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Cardiogenic Shock

Physiological and Biochemical Concepts

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INTRODUCTION

Because cardiogenic shock is the culmination of cumulative abnormalities in the heart and because it is associated with the most dire of prognoses, any attempt at its diagnosis and appropriate management demands a clear understanding of the pathophysiological processes involved in the individual patient. For example, treating cardiogenic shock with aggressive diuresis to reduce the central venous pressure when the shock is predominantly secondary to extensive right ventricular infarction may significantly reduce filling of the left ventricle, thereby further exacerbating the cardiogenic shock. Similarly, a misplaced attempt at alleviating the distress of severe dyspnea secondary to acute pulmonary edema by using large doses of morphine or diamorphine may result in marked respiratory depression and precipitate respiratory arrest or alternatively may reduce the arterial pressure so as to compromise the coronary perfusion further, worsening the cardiogenic shock. Erroneous concepts lead to erroneous treatment.

Above all else, it is worth remembering that during cardiogenic shock, the cardiac pump is performing in an unstable state. As a mechanical pump, the heart is unusual in that its performance is somewhat dependent on its own output. When the aortic pressure that it generates falls below the critical pressure for coronary perfusion (usually a mean pressure of about 60 mm Hg), left ventricular myocardium is at risk for

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ischemia, which can then further impair its pumping performance. Timely treatment should therefore be directed at interrupting the vicious cycle by maintaining the coronary perfusion pressure, thereby ensuring continued cardiac viability. Measures required may include urgent coronary revascularization to salvage threatened viable myocardium, mechanical circulatory support, control of bradyarrhythmia or tachyarrhythmia, removal and counteraction of negative inotropic effects, and correction of metabolic derangement.

PATHOPHYSIOLOGY OF CARDIOGENIC SHOCK

There is more information about the pathophysiology of cardiogenic shock than can be included in this chapter. Therefore, this chapter is necessarily selective and includes only information that is directly relevant to the diagnosis and treatment of cardiogenic shock in clinical practice.

Cardiac and Extracardiac Determinants

When diagnosing cardiogenic shock, it is important to determine whether the presentation of shock is truly cardiogenic. Central cardiac factors need to be distinguished from peripheral and extracardiac factors. The presentation of shock in a coronary care unit does not necessarily preclude the occurrence of shock from other causes than the heart, such as hypovolemic (absolute or relative) shock, septicemic or anaphylactic shock, or shock secondary to a massive pulmonary embolism. It is also possible that more than one type of shock can be present concurrently. Nevertheless, because the heart is not the sole determinant of circulatory collapse, the central contribution of cardiac function and its inadequacy must be considered in relation to the state of the peripheries, including the vasculature, gas exchange, blood constituents, and volume.

Other compounding factors such as intercurrent infection, anemia, hypoxia (secondary to respiratory diseases), hypothermia, hyperpyrexia, dysthyroidism, thiamine deficiency, Addisonian crisis, or other systemic disorders may play a role. Prompt recognition and identification of these compounding factors are necessary before appropriate correction of these defects can be instituted. Drugs with myocardial depressant actions or hypotensive agents (e.g., morphine, diamorphine, β -blockers, arterial vasodilators, streptokinase) may be precipitating or contributory factors toward the onset of shock. Prompt recognition, withdrawal, or counteraction of such harmful effects of drugs may alter the nature and course of shock.

Etiology and Sequence of Events

In true cardiogenic shock, the initiating event occurs in the heart. Most clinicians associate it with myocardial infarction, although the etiology of cardiogenic shock can be the result of any defect in the heart, be it affecting the myocardial function (e.g., ischemia, infarction, stunning, contusion, arrhythmia, heart block, myocarditis), or the integrity of valves (e.g., chordal or papillary muscle rupture, acute regurgitation in endocarditis), or the integrity of cardiac structures (e.g., acute ventricular septal defect [VSD], acute tamponade). Urgent measures should be put in place to deal with these lesions, but while the definitive procedures are being planned and arranged, it is crucial to deal with the hemodynamic and metabolic consequences of the shock.

In addition to a decline in systolic function, there is also a substantial decrease in left ventricular compliance, increasing the filling pressure at a given end-diastolic volume (1–4). The increased left ventricular end-diastolic pressure causes pulmonary congestion, leading to hypoxemia and ischemia, which further reduces coronary perfusion pressure. Myocyte swelling occurs (5) as a consequence of an intracellular accumulation of sodium and calcium resulting from anaerobic glycolysis, further decreasing left ventricular compliance (6). The further reduction in compliance and the myocyte swelling lead to an increase in ventricular wall stress, elevating myocardial oxygen requirements. As the myocardium becomes less compliant, the pumping capacity of the heart becomes less efficient, increasing the imbalance between myocardial oxygen requirements and supply.

