the patient's syndrome is severe and resistant to the combination of colchicines and ibuprofen. It is not advisable to commence corticosteroids solely for the relief of pain, because these agents may increase viral replication. Recurrence of pericarditis and a bothersome, corticosteroid-dependent, and disabling syndrome have been ascribed to corticosteroid therapy, albeit, rarely. Corticosteroids are indicated when there is total failure of high-dose NSAIDs and colchines used over several weeks and with relapsing pericarditis not controlled by NSAIDs and colchines.

Dexamethasone. A dosage of 4 mg intravenously (IV) may relieve pain in a few hours.

Prednisone. A dosage of 60 mg daily for a few days is used and decreased by 10 mg every 3–5 days until a dose of 15 mg is reached. If symptoms are controlled, it is advisable to give 15 mg on alternate days for 5 days and then 10 mg alternate days for 5 days, 5 mg alternate days for 5 days, and discontinue. The course of prednisone should be tapered as quickly as feasible. NSAIDs are added at an adequate dosage, when the corticosteroid dose has reached 15 mg daily.

Recurrent Pericarditis

- Colchicine dosage: 2 mg loading dose, then 1 mg daily. Approximately 25% of patients experience recurrence; if effusion develops, the risk of tamponade is high in this subset. In the absence of heart failure (HF) or tamponade, colchicine causes beneficial effects and is advisable.
- The salutary effects may be caused by colchicine binding to membrane proteins and interference with polymorph leukocyte function.
- Patients with chest pain unrelieved by adequate doses of NSAIDs and colchicines may require corticosteroids for control of pain, fever, and shortness of breath. Alternate-day therapy carries less risk of adverse effects.
- In patients with relapsing pericarditis who do not respond to drug therapy, particularly chronic colchicine use, peri-cardiocentesis may be required.

Specific Causes of Pericarditis

POSTINFARCTION PERICARDITIS

Acute pericarditis occurs in approximately 10% of patients within 10 hours–10 days after infarction. The pain may be confused with postinfarction angina, extension of infarction, or pulmonary embolism. Most cases occur on the third or fourth day postinfarction. Chest pain is best treated with aspirin. NSAIDs, such as indomethacin, ibuprofen, naproxen, and cyclooxygenase-2 (COX-2) inhibitors should be avoided because they appear to interfere with the healing of infarcted tissue and have been shown to cause infarct expansion and accelerate remodeling.

Dressler's syndrome occurs in less than 0.1% of patients, usually weeks or months after MI, and may be an immune reaction. This condition is currently no longer observed.

PURULENT PERICARDITIS

Purulent pericarditis usually occurs during septicemia caused by *pneumococcus*, *meningococcus*, *hemophilus*, *gonococcus*, and other organisms. Pericardiocentesis is indicated in patients suspected of purulent pericarditis to isolate micro-organisms and determine sensitivities and the appropriate choice of antibiotics. Cardiothoracic surgical assistance often is required for open pericardial drainage or creation of a pericardiopleural window.

TUBERCULOUS PERICARDITIS

In Asia, Africa, the Middle East, Latin America, and some nonindustrialized countries, tuberculosis is the most common cause of pericarditis. In North America and Europe, tuberculosis is responsible for about 4%, 7%, and 6% of acute pericarditis, tamponade, and constrictive pericarditis, respectively.

Diagnosis requires isolation of mycobacterium tuberculosis in pericardial fluid or a histological examination of pericardial tissue or proven active tuberculosis in other organs.

Tuberculous pericarditis is more common in blacks, is commonly seen in patients with acquired immunodeficiency syndrome (AIDS), and has a peak incidence in patients between 30 and 60 years of age.

Symptoms and signs include the following:

- Cough; weight loss; dyspnea, occasionally orthopnea; fever, chills, and night sweats may be present for several months before signs of pericarditis occur; cardiomegaly; a pericardial friction rub plus signs of tamponade may develop; hepatomegaly occurs in over 90% of patients; and ascites is fairly common.

Echocardiographic and computed tomography (CT) examination may reveal pericardial effusion and pericardial thickening. The patient should be hospitalized, observed for tamponade, and given therapy with isoniazid (300 mg), pyridoxine (50 mg), rifampin (600 mg), and ethambutol (15 mg/kg) daily for at least 9 months, allowing a minimum of 6 months of drug treatment after culture conversion. The combination of isoniazid (300 mg) and rifampin (600 mg) daily for 9 months has been shown to produce a satisfactory response in 95% of patients with extrapulmonary tuberculosis.

Corticosteroid Therapy

Corticosteroid therapy is indicated for recurrent or persistent pericardial effusion in patients receiving adequate courses of antituberculous therapy. This therapy may avoid constrictive pericarditis and pericardial resection, which appears to be required in 7–40% of patients adequately treated with antituberculous drugs. Although some series show a high incidence of pericardial constriction, pericardiectomy is not routinely recommended. In a study by Strang et al., only 17 of 240 patients treated with prednisolone in addition to antituberculous drugs for 11 weeks required pericardiectomy, and prednisolone therapy reduced overall mortality from 14 to 3%.

A 40–60 mg dosage of prednisone or prednisolone daily is given in two divided doses.

Uremic Pericarditis

Pericardiocentesis is required only if there is suspicion of purulent infection or tamponade. The condition usually subsides with more frequent dialysis. Recurrent effusions uncontrolled by dialysis may respond to instillation of triamcinolone into the pericardial sac.

The instillation of sclerosing agents is of benefit in some patients with neoplastic pericarditis.

CARDIAC TAMPONADE

Tamponade may occur acutely secondary to the following:

- Cardiac surgery or chest trauma: an individual who has sustained recent chest trauma and appears in shock with increased venous pressure should be suspected of having cardiac tamponade.
- Acute MI with free-wall rupture (*see* Chapter 2).
- Dissecting aneurysm.
- Acute or subacute presentations occasionally occur with neoplastic involvement, non-specific pericarditis, and uremia or purulent infections

Diagnostic Hallmarks

Sudden progressive severe shortness of breath, chest tightness, dysphagia, and peripheral cyanosis may herald the shock-like state. The JVP is usually elevated. Acute hemo-pericardium may cause jugular pulsations without much distention because there is not sufficient time for blood volume to increase. Dilation of veins in the forehead, scalp, and fundi, may be observed. Hypotension and tachycardia are usually present. A pericardial rub may be present particularly in patients with inflammatory effusions.

- Cardiac tamponade is a form of cardiogenic shock and the differential diagnosis includes causes of cardiogenic shock (*see* Chapter 3, [Table 3.1.](#)).

- Significant pulsus paradoxus is usually detectable except when severe hypotension or elevation of the diastolic pressure of either ventricle is present. Studies between 1991 and 1999 give its prevalence between 12 and 75%.

Thus, the physician should not be lulled into a sense of false security by the absence of paradoxus.

- Pulsus paradoxus is an exaggeration of the normal inspiratory decline of systemic arterial pressure and is therefore not actually “paradoxical.” To determine the presence of significant pulsus paradoxus, the patient’s respirations are observed while slowly deflating the blood pressure (BP) cuff. Initially, the Korotkoff sound is heard only on expiration, but as the cuff pressure is lowered, Korotkoff sounds are heard during inspiration; the difference in systolic blood pressure (SBP) recorded at the commencement of the Korotkoff sounds in inspiration and expiration is an estimate of pulsus paradoxus.
- Normally, this difference is less than 10 mmHg. Pulsus paradoxus greater than 12 mmHg is significant.

In patients with a very low cardiac output pulsus paradoxus is often not detected by this method and a catheter is needed for it to be identified. Pulsus paradoxus may be palpable in muscular arteries.

Muffled heart sounds represent another characteristic feature, although not a diagnostic hallmark.

Pulsus paradoxus may be observed in several conditions, including the following:

- Severe chronic obstructive pulmonary disease (COPD), status asthmaticus.
- Pneumothorax.
- Massive pulmonary embolism.
- The many forms of severe hypotension including profound hemorrhagic shock.

In COPD and asthma, the JVP falls normally on inspiration. With right ventricular (RV) infarction, the venous pressure is high but increases on inspiration (Kussmaul’s sign), and pulsus paradoxus is absent. Massive pulmonary embolism may produce a shock-like state with markedly elevated JVP and represents a diagnostic challenge, but the clinical setting usually assists in differentiating the two conditions.

Severe HF causing marked elevation of JVP can be confused with cardiac tamponade. It is important to differentiate the two conditions, because the use of diuretics is contraindicated in the presence of tamponade. Because the most common cause of right HF is left HF, pulmonary congestion is usually detectable with the presence of crackles, third heart sound, radiological evidence of pulmonary congestion, and left ventricular (LV) failure.

Pulsus paradoxus is not a feature of severe HF, and the presence of a V-wave in the venous pulse indicates tricuspid regurgitation.

Conditions that they cause in the absence of diagnostic pulsus paradoxus in patients with cardiac tamponade include the following:

- Cardiac regional tamponade causing hemodynamic deterioration may occur within the first 2 weeks of cardiac surgery or in conditions causing adhesions and local cardiac compression by loculated fluid. In these situations, pulsus paradoxus may be absent and the echocardiogram may fail to show effusion all around the heart.
- Extreme hypotension that may occur during severe tamponade may make respiration induced pressure changes.
- Unmeasurable pericardial adhesions particularly over the right heart that impede volume changes.

- Acute LV failure caused by MI with effusion causing tamponade.
- Severe aortic regurgitation with or without severe LV failure may produce sufficient regurgitant flow to dampen respiratory fluctuations.

ECG Findings

Electrial alternans; combined P and QRS alternation is a diagnostic hallmark, virtually specific for cardiac tamponade (Fig. 13.2.).

Alternation confined to the QRS complex: every other QRS complex is of smaller voltage is more common than combined P and QRS alternation, but rare cases of very large effusions without tamponade may cause QRS alternans.

Chest X-Ray

- More than 200 mL of fluid must accumulate before the cardiac dimensions and silhouette are affected.
- The volume of most nonhemorrhagic effusions that cause tamponade is 300–600 mL. Definite pericardial-fat lines observed on the lateral film indicate a large effusion.
- A large cardiac silhouette in a patient with clear lung fields associated with severe acute shortness of breath, elevated JVP and hypotension or cardiogenic shock state suggests tamponade. Although the chest X-ray is not diagnostic, it is often done initially in the workup of virtually all patients with a shocklike state.

Echocardiography

In patients with suspected cardiac tamponade, urgent echocardiography is mandatory.

Echocardiographic hallmarks are: diastolic chamber collapses of the right atrium, right ventricle, or both, occasionally the left atrium and rarely the left ventricle.

- An early finding of diastolic right atrial collapse, which occurs in most cases except regional tamponade, in which right or left atrial collapse may be observed (Fig. 13.2.); right atrial collapse is more specific if inward movement occupies more than 30% of the cardiac cycle. Right atrial collapse is seen also in some patients with hypovolemia without tamponade; this may occur in patients with multiple trauma with chest and pericardial involvement because bleeding elsewhere depletes blood volume.
- Diastolic right ventricular collapse is a less sensitive, but specific finding.
- Left atrial collapse is highly specific, but occurs in less than 25% of patients.
- A swinging heart and electrical alternans may occur (Fig. 13.2.).

Management

Management of tamponade involves the maintenance of an adequate preload so as to generate stroke volume.

Thus, diuretics and preload-reducing agents, such as nitrates and angiotensin-converting enzyme (ACE) inhibitors, must be avoided. Volume expansion with saline and even transfusion with packed red cells may provide hemodynamic stability until pericardiocentesis is accomplished. It is important to maintain volume expansion so that right atrial pressure may be maintained above intrapericardial pressure to prevent right atrial or ventricular collapse.

The volume expansion strategy is controversial, however, and is instituted only as a temporary measure until pericardiocentesis is done. A 16 or 18 gage polytetrafluoroethylene sheathed needle with a steel core is used, and the steel core withdrawn when the pericardial-fluid area is reached.

Pericardiocentesis should be carried out by an experienced cardiologist under echocardiographic control or by a cardiac thoracic surgeon.

A paraxiphoid needle insertion is advised. The needle should be aimed toward the left shoulder. Insert the needle between the xiphoid process and left costal margin, then angle the hub of the needle about 15° above the skin to bypass the costal margin. The hub is then depressed so the point of the needle is aimed toward the left shoulder and advanced to pierce the pericardium with echocardiographical guidance if an apical insertion is used the needle is aimed internally.

An indwelling pericardial catheter with multiple side holes (pigtail angiographic catheter) may be used for drainage and for installation of antibiotics, triamcinolone, or chemotherapeutic agents. Failure of pericardiocentesis is usually owing to a posteriorly located effusion. Reaccumulation of fluid and recurrent tamponade are indications for subxiphoid pericardial window drainage carried out by a cardiothoracic surgeon.

CONSTRUCTIVE PERICARDITIS

The proper management of constrictive pericarditis begins with correct diagnosis. Common causes include the following:

- Neoplastic disease, especially carcinoma of lung or breast, asbestosis and lymphoma.
- Mediastinal irradiation.
- Nonviral pericardial infections.
- Postviral pericarditis.
- Tuberculosis (the most common cause in third-world countries).
- Postcardiac surgery.
- Chest trauma.
- Connective tissue diseases, particularly rheumatoid arthritis.
- Chronic renal failure and dialysis.

Diagnostic Hallmarks

If the JVP is both markedly and chronically elevated and the patient's history and physical examination fail to suggest an apparent cardiac cause in the presence of a small quiet heart, then a restrictive syndrome must be considered, the most common cause being constrictive pericarditis.

Neck vein examination should reveal Kussmaul's sign, which may be difficult to elicit when the venous pressure is severely elevated. The venous pulse usually has a prominent y-descent (a major negative wave), coincident with the early rapid diastolic filling of the ventricle. A prominent x-descent, coincident with filling of the atrium, is often observed in patients with sinus rhythm. The exaggerated x- and y-descents give the venous pressure a characteristic M- or W-shaped pattern ([Table 13.3](#)).

Auscultation should reveal the presence of an early high-frequency third heart sound (S_3) caused by abrupt cessation of early diastolic filling. This sound, referred to as a pericardial knock, occurs earlier than the conventional S_3 of HF and has a sharp high-pitched quality that is easily heard with the diaphragm and may mimic an opening snap or early filling sound heard in endomyocardial fibrosis.

Atrial fibrillation (AF) occurs in approximately 33% of cases of constrictive pericarditis.

The presence of marked ascites, occurring days to weeks before the presence of significant edema, points strongly to constrictive pericarditis and serves to distinguish the condition from HF, in which prominent edema occurs and is followed weeks later by mild

Table 13.3.
Constrictive Pericarditis vs Restrictive Cardiomyopathy

	<i>Constrictive pericarditis</i>	<i>Restrictive cardiomyopathy</i>
Clinical features		
Heart size	Usually normal	Usually large
Heart impulse	Quiet	LV and/or right ventricular dilatation
JVP	M-pattern ^a	M-pattern
Kussmaul's sign	Present	Present
Systolic (v) waves	Absent	Present (tricuspid regurgitation)
Systolic murmurs	Rare	Common
S ₃ gallop ^b	Present	Present (except in amyloid)
Chest X-ray	Clear lung fields	Similar
	Normal heart size	Similar or moderately enlarged
	Pericardial calcification (50%)	Rare
		Myocardial calcification not uncommon
ECG	P-mitrale	Uncommon
	Atrial fibrillation 33%	Common
	Conduction defects uncommon	Common
	Flat or inverted T-waves	Widespread T-wave inversion common
	May show low voltage	Low voltage common
	Q-waves very rare	QS precordial leads pseudoinfarction pattern common
Echocardiogram	Thickened pericardium	
	Calcified pericardium	No pericardial calcification, myocardial calcification
	Normal septal motion	
Systemic disease (associated)	Tuberculosis	Amyloid; sarcoid; tuberculosis
CT or MRI	Thickened pericardium	Normal pericardium

^aDue to exaggerated x- and y-descents.

^bPericardial knock.

JVP, jugular venous pressure; CT, computed tomography; MRI, magnetic resonance imaging; LV, left ventricular.

ascites. In a few patients with long-standing constriction and congestion, protein-losing gastroenteropathy may ensue.

Differential Diagnosis

Patients who present with noncalcific constrictive pericarditis pose a diagnostic problem.

HEART FAILURE

HF not caused by constrictive pericarditis can be difficult to differentiate. The presence of a pericardial knock and marked ascites developing before leg edema favor the diagnosis of constrictive pericarditis. Also, severe HF causing chronically elevated JVP is invariably associated with tricuspid regurgitation and prominent V-waves. The heart size is usually normal with constrictive pericarditis, and calcification may be apparent, depending on the causation.

RV INFARCTION

RV infarction may produce a similar picture. RV infarction usually presents, however, in the setting of an acute MI and often with inferoposterior involvement. The condition is acute and presents with a high JVP associated with hypotension. Constrictive pericarditis is a chronic condition with insidious appearance of symptoms and signs.

RIGHT ATRIAL MYXOMA

Myxoma should produce a prominent A-wave in the venous pulse, may mimic tricuspid stenosis and requires echocardiographical exclusion.

RESTRICTIVE CARDIOMYOPATHY

Restrictive physiology owing to amyloid and endomyocardial fibrosis may mimic the hemodynamic findings of constrictive pericarditis. [Table 13.3](#) gives diagnostic points for constrictive pericarditis versus restrictive cardiomyopathy. The presence of cardiac enlargement, prominent murmurs, and/or tricuspid regurgitation with prominent systolic V-waves supports the diagnosis of restrictive cardiomyopathy. ECG findings may be similar in both conditions, but pseudoinfarction pattern favors restrictive disease. Diagnosis can be difficult if pericardial calcification or pericardial thickening is not observed on echocardiography or CT or in patients with LV diastolic pressures equal to RV diastolic pressures. MRI may be helpful in identifying thickening of the pericardium. In patients with suspected myocardial disease, endomyocardial biopsy is desirable.

Investigations

A few or all of the following investigations may be required to be certain of the diagnosis:

- Chest X-ray may show pericardial calcification, especially of the apex and posteriorly, which is best seen on lateral views, the heart size is usually normal.
- ECG is virtually always abnormal but nonspecific and shows diffuse flat or inverted T-wave in over 75%; the depth of inversion of the T-waves is usually proportional to the degree of pericardial adherence to the myocardium, which may make stripping difficult; low voltage is present in approximately 50% of cases, along with abnormal P-waves, P-mitrale if in sinus rhythm. AF is present in approximately 33% of patients.
- Echocardiography is of limited value in identifying thickened pericardium, unless calcification is present. Doppler echocardiography shows typical Doppler features in both mitral and hepatic vein flow in approximately 85% of patients with constriction amenable to surgery. In amyloid heart disease, the atrial septum is characteristically thickened, as also may be the case with valves.
- Ultrafast cine-CT and/or MRI give fairly accurate assessment of pericardial thickness, pericardial impingement on the right ventricle, and the degree of dilation of the vena cava and hepatic veins.
- Cardiac catheterization findings are listed in [Table 13.4](#). Elevation and equalization of all diastolic pressures and the dip and plateau or square root sign are typical findings, but these may be observed in some patients with restrictive cardiomyopathy; as outlined above, MRI is useful in differentiating these two categories of patients.
- It is important to avoid diuretics before catheter studies, because sodium and water loss may cause equalization of LV and right ventricular filling pressures in patients with restrictive cardiomyopathy.

Table 13.4.
Catheterization Data

<i>Parameters</i>	<i>Constrictive pericarditis</i>	<i>Restrictive cardiomyopathy</i>
Diastolic pressure	Equalization of early and late diastolic pressures	LV > right ^a Rarely LV- right and resembles constrictive
LVEDP-RVEDP ≤6 mmHg (predictive value 87%) ^b	Pericarditis Usual finding (few exceptions)	Usually >6, but significant Overlap
LA pressure	Equal right	Higher than right; may equalize with severe tricuspid regurgitation
RV pressure square root	Always present: early dip and plateau during diastole	Present, but may disappear with therapy regurgitation
Sign		
Pulmonary hypertension	Mild	Moderate or severe
RV systolic pressure ≤52 mmHg ^b (predictive value 71%)	Usual finding	Wide range (30–85 mm Hg)
RVEDP/RV systolic ≥0.38 ^b (predictive value 83%)	Usual finding	Variable, significant overlap

^aBoth measured simultaneously.

^bModified from Am heart J 1991;122:1431.

LV, left ventricular; RV, right ventricular; EDP, end diastolic pressure; LA, left atrial.

Therapy

If chest X-ray, CT, or MRI reveal a calcified pericardium and if endomyocardial biopsy is unavailable, surgery should be pursued in this setting.

Depending on findings on cardiac catheterization with left- and right-heart hemodynamics, the following is recommended:

- If CT or MRI imaging shows thickened pericardium and one or more hemodynamic criteria for constriction, a high probability of constriction is indicated and surgery is advisable.
- If discordant imaging and hemodynamic data are indeterminate, biopsy is advisable; if this shows infiltrative myopathy, medical therapy is advised, if the chest X-ray, CT, or MRI shows a calcified pericardium on a negative biopsy, surgery is advisable.
- If imaging shows a normal pericardium and less than 2 hemodynamic criteria for constriction, there is a low probability of constriction and observation and medical therapy are rational strategies.

Surgical pericardiectomy is needed when medical therapy, with the judicious use of diuretics and digoxin for control of the ventricular response in patients with AF, fails to reduce markedly elevated JVP and when symptoms are persistent and bothersome. Early surgical mortality is approximately 5%. In patients with severe calcific disease, recovery may be delayed for weeks or months. If constriction and restriction are both present, pericardiectomy may not cause symptomatic improvement. If myocardial fibrosis is present also, improvement from operation will be limited.

MYOCARDITIS

Acute myocarditis is a disease that can cause a fulminant illness that may result in functional impairment or death. Myocarditis appears to be a precursor in some patients with dilated cardiomyopathy. Confirmation of a diagnosis of myocarditis requires fulfillment of the Dallas criteria.

Etiology

It is clinically helpful to consider the etiology of myocarditis under six or more categories:

- **Active viral:** it appears that viruses may induce myocarditis in genetically susceptible individuals. In humans, viral involvement and a later immunological modulation appear to be important. Viral myocarditis can be induced in genetically susceptible mice by viruses and can be prevented by vaccines or by interferon. Enteroviruses of the Picornaviridae family, in particular Coxsackie B, are implicated in most cases. In approximately 50% of patients with human immunodeficiency virus (HIV) who develop a dilated cardiomyopathy, associated myocarditis has been observed on biopsy. Also, 52% of 71 AIDS patients was observed to have a myocarditis at autopsy. The HIV or cytomegalovirus appears to be the cause of myocarditis in patients with AIDS. Acute myocarditis has been associated with infection by Coxsackie B₃ and B₅, mumps, Epstein-Barr, influenza, and other viruses.
- **Lymphocytic:** also called postviral myocarditis, or idiopathic. The term lymphocytic appropriately describes the histological findings. The etiology of this form of myocarditis is unclear. It is believed to be the result of a pathological immune response to recent viral infection that is often subclinical. Two molecular biological techniques, polymerase chain reaction and *in situ* hybridization, have supported the etiological role of enteroviruses in human myocarditis.
- **All other infectious causes:** Chagas' disease is the most common cause of myocarditis in Latin America. Other organisms implicated include toxoplasmosis and diphtheria.
- **Autoimmune:** associated with lupus erythematosus and Kawasaki syndrome.
- **Giant cell:** in this condition, investigators found large nucleated cells with the characteristics of macrophages next to myocytes. An autoimmune process appears likely because this condition has been seen in association with Sjögren's syndrome, giant-cell arteritis, thymoma, myasthenia gravis, chronic active hepatitis, and ulcerated colitis. Patients with giant-cell myocarditis appear to have a prognosis worse than that of lymphocytic myocarditis.
- **Hypersensitivity to drugs and other exogenous agents.**

Clinical Hallmarks

A viral illness in the preceding weeks is observed in over 85% of cases. Any one or more of the following may be manifest:

- Chest pain in over 20% of patients, associated with pericarditis and its signs and symptoms; chest pain may occur suddenly and last for several hours without features of pericarditis and mimic acute MI (these patients may have recurrent or intractable chest pain over several days).
- Palpitations in approximately 33%.
- Symptoms and signs of HF with a small pericardial effusion.
- An easily heard S₃ gallop is commonly present with acute myocarditis and is an expected finding in patients with significant myocardial involvement; an S₃ may persist for several weeks.

- Subclinical illness is not uncommon.
- ECG shows ST-T-wave changes, often with low T-wave and QRS voltage. Conduction defects and atrial or ventricular arrhythmias commonly occur. The ECG may show Q-waves and a pattern simulating acute MI. Serial ECG tracings over the next few days, however, do not show the evolutionary changes that are hallmarks of acute MI.
- Creatine kinase (CK) and CK-MB may simulate MI, but with a different time course. Myocardial biopsy is rarely required, except for research purposes or before prescribing immunotherapy. A negative gallium scan is reassuring, because it excludes myocarditis in over 96% of all cases. Also, a negative gallium predicts a negative myocardial biopsy. In a multicenter study, only 9.4% of 2000 patients with presumed myocarditis had a positive biopsy. Antimyosin scintigraphy has a sensitivity of approximately 55% and a negative predictive value of 95%. A negative scan is usually associated with a biopsy negative for myocarditis. A diffused faint and heterogenous uptake indicates a positive scan for myocarditis. With MI, an intense localized myocardial uptake of antibody occurs in the region of the infarct-related coronary artery, but the scan basically reveals cardiac damage and does not necessarily indicate the cause.

Prediction of Outcome

More than 90% of patients recover completely over days, weeks, or months. In a few cases, HF is manifest and clears over weeks with conventional antifailure therapy. Rarely, HF becomes progressively worse and is unabated, except when corticosteroids or cyclosporin cause some amelioration.

Nonsustained ventricular arrhythmias should not be treated with antiarrhythmics, because these agents may cause deterioration owing to their negative inotropic and proarrhythmic effects. In the presence of lethal or potentially lethal arrhythmias, the use of amiodarone may be lifesaving.

HF Therapy

Therapies for treating HF include the following:

- Modified bedrest: bed to chair for 1 week and then slow ambulation over weeks.
- Avoid digoxin because there is increased sensitivity; thus, the drug is used only for AF with a fast ventricular response or with severe HF along with furosemide and ACE inhibitors (*see* Chapter 5).
- Diuretics must be used judiciously, taking care to prevent potassium and magnesium depletion; ACE inhibitors are necessary to decrease afterload and appear to provide salutary effects.
- Corticosteroids are advisable if symptoms persist or continue to progress in an unabated fashion. Corticosteroids may be given a trial, especially if the illness is beyond 3 weeks. During the first few weeks, there is a fear that corticosteroids may increase viral replication and worsen myocarditis.

A multicenter randomized study using corticosteroids and cyclosporin in patients with biopsy-proven myocarditis showed no improvement in survival or LV function. Thus, a conservative approach is suggested, except where life appears to be threatened.

BIBLIOGRAPHY

- Adler Y, Finkelstein Y, Guindo J, et al. Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998;97:2183–2185.
- Angel J, Anivarro I, Domingo E, Soler-Soler J. Cardiac tamponade: risk and benefit of fluid challenge performed while waiting for pericardiocentesis. *Circulation* 1997;96:Suppl I:I–30.

- Bommer WJ, Follette D, Pollock M, Arena F, Bogнар M, Berkoff H. Tamponade in patients undergoing cardiac surgery: a clinical-echocardiographic diagnosis. *Am Heart J* 1995;130:1216–1223.
- Callahan JA, Seward JB. Pericardiocentesis guided by two-dimensional echocardiography. *Echocardiography* 1997;14:497–504.
- D’Cruz I, Rehman AU, Hancock HI. Quantitative echocardiographic assessment in pericardial disease. *Echocardiography* 1997;14:207–214.
- Figulla HR, Stille-Siegenger M, Mall G, et al. Myocardial enterovirus infection with left ventricular dysfunction: a benign disease compared with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1995;25:1170.
- Fowler NO. Tuberculous pericarditis. *JAMA* 1991;266:99.
- Garcia MJ. Constriction vs restriction: how to evaluate? *J Am Coll Cardiol ACC J Rev* 2003; July/August: 49–53.
- Hare JM, Baughman KL. Myocarditis: current understanding of the etiology pathophysiology, natural history and management of inflammatory diseases of the myocardium. *Cardiol Rev* 1994;2:154.
- Hashim R, Frankel H, Tandon M, Rabinovici R. Fluid resuscitation-induced cardiac tamponade. *Trauma* 2002;53:1183–1184.
- Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial effusion in AIDS: incidence and survival. *Circulation* 1995;92:3229.
- Imazio M, Demichelis B, Cecchi E, et al. Cardiac troponin I in acute pericarditis. *J Am Coll Cardiol* 2003;42:2144–2148.
- Imazio M, Demichelis B, Parrini I, et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. *J Am Coll Cardiol* 2004;43:1042–1046.
- Kirchhoff LV. American trypanosomiasis (Chagas’ disease)-a tropical disease now in the United States. *N Engl J Med* 1993;329:639.
- Lange RA, Hillis LD. Acute pericarditis. *N Engl J Med* 2004;351:2195–2202.
- Maron BJ. Sudden death in young athletes. *N Engl J Med* 1993;329:55.
- Mason JW. Distinct forms of myocarditis. *Circulation* 1991;83:1110.
- Mason JW, O’Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;333:270.
- Merce J, Sagrista-Sauleda J, Permanyer-Miralda G, Soler-Soler J. Should pericardial drainage be performed routinely in patients who have a large pericardial effusion without tamponade? *Am J Med* 1998;105:106–109.
- Narula J, Khaw BA, Dec GW, et al. Recognition of acute myocarditis masquerading as acute myocardial infarction. *N Engl J Med* 1993;329:100.
- Newby LK, Ohman EM. Troponins in pericarditis: implications for diagnosis and management of chest pains patients. *Eur Heart J* 2000;21:798–800.
- Palka P, Lange A J, Donnelly E, et al. Differentiation between restrictive cardiomyopathy and constrictive pericarditis by early diastolic doppler myocardial velocity gradient at the posterior wall. *Circulation* 2000;102:655–662.
- Ramsaran EK, Benotti JR, Spodick DH. Exacerbated tamponade: deterioration of cardiac function by lowering excessive arterial pressure in hypertensive cardiac tamponade. *Cardiology* 1995;86:77–79.
- Reydel B, Spodick DH. Frequency and significance of chamber collapses during cardiac tamponade. *Am Heart J* 1990;119:1160–1163.
- Sargrista-Sauleda J, Angel J, Sánchez A, et al. Constrictive pericarditis. *N Engl J Med* 2004;350:469–475.
- Sekiguchi M, Richardson PJ (eds). Prognosis and treatment of cardiomyopathies and myocarditis. *Cardiomyopathy Update 5*. Tokyo: University of Tokyo Press, 1994.
- Spodick DH, Greene TO, Saperia G. Acute myocarditis masquerading as acute myocardial infarction. *Circulation* 1995;91:1886.
- Spodick DH. Truly total electric alternation of the heart. *Clin Cardiol* 1998;21:427–428.
- Spodick DH. Pericardial diseases. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: a textbook of cardiovascular medicine*, sixth edition. Vol. 2. Philadelphia, PA: W.B. Saunders, 2001:1823–76.
- Spodick DH. Acute cardiac tamponade. *N Eng J Med* 2003;349:684–690.
- Spodick DH. Current Concepts and Practice *JAMA* 2003;289:1150–1153.
- Vaitkus PT, Kussmaul WG. Constrictive pericarditis versus restrictive cardiomyopathy: a reappraisal and update of diagnostic criteria. *Am Heart J* 1991;122:1431.
- Wang K, Asinger RW, Marriott HJL. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003;349:2128–2135.

CONTENTS

HYPERTROPHIC CARDIOMYOPATHY
PATHOPHYSIOLOGY
CLINICAL HALLMARKS
INVESTIGATIONS
THERAPY
APICAL HCM
DILATED CARDIOMYOPATHY
RESTRICTIVE CARDIOMYOPATHY
SPECIFIC HEART MUSCLE DISEASE
BIBLIOGRAPHY

Cardiomyopathies are classified as follows:

- Hypertrophic cardiomyopathy.
- Dilated cardiomyopathy.
- Restrictive cardiomyopathy.
- Arrhythmogenic right ventricular (RV) cardiomyopathy (RV dysplasia).
- Unclassified cardiomyopathy: diseases that do not have features of 1 to 4 and include fibroelastosis and mitochondrial disease.
- Specific cardiomyopathies (specific heart muscle diseases formerly termed secondary cardiomyopathy).

Most of these diseases are rare, but hypertrophic cardiomyopathy has become well-known because it is one of the causes of sudden death in young athletes and young individuals.

Heart muscle disease from known causes, particularly infiltrative or systemic disease, formerly termed secondary cardiomyopathy, is currently referred to as specific cardiomyopathy and is discussed at the end of this chapter.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) refers to a condition in which massive ventricular hypertrophy occurs in the absence of any definite cause.

- The term HCM is preferred, because not all affected patients have idiopathic hypertrophic subaortic stenosis (IHSS) or features of hypertrophic obstructive cardiomyopathy (HOCM).

From: *Contemporary Cardiology: Heart Disease Diagnosis and Therapy:
A Practical Approach, Second Edition*

Edited by: M. Gabriel Khan © Humana Press Inc., Totowa, NJ

- Approximately 33% of patients have no significant left ventricular (LV) outflow tract gradient at rest or on provocation.
- The prevalence of HCM is 1 in 500; thus, approximately half a million individuals in the United States have this disease at any time.
- HCM is the most common genetic cardiovascular disease and it is the most common cause of sudden cardiac death in young individuals, including athletes.

HCM is a disease caused by a wide variety of mutations in genes encoding cardiac sarcomeric proteins that leads to inappropriate and often severe hypertrophy of the myocardium. Approximately 60% of cases are familial and are inherited in a Mendelian single gene autosomal dominant fashion. The genetic cardiac disorder is caused by a missense mutation in one of at least 10 genes that encode the proteins of the cardiac sarcomere.

There are at least 10 culprit genes and more than 125 specific mutations. The most common of these culprit genes that encode sarcomeric contractile polypeptides include the following:

- β -Myosin heavy chain (β -MHC) (MYH7, ~35%).
- Cardiac troponin (TNNT2, ~15%).
- Myosin-binding protein C (~15%) genes.
- α -Tropomyosin.
- Essential myosin light chain.
- Troponins I.
- α -Cardiac actin.
- Regulatory myosin light chain.

Familial HCM can be caused by genetic defects at more than one locus and therefore is a genetically heterogenous disease. The mutations of the troponins-T and some mutations of the β -MHC appear to be associated with sudden death more often than other mutations. Some mutations may be associated with a high incidence of sudden cardiac death, whereas others appear to have a more benign course. This has led to the hypothesis that genotyping may facilitate the identification of individuals at risk of sudden death. There is extreme variability, however, and even mutations that were considered by some to be malignant MYH7 and TNNT2, often run a benign course.

In a study by Ackerman et al., so-called “malignant” mutation was found in only 1% of 293 study patients. The authors concluded that, given the low prevalence of malignant MYH7 and TNNT2 mutations in a large study, genetic testing was unlikely to contribute significantly to risk assessment.

Mutations of the troponins-T gene usually results in only mild or no heart muscle hypertrophy. Some of the sporadic forms of the disease are caused by spontaneous mutations. In some patients with an abnormal gene and normal echocardiography, an abnormal electrocardiogram (ECG) points to the underlying HCM.

The myofibrillar disarray commonly seen in HCM is believed to be caused by an aberration of catecholamine function in the heart of the embryo or by polypeptides produced by the cardiac β -MHC gene.

Familial cases show an autosomal dominant trait linked to chromosome 14q1. In some families, HCM is caused by mutation in the cardiac heavy myosin gene, mainly in the β -MHC gene (chromosome 14q11–q12). Approximately 50% of cases occur in families with an autosomal-dominant transmission, and 40% of cases are sporadic.

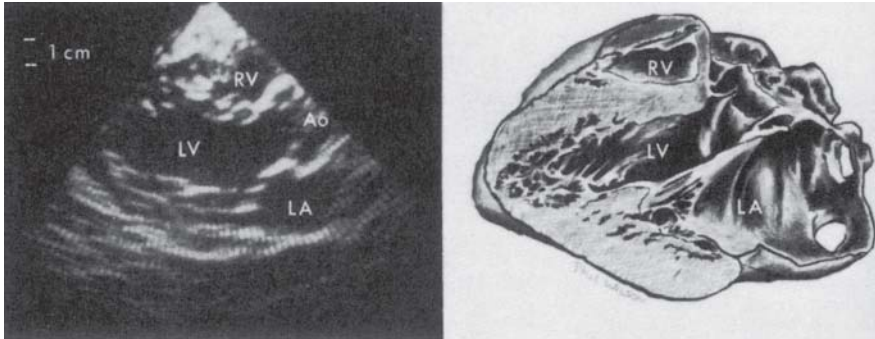


Fig. 14.1. Two-dimensional long-axis echocardiogram and a drawing of the corresponding anatomic specimen with the heart slices through its long axis. RV, right ventricle; LV, left ventricle, Ao, aorta; LA, left atrium. From Rogers EW, Feigenbaum H, Weyman AE. Echocardiography for quantitation of cardiac chambers. In: Yu PN, Goodwin JF, eds. *Progress in Cardiology*. vol. 8. Philadelphia, PA: Lea & Febiger, 1979. Reprinted with permission.

PATHOPHYSIOLOGY

Most patients show asymmetric hypertrophy of the septum and a hypertrophied nondilated left and/or right ventricle. But the septum may be diffusely hypertrophied or only in its upper, mid, or apical portion. Hypertrophy extends to the free wall of the left ventricle.

- [Figure 14.1](#). shows a normal echocardiogram.
- [Figure 14.2](#). shows a patient with HCM who exhibits uniform hypertrophy of the entire left ventricle.
- [Figure 14.3](#). shows the same patient showing total cavity obliteration during systole.
- [Figure 14.4](#). illustrates hypertrophy of the proximal two thirds of the intraventricular septum.
- Decreased compliance and incomplete relaxation of the left ventricle cause impedance to diastolic filling.
- Rapid powerful contraction of the hypertrophied left ventricle expels most of its contents in the first half of systole. This hyperdynamic systolic function is apparent in most patients with HCM.
- The anterior leaflet of the mitral valve is displaced toward the hypertrophied septum, causing obstruction in midsystole. [Figure 14.5](#). shows systolic anterior motion of the anterior mitral leaflet.
- Mitral regurgitation is virtually always present in the obstructive phase of the disease. The sequence of events is eject, obstruct, leak.
- A variable LV outflow pressure gradient at rest occurs in approximately 35% of patients. A further 25% develop a similar gradient precipitated by conditions that increase myocardial contractility or decrease ventricular volume. Thus, diuretics and other causes of hypovolemia and preload-reducing agents that reduce the volume of the small ventricular cavity may worsen outflow tract obstruction.
- Fibrosis and occlusive disease in small coronary arteries and arterioles may occur. The major coronary arteries are wide and patent unless occlusive atherosclerotic coronary disease occurs as a chance association.

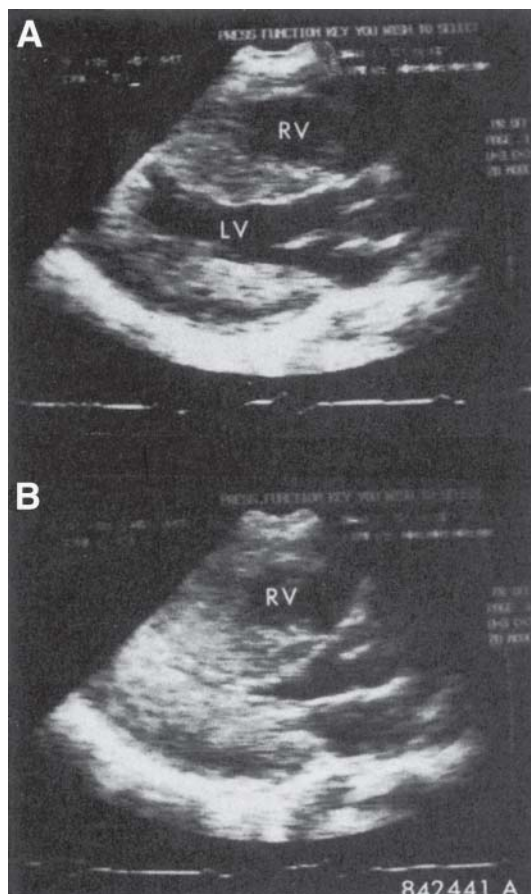


Fig. 14.2. Long-axis two-dimensional echocardiogram of a patient with hypertrophic cardiomyopathy who exhibits uniform hypertrophy of the entire left ventricle (LV). LV, left ventricle; RV, right ventricle; (A) diastole; (B) systole. From Feigenbaum H. Echocardiography. Fourth edition. Philadelphia: Lea & Febiger, 1986:518. Reprinted with permission.

CLINICAL HALLMARKS

Symptoms

- Dyspnea caused by raised LV end-diastolic pressure.
- Angina resulting from reduced diastolic coronary perfusion.
- Presyncope or syncope during exercise, normal activities, or at rest, not simply related to failure or to increase cardiac output on exercise.
- May present with palpitations or symptoms and signs of heart failure (HF). [Table 14.1](#) gives the predominant symptoms and signs and their approximate incidence.

Physical Signs

General physique is usually normal and well-developed.

The palpable left atrial beat preceding the LV thrust is a most important sign because it can occur in the absence of gradient or murmur; this palpable fourth heart sound reflects impaired LV relaxation.

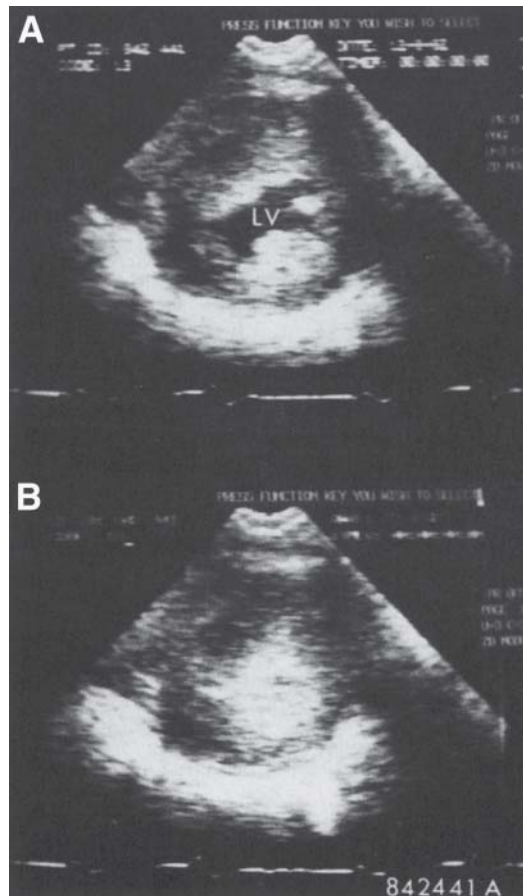


Fig. 14.3. Short-axis two-dimensional echocardiogram in diastole (A) and systole (B) of the same patient illustration in Figure 14.2. During systole there is total cavity obliteration. LV, left ventricle. From Feigenbaum H. Echocardiography. Fourth edition. Philadelphia, PA: Lea & Febiger, 1986. Reprinted with permission.

The murmur has typical features:

- Crescendo–decrescendo starts well after the first heart sound (S_1) and ends well before the second heart sound (S_2). It is best heard between the apex and left sternal border.
- Radiates poorly to the neck, if at all.
- Intensity increases with maneuvers or drugs that decrease preload (Valsalva, standing, amyl nitrite) and decreases in intensity with an increase in afterload (squatting, hand grip, phenylephrine).
- Because echocardiography can be diagnostic and is available in most centers, it is imprudent to rely on the maneuvers outlined to differentiate the murmur of HCM from valvular aortic stenosis. But technique and skilled interpretation are essential. Two-dimensional and Doppler studies are needed. *“Casual” or “occasional” echocardiography can be dangerously misleading.*
- Easy to distinguish from aortic valvular stenosis, in which the murmur starts soon after the S_1 and radiates well to the neck.

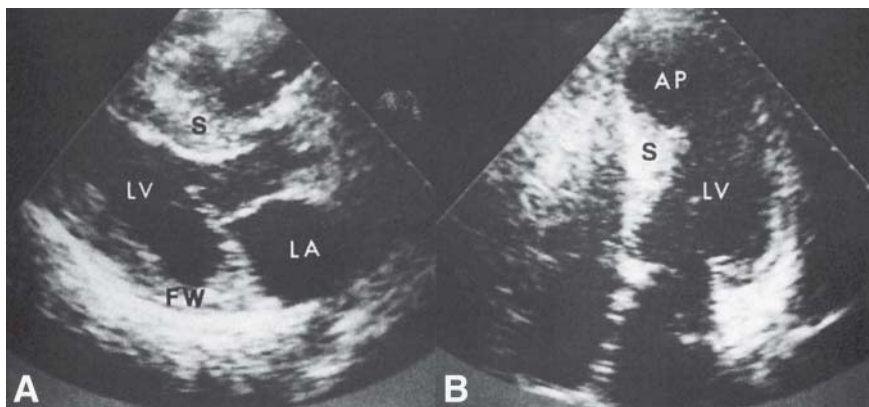


Fig. 14.4. Long-axis (A) and apical four chamber (B) echocardiograms of a patient with hypertrophic cardiomyopathy whose hypertrophy primarily involves the proximal two-thirds of the interventricular septum (S). The apex (AP) is spared from the hypertrophic process. LV, left ventricle; FW, left free wall; LA, left atrium. From Feigenbaum H. Echocardiography. Fourth edition. Philadelphia: Lea & Febiger, 1986:519. Reprinted with permission.

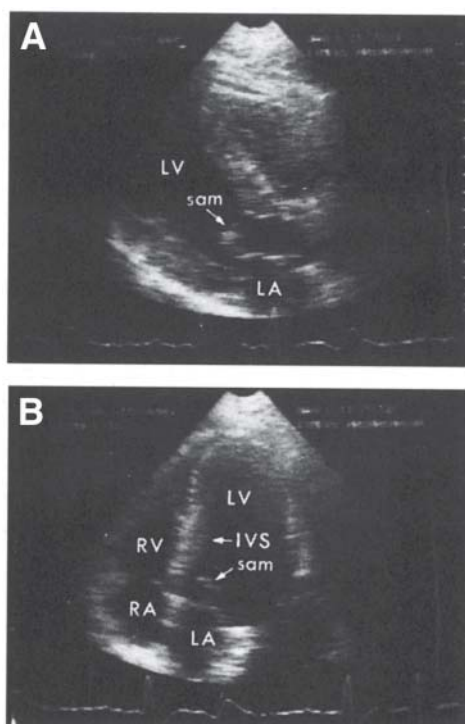


Fig. 14.5. Long-axis (A) and apical four chamber (B) echocardiograms of a patient with hypertrophic cardiomyopathy and a prominent systolic anterior motion (SAM) of the anterior mitral leaflet. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; IVS, interventricular septum. From Feigenbaum H. Echocardiography. Fourth edition. Philadelphia, PA: Lea & Febiger, 1986:526. Reprinted with permission.

Table 14.1.
Clinical Hallmarks of Hypertrophic Cardiomyopathy

<i>Symptoms and signs</i>	<i>Approximate incidence (%)</i>	<i>Factors</i>
Dyspnea	80	Diastolic dysfunction
Angina	60	Decreased coronary reserve, small vessel disease, or associated coronary heart disease
Presyncope	50	Even at rest
Syncope	20	Postexertional and normal activities
Sudden death/annual		
Adult	2.5	Mainly arrhythmic
Children	6	
Annual mortality	4	
Brisk carotid upstroke	90	
Atrial fibrillation	15	
Left atrial beat	50	
Left ventricular thrust	60	
Fourth heart sound	50	
Third heart sound	30	
Systolic murmur, late onset crescendo–decrescendo	90	Begins well after S ₁ Little or no radiation to neck: outflow gradient
Mitral systolic murmur	50	Mitral regurgitation, radiates to axilla

- A mitral regurgitant murmur is often heard in the last half of systole with radiation to the axilla. It is usually associated with an outflow tract gradient. A mitral diastolic rumble may be detected. The S₂ may be single or paradoxically split.

It must be emphasized that the physical examination may be relatively unremarkable in HCM; attention is necessary to elucidate the following three subtle signs:

- Rapid carotid upstroke.
- Abnormal cardiac impulse with a palpable left atrial beat.
- Gallop sounds.

HCM causes a brisk carotid upstroke because of the dynamic LV emptying, giving an ill-sustained quality, whereas aortic valvular stenosis produces a slow-rising pulse, pulsus tardus et parvus, with a delayed carotid upstroke.

Signs of obstructive HCM include a bifid arterial pulse and a double systolic or triple apex beat, and reversed splitting of the S₂.

Supraventricular arrhythmias occur in 20–50% of patients and ventricular arrhythmias occur in almost all patients.

Sudden Death

Efforts at prevention of sudden death represent important clinical challenges in HCM and can only result from better methods of identification of high-risk patients.

Major risk factors for sudden death are:

- Cardiac arrest (ventricular fibrillation [VF]).
- Spontaneous sustained ventricular tachycardia (VT).
- Family history of sudden death in two or more first-degree relatives younger than age 40; but defined by some as sudden death in one or more first-degree relatives younger than age 40.

Clinical parameters that may assist in the assessment of risk for sudden death however, remain unsystematic and haphazard. McKenna et al. make the point that, at best, clinical risk markers are only modestly predictive of short- to medium-term risk of sudden death. The presence of a severe outflow tract gradient does not correlate with the risk of sudden death.

- Marked left ventricular hypertrophy (LVH): Current evidence indicates that marked LVH should not be relied upon: some studies indicate that LV wall thickness greater than 30 mm significantly increases the risk of sudden death. In a study by Spirito et al., sudden death occurred in less than 1% of patients with maximal thickness less than 20 mm and in 16% of patients with maximal thickness, more than 30 mm over the average follow-up of 7 years. Unfortunately, at least 10% of patients in most survival studies show a LV wall thickness greater than 30 mm. Most important, the majority of sudden cardiac deaths in patients with HCM occur in those with wall thickness of less than 30 mm.
- Survivors of cardiac arrest: a high-risk group that is easy to define are those individuals who have survived an episode of sustained VT. These patients have an approximately 8% chance of a further cardiac event in 5 years.
- Family history and/or syncope: a history of sudden death in the family or syncope in the individual is worrisome and there is considerable anecdotal evidence to suggest that these two features carry a sizable predictive risk. The worry to the family and individual is understandable. The outcome statistical analyses in large series show that they are not reliable indicators, however, for the prediction of sudden death. Syncope is more sinister in children with HCM than in adults.
- Arrhythmias and abnormal exercise blood pressure (BP) response to: finding of nonsustained ventricular tachycardia on Holter electrocardiographic ambulatory monitoring, and an abnormal BP response on exercise taken in association with the clinical evaluation (massive LVH) and family history (unexplained syncope, family history of sudden death) is a useful strategy. In a prospective study in which these parameters were present there was an annual sudden death risk of approximately 3%.

Most important, a group at low-risk of sudden death may be identified:

- Asymptomatic patients with LV thickness less than 20 mm.
- Absence of nonsustained VT on Holter monitoring.
- Normal exercise BP response and no family history of sudden death.

Atrial Fibrillation in HCM

Atrial fibrillation (AF) occurs in approximately 15% of patients with HCM. The loss of atrial systole with a fast ventricular response may precipitate pulmonary edema and, occasionally, severe hypotension.

The outcome for patients with HCM and AF is not as bleak as envisaged in the 1970s and 1980s, however. The outlook is not significantly worse for patients with AF and failure to convert than it is for patients with sinus rhythm. Functional class does deteriorate with the onset of AF, but it improves with conversion and control of ventricular response or when chronic AF with controlled ventricular response is achieved.

Endocarditis

Infective endocarditis may occur on aortic or mitral valves. It should be suspected if unexpected HF or symptoms or signs of endocarditis occur or if a procedure has been carried out without antibiotic cover.

INVESTIGATIONS

Chest X-Ray

The chest X-ray may be normal but often shows some left atrial enlargement; the left ventricle ranges from normal to severe enlargement. Aortic valve calcification is absent in HCM, but annular calcification of the mitral valve occurs.

ECG Findings

- Virtually always abnormal (97%) in patients with significant symptomatic HCM and about 90% abnormal in asymptomatic patients and may be abnormal when the echocardiogram shows no LVH; the ECG is an inexpensive screening test.
- AF in 15%; an additional 33% have paroxysmal episodes.
- Other supraventricular and ventricular arrhythmias, nonsustained VT is common, but sustained VT occurs in approximately 3%.
- Deep, narrow Q-waves in about 30% in leads II, III, aVF, V₅ and V₆, or in I, aVL, V₅ and V₆, and rarely V₁ through V₃, which at times reflect septal hypertrophy and may mimic infarction (Fig. 14.6.).
- Intraventricular conduction delay in over 70%.
- High QRS voltage LVH.
- Diffuse T-wave changes in some patients or T-waves of LVH.
- Giant inverted T-waves, very high precordial QRS voltage with apical HCM.
- Supraventricular tachycardia (SVT) segment depression in some.
- PR interval occasionally short; pre-excitation may be seen.

Echocardiogram

Two-dimensional echocardiographic observation of a LV myocardial segment of 1.5 cm or more in a normal-sized adult is considered diagnostic if there is no other evident cause. Asymmetric hypertrophy is supporting evidence. Myocardial mass increases with age and size. Continuous-wave Doppler echocardiography defines the degree of LV outflow-tract gradient. Figures 14.2.–14.5. and 14.7. illustrate features of HCM. Table 14.2. gives echocardiographic hallmarks.

Holter Monitoring

A 48-hour Holter monitor is necessary because a 24-hour study detects less than 50% runs of nonsustained VT. Repeated studies may be required.

Where facilities exist, a signal-averaged ECG is advisable, especially in younger patients. In this subgroup, an abnormal signal-averaged ECG appears to be a marker for sudden death. Further studies are necessary to confirm the role of the signal-averaged ECG in patients with HCM.

THERAPY

Management of the patient with HCM includes the following:

- Counseling and screening of all first-degree relatives with echocardiography every 5 years. Importantly, hypertrophy may not be appreciable until the sixth to seventh decade.

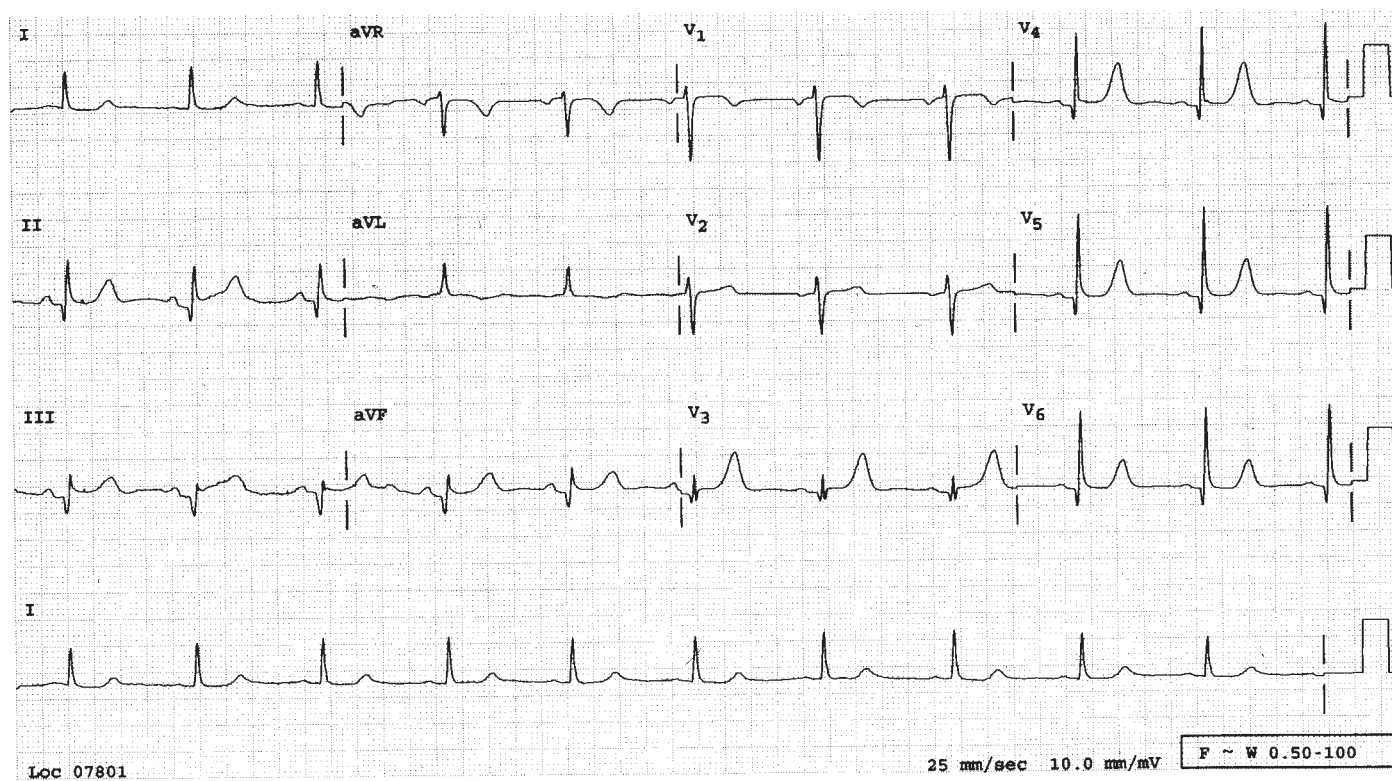


Fig. 14.6. Hypertrophic cardiomyopathy simulating inferolateral infarction.

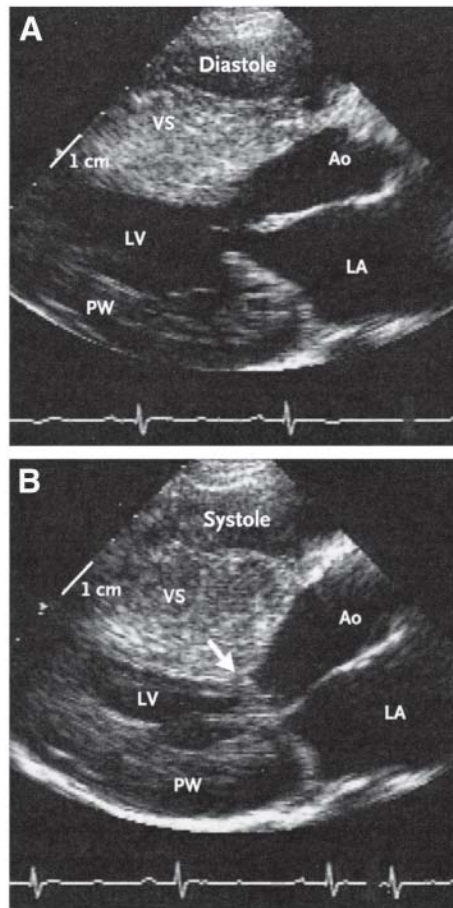


Fig. 14.7. Two-dimensional echocardiogram from a patient with severe symptomatic hypertrophic obstructive cardiomyopathy. (A) shows a still frame obtained during diastole. There is a marked increase in the thickness of the ventricular septum. (B) shows a still frame obtained during systole. Systolic anterior motion of the mitral valve apparatus causes obstruction of the left ventricular outflow tract (arrow). Ao, aorta; LA, left atrium; PW, posterior wall, VS, ventricular septum; LV, left ventricular. From Nishimura RA, Holmes DR Jr. Hypertrophic obstructive cardiomyopathy. *N Engl J Med* 2004;350:1320–1327. Reproduced with permission from N Engl J Med ©2004 Massachusetts Medical Society. All rights reserved.

- Patients must be instructed to avoid strenuous competitive exercise because it can cause sudden death. Intense physical activity involving bursts of exertion or repeated isometric exercise should be avoided.
- Avoid dehydration. A decrease in ventricular volume or increase in ventricular contractility increases the outflow gradient. Thus, dehydration and the use of preload-reducing agents, such as diuretics, nitrates, or angiotensin-converting enzyme (ACE) inhibitors are hazardous.
- All patients should be offered instructions for prophylaxis against infective endocarditis.
- β -Agonists increase contractility and are contraindicated.
- Digoxin increases contractility and its use should be avoided, except in the management of chronic AF, a fast ventricular response uncontrolled by amiodarone, β -blockers, or verapamil. Also useful in patients with end-stage disease with HF (*see Table 14.3*).

Table 14.2.
Echocardiographic Hallmarks of Hypertrophic Cardiomyopathy

Disproportionate septal thickness, septum to posterior wall ratio >1.5
LV myocardial segment > 1.5 cm in thickness
Poor septal contraction, hypercontractile free posterior wall
Systolic anterior motion of the mitral valve when outflow tract gradient >30 mmHg
Mid systolic aortic valve closure
Small LV cavity, typically with virtual elimination in systole
Mitral regurgitation frequently present
LV outflow tract gradient at rest in about 35% of patients

- Drugs that decrease myocardial contractility or produce myocardial relaxation, particularly β -blockers, play a role in the control of symptoms.
- Patients without significant obstruction with moderate mitral regurgitation and end-stage disease with HF and ventricular dilatation may benefit from the judicious use of ACE inhibitors (Table 14.3.).

Pharmacological Agents

Symptomatic relief can be attained in many patients by pharmacological therapy designed to achieve the following:

- Block the effects of catecholamines that exacerbate the outflow tract obstruction.
- Slow the heart rate to 50–60 beats per minute (BPM) to enhance diastolic filling.

β -Adrenergic Blocking Agents

Clinical trials have documented the role of β -blockers in the management of HCM. β -blockers and verapamil are equally effective for the management of symptoms, but β -blockers generally are safer and therefore are considered first-line therapy. Beneficial effects of β -adrenergic blocking drugs include the following:

- Decrease in myocardial contractility causes a decrease in “venturi” effect and therefore less obstruction.
- Relief of dyspnea in about 40% of patients.
- Significant relief of angina in 33–66% of patients.
- The heart rate should be maintained between 52 and 60 BPM; this results in an improvement in ventricular filling during prolonged diastole; also increased coronary filling occurs because of prolongation of the diastolic interval.
- Improvement in diastolic dysfunction.
- Partial control of supraventricular and ventricular arrhythmias.

Angina, at times, may be caused by coincident atheromatous obstruction of major coronary arteries but is commonly a result of small vessel disease and decreased coronary flow reserve. Large doses of β -blockers are often required to produce adequate β -adrenergic blockade.

The therapeutic activity of β -blockers, particularly propranolol, metabolized in the liver, and calcium antagonists is blunted by cigarette smoking. It is important for patients with HCM to desist smoking because of other adverse effects, as well as the decrease in effectiveness of the two major pharmacological interventions. β -Blockers do not appear to decrease the risk of sudden death in these cardiac patients. But clinical trials have

Table 14.3.
Pharmacologic and Surgical Interventions for Hypertrophic Cardiomyopathy

<i>Intervention</i>	<i>Obstructive phase</i>	<i>End stage</i>
Negative inotropes		
β-blockers	Yes (especially with latent obstruction)	Small dose considered
Verapamil	Yes	Contraindicated
Disopyramide	Yes	Contraindicated
Digoxin	Contraindicated	Needed and useful
Diuretics	Contraindicated	Needed and useful
Afterload-reducing agent		
ACE inhibitors	Contraindicated	Of some benefit in patients with ventricular dilatation and heart failure
Surgery	Septal myectomy	Transplant

included only small numbers of patients, and this is a possible reason for the lack of documentation of a decrease in the risk of sudden death with β-blocker therapy. These agents are particularly useful in patients with latent “obstruction.” Clinical experience has been mainly with propranolol; nonselective agents are preferred. β-Blockers with significant partial agonist activity, such as pindolol and acebutolol, are less desirable.

Contraindications to β-blocker therapy include asthma, HF, severe peripheral vascular disease, sick sinus syndrome, marked bradycardia, and second- or third-degree atrioventricular (AV) block.

PROPRANOLOL

This is supplied as 20-, 40-, 80-, and 120-mg tablets (Inderal LA: 80, 120, and 160 mg). A dosage of 10 mg three times daily is given and increased slowly to 120–240 mg daily. A slow buildup of the dosage to 320 mg may be required.

METOPROLOL

100–200 mg daily.

SOTALOL

This is a nonselective hydrophilic nonhepatic-metabolized β-blocker that, among the β-blockers, has a class 3 antiarrhythmic activity and therefore may decrease the risk of sudden death. Where amiodarone is contraindicated or produces adverse effects, sotalol may be tried for supraventricular and ventricular arrhythmias.

This is supplied as 80- and 160-mg tablets, or 40- and 80-mg tablets in the United Kingdom. A dosage of 80–240 mg daily is used. Start with 40–80 mg twice daily and then increase, if needed, to a maximum of 240 mg daily. The drug can be given once daily, but it makes more sense to give smaller divided doses so that in the event of adverse effects, the evening dose can be discontinued. Maintain normal serum potassium and watch especially for precipitants of hypokalemia resulting from diuretic use and persistent diarrhea.

Caution: Hypotension, do not use with potassium-losing diuretics. Care must be taken to maintain normal serum potassium to avoid the rare risk of torsades de pointes. Do not use in patients with renal failure.

β -Blockers interact with amiodarone, diltiazem, verapamil, diuretics, quinidine, and class 1A antiarrhythmics.

Calcium Antagonists

Verapamil enhances LV diastolic filling by improving ventricular relaxation, actions similar to those produced by β -adrenergic blockade. Considerable experience with verapamil is now available, but the initial high expectations have not materialized, and the drug has caused deaths. Verapamil decreases dyspnea and increases exercise capacity in some patients but does not improve survival and has precipitated life-threatening pulmonary edema in a significant number of patients; these vasodilators can unpredictably increase the obstruction with resultant pulmonary edema, cardiogenic shock and death. It is contraindicated in patients with severe obstruction or end-stage disease associated with ventricular dilation and HF.

This is supplied in 80- and 120-mg tablets (SR 240 mg; United Kingdom: 40 mg). A dosage of 40 mg three times daily or 80 mg twice daily is used and increases slowly over weeks to 240–360 mg daily under close observation. Preferably, administration of the drug is begun in the hospital setting.

Adverse effects include high-grade AV block, asystole, sinus arrest, acute pulmonary edema, and hypotension. The drug must not be combined with amiodarone and should not be used concomitantly with β -blockers, quinidine, or disopyramide.

Contraindications include the following:

- Orthopnea or paroxysmal nocturnal dyspnea. Deaths have occurred in these patients as a result of verapamil use.
- HF or end-stage disease ([Table 14.3](#)).
- Sick sinus syndrome.
- AV block and conduction defects.

Amiodarone

Amiodarone has gained widespread acceptance as a major advance in the management of patients with AF and, in others, to reduce the incidence of ventricular arrhythmias and sudden death where the risk is assessed to be high.

Indications include the following:

- Syncope resulting from ventricular arrhythmia is an indication, provided that sick sinus syndrome and AV block are excluded. In the latter subset of patients, pacing and amiodarone are advisable.
- AF: prevention, conversion, and/or control of ventricular response. Amiodarone causes AF to convert to sinus rhythm in approximately 80% of patients and is especially effective in causing conversion to sinus rhythm when the duration of AF is short. Amiodarone also stabilizes the ventricular response. The drug appears to be successful in preventing the progression of paroxysmal fibrillation that has been present for less than 1 week to chronic AF. Direct current cardioversion is indicated in patients with recent-onset AF who show hemodynamic deterioration: effective anticoagulation is essential and amiodarone cover facilitates conversion.
- Suppression of potentially lethal arrhythmias.

Electrophysiological testing to select a drug that suppresses VT is generally not useful in these patients. Because amiodarone is the only drug that has been shown to decrease the risk of sudden death, it is used when indicated as the drug of first choice, regardless of testing. Electrophysiological testing should be reserved for patients who have repeated syncope or uncontrollable arrhythmias and in whom amiodarone is unacceptable; the choice often lies between administration of sotalol and implantation of an antitachycardia device.

This is supplied 200-mg tablets, and in the United Kingdom, in 100- and 200-mg tablets or 150-mg ampules. A dosage of 200 mg three times daily for 5–7 days and 200 mg twice daily for 2 weeks is given, after which, if no major adverse effects are seen and depending on effectiveness, the dose is reduced to 200 mg daily for 4–6 weeks and then 100 mg daily for 5 days per week. The exact cutoff point for reduction is controlled by the results of 48-hour Holter monitoring. The aim is for 50–100 mg daily.

Intravenous (IV) administration of amiodarone is reserved for patients with immediate life-threatening arrhythmias, including AF. The dosage is IV infusion: 1000 mg over 24 hours given as 150 mg over 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute for 18 hours (*see* Chapter 6).

Because of the significant potential for adverse effects and drug interactions, monitor the following at 2–4 weeks for 3 months and then at least monthly or at appropriate intervals:

- ECG for bradyarrhythmias, excessive QT prolongation, AF, or VT.
- Serum potassium (and magnesium) levels.
- Liver function tests, thyroid function tests.
- Digoxin level, if concomitant use of digoxin with dosage halved.
- Prothrombin time, international normalized ratio if on warfarin with dosage halved.
- Chest X-rays at 3 and 6 months and then every 6 months or annually thereafter or on occurrence of dyspnea is also important for early detection of pulmonary infiltrates.
- Lung function tests (*see* Chapter 6).
- Slit lamp examination for corneal deposits.

Contraindications include sinus bradycardia, sick sinus syndrome, and AV block, requires pacing if amiodarone is needed, clinical thyroid dysfunction is a relative contraindication, and pregnancy and breastfeeding.

Adverse effects include the following:

- Severe bradyarrhythmias; asystole; rarely, torsades de pointes, especially in patients with bradycardia or low serum potassium.
- Hypothyroidism or, less often, hyperthyroidism occurs in about 5% of patients.
- Corneal microdeposits are universal during chronic therapy but rarely become symptomatic.
- Hepatitis with grossly elevated transaminase occurs in a small minority of patients and, because this condition has a propensity to progress to cirrhosis, immediate discontinuation of amiodarone is necessary (*see* Chapter 6).
- Nervous system manifestations are common with sleep disturbances, paraesthesias, or twitching that usually responds to dose reduction.
- Photosensitivity, metallic taste, nausea, and vomiting.
- Slate grey skin is related to high loading and maintenance doses. The skin must be protected from direct and indirect ultraviolet light.
- Pulmonary infiltrates and alveolitis represent a life-threatening, usually late complication about which the patient should be warned, but this occurs in fewer than 1% of

patients. The aforementioned adverse effects are uncommon with modern conservative dosing schedules. Severe side effects are rare if minimal effective doses are used and are usually reversible, except severe pulmonary infiltrates and skin pigmentation.

Interactions include the following:

- Amiodarone increases the activity of oral anticoagulants; both drugs may be required in patients with AF or in patients with embolization.
- Verapamil and diltiazem may produce sinus arrest or AV block.
- Digoxin levels increase markedly.
- Quinidine levels increase and TdP may be precipitated.
- Sotalol in combination may precipitate TdP.
- Phenothiazines and tricyclics.

Patients with cardiac arrest or sustained VT, in whom amiodarone therapy has failed, deserve consideration for an antitachycardia pacemaker defibrillator.

Disopyramide

Disopyramide exerts a negative inotropic effect, and some studies indicate beneficial effects in some symptomatic patients during the obstructive phase, in whom β -blockers and/or amiodarone are contraindicated. The drug does not prolong life and is not effective for angina. A dosage of 150–800 mg daily is used, preferably as a twice-daily long-acting preparation (*see* Chapter 6).

Contraindications include sick sinus syndrome, AV block, and impaired ventricular systolic function ([Table 14.3.](#)).

Digoxin

Digoxin is contraindicated in HCM, except in patients with severe HF with end-stage disease unresponsive to very small doses of diuretics. If direct-current (DC) shock or amiodarone fails to convert AF to sinus rhythm and the ventricular response is more than 100 per minute, digoxin is advisable, especially if HF is present. If HF is not present, a β -blocker is advisable to decrease the ventricular response.

Interactions may occur with verapamil, diltiazem, and amiodarone.

Anticoagulants

Indications include the following:

- All patients with AF, to prevent embolism at the time of DC conversion, and when waiting for amiodarone to produce conversion.

Patients who remain in AF while on amiodarone should receive anticoagulants but with careful monitoring of international normalized ratio or prothrombin time because amiodarone enhances the activity of coumarins and life-threatening bleeding can be precipitated.

Antibiotics

Antibiotics should be given before dental work, endoscopy, abdominal, and other operations to prevent bacterial endocarditis (*see* Chapter 12).

Automatic Defibrillator

Implantation of a cardioverter-defibrillator may be lifesaving in patients at high risk for sudden death:

- History of cardiac arrest (VF).
- Documented, sustained VT.
- History of sudden cardiac death in two or more first-degree relatives younger than age 40.

The American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology 2002 guidelines designate the ICD as a class IIb indication for primary prevention of sudden death in HCM. The implantable cardioverter-defibrillator (ICD) has been shown to be the most effective prophylactic treatment for prevention of sudden death in HCM. Reportedly, ICDs reliably aborted potentially lethal VTs in approximately 25% of patients over a 3-year period, despite the substantial LV mass observed in these patients.

Septal Myectomy and Mitral Valve Surgery

Indications include the following:

- Patients who have had adequate trials of β -blockers, verapamil, or amiodarone plus β -blocker and remain severely symptomatic with angina and dyspnea.
- Outflow gradient greater than 50 mmHg at rest.
- Severe mitral regurgitation.
- Very thick ventricular septum. Small ventricular cavity, true obstruction.
- High LV end-diastolic pressure.

When surgery is indicated, a septal myotomy/myectomy is performed. A significant number of patients obtain symptomatic relief of symptoms. The Dusseldorf and Toronto experience shows an encouraging reduction in sudden death and syncope after successful myotomy/myectomy. In a cohort of patients from Toronto operated on between 1971 and 1986, the 5-year survival was 93%, with symptom relief for most patients. Mitral valve replacement is indicated only for severe mitral regurgitation dual-chamber pacing.

Alcohol-Induced Septal Ablation

Sigwart originally reported nonsurgical septal ablation with intracoronary alcohol that produced a localized infarct that was sufficient to eliminate symptomatic subaortic stenosis in three patients. Improvement was maintained for more than 12 months.

Nonsurgical septal ablation is characterized by the following:

- 100 % alcohol is infused selectively into a septal perforator artery or branch that perfuses the proximal septum to produce a localized myocardial infarct.
- Causes significant symptomatic improvement with a decrease in the outflow gradient from 60 to 70 mmHg to less than 20 mmHg in selected cases done by highly skilled operators.
- In experience centers heart block requiring pacing occurs in 20–30% of cases; also large infarcts and ventricular septal defects may occur.

Dual-Chamber Pacing

Pacing causes a variable and small reduction in the pressure gradient and may relieve symptoms in some, but has a placebo effect.

Nishimura et al. observed a less than 15% decrease in LV gradient. Exactly how pacing achieves modest beneficial hemodynamic effects is unknown; complete ventricular capture is necessary and requires optimization of the AV delay with β -blockers or verapamil. Results of randomized clinical trials (RCTs), however, show a large placebo effect and no significant improvement in objective measures of exercise capacity. At 5 years of follow-up, less than 40% of patients show improvements in symptoms.

Dual-chamber pacing may be considered in patients who have coexisting illnesses that are contraindications to other therapies or those who require pacing for bradyarrhythmias.

APICAL HCM

Apical HCM in Japanese people appears to have a low risk of sudden death and a benign prognosis; an outflow tract gradient does not develop. ECG shows typical giant inverted T-waves and high precordial QRS voltage. Angina, dyspnea, and arrhythmias may, however, occur. Syncope is uncommon.

HCM was associated with giant T-waves observed in a small group of Western patients and had the same outcome as in patients without giant T-waves. Giant T-waves are not a common feature of HCM in non-Asian patients. Giant T-waves in non-Japanese should be considered to be a dramatic ECG pattern and not a marker of outcome. Management with β -blockers is appropriate.

Digoxin is indicated if Af or HF supervenes. Amiodarone is indicated for paroxysmal AF with ventricular rates uncontrolled by digoxin and/or if VT or VF occurs. Prognosis appears relatively favorable in most patients with this form of HCM.

Mitral valve calcification is not uncommon in the elderly and may cause difficulties in differential diagnosis from rheumatic mitral valve disease, especially if AF is present.

Systemic hypertension is also not uncommon in the older patients in whom it can be difficult to know whether the ventricular hypertrophy is caused by the hypertension, or apical HCM. Echocardiography should establish the difference between HCM and hypertensive heart disease.

DILATED CARDIOMYOPATHY

A diagnosis of dilated cardiomyopathy (DCM) should be considered in a patient with right and left HF, documented global hypokinesis and dilatation of the left and/or right ventricles, and reduced systolic function in the absence of evidence of coronary artery disease (CAD), congenital, specific valvular, hypertensive, or specific heart muscle disease and chronic excessive alcohol consumption.

DCM is not caused by alcohol but can be exaggerated by it. A previous viral infection has been suspected in up to 50% of cases. Although previously considered to be only rarely familial, it is now known that a genetic basis exists; the locus affected appears to be associated with immunoregulation.

Patients usually present at age 20–50, but the disease also occurs in children and in the elderly. More than 75% of patients present with an initial episode of HF, New York Heart Association class III or IV.

Clinical Hallmarks

Clinical hallmarks of DCM include the following:

- Progressive dyspnea on exertion over weeks or months, culminating in orthopnea, paroxysmal nocturnal dyspnea, and edema, which are common features. Physical signs of

right and left HF are prominent in late cases. The extremities tend to be cool and pale owing to vasoconstriction.

- The apex beat is displaced downward and outward to the left because of LV dilatation.
- Left lower parasternal lift or pulsation indicates RV dilatation.
- The jugular venous pressure may be elevated and may show a systolic wave of tricuspid regurgitation.
- A soft grade I–II/VI systolic mitral murmur and a soft tricuspid systolic murmur are commonly present because of mitral and tricuspid regurgitation as a result of dilatation of the ventricles and valve rings as well as papillary muscle dysfunction.
- The fourth heart sound (S₄) and the third heart sound (S₃) are constantly present, as well as sinus tachycardia; thus, a summation gallop is a frequent finding.
- The loud S₃ is present in virtually all cases and is often heard when HF is absent. This hallmark serves to differentiate DCM from a class 4 ventricle owing to CAD where a soft S₃ is heard during episodes of HF but is frequently absent or quite soft when the individual is assessed not to be in HF, and in the absence of LV aneurysm.
- BP is frequently low, hypotension carries a poor prognosis.

Aortic systolic or diastolic murmurs are usually absent and serve to exclude specific valvular heart disease as a cause of severe HF. But, occasionally, an aortic diastolic murmur is heard in DCM. Echocardiographical diagnosis can be made before overt HF has developed.

Investigations

ECG

ECG features include the following:

- Sinus tachycardia.
- Flat or inverted T-waves.
- Modest LVH may be masked by low voltage.
- AF occurs in about 25%.
- Conduction abnormalities occur in more than 75% of cases: nonspecific intraventricular conduction delays, left anterior hemiblock, left bundle branch block (LBBB) is observed in a significant minority, right bundle branch block (RBBB) is uncommon.
- Poor R-wave progression (V₂ through V₄) or Q-waves of pseudoinfarction may suggest an incorrect diagnosis of ischemic heart disease.

CHEST X-RAY

The heart is enlarged, commonly involving all four chambers. There is usually evidence of a raised left atrial pressure in the pulmonary vascular pattern; pleural effusions may be present.

ECHOCARDIOGRAM

Echocardiographic features include the following:

- Severe dilatation of both ventricles ([Fig. 14.8.](#)); there is global hypokinesis and commonly paradoxical movement of the septum.
- Increased end-systolic and end-diastolic dimensions.
- Ejection fraction (EF) usually less than 35%; in the presence of HF, EF is usually 10–30%.
- Atrial enlargement and ventricular thrombi are commonly seen.
- A small pericardial effusion is frequent.

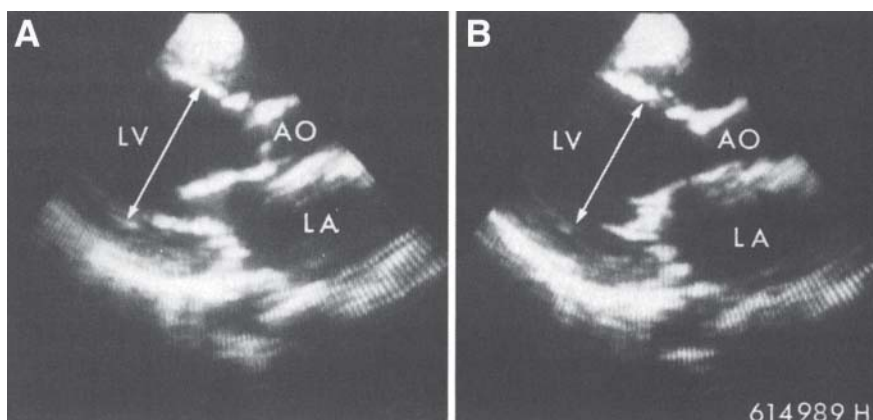


Fig. 14.8. Long-axis parasternal two-dimensional echocardiogram in diastole (**A**) and systole (**B**) of a patient with dilated cardiomyopathy. Little difference in the left ventricular diameter exists between the two recordings. The mitral valve opening in (**B**) is also markedly reduced. LV, left ventricle; AO, aorta; LA, left atrium. From Feigenbaum H. *Echocardiography*. Fourth edition. Philadelphia, PA: Lea & Febiger, 1986:532. Reprinted with permission.

ENDOMYOCARDIAL BIOPSY

This is used as a research tool to exclude suspected known heart muscle disease and to detect evidence of myocarditis or viral particles. Pathological features include degeneration of myocytes, varying degrees of loose interstitial fibrosis, and myocytic hypertrophy. But histological changes may be unremarkable in some cases. The presence of interstitial fibrosis suggests the possibilities of previous viral myocarditis. The diagnosis of myocarditis by pathology must satisfy the Dallas criteria.

HOLTER MONITORING

The results of Holter monitoring carried out for 48 hours help to define patients with potentially lethal ventricular arrhythmias.

Etiological Evaluation. Up to 50% of cases of myocarditis and DCM appear to be associated with enteroviral infections; however, causality has not been established with certainty. Molecular hybridization techniques have linked enteroviral infections to both human myocarditis and DCM. More than 20% of patients with DCM have at least one first-degree relative with cardiomegaly and decreased EF.

Organ-specific cardiac autoantibodies have been detected in about 26% of patients with DCM, as opposed to fewer than 3% of patients with known cardiac disease. An immunological process associated with a viral infection is observed in a minority of patients with DCM. The autoimmune process may have a genetic basis, and future studies are awaited to clarify and document the causes of DCM.

PROGNOSIS

The 1-year mortality of about 25% in earlier studies has improved to about 10%. The 5-year mortality of approximately 50% has shown some improvement in more recent population based studies with a reported mortality of 20%. The improvement in mortality is likely owing to earlier detection of HF and better management, including the use of ACE inhibitors. Mortality after documented HF has been reported as about 50% in 1 year. However, reports indicate an improved prognosis with 50% survival at 5 years, probably

owing to earlier diagnoses, better methods of investigation, and improved therapy. The most important indication of prognosis is cardiac function. Patients with the lowest EF have the worst prognosis.

Advice to patients and relatives regarding prognosis is fraught with difficulty because we have poor parameters from which to predict outcome. A patient presenting with severe HF with global hypokinesia and EF less than 20% and/or LBBB with associated potentially lethal ventricular arrhythmias has a poor prognosis and is unlikely to survive beyond 12 months. Patients with these diagnoses may survive for 2 years or more, however, and caution is necessary in discussions with both the patient and family. A few small-group studies suggest a trend toward a modest increased survival with the use of low-dose amiodarone to control arrhythmias, in addition to the usual measures for control of HF.

The prognosis of HF has been improved with the use of hydralazine combined with nitrate, and the Vasodilator Heart Failure Trial II (VHeFT II) study has shown ACE inhibitors to be superior to this combination (*see* Chapter 5). The Studies of LV Dysfunction (SOLVD) confirmed the salutary effects of ACE inhibitors. The VHeFT II and SOLVD, however, randomized only 9.5–32% of patients with DCM.

Therapy

The most important aspect of management of DCM is the prevention and control of HF, arrhythmias, and embolization. The following standard management for HF should be instituted:

- Bed to chair rest for several days.
- Oxygen and a sedative at night to allow restful sleep, which adds to the patient's comfort and reduces the workload of the failing myocardium.
- Salt restriction.
- Avoidance of alcohol is necessary in all patients with HF and especially in the patient with a class 3 or 4 ventricle, because alcohol decreases the EF. Patients should be assessed for the presence of macro-ovalocytes, decreased platelet counts, and increased levels of γ -glutamyltransferase, which may indicate alcohol abuse with patient's denial.

DIGOXIN

Digoxin provides some benefit in HF patients in sinus rhythm and is indicated for AF with uncontrolled ventricular response. The dose should be adequate, but care is needed to avoid digitalis toxicity.

DIURETICS

Diuretics play a vital role in the relief of symptoms and cannot be replaced by ACE inhibitors. The three groups of drugs—diuretics, digoxin, and ACE inhibitors—are complementary.

FUROSEMIDE

A dosage of 40–80 mg daily is used. Increase only if shortness of breath and pulmonary congestion are not controlled by the addition of adequate doses of an ACE inhibitor; the use of ACE inhibitors is often limited by hypotension. Patients with poor systolic function often have low systolic pressures (<110 mmHg), and it is sometimes necessary to discontinue diuretics for 24–48 hours to permit the selected ACE inhibitors to be commenced. Caution is needed to avoid hypokalemia and magnesium depletion. The latter can be treated with magnesium glycerophosphate (3–6 g daily).

SPIRONOLACTONE (ALDACTONE)

The addition of spironolactone to HF medications has been shown in RCTs to cause a significant reduction in the risk of death in patients with EF <40%; hospitalization for recurrent HF is significantly reduced. Spironolactone causes gynecomastia.

EPLERENONE (INSPIRA)

A new agent, eplerenone, is a selective aldosterone blocker and has been shown in the Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study clinical trial to significantly reduce mortality and morbidity but does not cause gynecomastia. A dose of 25 mg is titrated up to maximum 50 mg daily. Hyperkalemia occurs in about 4% of patients; these agents are not advisable in patients with serum creatinine greater than 1.4 mg/dL (123 μ mol/L) or in Type 2 diabetics.

ACE Inhibitors and ARBs

These agents have made a major contribution to survival of patients with HF; however, diastolic dysfunction in patients with DCM tends to worsen with ACE inhibitor therapy. The dosage and pharmacological profile of ACE inhibitors are discussed in Chapter 5.

CAPTOPRIL (CAPOTEN)

The first dose(s) are given when the patient will be recumbent for at least 6 hours in the situation that first-dose severe hypotension occurs. A test dose of 3–6.25 mg is given; if hypotension is not precipitated, give 6.25 mg twice daily for 1–2 days and increase to 12.5 mg twice daily. Over days to weeks thereafter, increase to 25 mg twice daily to a maximum of 50 mg daily. A daily dose in excess of 100 mg provides little added benefit for these patients, and there is a risk of a lowered diastolic pressure with consequent poor coronary perfusion that may trigger an arrhythmic death.

The renin-angiotensin system is usually blocked by a daily captopril dosage of 25 mg, and a daily maintenance dose of 37.5–75 mg is recommended. When the patient is stabilized on 25 mg of captopril daily or an equivalent dose of the selected ACE inhibitor, the dose of furosemide can be increased as required to relieve congestion and shortness of breath.

ENALAPRIL (VASOTEC, INNOVACE IN THE UK)

A dosage of 2.5 mg is given; observe for 4 hours. If there is no hypotension or other adverse effects, give 2.5 mg twice daily for 1–2 days and then increase slowly over days or weeks to 5–10 mg once or twice daily. Increase dose interval or do not use in patients with renal failure (serum creatinine greater than 2.3 mg/dL [203 μ mol/L]). Dosages of ACE inhibitors and ARBs are given on p. 320 and in [Table 8.4](#).

ACE inhibitors and ARBs are contraindicated in the following:

- Renal artery stenosis of a solitary kidney or severe bilateral renal artery stenosis.
- Aortic stenosis.
- Restrictive cardiomyopathy (RCM), HCM with obstruction.
- Severe carotid artery stenosis; severe anemia.
- Pregnancy and during breastfeeding.
- Relative contraindications include patients with collagen vascular diseases or concomitant use of immunosuppressive therapy, because neutropenia and rare agranulocytosis observed with ACE inhibitors appear to occur in these patients.

Adverse effects include the following:

- Hypotension.
- ACE inhibitors may cause transient decrease in renal function and hyperkalemia in patients with renal failure.
- Pruritis and rash in about 10%.
- A very rare but important adverse effect is angioedema of the face, mouth, or larynx, which may occur in approximately 0.2% of treated patients and can be fatal.
- Neutropenia and agranulocytosis are rare and occur mainly in patients with serious intercurrent illness, particularly immunological disturbances.
- Cough occurs in about 20% of patients and an ARB can be substituted (*see* Chapter 5 for ARBs).

Interactions may occur with allopurinol, acebutolol, hydralazine, nonsteroidal antiinflammatory drugs (NSAIDs), procainamide, pindolol, steroids, tocainide, immunosuppressives, and other drugs that alter immune response. Utilize care with drugs that increase serum potassium levels.

β-Adrenergic Blockers

Judicious use of β-blockers appears, however paradoxically, to benefit some patients with DCM, especially individuals with resting sinus tachycardia and/or diastolic dysfunction. Removal of sympathetic drive on myocytes and restoration toward normal of the downgrading of β-adrenergic receptors in HF appear to provide benefits.

Reduction in heart rate decreases myocardial oxygen demand and also improves coronary blood flow. Prevention of arrhythmias, with even modest reduction in sudden deaths, is a potential benefit of careful β-adrenergic blockade. Clinical trials have shown mixed results, however, and large-scale trials are underway.

Fortunately, all β-blockers are not alike, and reports of studies using carvedilol, labetalol, and metoprolol indicate beneficial effects that must be assessed in large-scale trials. In a randomized trial of 338 patients with DCM and HF, EF less than 40%, metoprolol commenced at very small doses that were gradually increased, prevented clinical deterioration, and improved symptoms and cardiac function. There were too few deaths for the trial to detect an effect on all cause mortality (*see* Chapter 5 for β-blockers in HF).

CARVEDILOL (COREG)

Supplied: tablets 3.125, 6.25, 12.5, 25 mg daily.

Carvedilol is strongly recommended as a β-blocker choice in patients with HF. The Carvedilol Prospective Randomized Cumulative Survival trial studied 2289 patients with severe HF EF 16–24%. Carvedilol caused a significant 35% reduction in all cause mortality.

An initial test dose of 3.125 mg increased to twice daily with food over two weeks; if tolerated, increased 6.25 mg twice daily; double the dose every week to the highest tolerated, usually 25 mg twice daily, in patients less than 85 kg, 50 mg if more than 85 kg. Decrease dose if dizziness or hypotension occurs.

METOPROLOL

A dosage of 2.5 mg twice daily is used and increased slowly over 8–20 weeks to a dose of 25–50 mg with a careful watch for worsening of HF. Benefit may not be observed for several months and, at times, even after early deterioration.

ORAL ANTICOAGULANTS

Warfarin is advisable in most patients to prevent embolization from atrial and ventricular thrombi; it is essential if there is AF. Pulmonary embolism and systemic embolization occur fairly frequently and worsen the dismal prognosis. In addition, immobilization during periods of HF predisposes deep vein thrombosis and pulmonary emboli.

Arrhythmia Control

AMIODARONE

Neither significant clinical benefit nor improved survival has been documented with antiarrhythmic agents, except for a modest effect of amiodarone.

A dosage of 200 mg three times daily for 1–2 weeks is given and then 100–200 mg daily, reducing to 5–6 days weekly. Consult the earlier discussion in this chapter and in Chapter 6 for advice on dosage, contraindications, and monitoring of adverse effects.

Sudden death in DCM is the result of a combination of pump failure and potentially lethal arrhythmias. Amiodarone is advisable if repeated 48-hour Holter monitoring reveals nonsustained VT or frequent multiform ventricular ectopics and in patients with sustained VT or survivors of cardiac arrest. Survival appears to be improved after amiodarone therapy in this subset. These small group studies require support from further well-designed clinical trials that are presently being conducted. DCM has a 50% 2-year mortality rate; with HF, the mortality rate is 50% in 1 year. Therefore, significant bothersome amiodarone toxicity, which usually appears after about 3 or more years of low-dose therapy, is not a deterrent to the use of a drug that presently provides the only hope for improved survival.

In selected patients with malignant ventricular arrhythmias who fail to respond to amiodarone or require discontinuance of the drug because of adverse effects, consideration should be given to the use of a multiprogrammable pacemaker cardioverter-defibrillator. Electrophysiological testing in patients with DCM, as in other patients with severe LV dysfunction, does not appear helpful. Also, the multiprogrammable cardioverter-defibrillator is of little benefit to patients with severely impaired ventricular function. Consideration must be given to these patients for cardiac transplantation.

Cardiac Transplantation for DCM

Young patients with refractory HF, class IV ventricle, maximal oxygen uptake below 12 mL/kg body weight/minute (on cardiopulmonary exercise testing)—EF less than 12%, causing very poor quality of life—and without contraindications listed should be considered for cardiac transplantation. Patients who have been relatively stable may suddenly deteriorate markedly; if so, transplantation becomes urgent and life support by means of intra-aortic balloon pump or mechanical heart assist device may be needed. Cardiomyoplasty is a possible option.

Contraindications include noncardiac underlying diseases: pulmonary, renal, hepatic, hematological, neurological, diabetic, or psychiatric; and alcoholism.

RESTRICTIVE CARDIOMYOPATHY

The major abnormality is a restriction of ventricular filling, thus an increase in filling pressures. RCM is a member of the group of diastolic HF in which diastolic function is impaired earlier and more severely than systolic function. The usual abnormality is

impaired relaxation and compliance. Restrictive pathophysiology may occur at the pericardial, myocardial, or endomyocardial level.

The most common cause of RCM is endomyocardial fibrosis (EMF) in tropical regions. In temperate climates, hypereosinophilic heart disease (Löffler's disease) may involve organs other than the heart. Myocardial involvement by amyloid, not associated with multiple organ involvement, is another cause of RCM in the Western world. Cardiac disease resulting from amyloid-associated multiple organ involvement, sarcoid, hemochromatosis, eosinophilic syndromes, scleroderma, adriamycin toxicity, and infectious agents, including tuberculosis, causing restrictive physiology is considered specific heart muscle disease. HCM may produce diastolic abnormalities similar to those in RCM.

Clinical Hallmarks

Hallmarks of RCM include the following:

- Intermittent fever, shortness of breath, cough, palpitations, edema, and tiredness.
- Hypereosinophilia with abnormal eosinophil degranulation is seen in temperate climates (hypereosinophilic heart disease).
- Hypereosinophilia is less severe in tropical EMF.
- S₃ and S₄ gallops may be visible and audible in the absence of HF.
- Symptoms and signs of HF and of moderate-to-severe mitral and tricuspid regurgitation owing to involvement of the papillary muscles serve to differentiate RCM from constrictive pericarditis, as does the greater degree of cardiac enlargement on chest X-ray in the former condition (Table 13.3.).
- During the early stages, EMF may mimic the hemodynamic and clinical features of constrictive pericarditis. Table 13.4. gives hemodynamic differences but significant overlap occurs.
- The chest X-ray in patients with EMF may show calcification of the RV or LV apical myocardium.
- Echocardiogram shows obliteration of the apices of the ventricles by echogenic masses, likened to a boxing glove. Numerous echogenic areas are usually observed throughout the ventricular myocardium (Fig. 14.9.). Also, myocardial calcification may be detected, and in later stages, mitral and tricuspid regurgitation may require echocardiographic assessment.
- The idiopathic endocardial fibrosis and associated thrombus may progressively obliterate the LV or RV cavities. Severe enlargement of the right atrium may occur.
- ECG findings are nonspecific. Marked ST-T-wave changes and LVH may be observed with LV involvement (Fig 14.10.).

Therapy

Medical therapy is unrewarding because of the following:

- Steroids may be helpful in the early acute inflammatory phase associated with hypereosinophilia. Hydroxyurea and vincristine have been used.
- Anticoagulants are necessary because thromboembolism is common.
- Restriction to filling does not respond to digoxin, diuretics, or vasodilators. Digoxin may be required to control the ventricular rate in patients with AF. If dyspnea is prominent, judicious trial of 2.5–5 mg of enalapril daily, should be tried; a salutary response has been observed in some patients. Arrhythmias may respond to small doses of β -blockers, and potentially lethal arrhythmias may require amiodarone therapy.

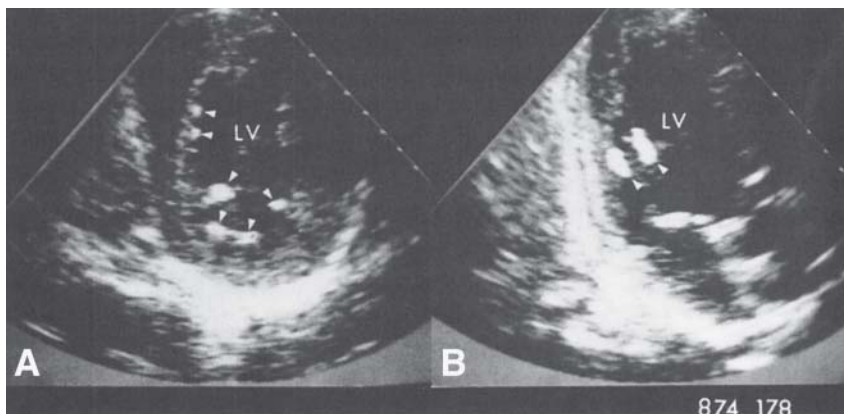


Fig. 14.9. Short-axis (A) and apical two chamber (B) two-dimensional echocardiograms of a patient with endomyocardial disease and eosinophilia. Numerous echogenic area (arrowheads) can be seen throughout the left ventricular endocardium. LV, left ventricle. From Feigenbaum H. Echocardiography. Fourth edition. Philadelphia, PA: Lea & Febiger, 1986:539. Reprinted with permission.

- Resection of masses of obliterating endocardial tissue with valve repair has produced apparent relief for a few years in some patients with EMF.
- Cardiac transplantation may require consideration in intractable cases.

SPECIFIC HEART MUSCLE DISEASE

Specific heart muscle disease usually produces a dilated form of cardiomyopathy with impaired systolic function. The principal causes of specific heart muscle disease are shown in [Table 14.4](#).

Restrictive physiology is seen with amyloid, sarcoid, neoplasm, radiation, scleroderma, hemochromatosis, and eosinophilic endomyocardial disease, in which eosinophilia is usually present. Rarely, myocardial tuberculosis is present with restrictive features. Amyloid heart disease and EMF are usually considered examples of RCM, but when cardiac involvement is associated with multiple organ disease, they qualify as specific heart muscle disease.

The findings of systemic disease of other organs, especially the liver, lymph nodes, and skin, which can be easily submitted to biopsy, assist in defining the underlying cause. Endomyocardial biopsy is often required but may not be helpful in patchy disease, such as sarcoid.

Therapy

Treatment should be directed at the underlying disease ([Table 14.4](#)). Occasionally, cardiac pacing is required for the management of complete heart block owing to involvement of conduction tissue by sarcoid, scleroderma, or hemochromatosis.

Other heart muscle diseases include involvement owing to infectious disease; Chagas owing to *Trypanosoma cruzi* is transmitted by a triatoma bug. The disease is prevalent in South America but does occur in the southern United States where more than 75,000 Latin Americans are believed to be infected with *T. cruzi*. The risk of transmission in the United States is mainly by blood transfusion by this immigrant population.

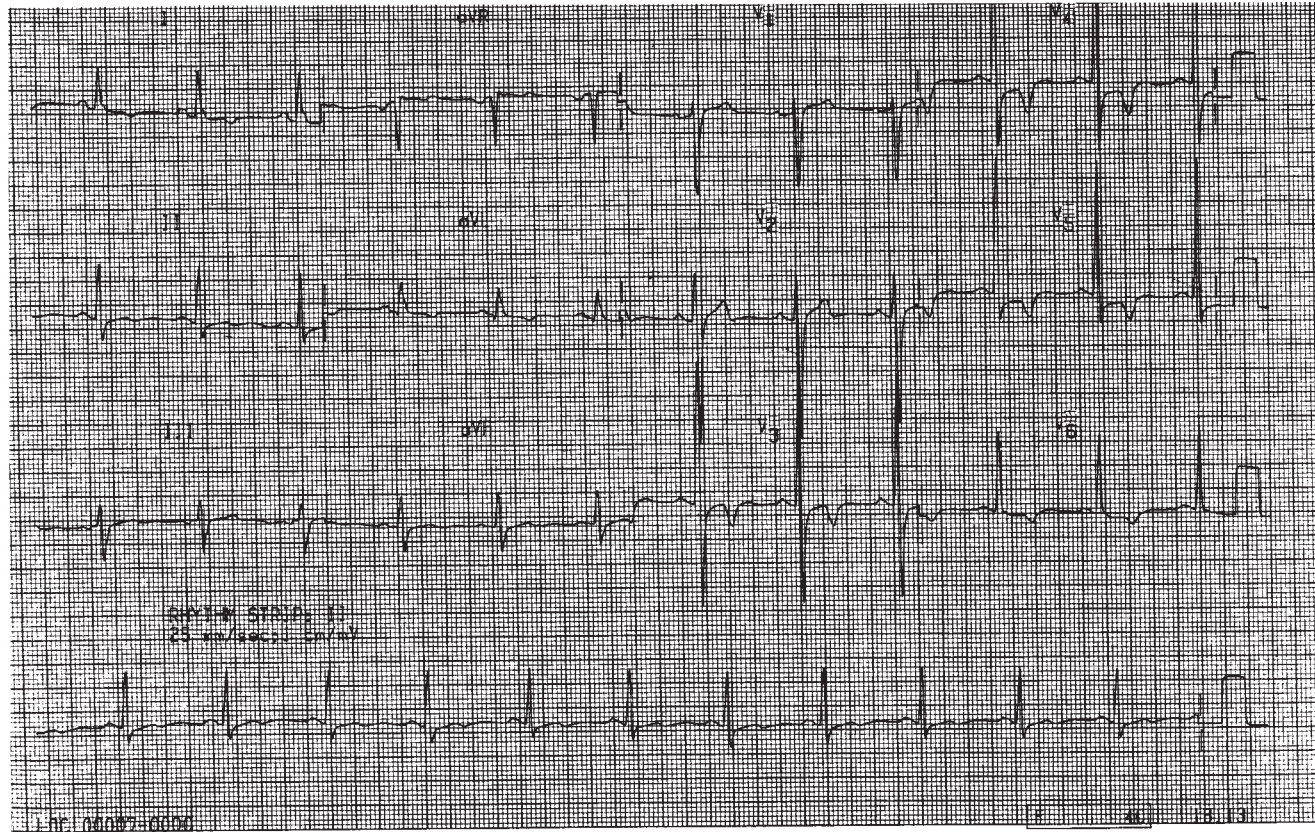


Fig. 14.10. ECG recording from a 29-year-old male with endomyocardial fibrosis; left ventricular hypertrophy and diffuse ST-T changes.

Table 14.4.
Principal Causes of Specific Heart Muscle Disease

Infectious	
Bacterial	Diphtheria, tuberculosis
Parasitic	Chagas' disease, toxoplasmosis, trichinosis, Echinococcus
Viral	Coxsackie, cytomegalovirus, HIV, Epstein-Barr, Kawasaki disease
Collagen vascular	Lupus erythematosus, scleroderma, mixed connective tissue disease, polyarteritis nodosa, rheumatoid arthritis
Metabolic	
and dietary disorders	Thiamine, selenium deficiency; glycogen storage disease
Toxic	Adriamycin, doxorubicin, cocaine, cobalt, ethanol, lead mercury, prednisone, zidovudine, X radiation
	Chemotherapeutic agents and allergic reactions
Neuromuscular	Duchenne's muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
Endocrine	Thyroid heart disease, pheochromocytoma, Addison's disease
Granulomata	Sarcoidosis
Others	Amyloid, hemochromatosis

The incidence of human immunodeficiency virus (HIV) is increasing, and myocarditis with pericardial effusion and cardiac tamponade is now surfacing in victims of acquired immunodeficiency syndrome. Myocardial involvement might be owing to the HIV virus; although this is unproven, involvement by Kaposi, opportunistic infections, and effects of medications must also be excluded. Rare involvement of cardiac muscle is seen with polymyositis, progressive muscular dystrophy, Friedreich's ataxia, and Fabry's disease.

Drugs, especially cocaine and toxins, may affect the myocardium; known toxins include cobalt (beer), chloroquine and emetine, phenothiazines, methysergide, and cancer chemotherapeutic agents (adriamycin, daunorubicin, doxorubicin, cyclophosphamide); also, methyl dopa and phenindione rarely cause a hypersensitivity myocarditis. Overdose with toxic doses of acetaminophen or cocaine may cause myocardial necrosis and arrhythmias, including torsades de pointes.

Treatment of these disorders involves removal and treatment of the infective agent or toxin, where possible.

BIBLIOGRAPHY

- Ackerman MJ, McKenna WJ, Thierfelder L, et al. mutations in the genes for cardiac troponins T and alpha tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;332:1058–1064.
- Andersson B, Hamm C, Persson S, et al. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. *J Am Coll Cardiol* 1994;23:1397.
- AVID: The Antiarrhythmic Versus Implantable Defibrillators Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576–1583.
- Borlani G, Maron BJ, Shen Win-Kuang, et al. Prevention of sudden death in hypertrophic cardiomyopathy: but which defibrillator for which patient? *Circulation* 2004;110:e438–e442.
- Bowles NE, Richardson PJ, Olsen EGJ, et al. Detection of Coxsackie-B virus specific RNA sequence in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. *Lancet* 1986;1:1120.
- Braunwald E, Seidman CE, Sigwart U. Contemporary evaluation and management of hypertrophic cardiomyopathy. *Circulation* 2002;106:1312–1316.

- CAPRICORN Investigators. The effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction. The CAPRICORN randomized trial. *Lancet* 2001;357:1385–1390.
- Cice G, Ferrara L, Benedetto AD, et al. Dilated cardiomyopathy in dialysis patients: beneficial effects of carvedilol double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2001;57:47–111.
- COPERNICUS: carvedilol prospective randomized cumulative survival study group effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–1658.
- Corrado D, Nava A, Buja G, et al. Familial cardiomyopathy underlies syndrome of right bundle branch block, ST segment elevation and sudden death. *J Am Coll Cardiol* 1996;27:443.
- Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 2003;42:1959–1963.
- Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med* 1994;331:1564.
- Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol* 1992;9:43.
- Elliott PM, Blanes G, Mahon JR, et al. A relation between the severity of left ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Am J Med* 2001;357:420–424.
- EPHESUS: Pitt B, Remme W, Zannad F, et al., Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321.
- Eriksson MJ, Sonnenberg B, Woo A, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;39:638–645.
- Fananas L, O'Connor RO, Tripodi D, et al. Impact of dual chamber permanent pacing in patients with obstructive hypertrophic cardiomyopathy with symptoms refractory to verapamil and beta-adrenergic blocker therapy. *Circulation* 1992;85:2149.
- Goodwin JF, Olsen EGJ (eds). *Cardiomyopathies: realizations and expectations*. Berlin: Springer Verlag, 1993.
- Grody WW, Cheng L, Lewis W. Infection of the heart by the human immunodeficiency virus. *J Am Coll Cardiol* 1990;66:203.
- Hejtmancik JF, Brink PA, Towbin J, et al. Localization of gene for familial hypertrophic cardiomyopathy to chromosome 14q1 in a diverse US population. *Circulation* 1991;83:1592.
- Hess OM, Sigwart U. New treatment strategies for hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 2004;44:2054–2055.
- Kappenberger L. Pacing for obstructive hypertrophic cardiomyopathy. *Br Heart J* 1995;73:107.
- Kasper EK, Agema WRP, Hutchings GM, et al. The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive patients. *J Am Coll Cardiol* 1994;23:586.
- Leung WH, Lau CP, Wong CK, et al. Improvement in exercise performance and hemodynamic by labetalol in patients with idiopathic dilated cardiomyopathy. *Am Heart J* 1990;119:884.
- Lowes BD, Gilbert EM, Abraham WT, et al. Myocardial gene expression in dilated cardiomyopathy treated with beta blocking agents. *N Engl J Med* 2002;346:1357–1365.
- Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;287:1308–1320.
- Maron BJ, Estes NA 3rd, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. *Circulation* 2003;107:2872–2875.
- Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CAR-DIA Study. *Circulation* 1995;92:785.
- Maron BJ, Dearani JA, Ommen SR, et al. The case for surgery in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004;44:2044–2053.
- Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screenings strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardio* 2004;44:2125–2132.
- McKenna WJ, Mogensen J, Elliott PM. Role of genotype in risk factor assessment for sudden death in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;39:249–251.
- Nishimura RA, Hayes DL, Ilstrup DM, et al. Effect of dual-chamber pacing on systolic and diastolic function in patients with hypertrophic cardiomyopathy. Acute Doppler Echocardiographic and Catheterization Hemodynamic Study. *J Am Coll Cardiol* 1996;27:421.
- Nishimura RA, Holmes DR. Hypertrophic obstructive cardiomyopathy. *N Engl J Med* 2004;350:1320–1327.
- Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349.

- Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002;106:2194–2187.
- Roberts R, Sigwart U. New concepts in hypertrophic cardiomyopathies, part II. *Circulation* 2001;104:2249–2252.
- Ryan MP, Cleland JFG, French JA, et al. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. *Am J Cardiol* 1995;76:689.
- Shamim W, Yousufuddin M, Wang D, et al. Nonsurgical reduction of the interventricular septum in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2002;347:1326–1333.
- Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet* 1995;346:211.
- Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:1778–1785.
- Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;332:1058.
- Webb JG, Sasson Z, Rakowski H, et al. Apical hypertrophic cardiomyopathy: clinical follow-up and diagnostic correlates. *J Am Coll Cardiol* 1990;15:83.
- Wigle ED, Rakowski H, Kimball BP, et al. Hypertrophic cardiomyopathy: clinical spectrum and treatment. *Circulation* 1995;92:1680.
- Williams RG, Chen AY. Identifying athletes at risk for sudden death. *J Am Coll Cardiol* 2003;42:1964–1966.

15

Syncope

CONTENTS

PATIENT EVALUATION
NEURALLY MEDIATED SYNCOPE
POSTURAL HYPOTENSION
CEREBROVASCULAR DISEASE
CARDIAC CAUSES
UNEXPLAINED SYNCOPE
BIBLIOGRAPHY

Syncope is defined as transient loss of consciousness associated with the loss of postural tone that is a result of sudden transient and inadequate cerebral blood flow; an acute fall in systolic blood pressure to less than 70 mmHg causes an interruption of cerebral blood flow for more than 8 seconds. Syncope is a common problem representing up to 1% of medical admissions to general hospitals and 3 to 7% of all U.S. emergency room visits.

Causes of syncope are often elusive, and the following points deserve attention:

- An obvious cardiac cause can be defined by the history, physical examination, electrocardiogram (ECG), and Holter monitoring in approximately 10% of cases ([Fig. 15.1.](#) and [Table 15.1.](#)).
- Vasodepressor or vasovagal syncope, also termed neurally mediated syncope or neurocardiogenic syncope, the common form of which is the simple faint, accounts for approximately 40% of cases of syncope. It is therefore most important to exclude this benign problem.

A Framingham study of 822 patients with syncope revealed the following causes: unknown 36.6%; vasovagal 21.2%; cardiac 9.5%; orthostatic 9.4%; medication 6.8%; stroke or transient ischemic attack 4.1%; and others 7.5%.

The majority of patients with neurally mediated syncope do not sustain significant injuries. In a small subset of patients, syncope occurs without warning and serious injuries occur. I prefer to label this subset of patients as having *malignant vasovagal syncope* and clinical trials utilizing pacemakers, and medical therapy is required in this pure subset to obtain appropriate treatment strategies. Dr. Kapoor, in an excellent review, also makes this distinction.

Unexplained syncope constitutes a large group (35%), but in patients who have structural heart disease and unexplained syncope, electrophysiologic (EP) testing is rewarding in identifying a significant number of cardiac causes of syncope and increases the total

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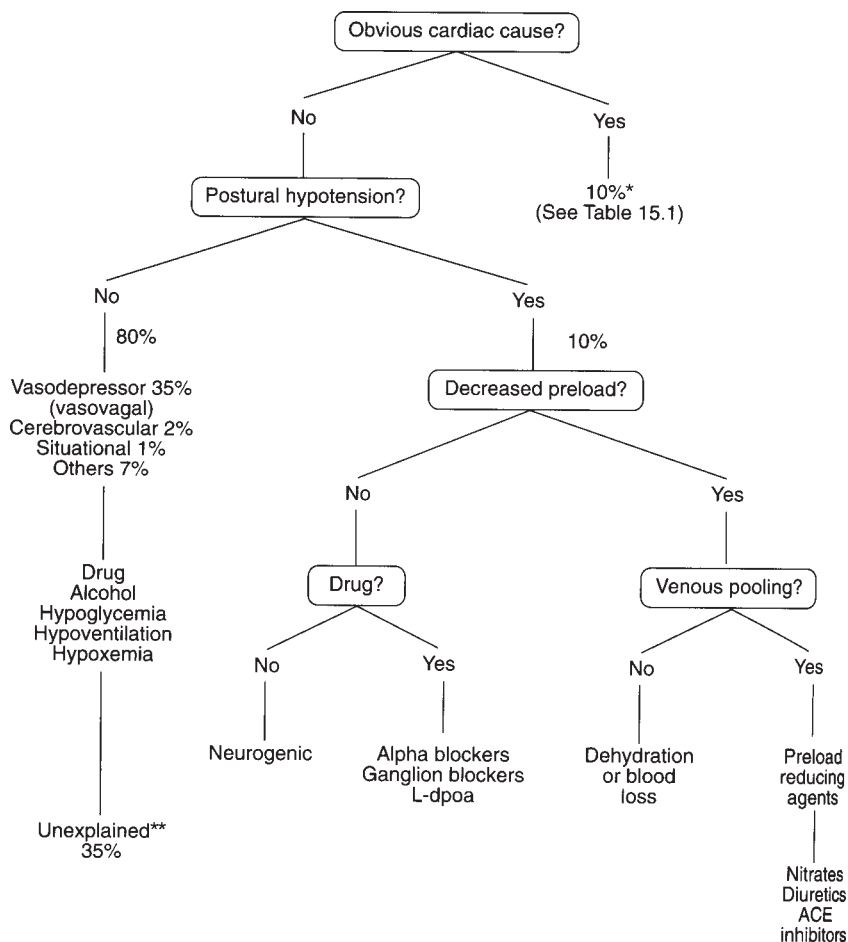


Fig. 15.1. Assessment of syncope. *Approximate incidence percent. **See Fig. 15.3.

cardiac cause of syncope to approximately 22%. Unfortunately, EP testing does not uncover all cases of sinoatrial (SA) and atrioventricular (AV) node disease or tachyarrhythmias.

Syncope may also be the clue to possibly life-threatening underlying cardiac diseases. Cardiac syncope carries a 24% incidence of sudden death in 1 year, as opposed to less than 2% sudden death per year in the remaining 78% of individuals. One-year mortality of patients with cardiac syncope ranges from 15 to 30%, versus less than 2% for individuals with unexplained syncope and without structural heart disease.

Postural hypotension is an important cause of syncope. It commonly occurs because of a decrease in preload and often occurs in patients on cardiac medications that cause venous pooling. Less often, syncope has a neurogenic cause, being a troublesome feature of autonomic neuropathy (Table 15.2.).

The assessment of syncope is often difficult, but intriguing. Figure 15.1. gives an algorithmic approach to the assessment of syncope.

Dizziness is often a feature of presyncope and has several causes that are difficult to determine. Figure 15.2. indicates steps to consider.

Table 15.1.
Obvious Cardiac Causes of Syncope and Approximate Incidence

<i>Causes</i>	<i>Approximate incidence (%)</i>
Tachyarrhythmias	45
Sustained and nonsustained VT	
Torsades de pointes	
Atrial fibrillation	
Supraventricular tachycardia	
Long QT syndrome	
WPW syndrome	
Pacemaker-mediated	
Bradyarrhythmias	35
Sinus node dysfunction (sick sinus syndrome)	
AV block: second and third degree	
Drug-induced	
Carotid sinus syncope	3
Obstruction to stroke volume	10
Aortic stenosis	
Hypertrophic cardiomyopathy	
Tight mitral stenosis	
Atrial myxoma or thrombus	
Cardiac tamponade	
Prosthetic valve dysfunction	
Pulmonary embolism	
Pulmonary hypertension	
Pulmonary stenosis	
Others	7
Brugada syndrome	
Mitral valve prolapse	
Myocardial infarction	
Severe ischemic heart disease	
Coronary artery spasm	
Pacemaker syndrome	
Aortic dissection	
Fallot's tetralogy	
Myocarditis	
Chagas' disease	

VT, ventricular tachycardia; WPW, Wolff-Parkinson-White; AV, atrioventricular.

PATIENT EVALUATION

The management of syncope entails the elucidation of the cause so that appropriate advice, medications, or corrective measures may be used to prevent bodily injury or threat to life. Because most cardiac causes pose a threat to life, it is important to use a methodical approach to solving the cause of syncope in a given individual. This medical solution calls for a sound knowledge of basic internal medicine and cardiology and should commence with a detailed history and physical examination.

Table 15.2.
Noncardiac Causes of Syncope

Vasodepressor (vasovagal) (neurally mediated syncope, neurocardiogenic syncope)
Postural hypotension
Decrease preload
Venous pooling, caused by extensive varicose veins, postexercise vasodilation, venous angioma in the leg
Drugs: nitrates, diuretics, ACE inhibitors
Decreased blood volume: blood loss, dehydration, vomiting, diarrhea, excessive sweating, Addison's disease
Drug-induced
α -Blockers
Ganglion blockers
Bromocriptine
L-Dopa
Neurogenic decrease autonomic activity
Bed rest
Neuropathies/diabetes
Shy Drager syndrome
Idiopathic
Mastocytosis
Cerebrovascular disease
Transient ischemic attack
Subclavian steal
Basilar artery migraine
Cervical arthritis, allanto-occipital dislocation compression vertebral artery
Situational
Cough, sneeze, micturition, defecation
Others
Drugs/alcohol
Hypoglycemia
Hypoxemia
Hypoventilation
Hysterical
Panic Attacks
Unexplained
See Figs. 15.2. and 15.3.

Differential diagnosis includes epilepsy, which can often be difficult to distinguish from syncope. Of the precipitants, prodromal symptoms and complaints during the spell and symptoms after the episode are useful in distinguishing syncope and seizures.

A confusional state postsyncope lasting minutes to hours indicates seizures, as this does not occur with syncope; patients are most often fully alert within a minute or two of a syncopal episode.

Syncope is usually associated with the following:

- Loss of consciousness precipitated by pain or occurring after exercise, micturition, defecation, and stressful events is generally owing to syncope, whereas aura may precede a seizure.
- Symptoms, such as sweating and nausea, during the episode are associated with syncope.

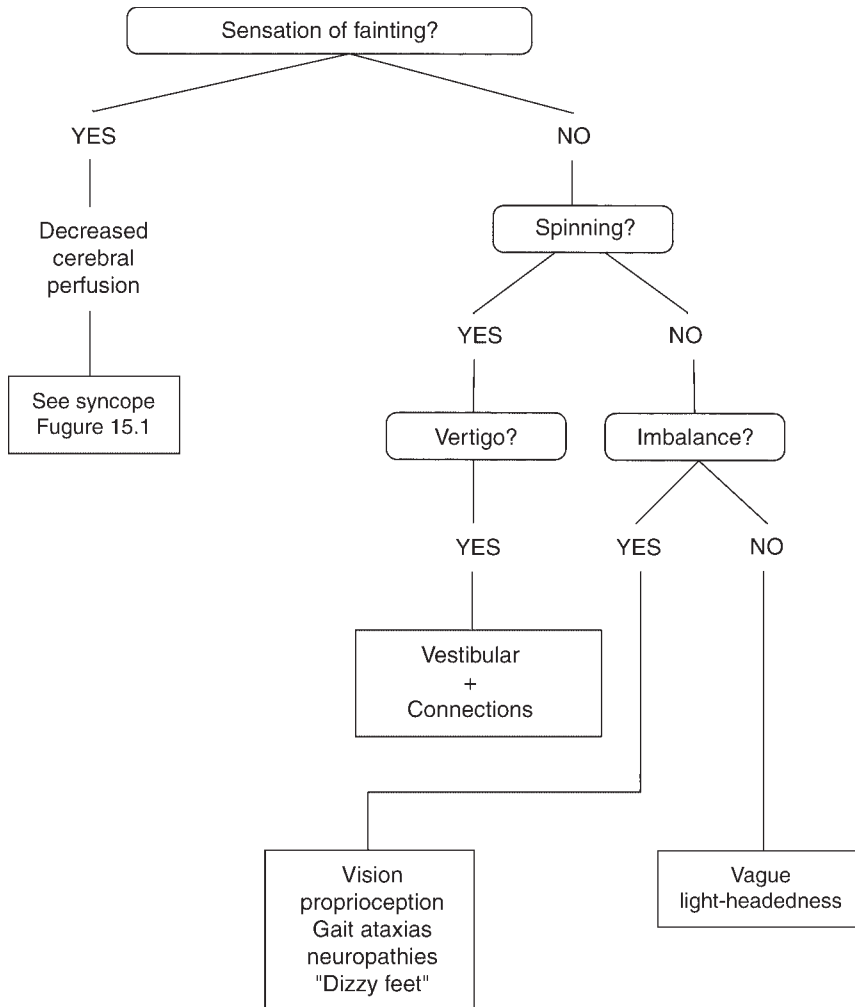


Fig. 15.2. Algorithm for evaluating patients with dizziness.

- A long duration of loss of consciousness (>5 minutes), disorientation after the event, and slowness of return to consciousness suggest a seizure. Rarely, syncope can result in seizure-like activity, but when rhythmic movements (such as clonic or myoclonic jerks) are reported, seizure is the likely diagnosis.

Those who should be admitted to a hospital include the following:

- Patients with suspected cardiac cause.
- Patients with significant bodily injury.
- The elderly patient in whom a readily identifiable cause is lacking.
- Recurrent syncope of undetermined etiology in patient who have no prodrome and are at risk for injury to themselves or others.

History and Physical Examination

A detailed relevant history and physical examination are mandatory and should include the following steps:

- Check the blood pressure (BP) on the patient recumbent for more than 3 minutes and then on standing, to elicit postural hypotension, if positive, assess causes of postural hypotension (Fig. 15.1.).
- Determine the BP in the arms and legs.
- Listen for bruits over the subclavian and carotid arteries.
- Look for finger clubbing and cyanosis as signs of congenital cyanotic heart disease.
- Perform a full cardiovascular examination. Check for left ventricular hypertrophy, presence of thrills, the murmur of aortic stenosis, hypertrophic cardiomyopathy (HCM), mitral stenosis, mitral valve prolapse, and the presence of prosthetic heart valve (Table 15.1. and *see* Chapter 11).
- Assess for tachyarrhythmias and bradyarrhythmias.

The history should exclude the most common cause of syncope, that is, vasodepressor or vasovagal syncope. All known causes of syncope should be methodically excluded (*see* Tables 15.1., 15.2., and Fig. 15.1.).

LABORATORY INVESTIGATIONS

After exclusion of the simple faint, obvious cardiac causes, postural hypotension, vasodepressor syncope, and cerebrovascular and situational causes, request complete blood count, electrolytes, blood urea, serum creatinine, and serum calcium. The following routine tests are not usually helpful:

- Chest X-ray.
- ECG.
- Echocardiogram.
- 24- or 48-hour Holter monitoring is advisable but has a low yield.
- Implantable loop recorder. Insertable loop recorders are the diagnostic test of choice to detect bradyarrhythmias in patients with rare recurrent symptoms.
- Head-up tilt testing. Head-up tilt testing has been used to delineate the pathophysiology, diagnosis, and management of patients with no detectable heart disease and unexplained syncope. Forty to 70% of patients with unexplained syncope experience syncope on being tilted 60° for 45 minutes. There is no standard protocol for the test, but current recommendations indicate the need for:
 - At least 60° tilt.
 - Duration of 15–45 minutes.
 - Use of foot-plate support rather than saddle.
 - Isoproterenol infusion improves sensitivity with decreased tilt time of 10 minutes at 80° tilt. The use of isoproterenol has the disadvantage of dosing difficulty and reduced specificity.

Isoproterenol infusion increased the provocation of symptoms produced by head-up tilt from 2 to 87% in individuals with unexplained syncope over a 10-minute study period and from 0 to 73% in those with diagnosed cardiopressor syncope, during a 15-minute tilt at 60°. However isoproterenol is not recommended in patients over age 50 because of cardiac adverse effects. Where edrophonium results in a negative head-up tilt test, isoproterenol does not reveal a positive test. In a study by Kapoor et al., isoproterenol

infusion resulted in a nonsignificant difference in the rate of positive tests in 20 young patients with unexplained syncope and controls matched by age, sex, and absence of underlying heart disease. The study by Kapoor et al. questions the low specificity of this test. As discussed in the section “Neurally Mediated Syncope,” there is very little reason for tilt testing if a meticulously relevant history and physical examination is completed. Head-up tilt testing confirms the diagnosis of neurocardiogenic syncope, but this diagnosis can be made in more than 90% of patients with this benign condition. Head-up tilt testing adds to the cost of health care and has little justification, particularly when this test has caused death in one patient and cerebral destruction in another and with other cases pending settlements.

Head-up tilt using 60° for 45 minutes does not appear to be useful in youthful subjects with typical vasovagal syncope, but in this group, the clinical diagnosis is usually apparent.

In unexplained syncope, both head-up tilt testing and EP evaluation are complementary and can identify the underlying cause in approximately 74% of patients presenting with unexplained syncope.

- The results of a positive tilt test are difficult to replicate on subsequent days, and thus it is difficult to use repeat tilt testing in treatment planning.
- Treatment of neurally mediated syncope is recommended only when syncope is recurrent or severe, and tilt testing should generally be reserved for these patients.
- Chemical stimulation with isoproterenol or sublingual nitroglycerin is required to achieve high rates of positive responses (65%) in unexplained syncope; nitroglycerin use is simpler and better tolerated, particularly in elderly and in patients with ischemic heart disease (IHD). Specificity and positive response rates are similar for both agents.
- There is an overuse of tilt testing for the workup of patients who have a benign ailment that should respond to increased salt intake and clarification of the prodrome, followed, if needed, by β -blocker therapy or disopyramide.
- Tilt testing causes minor degrees of asystole, but this can be occasionally prolonged and can cause cerebral damage, albeit rarely. A death has been reported, and one patient has suffered irreparable extensive brain damage. The court settlements do not adequately compensate the bereaved families. Other cases are before the courts. Calkins et al. made the point that it is distressing to observe the many patients with syncope who have been referred to tertiary centers. Diagnosis, in most cases, can be made clinically because of the prodromal symptoms, occurrence in the upright or seated position, and absence of confusion after syncope. The cost per patient is approximately \$4700 for Holter, echocardiogram, stress testing and unnecessary electroencephalogram, computed tomography and tilt testing. The test should be reserved for patients with unexplained syncope that has no prodrome and has caused injuries, that is, patients with malignant vasovagal syndrome.

NEURALLY MEDIATED SYNCOPES

The simple faint is the most common cause of syncope and is easily recognized. Neurally mediated syncope (also called neurocardiogenic syncope) virtually never occurs in a patient in the recumbent position. Precipitating circumstances are almost always present and typically occur in young individuals and, occasionally, in older patients in the setting of exhaustion, hunger, prolonged standing or sitting in a hot crowded room, sudden severe pain or trauma, venipuncture, fright, and sudden emotional stress.

The simple faint usually gives a warning of seconds to minutes. Some warnings include the following:

- The feeling of weakness, nausea, vague upper abdominal discomfort, diaphoresis, yawn, sighing, hyperventilation, unsteadiness, blurring of vision, and unawareness before fainting.
- Vertigo is not a symptom associated with a simple faint, and these patients do not get syncopal attacks. Thus, a good history identifies the faint and may save expensive and time-consuming investigations.
- Dizziness, presyncope, drop attacks, and vertigo do not lead to a loss of consciousness. Loss of consciousness for more than 5 minutes, disorientation after the event, and slowness of return to consciousness suggest a seizure.

Neurally mediated syncope may present as the following:

- Vasodepressor: a profound fall in peripheral vascular resistance and marked reduction in BP occurs, but the heart rate usually remains above 60 beats per minute (BPM).
- Vasovagal: predominantly cardioinhibitory; a fall in BP occurs, but there is marked vagal induced bradycardia of less than 60 BPM;
- A combination of vasodepressor and vasovagal features. The vasodepressor component with marked reduction in BP appears to play an important role in loss of consciousness. Bradycardia plays a secondary role. These features explain the poor response to atropine. Thomas Lewis, in 1932, in his classic paper, stated that “while raising the pulse rate up to, and beyond, normal levels during the attack, leaves the blood pressure below normal and the patient still pale and not fully conscious.” Abboud makes the relevant comment that “60 years later, Sra et al. can make the same statement with respect to the implantation of a pacemaker.” Thus, the marked vasodilatation causes temporary, but profound, hypotension, with SBP of less than 65 mmHg which produces syncope even when the heart rate is 60–80 BPM. The marked vasodilatation is caused by the inhibition of sympathetic vasoconstrictor activity at the very moment when arteriolar vasoconstriction is necessary to combat the marked fall in BP. In most patients, the onset of bradycardia is consistently preceded by hypotension. Sra et al. have shown that an increase in myocardial contractility and a decrease in left ventricular (LV) systolic dimensions occur 2–4 minutes before the onset of syncope.

The constant findings in vasodepressor syncope are the following:

- A sudden marked fall in total peripheral resistance, resulting in a drastic fall in BP.
- Decreased cerebral perfusion causing loss of consciousness.
- Loss of consciousness usually occurs within 10 seconds of onset of diminished perfusion.
- Return of consciousness in seconds to minutes if the individual remains flat with the legs elevated.
- Injuries are most uncommon with vasodepressor syncope.
- Bradycardia of less than 55 BPM is not a feature.

The exclusion of epilepsy is relatively easy, but occasionally syncope may be confused with akinetic seizures. Bradycardia in association with seizures has been described. The aura, if any, in epilepsy is transient but tells a story; convulsive movements occur with loss of consciousness. Injuries, including lip and tongue biting, and incontinence with a prolonged postictal state may occur.

In patients with neurocardiogenic syncope, the diagnosis can be made in virtually all patients from a relevant history and physical. Head-up tilt testing, although commonly done in tertiary hospitals, is not necessary for confirming this diagnosis. If symptoms are

bothersome and structural heart disease has been excluded, a trial of increased sodium intake is advisable. Patients with vasovagal syncope should be taught to recognize their prodromal symptoms and to try the following:

- crossing their legs and squeezing.
- sitting down or lying down abruptly and elevate the legs higher than the hips.

Because cardiac sympathetic overstimulation, vigorous LV contraction, and stimulation of intramyocardial mechanoreceptors (C fibers) appear to be important underlying mechanisms in the genesis of unexplained syncope without structural heart disease, β -blockers or disopyramide have been given as rational therapy and have proven successful in some patients with disabling syncope.

Atenolol (25 mg) or metoprolol (100 mg) or pindolol (5 mg) daily may produce a salutary response. IV esmolol may be used to predict the outcome of oral β -blocker therapy; the trial of timolol, a noncardioselective β -blocker with greater vasoconstrictive properties than selective agents, should be tested in clinical trials. One short-term randomized trial and a large number of uncontrolled studies of β -blockers claim effectiveness of these drugs, but several controlled trials did not show effectiveness. A randomized trial of paroxetine showed reduced recurrences at 2 years but needs further confirmation.

Although volume expansion with increased salt and fluid intake, moderate exercise, and tilt training are relatively safe measures, beneficial effects have not been documented in randomized trials.

Midodrine was shown to be beneficial in a small randomized trial when compared with no treatment, but there was no placebo arm to the study.

Fitzpatrick and Sutton described 40 patients who had syncope associated with injuries because these patients had no prodrome. Tilt testing showed mostly vasovagal syncope with a profound bradycardia; some patients had other forms of bradycardias. Dual-chamber pacing appeared to prevent syncope during a 2-year follow-up. These patients were, however, over age 65 and may have had undetected SA or AV node disease. It is unusual for patients with neurocardiogenic syncope to sustain injuries, and fortunately this type of patient is uncommon. In patients who experience no prodrome and sustain injuries, a full workup is necessary. If EP studies are negative, prognosis is usually good, but some patients may have undetected SA or AV node disease. If injuries continue to occur, a subcutaneous monitoring device (Medtronic, Inc.) can be used. An implantable “loop recorder” as described by Krahn and Klein et al. may provide helpful information. In 14 patients with previous syncopal episodes and negative head-up tilt, the recorder revealed sinus arrest in three, complete heart block in two, supraventricular tachycardia (ST) in one, ventricular tachycardia (VT) in one, vasodepressor syncope in two, hemodynamic in one, and psychogenic in one. These authors concluded that an implantable “loop recorder” is useful for making a diagnosis when episodes are too infrequent for standard monitoring techniques (*see* Fig. 15.3.).

Pacemakers

Pacemakers may be a treatment option in patients with severe recurrent syncope that have caused injuries (malignant vasovagal syndrome).

The few small clinical trials that have assessed this therapy had many flaws and most were negative and have not clarified the role of pacemakers.

The Vasovagal Pacemaker Study (VPS) II study by Connolly et al., addressed the issue of the placebo effect associated with pacemaker intervention. Of the 52 patients random-

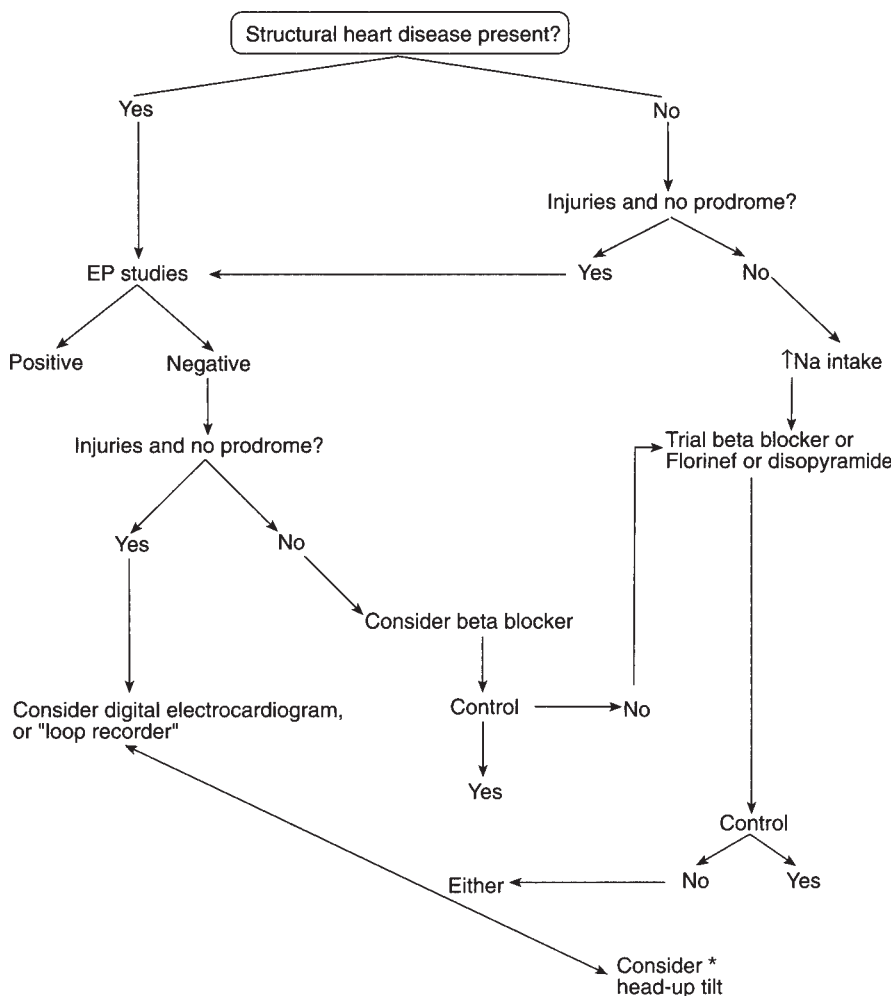


Fig 15.3. Algorithm for the management of unexplained syncope. *Use is abused: may not assist further with therapeutic strategies and is not without dangers of cortical damage.

ized to a pacemaker with sensing but without pacing. Twenty-two (42%) had recurrent syncope within 6 months versus 16 (33%) of 48 patients in the pacemaker with rate-drop response. Lead dislodgement or repositioning occurred in seven patients. Vein thrombosis, pericardial tamponade leading to removal of the pacemaker system, and infection involving the pacemaker generator occurred in three patients. In only 15 to 23% of the patients, the lowest heart rate recorded was less than 40 BPM.

The authors concluded that pacing therapy did not reduce the risk of recurrent syncope in patients with vasovagal syncope. Because of the weak evidence of efficacy of pacemaker therapy and the risk of complications, pacemaker therapy should not be recommended as first-line therapy for patients with recurrent vasovagal syncope. It must be reemphasized that this was not a study of the malignant vasovagal syndrome.

In VASIS, the Vasovagal Syncope International Study, 42 patients who had experienced three or more episodes of syncope during the past 2 years and had a cardioinhibitory response on tilt testing (almost all without drug provocation), which was defined as

a heart rate of less than 40 BPM for more than 10 seconds or asystole for more than 3 seconds received a pacemaker with rate hysteresis. During a mean follow-up period of 3.7 years, syncope recurred in 5% of patients with pacemakers and 61% of patients without pacemakers.

Most importantly, the results of the four trials raises the question of whether the differences in the study results could be owing to differences in the study populations or in tilt testing methods. In VPS and VPS II, fewer than 30% of patients had relatively severe bradycardia that was prominent in VASIS and the Syncope Diagnosis and Treatment Study (SYDIT); 85% of patients in VASIS and 60% of patients in SYDIT had asystole.

Relative bradycardia on tilt testing does not appear to be an important predictor of the response to pacemakers but that asystole is. In VASIS and SYDIT, tilt testing was reasonably standardized, but it was not standardized in VPS or VPS II.

Pacemakers are not expected to benefit patients with neurally mediated syncope who manifest prominent vasodilatation (vasodepressor).

Importantly, patients in VASIS and SYDIT were older, and a different pathophysiological mechanism may operate in this subset of patients, requiring different treatments.

POSTURAL HYPOTENSION

Several cardiac medications may cause orthostatic hypotension, particularly in the elderly. Assess the following:

- Check the BP with the patient recumbent for at least 3 minutes and then on standing; a reduction in SBP of 20 mmHg or more represents orthostatic hypotension.
- Check for evidence of decrease in preload, which may manifest itself by venous pooling that may occur on sudden standing after vigorous exercise or because of extensive varicose veins. Preload reducing agents, particularly, nitrates. Angiotensin-converting enzyme inhibitors or α -blockers may be implicated. Blood loss and dehydration are obvious causes, but an occult cause of the latter is Addison's disease.
- If conditions causing a decrease in preload are not present, inquire about the use of medications that cause arterial dilatation, particularly α_1 -adrenergic blockers, such as prazosin and labetalol, ganglion-blocking drugs, L-dopa, bromocriptine, and rarely, nifedipine.
- If drug use is excluded, postural hypotension may be caused by autonomic imbalance or neurological diseases. Complete bed rest and a lack of leg exercise, plus a decrease in autonomic activity, commonly result in postural hypotension. Neuropathy, especially owing to diabetes, Shy Drager, and other neurologic problems must be excluded.

Standing from a recumbent or sitting position causes immediate pooling of blood in the lower limbs and a consequent fall in BP that normally triggers a baroreceptor response and sympathetically mediated vasoconstriction and an increase in heart rate. As indicated above, conditions that impair baroreceptor function and decrease sympathetically mediated α_1 vasoconstriction may precipitate postural hypotension.

Orthostatic hypotension as a consequence of autonomic neuropathies and autonomic failure is difficult to treat successfully. It may respond to increased sodium intake or fludrocortisone (Florinef), 0.1–0.2 mg daily. The management of orthostatic hypotension caused by autonomic failure can be successfully managed in properly selected patients with midodrine (Amatine), a selective peripherally acting postsynaptic α_1 ad-

energetic agonist. Salutory effects are caused by an increase in arterial and venous tone; venous pooling is prevented. An initial dosage of 2.5 mg three times daily with monitoring of supine BP is used and then increased in 2.5-mg increments at weekly intervals to a maximum of 10 mg three times daily. Caution is needed because the action of midodrine is identical to that of other α -adrenergic receptor stimulants, such as methoxamine or phenylephrine; an increase in total systemic resistance may cause supine hypertension that can precipitate heart failure (HF), myocardial ischemia, infarction, or stroke in susceptible individuals. Supine hypertension is more common during the initiation of midodrine therapy; during the titration period, adverse effects include supine hypertension, which may cause headaches and pounding in the ears. Reflex bradycardia may occur, and caution is needed when the drug is combined with agents that cause bradycardia (digoxin, β -blockers, diltiazem, and verapamil). Urinary retention is an important adverse effect in elderly males. The drug is contraindicated in patients with significant coronary heart disease, HF, renal failure, urinary retention, thyrotoxicosis, and pheochromocytoma. Midodrine is renally excreted, and care is necessary to decrease the dose and increase the dosing interval in patients with renal dysfunction.

In patients who are not responsive to midodrine or fludrocortisone and have sustained injuries, atrial pacing with a heart rate of 100 BPM may afford some amelioration if combined with increased salt intake, fludrocortisone, elevation of the head of the bed during sleep, and full-length leotards to enhance venous return.

A release of histamine, prostaglandin D, and other vasodilators from mast cell proliferation (mastocytosis) causes vasodilatation and is a rare cause of postural hypotension.

Instruct the patient to change posture slowly and to engage in calf muscle flexion before standing. Elevating the head of the bed and a gradual change in posture may provide a salutary response.

CEREBROVASCULAR DISEASE

Subclavian Steal

Occlusion of the subclavian artery proximal to its vertebral branch may produce symptoms when exercising the arm on the affected side. Blood is directed from the basilar system down the vertebral artery to the arm. The steal of blood may be sufficient to cause clouding of consciousness and syncope. A bruit maximal over the supraclavicular area near the origin of the vertebral artery may be heard. Subclavian steal is not common, and syncope is a rare occurrence.

Transient Ischemic Attack

Syncope occurs in approximately 7% of individuals with transient ischemic attack (TIA) and is more common with vertebral-basilar artery TIA. Associated symptoms include vertigo, diplopia, ataxia, and loss of postural tone in the legs. A drop attack without loss of consciousness is more common than syncope. Treatment with enteric-coated aspirin (80–325 mg once daily) is advisable. Patients who are unable to take aspirin should be tried on clopidogrel. Poor responders should be considered for stenting.

Aortic Arch Syndrome

Pulseless disease (Takayasu's disease) is an arteritis-producing occlusion of the aortic arch vessels, and syncope may result. The BP is lower in the arms than the legs.

CARDIAC CAUSES

The major determinant in cardiac syncope is a decrease in cardiac output owing to reduced heart rate or ineffectual cardiac contractions secondary to arrhythmia. A diagnosis of cardiac syncope connotes a guarded prognosis with a mortality of up to 24% in 1 year, although this varies greatly according to the mechanism of the arrhythmia. Early diagnosis with appropriate therapy is lifesaving. Obvious causes of cardiac syncope are listed in [Table 15.1](#).

Tachyarrhythmias sustained rapid ventricular tachycardia (VT), that is, VT duration greater than 30 seconds, or symptomatic nonsustained VT commonly causes syncope. When VT is not apparent on the ECG rhythm strip or Holter monitoring, the underlying mechanism may be revealed by EP testing.

Atrial fibrillation or other ST with fast ventricular rates may cause syncope, especially in the elderly, or when rapid rates supervene in patients with Wolff-Parkinson-White (WPW) syndrome.

Torsades de Pointes

This arrhythmia is usually caused by class IA agents (quinidine and procainamide) and class III agents (sotalol causes syncope mainly in the presence of hypokalemia; amiodarone rarely causes torsades). Because torsades is a brady-dependent arrhythmia, acceleration of the heart rate using isoproterenol or by pacing constitutes effective modes of therapy. Magnesium sulfate IV will usually terminate the attacks pending initiation of more definitive therapy (*see* Chapter 6).

Aortic Stenosis and HCM

Syncope in aortic stenosis is typically exertional and suggests significant disease with life expectancy of 1–3 years. With HCM, syncope may be precipitated by exercise but can occur with normal activities or at rest (*see* Chapters 11 and 14).

Acute Myocardial Infarction

Syncope is an uncommon mode of onset of myocardial infarction (MI). Approximately 64% of patients with acute inferior MI have significant bradycardia and hypotension that predispose syncope. Rarely, patients with extensive coronary artery (CAD) disease present with exertional syncope.

Sinus Node Dysfunction and Sick Sinus Syndrome

Severe bradycardia (30–40 BPM), sinus arrest, and brady- or tachyarrhythmias may cause lightheadedness, dizziness, confusion, memory loss, or presyncope. One or more of these associated symptoms usually produce a 1- to 10-second warning before syncope; however, syncope can occur without warning in this category of patients and injuries may occur.

The setting is usually IHD with old infarction. The ECG may be normal or show evidence of old infarction, bradycardia, or sinus arrest. A 48-hour Holter gives about a 70% chance of detecting a significant arrhythmia, with symptoms noted in the patient's diary, as opposed to less than 48% with a single 24-hour Holter monitoring. Fairly often, repeat 48-hour Holter monitoring is necessary once or twice over a couple of weeks to identify a bradyarrhythmia that is symptomatic. Treatment of sinus node dysfunction is

given in Chapter 17. Sinus node dysfunction and severe bradycardia causing presyncope or syncope may be owing to drug therapy that inadvertently depresses sinus node function. Verapamil, diltiazem, digitalis, β -blockers, class I antiarrhythmic agents, amiodarone, and especially their combinations, may cause severe bradycardia, AV block, and asystole in susceptible individuals. Discontinuation of the causative agent or agents is unfortunately rarely practical and pacing is usually indicated.

AV Block and Stokes-Adams Attacks

Patients with Mobitz type II or third-degree AV block may suddenly have an occurrence of transient asystole or ventricular fibrillation (VF) with complete cessation of cerebral blood flow. Because VF is instantaneous, the cerebral circulation is suddenly deprived of perfusion, resulting in loss of consciousness usually without warning. Episodes can happen while sitting, lying, or walking. The unconscious patient appears very pale and, on arousal, becomes flushed as blood rushes to the head. When a patient is assessed hours or days later, ECG may show manifestations of Mobitz type II or complete AV block, right bundle branch block or left bundle branch block (LBBB), or bilateral disease. Cardiac pacing should be instituted.

Prolonged QT Syndrome

Recurrent syncope in children and young adults with a positive family history may be owing to the prolonged QT syndrome. Episodes of life-threatening arrhythmias appear to be precipitated by increased sympathetic stimulation. Thus, β -blockers have a role in management, despite a tendency for bradycardia in many of these patients. Propranolol in doses of 80–160 mg daily or a similar noncardioselective β -blocker without agonist activity is preferred.

When recurrent syncope is uncontrolled by β -blockers, combined pacing and β -blocker therapy may be required. In uncontrolled cases, excision of the left stellate ganglion may be a last resort (*see* Chapter 6).

Carotid Sinus Syncope

Carotid sinus syncope produces loss of consciousness most often by a cardioinhibitory bradycardiac mechanism and rarely, by vasodepressor effects. This uncommon condition represents less than 3% of patients with cardiac syncope and occurs mainly in men aged 61–76 years. Males outnumber females 4:1. The history of syncope occurring with sudden turning of the head, shaving, or a tight shirt collar should alert the physician. Episodes may occur in clusters or with dizzy spells. In some patients, attacks are rarely associated with any head movement or pressure on the neck. Right, left, or bilateral carotid sinus involvement occurs in approximately 60, 22, and 22%, respectively. In a 17-year follow-up of 89 patients, hypersensitivity of the right carotid sinus was 7:1 compared with the left. Because carotid sinus massage, even for 2–3 seconds, carries a risk in the elderly male, a provisional diagnosis is made by exclusion of other causes before attempting carotid sinus massage, which typically results in ventricular asystole for more than 3 seconds or a decrease in BP of 30–50 mmHg, without change in heart rate. Carotid sinus massage is best done in a hospital setting with resuscitative equipment standby, although if necessary, the transient asystole is usually easily terminated by asking the patient to cough or by giving one or more light chest thumps. Complications are TIA, rare hemiplegia, and asystole.

Because of the high spontaneous remission rate and good outcome in patients with carotid sinus syncope, only patients with recurrent syncope, particularly those with organic heart disease, should be considered for ventricular pacing and with programming the pacemaker rate well below the patient's sinus rate. In a 2- to 8-year follow-up study by Brignole et al., patients with carotid sinus syncope had an overall mortality rate that was not significantly different from control patients (5.8/100 person-years).

Other Causes of Cardiac Syncope

Additional causes of cardiac syncope include the following:

- Obstruction of blood flow may occur with massive pulmonary embolism.
- Myxoma and left atrial thrombosis may cause syncope precipitated by suddenly sitting up or leaning forward.
- Syncope occurring in patients with a prosthetic heart valve presents a particularly life-threatening emergency requiring admission to exclude prosthetic valve malfunction or obstructing thrombus (*see* Chapter 11).
- WPW syndrome or cardiac tamponade should present no problems in diagnosis. Fallot's tetralogy produces hypoxic spells that cause arterial vasodilatation. β -Blockers inhibit right ventricular contractility and decrease the right to left shunt; also, these agents produce peripheral vasoconstriction. supraventricular tachycardia is controlled. These actions may ameliorate hypoxic syncope.

UNEXPLAINED SYNCOPE

Approximately 35% of syncopal attacks occur without a readily defined cause. From 10 to 25% of total EP studies done in several large EP laboratories in the United States are for the resolution of the diagnosis of unexplained syncope. An algorithm for the management of unexplained syncope is given in [Figure 15.3](#).

EP Study

A provocative EP study is useful in revealing a cardiac cause in more than 33% of patients with unexplained syncope. Approximately 21% of these patients with negative studies is subsequently diagnosed as having intermittent high-degree AV block or sinus node disease. Caution is therefore necessary because an EP study is not a sensitive test to expose symptomatic bradycardia.

EP studies have been shown to initiate sustained monomorphic VT in approximately 18% of patients and nonsustained VT in approximately 23%. Nonsustained VT, especially if only for a few seconds duration, carries a minimal risk in patients with syncope and requires no arrhythmia therapy. Patients with syncope and sustained monomorphic VT do not appear to benefit from antiarrhythmic therapy, and the incidence of syncope is not reduced except when amiodarone is used as therapy.

The exact incidence of sudden death is unknown but appears to be low in patients with syncope unresolved by extended Holter monitoring and EP testing.

In patients with structural heart disease, especially IHD or cardiomyopathy, and severely impaired ventricular function, with Holter manifesting sustained monomorphic VT or EP-initiated sustained VT, amiodarone therapy is advisable. Holter monitor documentation of sustained VT is a strong predictor of EP-induced sustained monomorphic VT, but the use of EP testing is of dubious value in these patients.

Signal-averaged ECG in the absence of LBBB and LV ejection fraction (EF) of less than 30% correlates well with the EP induction of sustained monomorphic VT, but signal-averaged ECG is not advisable because regardless of results, EP studies are indicated in virtually all patients with structural heart disease and unexplained syncope.

EP studies appear to be justifiable in patients who have a high probability of induction of sustained monomorphic VT, such as the following:

- Post-MI patients with unexplained syncope.
- LVEF less than 30%.
- LV aneurysm.
- Complex ventricular ectopy on Holter.

Patients who have undergone a detailed assessment, including a relevant history and physical investigation, and remain with syncope of unknown cause and a negative EP study, have a low (2%) incidence of sudden death. EP studies are falsely negative in over 20% of patients who continue to have syncope. Close follow-up with extended Holter monitoring or a second assessment of HV intervals (the conduction time from the *His* bundle to the ventricle) and tests of sinus node function may reveal sinus node dysfunction or high-degree AV block.

In patients with recurrent symptoms, particularly in those with unexplained syncope that result in injuries insertable loop recorders are the diagnostic test of choice. A loop recorder may be implanted subcutaneously. The device is able to record 7–15 minutes of continuous ECG signal and is triggered by magnet application by the patient or companion. The data can be retrieved by telemetry. An event recorder has a role in patients who have sufficient warning to activate the instruction and the event is retrieved by telemetry.

β-Adrenergic Blocker

Patients without structural heart disease and neurocardiogenic syncope respond to increase salt intake and a trial of 0.1 mg of Florinef and a β-adrenergic blocking drug daily should be given a trial. These agents have been shown to prevent neurocardiogenic syncope in 50–75% of patients. Atenolol (25 to maximum 50 mg), metoprolol sustained release (100 mg), 5 mg of timolol twice daily, or nadolol (20 mg). Propranolol is beneficial, but adverse effects are often bothersome. Sra et al. have shown esmolol to be effective in predicting the outcome of head-up tilt response to oral metoprolol. All patients who had a negative head-up tilt test response with esmolol IV had a negative test during oral metoprolol therapy. Timolol, a nonselective β-blocker, causes greater arteriolar vasoconstriction than does atenolol or other cardioselective β-blockers and should provide salutary effects without the need for an abuse of tilt testing.

Disopyramide has a negative inotropic effect and a tendency to increase peripheral vascular resistance. Disopyramide (100–150 mg) sustained-release twice daily may be given a trial in patients in the absence of structural heart disease and in patients who have failed to respond to β-blockers.

BIBLIOGRAPHY

- Abboud FM. Neurocardiogenic syncope. *N Engl J Med* 1993;328:1117.
- Abboud FM. Ventricular syncope. Is the heart a sensory organ? *N Engl J Med* 1989;320:390.
- Akhtar M, Jazayeri M, Sra J. Cardiovascular causes of syncope. Identifying and controlling trigger mechanisms. *Postgrad Med* 1991;90:87.

- Ammirati F, Colivicchi F, Santini M. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation* 2001;104:52–57.
- Benditt DG, Ferguson DW, Grubb BP, et al. ACC expert consensus document: tilt table testing for assessing syncope. *J Am Coll Cardiol* 1996;28:263–275.
- Benditt DG, Fahy GJ, Lurie KG, et al. Pharmacotherapy of neurally mediated syncope. *Circulation* 1999;100:1242–1248.
- Brignole M, Oddone D, Cogorno S, et al. Long-term outcome in symptomatic carotid sinus hypersensitivity. *Am Heart J* 1992;123:687.
- Brignole M, Alboni P, Benditt D, et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;22:1256–1306.
- Calkins H, Byrne M, El-Atassi R, et al. The economic burden of unrecognized vasodepressor syncope. *Am J Med* 1993;95:473.
- Connolly SJ, Sheldon R, Roberts RS, et al. The North American Vasovagal Pacemaker Study (VPS): a randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *Am J Coll Cardiol* 1999;33:21–23.
- Di Girolamo E, Di Iorio C, Sabatini P, et al. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999;33:1227–1230.
- Fitzpatrick AP, Theodorakis G, Vardas P, et al. Methodology of head-up tilt testing in patients with unexplained syncope. *J Am Coll Cardiol* 1991;17:125.
- Fitzpatrick A, Sutton R. Tilting towards a diagnosis in recurrent unexplained syncope. *Lancet* 1989;1:658.
- Grubb BP, Temeszy-Armos P, Halm H, et al. Utility of upright tilt-table testing in the evaluation and management of syncope of unknown origin. *Am J Med* 1991;90:6.
- Kapoor WN. Is there an effective treatment for neurally mediated syncope? *JAMA* 2003;289:2272–2275.
- Krahn AD, Klein GJ, Yee R, et al. Randomized Assessment of Syncope Trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;104:46–51.
- Linzer M, Yang EH, Estes NA, et al. Diagnosing syncope: part 1: value of history, physical examination, and electrocardiography. The clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997;126:989–996.
- Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med* 1997;29:495–466.
- Morillo CA, Leitch JW, Yee R, et al. A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993;22:1843.
- Kapoor WN, Brant N. Evaluation of syncope by upright tilt testing with isoproterenol: a nonspecific test. *Ann Intern Med* 1992;116:358–363.
- Natale A, Aktar M, Jazayeri M, et al. Provocation of hypotension during head-up tilt testing in subjects with no history of syncope or presyncope. *Circulation* 1995;92:54–58.
- Kapoor W, Peterson J, Wieand HS, et al. Diagnostic and prognostic implications of recurrences in patients with syncope. *Am J Med* 1987;83:700–708.
- Kapoor WN. Current Evaluation and Management of Syncope. *Circulation* 2002;106:1606.
- Lipsitz LA, Pluchino FC, Wei YC, et al. Syncope in institutionalized elderly: the impact of multiple pathologic conditions and situational stress. *J Chron Dis* 1986;39:619–630.
- Mahanonda N, Bhuripanyo K, Kangkagate C, et al. Randomized double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. *Am Heart J* 1995;130:1250–1253.
- Madrid A, Ortega I, Rebollo GJ, et al. Lack of efficacy of atenolol for prevention of neurally-mediated syncope in highly symptomatic population: a prospective double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 2001;37:554–547.
- Raviele A, Brignole M, Sutton R, et al. Effect of etilefrine in preventing syncopal recurrence in patients with vasovagal syncope: a double-blind, randomized, placebo-controlled trial. The Vasovagal Syncope International Study. *Circulation* 1999;99:1452–1457.
- Raviele A, Giada F, Brignole M, et al. Diagnostic accuracy of sublingual nitroglycerin test and low-dose isoproterenol test in patients with unexplained syncope: a comparative study. *Am J Cardiol* 2000;85:1194–1198.
- Salim MA, Di Sessa TG. Effectiveness of fludrocortisone and salt in preventing syncope recurrence in children. A double-blind, placebo-controlled randomized trial. *J Am Coll Cardiol* 2005;45:484–488.

- Sarasin FP, Louis-Simonet M, Carballo D, et al. Prospective evaluation of patients with syncope: a population-based study. *Am J Med* 2001;111:177–184.
- Sheldon R, Rose S, Flanagan P, et al. Effects of beta blockers on the time to first syncope recurrence in patients after a positive isoproterenol tilt table test. *Am J Cardiol* 1996;78:536–539.
- Sutton R, Brignole M, Menozzi C, et al. Dual-chamber pacing in treatment of neurally mediated tilt-positive cardioinhibitory syncope. Pacemaker versus no therapy: a multicentre randomized study. *Circulation* 2000;102:294–299.
- Ward CR, Gray JC, Gilroy JJ, et al. Midodrine: a role in the management of neurocardiogenic syncope. *Heart* 1998;79:45–49.

16

Preoperative Management of Cardiac Patients Undergoing Noncardiac Surgery

CONTENTS

PATHOPHYSIOLOGY OF CARDIOLOGIC COMPLICATIONS

FROM SURGERY

RISK STRATIFICATION AND PLAN OF MANAGEMENT

PATIENT ASSESSMENT

CARDIAC DISEASES, ASSESSMENTS, AND THERAPY OPTIMIZATION

STRATEGIES FOR PREVENTION

BIBLIOGRAPHY

Cardiovascular complications account for approximately 50% of deaths in patients submitted to major noncardiac surgery, and more than 90% of these occurs in patients with coronary heart disease (CHD). In the United States, approximately one million patients have a cardiac death, congestive heart failure, myocardial infarction (MI), or myocardial ischemia after noncardiac surgery. The cost of in-hospital cardiac morbidity exceeds 10 billion dollars annually.

Cardiac patients with a high risk of postoperative infarction and cardiac death can be identified by careful elucidation of the history and a physical examination, followed by electrocardiogram (ECG), chest X-ray, and, where needed, Holter monitoring, echocardiogram, and exercise stress test.

In patients with CHD, it is necessary to carefully evaluate the following:

- Left ventricular (LV) reserve.
- Coronary reserve or ischemic burden.

These findings and an understanding of the complications that may occur in patients with CHD, when submitted to the intensive stress of catecholamines, hypotension, decreased preload or hypervolemia, myocardial depressant effect, and interactions of cardiac medications, are vital for the formulation of a rational plan of management.

PATHOPHYSIOLOGY OF CARDIOLOGIC COMPLICATIONS FROM SURGERY

Activation of the sympathetic nervous system and sensitization of the ischemic myocardium to increase catecholamines appear to play a major role in initiating ischemic

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complications. Poorly perfused myocardium is in jeopardy during the increased demands imposed by the cardiac response to intense sympathetic/catecholamine stimulation, which occurs perioperatively and maximally in the postoperative period.

The 12- to 72-hour postoperative hypermetabolic state imposes considerable demands that require adequate LV function and coronary flow reserve. Holter monitoring indicates an increased incidence of painless ischemia before adverse cardiac outcomes during the 2- to 5-day postoperative period. The inadvertent withdrawal of antianginal or antihypertensive medications may predispose intraoperative and postoperative complications. Also, surgical trauma promotes activation of new platelets, which, with added stasis, are linked to the initiation of venous thromboembolism.

RISK STRATIFICATION AND PLAN OF MANAGEMENT

Mukherjee and Eagle advise the following routine:

- Assess the patient's clinical features.
- Evaluate functional status.
- Consider the patient's surgery-specific risk.
- Decide if further noninvasive evaluation is needed.
- Decide when to recommend invasive evaluation.
- Optimize medical therapy.
- Perform appropriate perioperative surveillance.
- Design maximal long-term therapy.

Minor surgery (ophthalmologic, transurethral resection of the prostate, herniorrhaphy, hysterectomy, and orthopedic surgery) usually causes no complications in cardiac patients, provided that these individuals are hemodynamically stable and do not have major contraindications to elective surgery (Table 16.1.).

Major surgery is tolerated relatively well by cardiac patients, except in those with MI less than 6 months previously, unstable angina, overt heart failure (HF), severe aortic stenosis, and angina class 2 and 3 in association with peripheral vascular disease and a strongly positive stress test or abnormal dipyridamole-thallium scan.

Patients undergoing vascular surgery are at highest risk for cardiac events. Patients with aortic abdominal aneurysms pose a considerable risk because of the magnitude of myocardial stress imposed during aortic cross clamping. Virtually all patients with abdominal aortic aneurysms have at least one of the following: significant CHD, hypertension, or renovascular disease.

Further estimation of risk requires consideration of the following:

- Emergency surgery for life-threatening conditions must be done regardless of risk and is performed under hemodynamic monitoring, with rapid optimization of medical therapy that must not delay surgical intervention.
- In patients where surgery is elective but promptly required, the consultant's major task is quickly to optimize medical therapy, assess risks, and determine, if necessary, how long surgery should be deferred.

The Goldman Cardiac Risk Index does not take into consideration vital information that may be gleaned from echocardiography, ejection fraction (EF), exercise stress testing, dipyridamole thallium scintigraphy, and Holter monitoring for silent ischemia. The Goldman classification was devised in the 1970s in cardiac and noncardiac patients and underestimates risks in class 4 patients. It excludes the history of angina, pulmonary

Table 16.1.
Cardiac Contraindications to Elective Noncardiac Surgery

Myocardial infarction <6 months ^a
Overt heart failure
Severe aortic stenosis
Unstable angina
Mobitz Type II, complete AV block, sick sinus syndrome

^aElective but promptly needed surgery justifiable after 3 months postmyocardial infarction with full hemodynamic monitoring (*see* Table 16.2.); emergency surgery can be done earlier.

edema, and the proximity of prior HF. Apart from it being cumbersome, it is of limited value in patients undergoing vascular surgery and in the elderly. The Detsky index is an improvement, but has several limitations.

Estimation of risk is an academic exercise in patients requiring emergency surgery for conditions that pose an immediate serious threat to life, such as aortic dissection, perforated viscus, ruptured spleen, or continued massive hemorrhage with marked hemodynamic deterioration. In these patients, the risks are well-known to the surgeon and anesthesiologist and should be communicated to the patient or next of kin, and the role of the consultant cardiologist in this setting is to assist with prompt hemodynamic stabilization of the patient.

Mortality is clearly related to the following:

- Age over 75 years: mortality is up to 10 times higher than in patients under age 65.
- Type of major surgery.
- Previous MI.
- Unstable or class 3 and 4 angina (*see* Chapter 4).
- Cardiac failure, present or recent past.
- Severity of aortic stenosis.
- Presence of significant arrhythmia.

Studies in the 1970s indicated that post-MI patients less than 3 months have a postoperative reinfarction rate of about 24%. Recent studies indicate that intensive hemodynamic monitoring can reduce postoperative infarction rates to less than 6% at 3 months and to approximately 3% at 3–6 months (Table 16.2). A high mortality rate is to be expected in patients less than 3 months post-MI, unstable angina, overt HF, and moderate-to-severe aortic stenosis. Elective surgery should be postponed or canceled in these subgroups.

Patients with class 2 to 3 angina with peripheral vascular disease and a positive stress test if at low workload, heart rate less than 120 beats per minute (BPM) have a high risk of infarction (20–25%).

Up to 60% of intraoperative and postoperative infarcts occur silently and with a high mortality rate. About 90% of postoperative cardiac events occur in patients with CHD, whereas valvular, hypertensive, and other heart disease account for the remaining patients with a low incidence of serious events.

Cardiac patients at high risk for elective noncardiac surgery are listed in Table 16.3. Most of the remaining large pool of cardiac patients undergo elective major surgery without significant risk, and it makes no sense to label them as low or good risk patients.

Table 16.2.
Approximate Incidence of Postoperative MI

<i>Studies</i>	<i>No MI</i>	<i>MI >6 mo</i>	<i>3–6 mo</i>	<i><3 mo</i>
1970s	0.5%	5%	15%	30%
1980s ^a		<1%	3%	6%

Angina class 2 and 3 + peripheral vascular disease and abnormal dipyridamole-thallium scan (15–30%).

^aFull hemodynamic monitoring.

Table 16.3.
High-Risk Cardiac Patients for Elective Noncardiac Surgery^a

Angina class 3 + PVD
 Angina class 3, no PVD, strongly positive stress test
 Angina class 2, no PVD, strongly positive stress test
 Angina class 2 + PVD, positive dipyridamole-thallium scan
 >6 months post-MI and any of the above categories
 >6 months post-MI moderate hypertension and/or diabetes
 Holter evidence of silent ischemia in above categories of patients
 Episodes of VT or frequent multiform ventricular ectopy
 Bradyarrhythmias
 Heart failure: more than one episode
 Heart failure: one episode necessitating triple therapy^b
 Ejection fraction <35%
 Aortic stenosis: moderate
 Hypertrophic or dilated cardiomyopathy
 Tight mitral stenosis

^aExcluding causes contraindicating surgery (Table 16.2.).

^bDigoxin, diuretic, and angiotensin-converting enzyme inhibitor.
 PVD, Peripheral vascular disease.

PATIENT ASSESSMENT

History

A careful relevant history backed up, if needed, by a spouse or relative is vital. The assessment of the patient should result in a clear knowledge of the following

- LV reserve, taking into account information gleaned from the history, physical, chest X-ray, and echocardiography with evaluation of the LV function.
- Coronary reserve, as derived from assessment of effort tolerance, exercise stress testing (see Chapter 4), and/or dipyridamole-thallium scintigraphy and, occasionally, coronary angiography.
- Extent of hypertension, if present.
- Significance of a detectable aortic systolic murmur or mitral stenosis.

The preoperative assessment should focus on the following:

- Functional status: poor functional status is defined as the inability to walk 6 minutes, two blocks or climb two flights of stairs.

- The proximity of HF.
- The proximity of MI.
- Exploring the history of angina.
- The severity of aortic stenosis.
- The significance of arrhythmias.

In addition, the assessment should include a meticulous review of all drugs the patient is taking. The number and usage of cardiac medications may give clues to the extent of underlying disease and continuation of some, but discontinuation of others may be necessary to ensure salutary effects.

β -Blockers have been proven to decrease morbidity and mortality in patients undergoing a variety of surgery. β -Blockers must not be stopped before surgery, however, because they prevent tachycardia during intubation and may be beneficial in preventing perioperative and postoperative ischemic events (*see* Chapter 4 for intravenous [IV] and oral dosages).

I agree with Fleisher et al. that β -blocker therapy is strongly indicated for the following:

- Patients with coronary artery disease (CAD).
- HF in the past.
- Diabetes mellitus, because these patients are at high risk for cardiac events or complications.
- Poor functional status defined as the inability to climb two flights of stairs or walk four blocks or a 6-minute walk.
- Patients undergoing high risk surgery: that is, β -blockers are indicated for all major surgery and can be withheld for patients undergoing low-risk surgery, such as biopsies, endoscopies, and breast and cataract surgery.
- Renal insufficiency if caused by diabetes or vascular disease.

Other considerations:

- Aspirin is a commonly used drug in cardiac patients. In most patients, aspirin should be discontinued 5 days before most surgical procedures and 7 days before urological or ophthalmological surgery (except for cataracts). Small-dose aspirin (75–81 mg) should be commenced on the second or third postoperative day if there are no contraindications. Plavix must also be discontinued at least 5–7 days prior to surgery.
- Oral anticoagulants and nonsteroidal antiinflammatory drugs must be discontinued days before surgery.
- Calcium antagonists tend to decrease blood pressure (BP), which may be lowered further by anesthetic agents and sedatives. Calcium antagonist dosage may be decreased slightly if angina is stable, and to a greater extent if LVEF is less than 40% and systolic BP (SBP) is 95–110 mmHg.
- If nitrates are not being taken by the patient, they may have to be added with care, but not to cause a decrease in BP.
- IV nitroglycerin infusion may be required perioperatively.
- Antihypertensive agents, digoxin, and diuretics are discussed later in this chapter.

Physical Examination

- Examine the chest for abnormal precordial movement, indicating LV wall motion abnormalities.
- Look for cardiomegaly and/or third heart sound S₃ gallop, which indicates LV dysfunction.
- Determine whether an aortic systolic murmur exists. Verify if aortic stenosis is significant: symptoms include shortness of breath on moderate effort, chest pain or presyncope,

LV thrust, delayed carotid upstroke, decreased intensity or absence of the aortic second sound in the second right interspace or over the right carotid. If any one of these symptoms or signs is present, defer elective surgery pending results of Doppler echocardiography (*see* Chapter 11).

- Carefully evaluate internal jugular pulsations for prominent waves and pressure exceeding 2 cm above the sternal angle indicative of HF with or without the presence of crepitations over the lung bases.
- Assess cardiac rhythm disturbances: atrial fibrillation with a fast ventricular response must be controlled; ask the patient to walk for 1 or 2 minutes and assess the apical rate.
- Assess hypertension, hypotension, and check for postural hypotension.
- Deeply palpate the abdomen for the presence of abdominal aortic aneurysm and assess the carotid and peripheral circulation. Patients with peripheral vascular disease have a higher incidence of complications indicative of widespread occlusive atheromatous vascular disease.

Investigations

ELECTROCARDIOGRAM

It is customary for all patients over age 40 to have a resting ECG performed within a few days before surgery, and consideration should be given to the following:

- This control tracing makes changes that may appear postoperatively more meaningful, for example, the sudden occurrence of P pulmonale, supraventricular tachycardia (SVT) depression V₁ to V₃, and/or right bundle branch block (RBBB) may suggest acute cor pulmonale caused by pulmonary embolism.
- If the resting ECG is abnormal, it should be compared with previous tracings to exclude recent or ongoing ischemia. If acute ischemia is confirmed, further investigations are necessary: request an exercise test if surgery is elective and the coronary reserve is questionable.
- Multifocal ventricular premature beats (VPBs) or other ventricular arrhythmias may require temporary control, but unifocal VPBs in the absence of ongoing ischemia or electrolyte abnormality are not of concern.
- The fast ventricular response with atrial fibrillation should alert the physician to the need for digoxin.
- ECG evidence of old infarction is particularly important in confirming the patient's history of old infarctions. An extensive infarct or anterior infarction carries a much higher surgical risk than inferior infarction.
- ST elevation present months after infarction strongly suggests LV aneurysm and increases surgical risk, as well as an increased incidence of LV systemic embolization. Left bundle branch block (LBBB) or other intraventricular conduction delay or LV hypertrophy (LVH) are indicative of an increased risk of perioperative infarction and/or death.
- Left atrial enlargement is an important finding in keeping with LVH or LV dysfunction overt LV failure or significant mitral stenosis and/or regurgitation.

DIPYRIDAMOLE-THALLIUM SCINTIGRAPHY

Some physicians claim that this is a useful test in detecting ischemic myocardial segments and appears to give prognostic information concerning the risk of cardiac event up to 2 years after surgery for peripheral vascular disease. A reversible defect and late redistribution after dipyridamole-thallium imaging are significant predictors of future cardiac events in patients with peripheral vascular disease.

Several studies have not confirmed the initially claimed accuracy of dipyridamole-thallium scintigraphy in predicting surgical risk. In a large prospective study, this test did not significantly predict cardiac complications. In a study by Baron et al., thallium redistribution was not significantly associated with the incidence of perioperative MI, ischemia, or other adverse outcomes. Patients with unstable angina, class 3 and 4 angina, or prior HF do not require assessment with dipyridamole, adenosine thallium scintigraphy, or dobutamine echocardiography because these patients are obviously at high risk. Coronary bypass surgery is indicated in these patients for the usual reasons. Patients with class 1 and 2 angina do not require the test because they usually undergo major surgery with little risk using modern anesthesiology techniques and, if required, hemodynamic monitoring. Thus, considerable financial savings can be achieved without endangering patient care.

The dipyridamole-nuclear scan is contraindicated in patients with unstable angina; angina at low level effort or at rest, stable class 3 or 4 angina; and patients with asthma or wheezing.

Adverse effects of dipyridamole-thallium scintigraphy are given in [Table 16.4](#). β -blocking drugs should be discontinued for 24 hours prior to the test if it is safe to do so; these agents retard the action of dipyridamole on coronary perfusion, and the test result may be erroneous (*see* Chapter 4).

HOLTER MONITORING

Preoperative Holter monitoring for 24–48 hours is helpful in detecting silent ischemia and is especially useful in patients with aortic aneurysms requiring surgery and in patients at high risk as listed in [Table 16.3](#). This investigation is not cost-effective, however, and reliability is critically dependent on details of the technique and equipment used at individual centers for detecting ischemia.

Studies using postoperative Holter monitoring indicate that at 1–4 days postoperative, 40–60% of patients with CHD develop “ischemic” changes that may herald an incidence of fatal or nonfatal infarction of 1–2%. It is probably not cost-justifiable, however, to monitor 100 cardiac patients in an attempt to save one fatal infarct or four nonfatal infarctions. MI is usually caused by occlusion of a coronary artery by thrombus overlying a fissured plaque of atheroma, the occurrence of which does not usually correlate with the presence of silent ischemia observed more than 12 hours before the events. Where arrhythmias are suspected, Holter monitoring is certainly relevant in the preoperative assessment of patients complaining of syncope or presyncope. Significant bradyarrhythmias that may require pacing or frequent multifocal or other wide complex ventricular ectopics may be uncovered in these patients.

ECHOCARDIOGRAPHY

Echocardiography is a valuable tool, but has a small role in patients like those listed in [Table 16.3](#). Patients with suspected LV dysfunction, valvular heart disease, or cardiomyopathy should have echocardiographic assessment.

The detection of regional wall motion abnormalities will greatly heighten the suspicion that significant CHD is present. LV systolic function is assessed, and an EF is reported by some echocardiographers if mitral regurgitation is absent.

The echocardiographical EF in patients with CHD is subjective to some errors in interpretation but is a useful guide for comparative studies, and echocardiography is necessary for evaluating the degree of aortic stenosis or other structural abnormalities.

Table 16.4.
Adverse Effects of Dipyridamole-Thallium Scintigraphy

<i>Adverse effect</i>	<i>Percentage</i>
Chest pain ^a	19
Death ^b	0.05
Nonfatal MI	2
Headache	12
Dizziness	20
Hypotension ^a	5
Wheezing in patients with asthma or bronchitis ^a	>20

^aQuickly relieved by stopping dipyridamole infusion and giving intravenous aminophylline (5 mg/kg over 20 minutes).

^bRepresents patients with unstable angina.

The radionuclide ECG-gated study cannot be used in patients with AF. Both studies give falsely high EF in patients with mitral regurgitation. Echocardiography is a more cost-effective test, although it is less accurate than radionuclide angiography for the measurement of EF; the cost of the latter is not justifiable.

CARDIAC DISEASES, ASSESSMENTS, AND THERAPY OPTIMIZATION

Ischemic Heart Disease

If the patient suffers from angina pectoris, assess if it is stable or unstable angina according to the following:

- Class 1: chest pain on extraordinary effort (*see* Chapter 4).
- Class 2: chest pain on normal activities that require moderate exertion, such as walking 0.5–1 mile briskly, with pain occurring mainly up hills and against a cold wind. Absence of rest angina except if emotionally precipitated.
- Class 3: chest pain on mild activities, such as walking three blocks or approximately 300 yards.
- Class 4: angina at rest.
- Unstable angina: new onset angina, a change in pattern and frequency, progressive angina (*see* Chapter 4).

Do not be lulled into satisfaction with the history of low pain frequency or low nitroglycerin consumption. Inactivity owing to intermittent claudication and peripheral vascular disease can decrease the frequency of chest pain and nitroglycerin consumption, such that severe obstructive CHD may be present with the patient only experiencing “mild” angina. Silent ischemia may occur, especially in patients with angina who have diabetes and in patients with unstable syndromes. A history of increasing angina, change in pattern, or angina at rest indicates severe CHD with limited coronary reserve. It must be reemphasized that rare or completely absent pain in an inactive patient is of little help in decision making.

Patients with stable class 2 angina without compromised LV function should undergo exercise stress testing before major elective surgery. The ability to complete more than 7 minutes of a Bruce or similar protocol without experiencing chest pain, ischemic changes, or an inappropriate fall in BP is evidence of adequate coronary reserve (*see*

Table 16.5.
Factors That Decrease Risk of Elective Noncardiac Surgery

Coronary artery bypass surgery
Role of angioplasty in patients with impaired coronary reserve, EF >40% ^a
Exercise stress test negative for ischemia
Absence of silent ischemia or frequent multiform ventricular ectopics on Holter
EF >40%
Pre-, peri-, and postoperative use of β -blockade if not contraindicated
Nitrates commencing 6 hours preoperative and for 48–96 hours postoperative: transdermal nitrate
q 6 hours \times 24–96 hours, then wean off
Low dose aspirin (80 to 162.5 mg daily from day 2) to prevent fatal or nonfatal MI or
thromboembolism ^a

^aStrongly advised (role to be defined by clinical trials).

Chapter 4) and suffices for most major surgery. In patients with class 3 angina (Tables 16.3. and 16.5.), particularly in those with EF less than 35%, elective surgery should be deferred until coronary angiography and revascularization are achieved. Both coronary artery bypass surgery (CABS) and angioplasty in patients with severe CHD have reduced the mortality that can be caused by noncardiac surgery (Table 16.5.). Patients with class 3 angina and those with MI within the previous 3–6 months constitute a high-risk group. If emergency surgery is necessary in this category of patients and in others considered at high risk, full hemodynamic monitoring should be instituted with arterial line, Swan-Ganz catheter, and continuous cardiac monitoring carried out during surgery and for about the next 5 days.

Progress in anesthesia and surgery allows surgical procedures to be performed successfully in patients who, in the 1960s and 1970s, would have been considered prohibitive surgical risks.

Heart Failure

Overt or minor HF is not an uncommon preoperative problem for which a cardiology consultation is required. Consideration must be given to the following:

- Document effort tolerance, degree of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and signs of HF.
- The presence of LV enlargement, S₃ gallop, and the history of two or more episodes of HF add to the risk and in these patients; optimization of medical therapy with the combination of angiotensin-converting enzyme (ACE) inhibitor, digoxin at correct dosage, and titrated use of furosemide should result in reduction in the risk of HF resulting from surgery. These patients require preoperative hemodynamic monitoring, and particular attention to the avoidance of fluid overload is required during their emergency surgery.
- It is important to recognize that HF may be present without clinical signs of congestion. Echocardiographic evaluation of LV systolic function is a useful assessment (*see* Chapter 5).
- Overt HF is a contraindication to elective surgery. If emergency surgery is required, the use of IV nitroglycerin, digoxin, and diuretics, as well as ACE inhibitors, may cause some amelioration in 48 hours to enable emergency surgery, but intensive hemodynamic monitoring is essential.
- If HF occurred more than 1 year before and an S₃ or marked cardiomegaly is absent with the patient stabilized on digoxin, a diuretic, and ACE inhibitor, elective surgery can proceed.

- For patients in the above groups, an echocardiogram is necessary to determine chamber size, ventricular contractility, presence or absence of aortic stenosis, degree of mitral regurgitation, and EF. It must be re-emphasized that the EF is not accurate in the presence of significant mitral regurgitation.
- Patients with prior HF and EF less than 30% are at high risk for the development of pulmonary edema in the postoperative phase. If surgery is mandatory, intensive hemodynamic monitoring is essential.
- Chest X-ray should be evaluated for the degree of cardiomegaly. Mild cardiomegaly is acceptable, but moderate-to-severe cardiomegaly requires echocardiographic evaluation correlated with the history and physical findings. Patients with severe CHD commonly exhibit no significant radiographic cardiomegaly, and the radiograph cannot be relied on in patients with CHD (the largest subset of cardiac patients). Thus, echocardiography has an increasing role in this category of patients.

Digoxin is indicated in cardiac patients with AF and an uncontrolled ventricular response. The drug is also indicated in patients with signs or symptoms of HF and in those with a history of HF (*see* Chapter 5). The use of digoxin, when indicated, does not increase the risk of a cardiac event, and studies that have tried to demonstrate this point fail to recognize that in these patients, mortality and morbidity are high, regardless of the use of digoxin. A digoxin level is not an essential requirement if one follows the rule that in patients under age 70 with a normal creatinine level, the maintenance dose should be 0.25 mg daily, and in patients over age 70 with normal serum creatinine, the dose is usually 0.125 mg daily.

An exception to the above guidelines is that AF with a fast ventricular response requires higher titrated dosage. If the dosage is not in accordance with the schedule given above or digoxin toxicity is in question, digoxin level should be estimated (*see* Chapter 5). A small dose of a β -blocker should be commenced and the patient stabilized on digoxin diuretic, ACE inhibitor, and β -blocker for a few months prior to surgery.

The combination of carvedilol and digoxin is superior to either drug alone.

Hypotension and Hypertension

Hypotension caused by hemorrhage or medications must be promptly corrected. In the management of hypotension, consider the following:

- Anesthesiologists correctly detest written advice to “avoid hypotension.”
- Patients with CHD are commonly prescribed a combination of β -blockers, ACE inhibitors, calcium antagonists, and nitrates; interaction with anesthetic agents and mild sedatives may cause a significant fall in BP.
- If the patient’s SBP is in the range of 95–105 mmHg on the aforementioned cardiac medications, it is wise to write an appropriate phrase: “Propensity to develop hypotension in view of relatively low BP and medications that predispose BP lowering.” The doses of the relevant agents, particularly calcium antagonists, which are not lifesaving agents, should be reduced to permit the SBP to increase to the range of 120–130 mmHg.
- When hypotension occurs in the operating room, an increase in IV saline is usually given to elevate BP. At times, this may precipitate subtle HF, which may go undetected because, in practice, not all cardiac patients are monitored with balloon flotation catheters.

Caution is necessary to avoid over prescribing transdermal nitrates for use during surgery in patients with borderline hypotension, SBP less than 110 mmHg. Also, the nitrate patch should not be applied to the anterior chest wall because a defibrillator paddle placed in contact with the nitrate patch may cause an explosion.

SBP greater than 220 mmHg and diastolic blood pressure (DBP) greater than 110 mmHg that does not respond to nifedipine (10 mg orally repeated in 2 hours if needed, plus or minus transdermal nitroglycerin) are considered a contraindication to elective surgery and require investigation and control before elective surgery. If emergency surgery is needed, BP control can be obtained with the use of IV nitroglycerin, labetalol, or nitroprusside. For dosage information, *see* Tables 4.9. (nitroglycerin) and 8.11. (nitroprusside). IV nitroglycerin is superior to nitroprusside in patients with CHD, because the latter agent may cause a coronary steal. If tachycardia is provoked by these agents, a short-acting β -blocker, such as esmolol IV or metoprolol, should be given (*see* Table 4.8.); propranolol has a longer duration of action at β -adrenergic receptors, and the negative inotropic action of this agent may persist for 12–16 hours and negative chronotropic effects may last up to 36 hours. Propranolol is commonly the only IV preparation available in some countries; 1 mg IV is equivalent to the 20 mg oral, and 1 mg IV can be given over 2 minutes and repeated if needed every 1–6 hours. Caution is necessary to avoid a β -blocker, including the α -, β -blocker labetalol, in patients who have asthma, HF, or in those who have severe LV dysfunction. Also, calcium antagonists are not all alike; verapamil and diltiazem are contraindicated in patients with EF less than 40%.

Antihypertensive agents should not be discontinued before surgery, except when drug treatment is inappropriate, causing unduly low BP or postural hypotension. Many patients with mild hypertension require no drug therapy. On admission, if a diuretic has been used, this can be discontinued until a few days before discharge. If a β -blocker is being given, this should be continued because of its salutary effects during induction of anesthesia and their cardioprotective effects in the peri- and postoperative periods.

The following antihypertensive agents must not be discontinued suddenly because rebound may occur:

- Clonidine.
- Guanfacine.
- Methyldopa.
- β -blockers or calcium antagonists.

Patients with mild-to-moderate hypertension that is not completely controlled, with SBP in the 180–210 range and DBP between 95 and 105, will benefit from an increase in medications and/or from the addition of transdermal nitroglycerin, and surgery should not be delayed.

High BP is usually well tolerated because premedication and anesthetic agents lower BP levels. The serum potassium should be maintained at a normal level greater than 4.0 mEq(mmol)/L, and metabolic alkalosis should be avoided because these conditions may increase the risk of cardiac events.

Abdominal Aortic Aneurysm

Patients with abdominal aortic aneurysms (AAA) are at high risk because they often have concomitant severe CHD and require extensive preoperative evaluation. These patients commonly have moderately severe hypertension that must be controlled. Also, CHD is nearly always present but may not be manifest, because the patient's exercise capacity usually is reduced because of intermittent claudication.

Evaluations include the following:

- Echocardiographic assessment of LV function.
- Holter monitoring to document arrhythmias and/or silent ischemia.

- Historic details of effort tolerance and an exercise stress test to evaluate coronary reserve. If the latter cannot be done, dipyridamole-thallium scintigraphy or similar noninvasive study should be considered, but such studies do not accurately define the risks.
- Baseline renal function.

Surgery is necessary when an AAA exceeds 5 cm. If the renal arteries are in proximity and require revascularization, the risk of precipitating severe irreversible renal failure may be prohibitive and the decision to proceed with surgery must be carefully considered. Also, the duration of surgery increases the incidence of cardiac death in patients with concomitant CHD. Coronary artery revascularization, therefore, is preferred in some patients before surgery for AAA, especially if class 3 angina or silent ischemia is documented.

Valvular Heart Disease

AORTIC STENOSIS

Severe aortic stenosis is a contraindication to elective surgery. It is usually not difficult to determine whether the murmur indicates severe aortic stenosis. In patients over age 50, more than 90% of aortic systolic murmurs are owing to calcific aortic sclerosis, less than 2% are owing to significant stenosis, and less than 1% are caused by severe stenosis. When stenosis occurs in this category of patients, however, the progression can be quite rapid over 6–12 months (*see* Chapter 11). Severe stenosis resulting from bicuspid and rheumatic valvular disease, and aortic sclerosis, nearly always causes one or more of the following cardinal symptoms or signs:

- Dyspnea on moderate activity.
- Exertional presyncope or syncope.
- Chest pain.
- A loud, harsh ejection systolic murmur over the aortic area that radiates into the neck, except when cardiac output is low.
- Delayed carotid upstroke, a useful sign in patients under age 65 (*see* Chapter 11).
- Decrease or loss of the second heart sound in the second left interspace or over the right carotid artery.
- Clinical or electrocardiographic LV hypertrophy.

If two of these cardinal features are present, surgery should be postponed pending the result of Doppler flow echocardiography. The mean Doppler gradient correlates well with the mean gradient obtained by catheterization; some laboratories report the maximal instantaneous gradient, which tends to be slightly higher than the aortic peak gradient obtained at catheterization.

Symptomatic patients with severe aortic stenosis, valve area less than 0.7 cm²/m², should undergo valve replacement before elective noncardiac surgery. In patients with moderate stenosis, valve area 0.8–1.2 cm²/m², the type of surgery and risks must be individualized (*see* Chapter 11).

Most patients with aortic sclerosis and mild aortic stenosis present no problems during surgery. Antibiotic prophylaxis is advised for patients with aortic valve disease (*see* Chapter 12).

AORTIC PROSTHETIC HEART VALVE

Discontinue anticoagulants 3 days before, or reverse the prothrombin time with fresh frozen plasma and vitamin K. Anticoagulants can be recommenced on the second postoperative day. The discontinuation of anticoagulants for surgery carries a risk of throm-

boembolism, and coverage with heparin may be required depending on the extent of the delay in the resumption of oral anticoagulants. After discontinuation of oral anticoagulants, vitamin K is given 36 hours before surgery if the atrial size is greater than 5 cm and if there is a previous history of thromboembolism. It is advisable to switch to IV heparin, and when the prothrombin time is less than 1.25 times the control, oral anticoagulants can be discontinued. Heparin is discontinued 6 hours preoperatively and cautiously recommenced 12-hours postoperatively, followed by oral anticoagulation. A 2-day overlap with heparin, until the prothrombin time or International normalized ratio is at the desired range for 2 days, is advisable.

MITRAL VALVE DISEASE

Critical mitral stenosis is fortunately rare, and elective surgery is postponed until valvotomy has been performed. Symptoms and signs are detailed in Chapter 11. Mitral regurgitation of all grades is usually well-tolerated, except if HF has occurred.

Patients with mitral valve disease and AF are at high risk for systemic embolism during the postoperative period.

HYPERTROPHIC CARDIOMYOPATHY

Approximately 33% of patients with hypertrophic cardiomyopathy (HCM) have a significant resting outflow tract gradient and an additional 33% obtain a gradient on provocation (*see* Chapter 14).

More than 80% of the stroke output occurs before the mitral valve impinges on the hypertrophied septum, producing a pressure gradient. This gradient is increased by hypovolemia or hypotension, as well as by preload-reducing agents, such as nitrates, which should be avoided. General anesthesia is safe in most patients with HCM provided that syncope, angina, or arrhythmia are not present. Spinal anesthesia appears to increase the operative risk because of associated hypotension.

ANTIBIOTIC PROPHYLAXIS FOR VALVULAR HEART DISEASE

Patients with prosthetic heart valves require antibiotic coverage for all procedures. All patients with valvular heart disease should receive coverage for dental and surgical procedures (except for a few procedures listed in Chapter 12). Mitral valve prolapse manifested by a murmur needs coverage.

Arrhythmias

SUPRAVENTRICULAR ARRHYTHMIAS

Patients with AF should be digitalized to control the ventricular response. The apical rate should remain between 70 and 90 and should not exceed 110 if the patient is walked down a 200-foot corridor or one flight of stairs.

Atrioventricular re-entrant tachycardia (AVNRT) is managed with digoxin or beta blockers. If AVNRT occurs during surgery, it can be controlled with short-acting esmolol, metoprolol, or with 1 mg of IV propranolol given over 2 minutes. The IV dosage of β -adrenergic blockers is given in Table 4.8. Verapamil should be avoided because of its negative inotropic effect, but it can be used in patients with good LV function. Adenosine, which has a half-life of less than 10 seconds, is as effective as verapamil, does not depress cardiac contractility, and is preferred in patients with LV dysfunction but must be avoided in patients with active ischemia (*see* Chapter 6).

VENTRICULAR ARRHYTHMIAS

Frequent multiform VPBs or ventricular tachycardia (VT) should be managed with lidocaine IV bolus (50–100 mg) and IV infusion (2–3 mg/minute) (Table 1.10.). Procainamide is rarely required for VT.

PACEMAKERS

Mobitz type I atrioventricular (AV) block does not require pacing. RBBB with left anterior hemiblock or Mobitz type I AV block does not require temporary pacing. An external transthoracic pacer should be available (*see* Chapter 17).

Mobitz type II, complete AV block, or significant sinus pauses require temporary pacing before emergency or elective surgery.

Electrocautery interference may transiently inhibit the output of implanted pulse generators despite electric shielding of the pacemaker. This is rare with the bipolar connections of newer pulse generators, however. A magnet should be available in the operating room to convert the pacing system, if necessary. The surgeon is advised to use the cautery in short 2- to 3-second bursts and to keep the equipment as far from the thorax as possible. The carotid and radial pulses must be monitored, because electrosurgery interferes with the ECG.

COR PULMONALE

Cor pulmonale carries a major risk because these patients have significant hypoxemia, with arterial oxygen pressure less than 55 mmHg arterial carbon dioxide pressure greater than 45 mmHg; the forced expiratory volume per second is commonly less than 30. These findings contraindicate elective surgery under general anesthesia and pose problems for emergency life-threatening conditions. If emergency surgery is necessary under general anesthesia, hemodynamic monitoring, optimization of respiratory medications, and ventilatory support in the intensive care unit setting is often necessary for days to weeks.

STRATEGIES FOR PREVENTION

There are no formulated strategies directed at prevention of postoperative fatal or nonfatal infarction. Some of the following steps are of proven value and some, although rational, must be tested by properly designed clinical trials. Table 16.5 gives factors that decrease the risk of cardiac events in high-risk patients undergoing elective surgery.

Consider the following:

- CABS or PCI helps reduce morbidity and mortality in categories 1–5 given in Table 16.3. but does carry its own risks, so individual decisions must be made. There is adequate proof from clinical trials that CABS patients usually undergo noncardiac surgery without significant complications. Coronary balloon angioplasty with stenting may provide similar protection but requires documentation in clinical trials.
- Exercise stress test is of value in selecting patients for coronary angiography with a view to coronary angioplasty or CABS.

Surgical intervention should be delayed in patients with the following:

- Recent acute MI, or unstable angina.
- Presence of clinical HF or HF within the prior 2 months.
- Severe valvular heart disease.

- Significant ventricular arrhythmias particularly if accompanied by syncope or presyncope. Patients who have had CABS in the past 5 years or percutaneous intervention (PCI) from 6 months to 5 years previously and are stable and without ischemia on physical activities can undergo surgery without stress testing. An echocardiogram should suffice to assess EF, abnormal LV wall motion abnormalities and cardiac dimensions.

β-BLOCKERS

The preoperative and perioperative use of a β-blocking agent (and for at least 1 week postoperative) may decrease morbidity and mortality, especially because the ischemic complications largely are mediated by sympathetic stimulation and catecholamines. β-Blockade is known to have a salutary effect and lifesaving potential in patients with CHD where ischemia is provoked by catecholamines.

NITRATES

Nitrates administered 1 hour preoperative and postoperative for 4–5 days, although unproven to decrease postoperative cardiac events, are advisable in patients at high risk. Transdermal nitroglycerin is used continuously for 2 or 3 days. It is then advisable to skip 10–12 hours daily to avoid tolerance.

SILENT ISCHEMIA

- Detection and prevention of silent ischemia is still in its infancy in terms of management. Silent ischemia is observed in the pre-, peri-, and postoperative period in approximately 70 and 84% of cardiac patients undergoing noncardiac surgery. In two reported studies indicating a high incidence of silent ischemia during the second to fourth postoperative days, however, the incidence of cardiac events was low (1–1.4% fatal infarction, 3 and 1.5% nonfatal infarction, 4 and 6.6% HF). Holter monitoring up to 4 days postoperative, as well as being technically difficult for ST segment monitoring, therefore, is not cost-effective.

The following steps may prove rewarding:

- The combination of low-dose aspirin and a β-blocking drug carries the best chance of preventing fatal or nonfatal reinfarction during the postoperative period.
- PCI is advisable preoperatively for patients with unstable coronary syndromes. The American College of Cardiology/American Heart Association guidelines recommend a wait of 4–6 weeks after coronary stenting to perform noncardiac surgery; this allows complete endothelialization and a full course of antiplatelet therapy, clopidogrel and aspirin to be administered. Aspirin (80 mg) or half of a regular aspirin given a few hours preoperative or 12–24 hours postoperative and then 160 mg daily for 2 weeks is advisable in patients at high risk for fatal or nonfatal infarction. As well, the incidence of thromboembolism is moderately reduced by postoperative aspirin therapy in some categories of surgical patients. It is unlikely that a small dose of 80 mg of aspirin given following surgery will significantly increase postoperative bleeding, but this agent must be avoided in ophthalmic surgery with the exception of cataract surgery.
- Because acute MI in the postoperative phase is silent in over 50% of cases, no therapy can be given for unrecognized silent disease. Thus, aspirin plus a β-blocker seems advisable for high-risk patients undergoing surgery.
- If MI is detected postoperatively, thrombolytic agents are contraindicated and PCI should be considered.

BIBLIOGRAPHY

- Baron JF, Mundler O, Bertrand M, et al. Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. *N Engl J Med* 1994;330:663.
- Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA* 2001;285:1865–1873.
- Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary. *J Am Coll Cardiol* 2002;39:542–553.
- Farwell DJ, Freemantle N, Sulke AN. Use of implantable loop recorders in the diagnosis and management of syncope. *Eur Heart J* 2004;25:1257–1263.
- Fleisher LA, Eagle KA, Shaffer T, et al. Perioperative- and long-term mortality rates after major vascular surgery: the relationship to preoperative testing in the medicare population. *Anesth Analg* 1999;89:849–855.
- Froehlich JB, Karavite D, Russman PL, et al. American College of Cardiology/American Heart Association preoperative assessment guidelines reduce resource utilization before aortic surgery. *J Vasc Surg* 2002;36:758–763.
- Hassan SA, Hlatky MA, Boothroyd DB, et al. Outcomes of noncardiac surgery after coronary bypass surgery or coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Med* 2001;110:260–266.
- Kaluza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000;35:1288–1294.
- Mangano DT, Goldman LG. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med* 1995;333:1750.
- Mukherjee D, Eagle KA. Clinician update: Perioperative cardiac assessment for noncardiac surgery eight steps to the best possible outcome. *Circulation* 2003;107:2771.
- O'Neil-Callahan K, Katsimaglis G, Teppe MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery. *J Am Coll Cardiol* 2005;45:336–342.

INDEX

A

- AAA. *See* Abdominal aortic aneurysm
- Abciximab, 44–45, 44f, 63, 64
for AMI, 41
- Abciximab and Carbostent Evaluation, 45
- Abdominal aortic aneurysm (AAA)
noncardiac surgery, 501–502
- Ablation therapy
for atrial fibrillation, 245–246
- Accelerated malignant hypertension, 326–327
- Accelerated malignant hypertension
drug therapy, 328t
- Accupril
daily dosage, 308t
dosages, 318t
for hypertension, 319
- ACE. *See* Angiotensin-converting enzyme
- Acebutolol
for arrhythmias, 276–277
dosage, 309t
- Acetazolamide
for heart failure, 192
- Acetyl salicylic acid
for AMI, 100
- Acute anterolateral infarction, 15f
- Acute coronary syndrome
drug therapy, 328t
- Acute cor pulmonale, 25, 30f
- Acute endocarditis, 420–422
- Acute Infarction Ramipril Efficacy (AIRE), 75
- Acute myocardial infarction, 1–64
ACE inhibitors, 58
activity levels, 47f
angiotensin receptor blockers, 58
balloon flotation right, 47
 β -blockers, 51–53
calcium antagonists, 58–60
clinically relevant pathophysiology, 3–6
clinical trials, 53–55
diagnosis, 7–8
echocardiography, 35–37
electrocardiogram, 9–14
infarction sites, 11–12
infarction size, 12–14
electrocardiogram changes simulating due to
other causes, 29f
emergency management, 40
hemorrhage into plaque, 6
incidence, 1
in-hospital mortality, 39t
lead aVR, 11
myocardial necrosis, 6
nitroglycerin, 57–58
nondiagnostic ECG, 11
PCI
clinical studies, 42–43
vs thrombolysis, 42f
pharmacological agents
selection of, 74t
physical signs, 8
physician interaction, 37–39
plaque rupture, 5–6
plaque vulnerability, 6–7
precordial leads, 34f
prevention, 3
primary angioplasty/stent, 41–45
public education, 37–39
risk stratification, 39
syncope, 485
thrombolytic therapy, 47–53
treatment, 40
vulnerable atheromatous plaques, 5
- Acute pericarditis
electrocardiography, 18–20, 19f
- Adalat Retard, 158
for hypertension, 324
- Adalat XL, 158
for hypertension, 324
- Adenocard
for AVNRT, 225–228
adverse effects, 228
caution, 228
contraindications, 227
dosage, 225–226
indications, 227
interactions, 228
- Adenosine
for antidromic tachyarrhythmias, 254
for arrhythmia, 223
for arrhythmias, 267
for AVNRT, 225–228
adverse effects, 228

- caution, 228
- contraindications, 227
- dosage, 225–226
- indications, 227
- interactions, 228
- for SVT in pregnancy, 230
- vs verapamil
 - for arrhythmia, 224–225, 226t
- Adenosine thallium scintigraphy, 142
- Adizem SR
 - daily dosage, 308t
- Afterload
 - heart failure, 182–183
- Aggrastat, 63–64
- AIRE. *See* Acute Infarction Ramipril Efficacy
- Alcohol-induced septal ablation
 - for hypertrophic cardiomyopathy, 459
- Alcohol intake reduction
 - for hypertension, 302
- Aldactone
 - for dilated cardiomyopathy, 464
 - for heart failure, 193
- Aldomet
 - dosage, 309t
 - for hypertension, 326, 501
 - for hypertension in pregnancy, 332, 334
- ALLHAT. *See* Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
- α -blockers
 - adverse effects, 311t
 - for hypertension, 307t, 324–326
- Altace
 - for AMI, 103
 - daily dosage, 308t
 - dosages, 318t
 - for heart failure, 196
 - postinfarction, 73, 75
 - for heart failure postinfarction, 73, 75
 - for hypertension, 319
- American β -Blocker Heart Attack Trial, 54, 91, 150, 310
- Amias
 - for AMI, 103
 - daily dosage, 308t
 - for heart failure, 189, 197
 - for hypertension, 320–321
- Amiloride
 - for arrhythmias, 277
 - for renovascular hypertension, 338
- Amiodarone
 - action, 278
 - for arrhythmias, 267, 277, 278–283
 - for atrial fibrillation, 85, 243
 - for cardiac arrest, 297
 - contraindications, 280
 - for dilated cardiomyopathy, 466
 - dosage, 265t, 278
 - drug interactions, 282t
 - for hypertrophic cardiomyopathy, 456–458
 - indications, 279–280
 - outside the United States, 280
 - interactions, 280
 - for late ventricular arrhythmias, 83
 - for orthodromic tachyarrhythmias, 253
 - for paroxysmal atrial tachycardia with block, 232
 - pharmacokinetics, 278–279
 - safety of, 219
 - for ventricular aneurysm, 94–95
 - for ventricular arrhythmias, 264t
- Amlodipine
 - for angina, 147
 - daily dosage, 308t
 - for hypertension, 304, 323
 - clinical effects, 322t
- Amoxicillin
 - for acute endocarditis, 421
 - for bacterial endocarditis prophylaxis, 424
 - for endocarditis, 420
- Ampicillin/sulbactam
 - for acute endocarditis, 421
 - for native valve endocarditis, 420
- Angilol
 - for AMI, 41t
 - for angina, 150, 151, 153
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for cardiac arrest, 295t
 - dosage, 309t
 - for hypertensive crises, 333
 - for hypertrophic cardiomyopathy, 455
 - pharmacologic features, 313t
 - for SVT in pregnancy, 230
 - for unstable angina, 160, 160t
- Angina, 127–171
 - calcium antagonists, 156–159
 - with β -blockers, 157
 - classification, 127–129
 - coronary artery bypass surgery, 170–171
 - echocardiography, 143–144
 - electrocardiogram, 140–141
 - electron beam tomography, 144–146
 - nitrates, 153–157
 - radionuclide myocardial perfusion imaging, 141–143
 - risk stratification, 162–163
 - treatment, 146–165
 - decision making, 149f
- Angiopeptin
 - stents, 169
- Angioplasty
 - for renovascular hypertension, 338
- Angiotensin-converting enzyme (ACE)
 - inhibition renal scintigraphy
 - for renovascular hypertension, 338

- Angiotensin-converting enzyme (ACE) inhibitors. *See also* specific types
adverse effects, 311t
for AMI, 102–103
for aortic regurgitation, 394–395
contraindications, 76
daily dosage, 308t
for dilated cardiomyopathy, 464
dosages, 318t
for heart failure postinfarction, 73–76
for hypertension, 307t, 316–321
advantages, 317
adverse effects, 319
contraindications, 319
disadvantages, 317
indications, 317
interactions, 319
NG monomethyl-L-arginine, 125
- Angiotensin receptor blockers (ARBs). *See also* specific types
daily dosage, 308t
for hypertension, 316–321
- Anisoylated Plasminogen Streptokinase Activator Complex (APSAC)
Multicenter Trial Group
cardiogenic shock, 114, 115
- Anistreplase
dosage, 48t
- Anterior infarction, 25f
- Anterolateral infarction, 24f
- Antiarrhythmic agents, 267–283
class IA, 267–272
class IC, 274–275
classification, 267
class II, 276–277
class III, 277–283
dosage, 265t
drug action, 271f
electrophysiologic agents, 269t
proarrhythmic effects of, 217–219
selection of, 217t
- Antibiotics
for hypertrophic cardiomyopathy, 458
- Anticoagulants
for atrial fibrillation, 243–244, 400–401
for atrial flutter, 236
for hypertrophic cardiomyopathy, 458
prosthetic valves, 388
- Antidromic circus movement tachycardia, 248–249
- Antidromic tachyarrhythmias
treatment, 254
- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 304, 315, 325
- Antihypertensive drugs
adverse effects, 311t
daily dosage, 308t
- Antiplatelet agents
for acute coronary syndrome, 61–64
- Aorta
atherosclerotic plaque predilection, 135
- Aortic arch syndrome, 484
- Aortic dissection, 369–373
diagnosis, 370–371
drug therapy, 328t
etiology, 370
imaging, 371
medical therapy, 371–372
surgery, 372–373
- Aortic prosthetic heart valve
noncardiac surgery, 502–503
- Aortic regurgitation, 389–397
diagnosis, 390
etiology, 390t
physical signs, 390–392
treatment, 392–397
valve replacement, 395–396
- Aortic stenosis, 375–389
etiology, 376t
hemodynamic parameters, 378t
natural history, 379–385
noncardiac surgery, 502
physical signs, 376
surgery, 381–385, 382t
survival, 377t
syncope, 485
therapy, 378
- Apo A-I Milano
for dyslipidemias, 365
- Apresoline
for hypertension, 325–326
in pregnancy, 332, 334
for hypertensive crises, 332, 333–334
for secondary hypertension, 336–337
- Aprinox
for hypertension, 315
- Aprovel
daily dosage, 308t
for heart failure, 197
- APSAC. *See* Anisoylated Plasminogen Streptokinase Activator Complex
- Arrhythmias, 81–86, 213–283
diagnostic guidelines, 213
early life-threatening, 45–47
etiology, 217t
management guidelines, 213–219
mechanism of, 217
mitral valve prolapse, 408
precipitating factors, 215–216
treatment, 221–230
- Arteries
atherosclerotic plaque predilection, 135
- Arthritis
rheumatic fever
treatment, 412

- Aspirin
 - for AMI, 40, 100
 - for early morning MI, 101t
 - for embolism prevention, 96
 - given within 24 hours of MI onset, 40t
 - MI, 3
 - for pericarditis, 97
- Assessment of Safety and Efficacy of Thrombolytic Regimen (ASSENT) 2, 49
- Assessment of Treatment With Lisinopril and Survival (ATLAS) trial, 195
- Asystole, 297
- Atacand
 - for AMI, 103
 - daily dosage, 308t
 - for heart failure, 189, 197
 - for hypertension, 320–321
- Atenolol
 - for angina, 150, 151, 152
 - for aortic dissection, 372
 - for arrhythmias, 276–277
 - dosage, 309t
 - for hypertensive crises, 333
 - for neurally mediated syncope, 481
 - pharmacologic features, 312t
 - for secondary hypertension, 336
 - for unexplained syncope, 488
 - for unstable angina, 160t
- Atherosclerotic plaque, 129–136
 - angiogenesis, 136
 - coronary arteries, 135–136
 - historical, 129–130
 - pathogenesis, 131f
 - response to injury hypothesis, 130–132
 - type III injury, 134–135
 - type II injury, 133–134
 - type I injury, 132–133
 - vessels predilection, 135
- ATLAS. *See* Assessment of Treatment With Lisinopril and Survival (ATLAS) trial
- Atorvastatin
 - for AMI, 40
 - for angina, 146
 - for dyslipidemias, 357–358
- Atrial fibrillation, 31f, 236–245, 237t, 239f, 240f, 400
 - in AMI, 84–85
 - diagnosis, 236–237
 - thromboembolism prevention, 244f
 - treatment, 241f
- Atrial flutter, 233–234, 234f, 235f
- Atrial tachycardia, 231
- Atrioventricular block
 - syncope, 486
- Atrioventricular nodal reentrant tachycardia (AVNRT), 219–220, 222f, 223f
 - chronic management, 230–236
 - treatment, 224f
- Atropine
 - for cardiac arrest, 295t
- Automatic defibrillator
 - for hypertrophic cardiomyopathy, 459
- Avapro
 - daily dosage, 308t
 - for heart failure, 197
- AVNRT. *See* Atrioventricular nodal reentrant tachycardia
- Azimilide
 - for arrhythmias, 283
- B**
- Bacterial endocarditis prophylaxis, 424–426
- Bacteroides
 - endocarditis, 422t
- Basel Antiarrhythmic Study of Infarct Survival, 279
- Baypress
 - dosage, 309t
 - for hypertension, 324
- Bedrest
 - for AMI, 46
 - for heart failure, 184
- Bedside commode
 - for AMI, 46
- Benazepril
 - daily dosage, 308t
 - dosages, 318t
 - for hypertension, 319
- Bendrofluzide
 - for hypertension, 315
- Bendroflumethiazide
 - dosage, 309t
- Benzthiazide
 - dosage, 309t
- Berkolol
 - for AMI, 41t
 - for angina, 150, 151, 153
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for cardiac arrest, 295t
 - dosage, 309t
 - for hypertensive crises, 333
 - for hypertrophic cardiomyopathy, 455
 - pharmacologic features, 313t
 - for SVT in pregnancy, 230
 - for unstable angina, 160, 160t
- Berkozide
 - for hypertension, 315
- β -adrenergic blockade, 4f
 - for aortic dissection, 372

- for arrhythmias, 267
- for dilated cardiomyopathy, 465
- for hypertrophic cardiomyopathy, 454–455
- for stable angina, 138
- for unexplained syncope, 488
- β-Blocker Heart Attack Trial (BHAT), 54, 91, 150, 310
- β-blockers
 - adverse effects, 56–57, 311t
 - for AMI, 40, 41t, 97–98
 - clinical trials, 97–98, 98t
 - for angina, 148–153, 148t
 - dosage, 150
 - selection of, 150–152
 - for arrhythmias, 46, 276–277
 - for atrial fibrillation, 400
 - classification of, 313t
 - dosage, 308–310, 309t
 - for hypertension, 306–311, 307t, 501
 - advantages, 310
 - contraindications, 311
 - disadvantages, 310–311
 - in pregnancy, 332
 - selection, 311–327
 - for hypertensive crisis, 341
 - for myocardial infarction
 - noncardiac surgery, 505
 - for orthodromic tachyarrhythmias, 253
 - pharmacologic features, 312t
 - potassium balance, 56
 - for renovascular hypertension, 338
 - safety of, 219
 - for secondary hypertension, 336
 - selection, 55–57
 - sudden cardiac death changes, 52f
 - for ventricular arrhythmias, 264t
 - with WPW, 252
- Betaloc, 55
 - for AMI, 41t
 - for angina, 151, 152
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for atrial fibrillation, 85
 - for cardiac arrest, 295t
 - for dilated cardiomyopathy, 465
 - dosage, 309t
 - for heart failure, 189, 198
 - for hypertension, 314
 - for hypertensive emergencies, 328t
 - for neurally mediated syncope, 481
 - for paroxysmal atrial tachycardia with block, 232
 - pharmacologic features, 312t
 - for secondary dyslipidemias, 346
 - for SVT in pregnancy, 230
 - for unexplained syncope, 488
 - for unstable angina, 160
- Betapace, 52
 - for arrhythmias, 277, 282–283
 - for atrial fibrillation, 243
 - for AVNRT, 230
 - dosage, 265t
 - for hypertrophic cardiomyopathy, 455–456
 - pharmacologic features, 313t
 - for secondary hypertension, 336
- Bethanidine
 - for arrhythmias, 277
- Betim
 - for angina, 150, 151, 153
 - dosage, 309t
 - pharmacologic features, 313t
 - for unexplained syncope, 488
- Bezafibrate
 - for dyslipidemias, 363
- BHAT. *See* β-Blocker Heart Attack Trial
- Bike riding
 - following AMI, 104
- Bile acid binding resins
 - for dyslipidemia, 361
- Bisoprolol, 55, 56
 - for angina, 150, 151
 - dosage, 309t
 - for hypertension, 314
 - pharmacologic features, 312t
- Bjork-Shiley spherical disc valve, 385
- Black patients
 - hypertension, 305, 306f
- Blocadren
 - for angina, 150, 151, 153
 - dosage, 309t
 - pharmacologic features, 313t
 - for unexplained syncope, 488
- BNP. *See* B-type natriuretic peptide
- Bradyarrhythmias, 85, 254, 297
- BRAVE, 44–45
- Bretylum
 - for arrhythmias, 277
- Brugada syndrome, 20–21, 267, 268f
 - mimic MI, 23f
- B-type natriuretic peptide (BNP)
 - heart failure, 178
- Bumetanide
 - dosage, 309t
 - for heart failure, 191
 - for secondary hypertension, 336
- Bundle branch block tachycardias, 260f
- C**
- CAD. *See* Coronary artery disease
- Cadura
 - for hypertension, 304, 325

- Calan
adverse effects, 166, 311t
for AMI, 101
for angina, 147, 156, 157, 158–159
for arrhythmia, 222, 223
for atrial flutter, 234
for AVNRT, 228–229, 230
dosage, 309t
drug interactions, 157
for hypertension, 324
clinical effects, 322t
drug interactions, 324t
for hypertrophic cardiomyopathy, 456
for paroxysmal atrial tachycardia with block, 232
for unstable angina, 161
with WPW, 252
- Calcium antagonists. *See also* specific types
advantages, 157
for AMI, 100–102
for angina, 148t
contraindications, 157
daily dosage, 308t
disadvantages, 157
for hypertension, 307t, 321–324, 501
advantages, 321–323
adverse effects, 323
clinical effects, 322t
contraindications, 323
drug interactions, 324t
for hypertrophic cardiomyopathy, 456
interactions, 157
for secondary hypertension, 336
for unstable angina, 160–162
- Calcium chloride
for cardiac arrest, 295t, 296
- Canadian Coronary Atherosclerosis Intervention Trial, 358
- Candesartan
for AMI, 103
daily dosage, 308t
for heart failure, 189, 197
for hypertension, 320–321
- Candesartan in Heart Failure (CHARM), 189, 320–322
alternative trial, 75
- Capoten, 58
for AMI, 59–60
daily dosage, 308ta
for dilated cardiomyopathy, 464
dosages, 318t
for heart failure, 188, 195
for heart failure postinfarction, 73, 75
for hypertension, 319
- CAPRICORN. *See* Carvedilol Postinfarction Survival Control in LV Dysfunction
- Captopril, 58
for AMI, 59–60
daily dosage, 308t
for dilated cardiomyopathy, 464
dosages, 318t
for heart failure, 188, 195
for heart failure postinfarction, 73, 75
for hypertension, 319
- Carace
dosages, 318t
for heart failure, 195
for hypertension, 304, 319
- Carbomedics bileaflet valve, 383f
- Cardiac arrest, 289–297
defined, 289–290
drug therapy, 294–297, 295t
etiology, 289–292
- Cardiac Arrhythmic Suppression Trial (CAST), 218
- Cardiac deaths, 357t
- Cardiac Insufficiency Bisoprolol Study II, 151
- Cardiac pacing, 86–88
- Cardiac pain
location, 139f
- Cardiac tamponade, 431f, 433–436
catheterization, 439t
chest x-ray, 435
diagnosis, 433–434
echocardiography, 435
electrocardiography, 435
investigations, 438
treatment, 435–436, 439
- Cardiac transplantation
for dilated cardiomyopathy, 466
- Cardiogenic shock, 109–125
cardiac medications worsening, 114t
clinical features, 114–115
definitive therapy, 122–123
etiology, 110–111
incidence, 111–114, 112t
initial reperfusion therapy, 124f
pathophysiology, 109, 111f
supportive therapy, 116–117
treatment guidelines, 113f, 115–116
- Cardiomyopathy, 443–470
- Cardiopulmonary resuscitation, 292–293
ABCs of, 291f
technique, 292–293
- Cardizem
adverse effects, 311t
for AMI, 58–59, 101, 102t
for angina, 157, 158
for atrial fibrillation, 238
for atrial flutter, 234
daily dosage, 308t
drug interactions, 157
for hypertension, 323
adverse effects, 323

- clinical effects, 322t
- drug interactions, 324t
- for secondary hypertension, 336
- for unstable angina, 161
- with WPW, 252
- Cardizem CD
 - for angina, 147
 - daily dosage, 308t
- Carotid sinus massage
 - for arrhythmias, 220–221
- Carotid sinus syncope, 486–487
- Carvedilol, 55, 56
 - for AMI, 41t
 - for angina, 150, 151, 152
 - for dilated cardiomyopathy, 465
 - dosage, 309t
 - for heart failure, 188, 198
 - for hypertension, 313–314
 - pharmacologic features, 312t
- Carvedilol Postinfarction Survival Control in LV Dysfunction (CAPRICORN), 54–55, 150, 310
- Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), 55, 150, 188, 310
- CAST. *See* Cardiac Arrhythmic Suppression Trial
- Catapres
 - dosage, 309t
 - for hypertension, 326, 501
- Catecholamine crisis
 - drug therapy, 328t
- Catecholamine surge
 - acute myocardial infarction, 7
- Catheter ablation
 - for antidromic tachyarrhythmias, 254
 - for atrial flutter, 236
 - for AVRNT, 231
- Cedocard
 - for angina, 156
 - for heart failure, 188
- Ceftriaxone
 - for endocarditis, 422
- Centrally acting agents
 - for hypertension, 326
 - for secondary hypertension, 337
- Centyl
 - for hypertension, 315
- Cerebrovascular disease, 484
- Chagas' disease, 468
 - electrocardiography, 31
- Chagasic myocarditis, 25
- CHARM. *See* Candesartan in Heart Failure
- Chest pain
 - acute myocardial infarction, 7–8
- Chest x-ray
 - aortic regurgitation, 391–392
 - aortic stenosis, 377
 - mitral stenosis, 398–399
- Chlamydia
 - endocarditis, 422t
- Chlamydia pneumoniae*, 134
- Chlorothiazide
 - dosage, 309t
- Chlorthalidone
 - dosage, 309t
- Cholesterol-lowering agents, 103
- Cholestyramine
 - for dyslipidemia, 361
- Chronic atrial fibrillation, 243–244
- CIBIS II, 56
- Cigarette smoking
 - with angina, 151
 - propranolol, 56
- Cilazapril
 - daily dosage, 308t
 - for heart failure, 196
 - for hypertension, 319
- Circus movement tachycardia, 250f, 251f
- CK-MB. *See* Creatine kinase MB
- Clindamycin
 - for bacterial endocarditis prophylaxis, 424
- Clonidine
 - dosage, 309t
 - for hypertension, 326, 501
- Clopidogrel, 64
 - for acute coronary syndrome, 61–62
 - for angina, 163
- Clopidogrel in Unstable Angina Recurrent Events (CURE), 62
- Cloxacillin
 - for acute endocarditis, 421
 - for endocarditis, 420
- Cluster headaches, 166
- Coarctation of the aorta
 - hypertension, 341–342
- Colchicine
 - for recurrent pericarditis, 432
- Colestid
 - for dyslipidemia, 361
- Colestipol
 - for dyslipidemia, 361
- Collapsing bounding pulse
 - etiology, 391t
- Computed tomography (CT)
 - for renovascular hypertension, 338
- Congenital aortic valvular stenosis, 389
- CONSENSUS. *See* Cooperative North Scandinavian Enalapril Survival Study
- Constrictive pericarditis, 436–439
 - diagnosis, 436–437
 - differential diagnosis, 437–438
 - vs reactive cardiomyopathy, 437t
- Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), 186, 187

- COPERNICUS. *See* Carvedilol Prospective Randomized Cumulative Survival
- Cordarone
 action, 278
 for arrhythmias, 277, 278–283
 for atrial fibrillation, 85, 243
 for cardiac arrest, 297
 for dilated cardiomyopathy, 466
 dosage, 265t, 278
 drug interactions, 282t
 for hypertrophic cardiomyopathy, 456–458
 indications, 279–280
 outside the United States, 280
 interactions, 280
 for late ventricular arrhythmias, 83
 for orthodromic tachyarrhythmias, 253
 for paroxysmal atrial tachycardia with block, 232
 pharmacokinetics, 278–279
 safety of, 219
 for ventricular aneurysm, 94–95
 for ventricular arrhythmias, 264t
- Cordilox
 adverse effects, 166, 311t
 for AMI, 101
 for angina, 147, 156
 for arrhythmia, 222
 for atrial flutter, 234
 for AVNRT, 228–229, 230
 dosage, 309t
 drug interactions, 157
 for hypertension
 clinical effects, 322t
 drug interactions, 324t
 for hypertrophic cardiomyopathy, 456
 for paroxysmal atrial tachycardia with block, 232
 for unstable angina, 161
 with WPW, 252
- Coreg, 55, 56
 for AMI, 41t
 for angina, 150, 151, 152
 for dilated cardiomyopathy, 465
 dosage, 309t
 for heart failure, 188, 198
 for hypertension, 313–314
 pharmacologic features, 312t
- Corgard
 for angina, 153
 for arrhythmias, 276–277
 dosage, 309t
 for secondary hypertension, 336
- Coronary angiography
 angina, 146
- Coronary artery bypass surgery
 indications for, 171
- Coronary artery disease (CAD)
 mortality, 2–3
- Coronary artery spasm, 4–5
- Coronary artery staging and prognosis, 138, 165–166
- Coronary balloon angioplasty
 angiographically acceptable lesions, 167t
 complications, 168t
 outcome, 168t
- Coronary disease
 LDL cholesterol, 350t
- Coronary heart disease
 incidence, 2
- Coronex
 for angina, 156
 for heart failure, 188
- Cor pulmonale, 28
- noncardiac surgery, 504
- Corticosteroids
 for pericarditis, 431–432, 433
- Corvert
 for antidromic tachyarrhythmias, 254
 for atrial fibrillation, 240
 for atrial flutter, 235
- Coversyl
 daily dosage, 308t
 dosages, 318t
 for hypertension, 319
- Coxiella burnetti*
 endocarditis, 422t
- Cozaar
 daily dosage, 308t
 for heart failure, 197
 for hypertension, 321
- C-reactive protein (CRP) levels
 unstable angina, 134, 140
- Creatine kinase MB (CK-MB), 9
- CREDO, 62–63
- Crestor
 for angina, 146
 for dyslipidemias, 360
- CRP. *See* C-reactive protein levels
- CT. *See* Computed tomography
- CURE. *See* Clopidogrel in Unstable Angina Recurrent Events
- ## D
- DANAMI-2, 43
- Daptomycin
 for acute endocarditis, 421
- DCM. *See* Dilated cardiomyopathy
- Deep venous thromboembolism
 after AMI, 95t
- Descending aorta
 dissection, 373
- Dexamethasone
 for pericarditis, 431
- Diabetes
 LDL cholesterol, 350t

- Diamox
 - for heart failure, 192
- Diastolic dysfunction
 - heart failure, 181–182
- Diazoxide
 - for hypertensive emergencies, 331
- Dibenzylamine
 - for hypertensive crisis, 340
- Diet
 - for AMI, 46
- Digoxin
 - for aortic regurgitation, 395
 - for arrhythmias, 222, 230
 - for atrial fibrillation, 84, 237–238, 400
 - for atrial flutter, 234
 - for AVNRT, 230
 - for dilated cardiomyopathy, 463
 - drug interactions, 157
 - for heart failure, 188, 500
 - for hypertrophic cardiomyopathy, 458
 - for postinfarction care, 76–77
 - for SVT in pregnancy, 230
 - with WPW, 252
- Dihydropyridine calcium antagonists
 - for angina, 157
 - contraindicated in stable angina, 138
- Diltiazem
 - adverse effects, 311t
 - for AMI, 58–59, 101, 102t
 - for angina, 157, 158
 - for atrial fibrillation, 85, 238
 - for atrial flutter, 234
 - daily dosage, 308t
 - drug interactions, 157
 - for hypertension, 323
 - adverse effects, 323
 - clinical effects, 322t
 - drug interactions, 324t
 - for secondary hypertension, 336
 - for unstable angina, 161
 - with WPW, 252
- Dilated cardiomyopathy (DCM), 460–466
 - arrhythmias, 466
 - chest x-ray, 461
 - clinical hallmarks, 460–461
 - echocardiography, 461, 462f
 - electrocardiogram, 461
 - endomyocardial biopsy, 462
 - Holter monitoring, 462–463
 - treatment, 463–464
- Diovan, 58
 - for AMI, 103
 - daily dosage, 308t
 - for heart failure, 197
 - for hypertension, 321
- Dipyridamole scintigraphy, 142
- Direma
 - dosage, 309t
 - for hypertension, 315
- Disopyramide
 - for arrhythmias, 268–269
 - dosage, 265t
 - for hypertrophic cardiomyopathy, 458
 - for unexplained syncope, 488
 - for ventricular arrhythmias, 264t
- Diuretics
 - for dilated cardiomyopathy, 463
 - dosage, 309t
 - for hypertension, 307t, 314–316
 - adverse effects, 315
 - interactions, 315
- Dizziness
 - evaluation, 477f
- Dobutamine
 - for cardiogenic shock, 117
 - infusion pump chart, 119t, 120t
 - pharmacologic effects, 118t
 - for postinfarction care, 78
 - for right ventricular infarction, 80
- Docusate
 - for AMI, 46
- Dopamine
 - for cardiogenic shock, 117–120
- Doxazosin
 - for hypertension, 304, 325
- Dual-chamber pacing
 - for hypertrophic cardiomyopathy, 459–460
- Dyazide
 - for hypertension, 316
- Dyslipidemias, 345–366
 - diagnostic blood levels, 347–348
 - dietary management, 351–356
 - drug therapy, 356–366
 - new drugs, 364–366
- E**
- Early morning sudden cardiac death
 - β -blockers for, 99t
- Early repolarization pattern, 15
- Echinococcal cyst
 - mimic old MI, 32
- Echocardiography
 - aortic regurgitation, 392
 - aortic stenosis, 377–378
 - mitral stenosis, 399
- Eclampsia
 - drug therapy, 328t
- Ehlers-Danlos syndrome, 370
- Electrocardiogram
 - aortic regurgitation, 391
 - aortic stenosis, 377
- Eminase
 - dosage, 48t
- Emory Angioplasty vs Surgery Trial, 171

- Enalapril
 - daily dosage, 308t
 - for dilated cardiomyopathy, 464–465
 - dosages, 318t
 - for heart failure, 188, 195
 - for hypertension, 319
- Enalaprilat
 - for hypertensive emergencies, 328t
- Endocarditis
 - mitral valve prolapse, 409
 - organisms causing, 422t
 - surgery
 - indications, 423–424
- Endomyocardial fibrosis
 - echocardiography, 469f
- Enterobacter
 - endocarditis, 422t
- Enterococci*
 - infective carditis, 418
- Enterococcus fecalis*
 - acute endocarditis, 421
- EPHESUS. *See* Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
- Epinephrine
 - for cardiac arrest, 294–296, 295t
 - pharmacologic effects, 118t
- Eplerenone
 - for dilated cardiomyopathy, 464
 - for heart failure, 188, 193
 - for hypertension, 316
- Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 188
- Eprosartan
 - daily dosage, 308t
 - for heart failure, 197
- Eptifibatide, 63
- Erythromycin
 - for bacterial endocarditis prophylaxis, 424
- Escherichia coli*
 - endocarditis, 422t
 - infective carditis, 419
- Esidrex
 - dosage, 309t
 - for hypertension, 315
- Esmolol
 - for AMI, 41t
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for atrial fibrillation, 84, 240–243
 - for unexplained syncope, 488
 - for unstable angina, 160t
- Essential hypertension, 301
- Eucardic, 55, 56
 - for AMI, 41t
 - for angina, 150, 151, 152
 - for dilated cardiomyopathy, 465
 - dosage, 309t
 - for heart failure, 188, 198
 - for hypertension, 313–314
 - pharmacologic features, 312t
- European Infarction Study, 52
- Everolimus
 - stents, 169
- Exercise
 - following AMI, 104
 - contraindications to, 105t
- Exercise stress test
 - angina, 140–141
- Ezetimibe
 - for dyslipidemias, 364–365
- Ezetrol
 - for dyslipidemias, 364–365
- F**
- Fasting
 - angina, 140
- Felodipine
 - dosage, 309t
 - for hypertension, 324
- Fenofibrate
 - for dyslipidemia, 362–363
- Fenoldopam
 - for hypertensive emergencies, 328t, 330
- Fibrates
 - for dyslipidemia, 361–364
- Fibrin, 3
- Fibrinolysis
 - for AMI, 41t
- Flecainide
 - for antidromic tachyarrhythmias, 254
 - for arrhythmias, 267, 274–275
 - for atrial flutter, 235
 - for AVNRT, 230
 - dosage, 265t
 - for ventricular arrhythmias, 264t
- Flucloxacillin
 - for acute endocarditis, 421
 - for endocarditis, 420
- Fluvastatin
 - for dyslipidemias, 360
- Foods
 - cholesterol content, 353t–355t
 - saturated fat content, 353t–355t
 - sodium content, 303t
- Fosinopril
 - daily dosage, 308t
 - dosages, 318t
 - for hypertension, 319
- 4S. *See* Scandinavian Simvastatin Survival Study
- Fungi
 - endocarditis, 422t

- Furosemide
for dilated cardiomyopathy, 463
dosage, 309t
for heart failure, 190
for heart failure postinfarction, 72
for renovascular hypertension, 338
for secondary hypertension, 336
- Fusobacterium
endocarditis, 422t
- G**
- Gated cardiac scan, 143
- Gemfibrozil
for dyslipidemia, 362
- Gentamicin
for acute endocarditis, 421
for native valve endocarditis, 420
for prosthetic valve endocarditis, 423
- Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO), 48–49
cardiogenic shock, 114, 115
- Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-IV, 64
- Gonococcus*
endocarditis, 422t
infective carditis, 418
- Gruppo Italiano per lo Studio della Strepto Survival trial, 38, 59–60
- Guanabenz
dosage, 309t
for hypertension, 326
- Guanfacine
dosage, 309t
for hypertension, 326, 501
- GUSTO. *See* Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
- H**
- HCM. *See* Hypertrophic cardiomyopathy
- Heart attack
psychosocial impact of, 103–104
- Heart catheter
for AMI, 47
- Heart failure, 175–198
ACE inhibitors, 193–198, 194t
angiotensin receptor blockers, 197
ARBS, 193–198
 β -blockers, 197–198
chest x-rays, 177–178
compensatory adjustments, 183–184
diagnosis, 176–181
diuretics, 189–193
echocardiogram, 179
electrocardiogram, 179
medications
 selection of, 185–187
noncardiac surgery, 499–500
nonspecific therapy, 184–185
pathophysiology, 176f, 181–184
physical signs, 177
postinfarction, 71–79
 pathophysiology, 71–72
 treatment, 72–73
precipitating factors, 181
randomized clinical trials, 187–189
renal response to, 184
symptoms, 176–177
underlying causes, 180
- Heart muscle diseases, 468–470
etiology, 470t
- Helicobacter pylori*, 134
- Helsinki Heart Study, 362
- Hemochromatosis
mimic old MI, 32
- Hemoglobin
angina, 140
- Heparin, 51
with aspirin
 for unstable angina, 162
- HIV. *See* Human immunodeficiency virus
- Holter monitor
angina, 146
- Human immunodeficiency virus (HIV)
heart disease, 470
- Hydralazine
for hypertension, 325–326
 in pregnancy, 332, 334
for hypertensive crises, 332, 333–334
for secondary hypertension, 336–337
- Hydrochlorothiazide
dosage, 309t
for hypertension, 315
- Hydro-diuril
dosage, 309t
for hypertension, 315
- Hydrodynamic stress
acute myocardial infarction, 7
- Hydroflumethiazide
dosage, 309t
- Hydrosaluric
dosage, 309t
for hypertension, 315
- 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors
for dyslipidemias, 357–358

- Hyperkalemia, 28f
- Hypertension, 299–342
 - diagnosis, 300–301
 - drug therapy, 304–311, 327–332
 - initial monotherapy, 305–306, 307t
 - noncardiac surgery, 500–501
 - nondrug therapy, 301–302
 - in pregnancy, 332–335
 - primary essential, 301
- Hypertensive crisis, 327
 - drug therapy, 328t
 - in pregnancy, 334
 - treatment, 339–341
- Hypertrophic cardiomyopathy (HCM), 25, 30f, 443–444
 - apical, 460
 - chest x-ray, 451
 - clinical hallmarks, 446–451, 449t
 - echocardiography, 446f, 448f, 451, 453f, 454t
 - electrocardiography, 31, 451
 - endocarditis, 451
 - Holter monitoring, 451
 - noncardiac surgery, 503
 - pathophysiology, 445
 - physical signs, 446–449
 - simulating inferolateral infarction, 452f
 - sudden death, 449–450
 - symptoms, 446
 - syncope, 485
 - treatment, 451–460, 455t
- Hypotension
 - noncardiac surgery, 500–501
- Hytrin
 - for hypertension, 325
- Hyzaar
 - for hypertension, 321
- I**
- IABP. *See* Intraaortic balloon pump
- Ibopramine
 - pharmacologic effects, 118t
- Ibutilide
 - for antidromic tachyarrhythmias, 254
 - for atrial fibrillation, 240
 - for atrial flutter, 235
- Iliac vessels
 - atherosclerotic plaque predilection, 135
- Impotence, 104
- Impress Study, 170
- Incessant atrial tachycardia, 231
- Indapamide
 - dosage, 309t
 - for hypertension, 316
- Inderal
 - for AMI, 41t
 - for angina, 150, 151, 153
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for cardiac arrest, 295t
 - dosage, 309t
 - for hypertensive crises, 333
 - for hypertrophic cardiomyopathy, 455
 - pharmacologic features, 313t
 - for SVT in pregnancy, 230
 - for unstable angina, 160, 160t
- Inderal
 - dosage, 309t
- Infective endocarditis, 415–426
 - bacteria causing, 418–419
 - blood cultures, 418
 - classification, 416–417
 - diagnosis, 415–419
 - echocardiography, 419
 - endocarditis complications, 417–418
 - physical signs, 417
 - predisposing factors, 416
 - treatment, 419–424
 - underlying disease, 417
- Inferior infarction, 17f
- Inferior wall MI, 87–88
- Inhibace
 - daily dosage, 308t
 - for heart failure, 196
 - for hypertension, 319
- Innovace
 - for dilated cardiomyopathy, 464–465
 - dosages, 318t
 - for heart failure, 188, 195
 - for hypertension, 319
- Inotrope
 - for cardiogenic shock, 117
- Inspira
 - for dilated cardiomyopathy, 464
 - for heart failure, 188, 193
 - for hypertension, 316
- Integrilin, 63
- Intercourse
 - return to, 104
- International Study of Infarct Survival, 114
- Intraaortic balloon pump (IABP), 117, 121
 - for cardiogenic shock, 122–123
 - contraindications, 80t
 - indications, 80t
 - and nitroprusside, 116
- Intubation
 - for postinfarction care, 77
- Irbesartan
 - daily dosage, 308t
 - for heart failure, 197
- Ischemic heart disease
 - noncardiac surgery, 498–499
- ISIS. *See* Italiano per lo Studio della Strepto Survival (ISIS-2) trial
- Iso-Bid

- for angina, 156
- for heart failure, 188
- Isolated systolic hypertension
 - drug treatment, 305t
- Isoptin
 - adverse effects, 166, 311t
 - for AMI, 101
 - for angina, 147, 156, 157, 158–159
 - for arrhythmia, 222, 223
 - for atrial flutter, 234
 - for AVNRT, 228–229, 230
 - dosage, 309t
 - drug interactions, 157
 - for hypertension, 324
 - clinical effects, 322t
 - drug interactions, 324t
 - for hypertrophic cardiomyopathy, 456
 - for paroxysmal atrial tachycardia with block, 232
 - for unstable angina, 161
 - with WPW, 252
- Isordil
 - for angina, 156
 - for heart failure, 188
- Isosorbide dinitrate
 - for angina, 156
 - for heart failure, 188
- Isosorbide mononitrate
 - for angina, 156
- Italiano per lo Studio della Strepto Survival (ISIS-2) trial, 38
- Italiano per lo Studio della Strepto Survival (ISIS-4) trial, 59–60
- J**
- Jogging
 - following AMI, 105
- K**
- Kabikinase, 50–51
 - dosage, 48t
 - for embolism prevention, 96
 - given within 24 hours of MI onset, 40t
 - for prosthetic valve obstruction, 387
- Klebsiella pneumoniae*
 - endocarditis, 422t
- L**
- Labetalol
 - adverse effects, 311t
 - dosage, 309t
 - for hypertension in pregnancy, 334–335
 - for hypertensive crises, 333
 - for hypertensive emergencies, 328t, 331
 - pharmacologic features, 313t
- Late ventricular arrhythmias, 83
- LBBC. *See* Left bundle branch block
- LDL-C. *See* Low density lipoprotein cholesterol
- Left bundle branch block (LBBB), 24
 - with AMI, 36f
 - with MI, 34f
 - new diagnostic clues, 33–35
 - old MI mimics, 27
 - precordial leads, 35f
- Left main coronary artery (LMCA), 12f
- Left-sided native valve endocarditis
 - risk stratification, 423
- Left ventricular dysfunction, 213–219
- Left ventricular failure (LVF)
 - with acute pulmonary edema
 - drug therapy, 328t
- Left ventricular hypertrophy (LVH), 24
 - old MI mimics, 27
- Left ventricular tachycardia, 216, 258f
- Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), 59
- Lescol
 - for dyslipidemias, 360
- Levatol
 - dosage, 309t
 - pharmacologic features, 313t
- Lidocaine
 - for arrhythmias, 267
 - for cardiac arrest, 295t, 296
 - dosage, 49t
 - toxicity, 49t
 - for ventricular tachycardia, 45
 - with WPW, 252
- Lignocaine
 - for arrhythmias, 267
 - for cardiac arrest, 295t, 296
 - dosage, 49t
 - toxicity, 49t
 - for ventricular tachycardia, 45
 - with WPW, 252
- LIMIT-2. *See* Leicester Intravenous Magnesium Intervention Trial
- Lipids
 - stable angina, 139–140
- Lipitor
 - for AMI, 40
 - for angina, 146
 - for dyslipidemias, 357–358
- Lipostat
 - for angina, 146
- Lisinopril
 - daily dosage, 308t

- dosages, 318t
- for heart failure, 195
- for hypertension, 304, 319
- LMCA. *See* Left main coronary artery
- LMWH. *See* Low-molecular weight heparin
- Lopressor, 55
 - for AMI, 41t
 - for angina, 151, 152
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for atrial fibrillation, 85
 - for atrial flutter, 234
 - for cardiac arrest, 295t
 - for dilated cardiomyopathy, 465
 - dosage, 309t
 - for heart failure, 189, 198
 - for hypertension, 314
 - for hypertensive emergencies, 328t
 - for hypertrophic cardiomyopathy, 455a
 - for neurally mediated syncope, 481
 - for paroxysmal atrial tachycardia with block, 232
 - pharmacologic features, 312t
 - for secondary dyslipidemias, 346
 - for SVT in pregnancy, 230
 - for unexplained syncope, 488
 - for unstable angina, 160
- Losartan
 - daily dosage, 308t
 - for heart failure, 197
 - for hypertension, 321
- Lotensin
 - daily dosage, 308t
 - dosages, 318t
 - for hypertension, 319
- Low-density lipoprotein cholesterol (LDL-C), 345, 346, 347
 - National Education Program modified guidelines, 348–350, 349f
- Low-molecular weight heparin (LMWH)
 - for embolism prevention, 96
 - for heart failure, 184
- Low sodium diet
 - for hypertension, 302
- Lozol
 - dosage, 309t
 - for hypertension, 316
- LVF. *See* Left ventricular failure
- M**
- MAGIC trial, 60
- Magnesium
 - for AMI, 59–60
 - for hypertension in pregnancy, 335
 - for paroxysmal atrial tachycardia with block, 232
- Magnesium sulfate
 - for cardiac arrest, 297
- Magnetic resonance angiography (MRA)
 - for renovascular hypertension, 338
- Marfan syndrome, 370
- Medtronic-Hall valve, 383, 383f
- MERIT. *See* Metoprolol CR Randomized Intervention Trial
- Methyldopa
 - dosage, 309t
 - for hypertension, 326, 501
 - for hypertension in pregnancy, 332, 334
 - for hypertensive emergencies, 332
- Metirosine
 - for hypertensive crisis, 341
- Metolazone
 - for heart failure, 192
- Metoprolol, 55
 - for AMI, 41t
 - for angina, 151, 152
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for atrial fibrillation, 85
 - for atrial flutter, 234
 - for cardiac arrest, 295t
 - for dilated cardiomyopathy, 465
 - dosage, 309t
 - for heart failure, 189, 198
 - for hypertension, 314
 - for hypertensive emergencies, 328t
 - for hypertrophic cardiomyopathy, 455a
 - for neurally mediated syncope, 481
 - for paroxysmal atrial tachycardia with block, 232
 - pharmacologic features, 312t
 - for secondary dyslipidemias, 346
 - for SVT in pregnancy, 230
 - for unexplained syncope, 488
 - for unstable angina, 160
- Metoprolol CR Randomized Intervention Trial (MERIT), 56, 189
- Metoprolol in Acute Myocardial Infarction (MI-AMI), 54
- Metyrosine
 - for hypertensive crisis, 341
- Mexiletine
 - for arrhythmias, 267, 273–274
 - dosage, 265t
 - safety of, 219
 - for ventricular arrhythmias, 264t
- Mexitil
 - for arrhythmias, 267, 273–274
 - dosage, 265t

- safety of, 219
 - for ventricular arrhythmias, 264t
 - MI. *See* Myocardial infarction
 - MIAMI. *See* Metoprolol in Acute Myocardial Infarction
 - Micardis
 - daily dosage, 308t
 - for heart failure, 197
 - Midodrine
 - for neurally mediated syncope, 481
 - MILIS. *See* Multicenter Investigation of the Limitation of Infarct Size
 - Minipress
 - for hypertension, 325
 - MIRACL. *See* Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
 - Mitral balloon valvuloplasty, 402–403, 403t
 - Mitral regurgitation, 404–406, 404t, 406f
 - with MI, 88–89
 - mitral valve prolapse, 408
 - surgery, 405–406
 - Mitral stenosis, 397–403
 - interventional management, 401–402
 - investigations, 398–399
 - medical therapy, 399–401
 - physical signs, 398
 - surgical open vs closed commissurotomy, 401–402
 - symptoms, 397–398
 - Mitral valve disease
 - noncardiac surgery, 503
 - Mitral valve prolapse, 406–407, 410t
 - complications, 408–409
 - physical signs, 407–408
 - prophylaxis, 424
 - symptoms, 407
 - treatment, 409–410
 - Mitral valve replacement, 403–404
 - Mitral valve surgery
 - for hypertrophic cardiomyopathy, 459
 - Moduret
 - for heart failure, 192
 - Moduretic
 - for heart failure, 192
 - for hypertension, 316
 - Monitan
 - dosage, 309t
 - Monitored Atherosclerosis Regression Study, 358
 - Monocor, 55, 56
 - for angina, 150, 151
 - dosage, 309t
 - for hypertension, 314
 - pharmacologic features, 312t
 - Mononitrate
 - for AMI, 59–60
 - Monopril
 - daily dosage, 308t
 - dosages, 318t
 - for hypertension, 319
 - Morphine
 - for AMI, 40
 - for cardiogenic shock, 116
 - for heart failure postinfarction, 72–73
 - for hypertensive emergencies, 328t
 - MRA. *See* Magnetic resonance angiography
 - Multicenter Antiatheroma Study, 358
 - Multicenter Cardiac Arrhythmia Pilot Study, 218
 - Multicenter Investigation of the Limitation of Infarct Size (MILIS), 33, 113, 114
 - Multifocal tachycardia, 233f
 - Myocardial contractility
 - heart failure, 183
 - Myocardial infarction (MI)
 - aneurysmectomy, 94–95
 - complications, 69–104, 71t
 - discharge medications, 97–98
 - electrocardiogram mimics, 15–33
 - free-wall rupture, 89–91
 - LV aneurysm, 93–94
 - mechanical complications, 88–89, 89t
 - mimics, 27–28
 - noncardiac surgery
 - prevention, 504–505
 - papillary muscle rupture, 92
 - rehabilitation, 104–105
 - risk stratification, 69–70, 70t
 - subacute rupture, 91–92
 - ventricular septal rupture, 92–93
 - Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL), 359
 - Myocarditis, 440–441
 - clinical hallmarks, 440–441
 - etiology, 440
 - HF therapy, 441
 - outcome, 441
 - Myotonic dystrophy
 - mimic old MI, 32
- ## N
- Nadolol
 - for angina, 153
 - for arrhythmias, 276–277
 - dosage, 309t
 - for secondary hypertension, 336
 - Nafcillin
 - for acute endocarditis, 421
 - for endocarditis, 420
 - Narrow QRS tachycardia
 - diagnosis, 220f
 - differential diagnosis, 214t
 - National Education Program modified guidelines, 348–351
 - Native valve endocarditis, 420
 - Natrilix

- dosage, 309t
 - for hypertension, 316
 - Neo-Naclex
 - for hypertension, 315
 - Neurally mediated syncope, 479–483
 - pacemakers, 481–483
 - NG monomethyl-L-arginine, 125
 - Nicardipine
 - dosage, 309t
 - Nicotinic acid
 - for dyslipidemias, 363–364
 - Nifedipine
 - adverse effects, 311t
 - for angina, 156
 - for aortic regurgitation, 393–394
 - dosage, 309t
 - for hypertension
 - adverse effects, 323
 - clinical effects, 322t
 - drug interactions, 324t
 - for hypertensive crisis, 340
 - for hypertensive emergencies, 331
 - for secondary hypertension, 336
 - for unstable angina, 161
 - Nifedipine Extended Release, 158
 - for hypertension, 324
 - Nitrates
 - advantages, 155
 - adverse effects, 155
 - for AMI, 100
 - for angina, 148t
 - antianginal effect mechanism, 153–154, 154f
 - contraindicated in stable angina, 138
 - contraindications, 155
 - disadvantages, 155
 - indications, 154
 - interactions, 155
 - for myocardial infarction
 - noncardiac surgery, 505
 - Nitrendipine
 - dosage, 309t
 - for hypertension, 324
 - Nitroglycerin
 - for AMI, 40, 100
 - for angina, 155–156
 - for cardiogenic shock, 121–122
 - for hypertensive emergencies, 328t, 332
 - infusion pump chart, 161t
 - pharmacologic effects, 118t
 - for postinfarction care, 78
 - for Prinzmetal's angina, 165
 - for right ventricular infarction, 80
 - for unstable angina, 160
 - Nitroprusside
 - for aortic dissection, 372
 - for cardiogenic shock, 116, 121
 - for hypertensive crisis, 340
 - for hypertensive emergencies, 328t, 329
 - infusion pump chart, 330t
 - pharmacologic effects, 118t
 - for postinfarction care, 79
 - for right ventricular infarction, 80
 - Noncardiac surgery
 - cardiac complications
 - pathophysiology, 491–492
 - cardiac contraindications, 493t
 - decreasing risk, 499t
 - dipyridamole-thallium scintigraphy, 496–497, 498t
 - echocardiography, 497–498
 - electrocardiogram, 496
 - high-risk cardiac patients, 494t
 - history, 494–495
 - Holter monitoring, 497
 - patient assessment, 494–498
 - physical examination, 495–496
 - postoperative MI
 - incidence, 494t
 - preoperative management, 491–505
 - risk stratification, 492–493
 - Noncardiogenic shock
 - incidence, 112t
 - Non-Q wave MI, 60–61
 - Non-ST elevation MI, 60–61
 - Norepinephrine
 - for cardiogenic shock, 120–121
 - pharmacologic effects, 118t
 - Normal ST elevations
 - electrocardiography, 20
 - Normodyne
 - adverse effects, 311t
 - dosage, 309t
 - for hypertension in pregnancy, 334–335
 - for hypertensive crises, 333
 - for hypertensive emergencies, 328t, 331
 - pharmacologic features, 313t
 - Norvasc
 - for angina, 147
 - daily dosage, 308t
 - for hypertension, 304, 323
 - clinical effects, 322t
 - Norwegian Postinfarction Timolol Trial, 54
 - Norwegian Post Myocardial Infarction Trial, 310
- O**
- Obstructive atherosclerotic CAD, 2
 - Old MI
 - mimics, 27–28
 - Omniscience valve, 383f
 - Oral anticoagulants
 - for dilated cardiomyopathy, 466

- Oretic
 - dosage, 309t
 - for hypertension, 315
- Orthodromic circus movement tachycardia, 248
- Orthodromic tachyarrhythmias
 - treatment, 253–254
- Orthostatic hypotension, 483–484
- Oxazepam
 - for AMI, 47
- Oxprenolol, 52
 - for angina, 151
- Oxygen
 - for AMI, 46
- P**
- Pacemakers
 - noncardiac surgery, 504
- Pain, 430f
 - pericarditis, 429–431
- Pancarditis
 - rheumatic fever
 - treatment, 412–413
- Paroxysmal atrial tachycardia with block, 231–232, 232f
- Paroxysmal supraventricular tachycardia (PSVT), 219–220
 - sites of origin, 221f
- PCI. *See* Percutaneous coronary intervention
- Penbutolol
 - dosage, 309t
 - pharmacologic features, 313t
- Penicillin
 - for acute endocarditis, 421
 - for native valve endocarditis, 420
- Percutaneous coronary intervention (PCI), 59–62, 166–168
 - acute myocardial infarction
 - clinical studies, 42–43
 - vs thrombolysis, 42f
 - for cardiogenic shock, 115
- Percutaneous coronary intervention (PCI) CURE study, 62
- Pericarditis, 96–97, 427–433
 - clinical hallmarks, 427–428
 - echocardiography, 429
 - electrocardiogram, 428–429, 429t
 - etiology, 428t, 432–433
 - idiopathic, 429–430
 - postinfarction, 432
 - purulent, 432
 - recurrent, 432
 - tuberculosis, 432–433
 - uremic, 433
 - viral, 429–430
- Perindopril Aceon
 - daily dosage, 308t
 - dosages, 318t
 - for hypertension, 319
- Permanent cardiac pacing
 - in AMI, 87
- Persistent atrial tachycardia, 231
- PET. *See* Positron emission tomography
- Pharyngitis
 - rheumatic fever
 - treatment, 412
- Phenoxybenzamine
 - for hypertensive crisis, 340
- Phentolamine
 - for hypertensive crisis, 339–340
- Phenylephrine
 - for arrhythmia, 224
 - for arrhythmias, 229–230
- Pheochromocytoma, 339
- Physicians Health Study
 - gastrointestinal bleeding, 101t
- Pindolol
 - for neurally mediated syncope, 481
 - pharmacologic features, 313t
- Platelet glycoprotein IIb/IIIa receptor blockers, 63
- Platelet receptor blockers
 - for angina, 163–165
- Plendil
 - dosage, 309t
 - for hypertension, 324
- Polygenic hypercholesterolemia, 345
- Polythiazide
 - dosage, 309t
- Positron emission tomography (PET), 143
- Postinfarction angina, 81
- Postural hypotension, 483–484
- Potassium
 - with angina, 151
- Potassium-sparing diuretics
 - for hypertension, 315
- PRAUGE study, 43
- Pravachol
 - for angina, 146
 - for dyslipidemias, 359–360
- Pravastatin
 - for angina, 146
 - for dyslipidemias, 359–360
- Pravastatin Limitations of Atherosclerosis in the Coronary Arteries trial, 358
- Prazosin
 - for hypertension, 325
- Prednisone
 - for pericarditis, 431
- Preload
 - heart failure, 181
- Primary dyslipidemias, 346–347
- Primary hypertension, 301
- Prinivil
 - daily dosage, 308t

dosages, 318t
 for heart failure, 195
 for hypertension, 304, 319
 Prinzmetal's angina, 129, 165
 Procainamide
 for antidromic tachyarrhythmias, 254
 for arrhythmias, 267, 269–270
 dosage, 265t
 for ventricular arrhythmias, 264t
 Procardia XL, 158
 for hypertension, 324
 Professional athlete
 benign ST and T-wave changes, 21f
 Prolonged QT syndrome
 syncope, 486
 Propafenone
 for arrhythmias, 267, 275–276
 for atrial flutter, 235
 for orthodromic tachyarrhythmias, 253
 for ventricular arrhythmias, 264t
 Propranolol
 for AMI, 41t
 for angina, 150, 151, 153
 for aortic dissection, 372
 for arrhythmias, 229
 for cardiac arrest, 295t
 dosage, 309t
 for hypertensive crises, 333
 for hypertrophic cardiomyopathy, 455
 pharmacologic features, 313t
 for SVT in pregnancy, 230
 for unstable angina, 160, 160t
 Prosthetic valve endocarditis, 422–423
 Prosthetic valves
 bacterial endocarditis, 387
 complications, 385, 386t
 failure, 385
 hemolysis, 387–388
 major bleeding, 386
 obstruction, 386–387
 selection of, 383–384, 384t
 systemic embolization, 387
 Proteus
 endocarditis, 422t
 Pseudoinferior infarction, 31f
Pseudomonas
 infective carditis, 418
Pseudomonas aeruginosa
 endocarditis, 422t
 PSVT. *See* Paroxysmal supraventricular tachycardia
 Pulmonary vein ablation
 for atrial fibrillation, 245–246
 Pulseless disease, 484
 Pulsus paradoxus, 434
 Pump failure, 77–78

Q

QRS tachycardia, 215t, 252f
 diagnosis, 220f
 differential diagnosis, 214t, 257f
 Questran Light
 for dyslipidemia, 361
 Quinapril
 daily dosage, 308t
 dosages, 318t
 for hypertension, 319
 Quinidine
 for arrhythmias, 267, 270–272
 dosage, 265t
 safety of, 219
 for ventricular arrhythmias, 264t

R

RADIANCE study, 188
 Ramipril
 for AMI, 103
 daily dosage, 308t
 dosages, 318t
 for heart failure, 196
 for heart failure postinfarction, 73, 75
 for hypertension, 319
 Randomized Intervention Trial of Unstable Angina (RITA 3), 162–163, 167
 Ranolazine
 for angina, 159
 RAVEL study, 169
 RBBB. *See* Right bundle branch block
 Regitine
 for hypertensive crisis, 339–340
 Renal dysfunction
 drug therapy, 328t
 Renedil
 dosage, 309t
 for hypertension, 324
 Renovascular hypertension, 337–338
 ReoPRO, 44–45, 44f, 63, 64
 for AMI, 41
 Restrictive cardiomyopathy, 438, 466–468
 Reteplase, 51
 Revascularization
 for cardiogenic shock, 123–125
 REVERSAL investigators, 359
 Rheumatic fever, 410–413
 clinical features, 410–412
 prevention, 413
 treatment, 412–413
 Right atrial myxoma, 438
 Right bundle branch block (RBBB), 20–21, 257f
 electrocardiography, 34–35
 not caused by MI, 37f
 Right main coronary artery (RMCA), 12f
 Right-sided endocarditis, 423

- Right ventricular hypertrophy (RVH)
 old MI mimics, 27
Right ventricular infarction, 17f, 79–81, 81t, 438
 treatment, 80–81
RITA 3. *See* Randomized Intervention Trial of
 Unstable Angina
RMCA. *See* Right main coronary artery
Rogitine
 for hypertensive crisis, 339–340
Rosuvastatin
 for angina, 146
 for dyslipidemias, 360
RVH. *See* Right ventricular hypertrophy
R-wave
 poor progression, 32f
- S**
- 4S. *See* Scandinavian Simvastatin Survival Study
Salmonella
 endocarditis, 422t
Sarcoidosis
 mimic old MI, 32
SAVE. *See* Survival and Ventricular Enlarge-
 ment
Scandinavian Simvastatin Survival Study (4S),
 358
Scleroderma
 mimic old MI, 32
Scotland Prevention study, 358
Secondary dyslipidemias, 345–346
 medications, 346
Secondary hypertension, 335–342
 renal parenchymal disease, 335–336
Sectral
 dosage, 309t
Septal myectomy
 for hypertrophic cardiomyopathy, 459
Serratia marcescens
 endocarditis, 422t
Serum creatinine
 angina, 140
Sexual activities
 return to, 104
SHEP. *See* Systolic Hypertension in the Elderly
 Program
SHOCK. *See* Should We Emergently
 Revascularize Occluded Coronaries for
 Cardiogenic Shock registry and trial
Shock, 77–78
Should We Emergently Revascularize Occluded
 Coronaries for Cardiogenic Shock
 (SHOCK) registry and trial, 109, 123, 125
Sick sinus syndrome
 syncope, 485–486
Silent ischemia, 166
 noncardiac surgery, 505
Simvastatin
 for angina, 146
 for dyslipidemias, 359
Single-photon emission computerized tomogra-
 phy (SPECT), 141
Sinus node dysfunction
 syncope, 485–486
Sinus tachycardia, 53
SIRIUS Trial, 169
SMILE. *See* Survival of MI Long-term Evalua-
 tion
Smoking cessation
 for hypertension, 302
Sodium bicarbonate
 for cardiac arrest, 295t, 296
Sodium restriction
 for heart failure, 184
SOLVD. *See* Studies of Left Ventricular Dys-
 function
Sorbitrate
 for angina, 156
 for heart failure, 188
Sotacor, 52
 for arrhythmias, 277, 282–283
 for atrial fibrillation, 243
 for AVNRT, 230
 dosage, 265t
 for hypertrophic cardiomyopathy, 455–456
 pharmacologic features, 313t
 for secondary hypertension, 336
Sotalol, 52
 for arrhythmias, 277, 282–283
 for atrial fibrillation, 243
 for AVNRT, 230
 dosage, 265t
 for hypertrophic cardiomyopathy, 455–456
 pharmacologic features, 313t
 for secondary hypertension, 336
SPECT. *See* Single-photon emission computer-
 ized tomography
Spironolactone
 for dilated cardiomyopathy, 464
 for heart failure, 193
SPORTIF. *See* Stroke Prevention Using Oral
 Thrombin Inhibitor in AF
Squatting and Valsalva maneuver
 for arrhythmias, 220–221
St. Jude valve, 383, 383f
Stable angina, 136–140
 blood work, 139–140
 classification, 127–128
 diagnosis, 138
 investigative evaluation, 138–139
 medical therapy, 144f
 pathophysiology, 136–138, 137f
Staphylococcus aureus
 acute endocarditis, 421
 endocarditis, 422t

- infective carditis, 418
- native valve endocarditis, 420
- Staphylococcus bovis*
 - acute endocarditis, 421
- Staphylococcus epidermidis*
 - infective carditis, 419
- Staphylococcus viridans*
 - acute endocarditis, 421
- Starr-Edwards ball and cage valve, 383, 383f
- Statins
 - adverse effects of, 360–361
 - for dyslipidemias, 357–358
- ST elevations
 - electrocardiography, 20
 - MI, 60–61
- Stent Restenosis (STRESS), 168
- Stents, 168–169
 - drug-eluting, 168
 - paclitaxel-eluting, 169
 - sirolimus-eluting, 168
- Stokes-Adams attacks
 - syncope, 486
- Streptase, 50–51
 - dosage, 48t
 - for embolism prevention, 96
 - given within 24 hours of MI onset, 40t
 - for prosthetic valve obstruction, 387
- Streptococcus anginosus*
 - infective carditis, 418
- Streptococcus bovis*
 - endocarditis, 422t
 - infective carditis, 418, 420
- Streptococcus durans*
 - acute endocarditis, 421
 - infective carditis, 418
- Streptococcus epidermidis*
 - endocarditis, 422t
- Streptococcus faecalis*
 - acute endocarditis, 421
 - endocarditis, 422t
- Streptococcus fecium*
 - acute endocarditis, 421
 - infective carditis, 418
- Streptococcus marcescens*
 - infective carditis, 418
- Streptococcus mitis*
 - infective carditis, 418
- Streptococcus mutans*
 - infective carditis, 418
- Streptococcus pneumoniae*
 - acute endocarditis, 421
 - infective carditis, 418
- Streptococcus salivarius*
 - infective carditis, 418
- Streptococcus viridans*
 - endocarditis, 422t
 - infective carditis, 418, 420
 - native valve endocarditis, 420
- Streptokinase, 50–51
 - dosage, 48t
 - for embolism prevention, 96
 - given within 24 hours of MI onset, 40t
 - for prosthetic valve obstruction, 387
- STRESS. *See* Stent Restenosis
- Stroke Prevention Using Oral Thrombin Inhibitor
 - in AF (SPORTIF), 244
- ST segment elevation, 10f, 13f, 14f, 15f
 - ACC/AHA guidelines, 40–41
 - acute myocardial infarction, 18f
 - AMI, 9–10
 - atrial fibrillation, 16f
 - electrocution, 26
 - fishhook appearance, 21f, 22f
 - hitched-up pattern, 24
 - inferior infarction, 16f
 - left bundle branch block, 26f
 - old anterior infarction, 31f
 - precordial repolarization patterns, 23f
 - scorpion stings, 26
- Studies of Left Ventricular Dysfunction (SOLVD), 187
- Subarachnoid hemorrhage, 25
- Subclavian steal, 484
- Sudden death
 - mitral valve prolapse, 408–409
- Sulbactam
 - for acute endocarditis, 421
 - for native valve endocarditis, 420
- Supraventricular arrhythmias, 84, 219–221, 222f
 - in AMI, 84t
 - noncardiac surgery, 503–504
- Supraventricular tachycardia (SVT)
 - pregnancy, 230
- Survival and Ventricular Enlargement (SAVE), 75
- Survival of MI Long-term Evaluation (SMILE), 75
- Sustained monomorphic ventricular tachycardia, 82–83
- Sustained ventricular tachycardia
 - treatment, 263f
- SVT. *See* Supraventricular tachycardia
- Swimming
 - following AMI, 105
- SYDIT. *See* Syncope Diagnosis and Treatment Study
- Syncope, 473–488
 - assessment, 474f
 - cardiac causes, 485–487
 - etiology, 475t

- noncardiac, 476t
 - history, 478–479
 - patient evaluation, 475–479
 - physical examination, 478–479
 - treatment, 482f
 - Syncope Diagnosis and Treatment Study (SYDIT), 483
 - Systemic embolism
 - mitral valve prolapse, 409
 - prevention of, 96
 - Systolic Hypertension in the Elderly Program (SHEP), 304, 305, 315
- T**
- Tachycardia
 - onset of, 216f
 - TACTICS. *See* Treat Angina with Aggrastat and Determine Costs of Therapy with Invasive or Conservative Strategies
 - Takayasu's disease, 484
 - TEE. *See* Transesophageal echocardiography
 - Telmisatran
 - daily dosage, 308t
 - for heart failure, 197
 - Temporary cardiac pacing, 86–87
 - Tenecteplase, 49, 51
 - dosage, 48t
 - Tenex
 - dosage, 309t
 - for hypertension, 326, 501
 - Tenormin
 - for angina, 150, 151, 152
 - for aortic dissection, 372
 - for arrhythmias, 276–277
 - for hypertensive crises, 333
 - for neurally mediated syncope, 481
 - pharmacologic features, 312t
 - for secondary hypertension, 336
 - for unexplained syncope, 488
 - for unstable angina, 160t
 - Terazosin
 - for hypertension, 325
 - Teveten
 - daily dosage, 308t
 - for heart failure, 197
 - TF. *See* Tissue factor
 - Thallium-201 SPECT, 142
 - Thiazide diuretics
 - adverse effects, 311t
 - for heart failure, 191–193
 - for hypertensive crises, 334
 - for secondary dyslipidemias, 346
 - Thromboembolism
 - prevention of, 95–96
 - Thrombolysis in Myocardial Infarction (TIMI)
 - risk score, 61
 - study, 162–163
 - Thrombolysis in Myocardial Infarction (TIMI)-2, 54
 - Thrombolysis in Myocardial Infarction (TIMI)-3, 43
 - Thrombolytic therapy, 38t, 48f
 - dosage, 48t
 - TIA. *See* Transient ischemic attack
 - TIBET. *See* Total Ischemic Burden European Trial
 - TIMI. *See* Thrombolysis in Myocardial Infarction
 - Timolol
 - for angina, 150, 151, 153
 - dosage, 309t
 - pharmacologic features, 313t
 - for unexplained syncope, 488
 - Tirofiban, 63–64
 - Tissue factor (TF), 3
 - Tissue plasminogen activator (tPA), 47
 - plus heparin, 48
 - TNKase, 49, 51
 - dosage, 48t
 - Tocainide
 - for arrhythmias, 267
 - for ventricular arrhythmias, 264t
 - Toprol XL, 55
 - for AMI, 41t
 - for angina, 151, 152
 - for aortic dissection, 372
 - for arrhythmias, 229
 - for atrial fibrillation, 85
 - for atrial flutter, 234
 - for cardiac arrest, 295t
 - for dilated cardiomyopathy, 465
 - dosage, 309t
 - for heart failure, 189, 198
 - for hypertension, 314
 - for hypertensive emergencies, 328t
 - for hypertrophic cardiomyopathy, 455a
 - for neurally mediated syncope, 481
 - for paroxysmal atrial tachycardia with block, 232
 - pharmacologic features, 312t
 - for secondary dyslipidemias, 346
 - for SVT in pregnancy, 230
 - for unexplained syncope, 488
 - for unstable angina, 160
 - Torcetrapib
 - for dyslipidemias, 365
 - Torsades de Pointes, 261–269, 266f
 - diagnosis, 261–262
 - syncope, 485
 - treatment, 262–263
 - Torsemide
 - for heart failure, 191
 - Total cholesterol
 - dyslipidemias, 348
 - Total Ischemic Burden Bisoprolol Study, 166

- Total Ischemic Burden European Trial (TIBET), 166
- tPA. *See* Tissue plasminogen activator
- Trandate
 adverse effects, 311t
 dosage, 309t
 for hypertension in pregnancy, 334–335
 for hypertensive crises, 333
 for hypertensive emergencies, 328t, 331
 pharmacologic features, 313t
- Trandolapril
 dosages, 318t
 for heart failure postinfarction, 75
- Transesophageal echocardiography (TEE)
 for cardiogenic shock, 116
 prosthetic valves, 389
- Transient ischemic attack (TIA), 484
- Transvenous temporary cardiac pacing, 87
- Treat Angina with Aggrastat and Determine Costs of Therapy with Invasive or Conservative Strategies (TACTICS), 63, 162–163
- Triglycerides
 dyslipidemias, 348
 elevated serum, 364
 National Education Program modified guidelines, 351
- Tritace
 for AMI, 103
 daily dosage, 308t
 dosages, 318t
 for heart failure, 196
 for heart failure postinfarction, 73, 75
 for hypertension, 319
- Troponin, 9
 with angina, 162
 pericarditis, 428–429
- ## U
- UKPDS. *See* United Kingdom Prospective Diabetes Study
- Uncomplicated postmyocardial infarction
 ambulation day, 96t
- Unexplained syncope, 487–488
 EP study, 487–488
- United Kingdom Prospective Diabetes Study (UKPDS), 55
- Unstable angina, 159–162
 β -blockers for, 160
 dosage, 160t
 classification, 128–219, 128t
 combination therapy, 162
 pathophysiology, 159
 treatment, 159–162
- Urapidil
 for hypertensive emergencies, 328t, 332
- Urizide
 for hypertension, 315
- Urokinase
 for prosthetic valve obstruction, 387
- ## V
- VALIANT. *See* Valsartan in Acute MI Trial
- Valsalva maneuver
 for arrhythmias, 220–221
- Valsartan, 58
 for AMI, 103
 daily dosage, 308t
 for heart failure, 197
 for hypertension, 321
- Valsartan in Acute MI Trial (VALIANT), 189, 321
- Valvular heart disease
 antibiotic prophylaxis
 noncardiac surgery, 503
- Vancomycin
 for endocarditis, 422
 for prosthetic valve endocarditis, 423
- Variant angina, 27f, 129, 165
- VASIS. *See* Vasovagal Syncope International Study
- Vasoactive drugs
 pharmacologic effects, 118t
- Vasopressin
 for cardiac arrest, 296
- Vasotec
 daily dosage, 308t
 for dilated cardiomyopathy, 464–465
 dosages, 318t
 for heart failure, 188, 195
 for hypertension, 319
- Vasovagal Pacemaker Study (VPS), 481
- Vasovagal Syncope International Study (VASIS), 482–483
- ## Veins
- atherosclerotic plaque predilection, 135
- Ventricular arrhythmias, 254–267
 diagnosis, 254–257
 grades, 254–258
 medications, 264t
 noncardiac surgery, 504
 treatment, 94–95, 258–261
 treatment guidelines, 262t
- Ventricular fibrillation
 treatment, 293–294, 294t
- Ventricular premature beats (VPB), 45, 82
- Ventricular tachycardia, 259f
 monomorphic vs polymorphic, 259f
- Ventricular thromboembolism
 after AMI, 95t
- Verapamil
 adverse effects, 166, 311t
 for AMI, 101
 for angina, 147, 156, 157, 158–159
 for arrhythmia, 222, 223

- for atrial flutter, 234
- for AVNRT, 228–229, 230
- dosage, 309t
- drug interactions, 157
- for hypertension, 324
 - clinical effects, 322t
 - drug interactions, 324t
- for hypertrophic cardiomyopathy, 456
- for paroxysmal atrial tachycardia with block, 232
- for unstable angina, 161
- with WPW, 252
- Very low-density lipoprotein (VLDL), 345
- Veterans Administration Cooperative Study, 171
- Veterans Administration Cooperative Vasodilator Heart Failure Trial (VHeFT) II, 187
- VHeFT. *See* Veterans Administration Cooperative Vasodilator Heart Failure Trial (VHeFT) II
- Vitamin K1
 - for atrial fibrillation, 245–246
- VLDL. *See* Very low-density lipoprotein
- VPB. *See* Ventricular premature beats
- VPS. *See* Vasovagal Pacemaker Study

W

- Walking
 - following AMI, 104
- Warfarin
 - for dilated cardiomyopathy, 466
- Weight reduction
 - for heart failure, 184
 - for hypertension, 301–302
- Wide QRS tachycardia, 215t, 252f
 - differential diagnosis, 257f

- Wolff-Parkinson-White (WPW) syndrome, 29,
 - 32f, 246–247, 247f, 248f, 249f
 - associated diseases, 250
 - drugs and increased risk, 252–253
 - risk stratification, 250–252
 - tachyarrhythmias, 253t
- Wytensin
 - dosage, 309t
 - for hypertension, 326

X

- Xanthomonas maltophilia
 - endocarditis, 422t
- Ximelagatran
 - for atrial fibrillation, 244–245

Z

- Zebeta, 55, 56
 - for angina, 150, 151
 - dosage, 309t
 - for hypertension, 314
 - pharmacologic features, 312t
- Zestril
 - daily dosage, 308t
 - dosages, 318t
 - for heart failure, 195
 - for hypertension, 304, 319
- Zetia
 - for dyslipidemias, 364–365
- Zocor
 - for angina, 146
 - for dyslipidemias, 359
- Zofenopril
 - for heart failure postinfarction, 75

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Heart Disease Diagnosis and Therapy

A Practical Approach

SECOND EDITION

M. Gabriel Khan, MD, FRCP(LONDON), FRCP(C), FACP, FACC

Associate Professor of Medicine, University of Ottawa; Cardiologist, The Ottawa Hospital, Ottawa, Canada

Foreword by

Henry J. L. Marriott, MD, FACP, FACC

University of South Florida School of Medicine, Tampa, FL

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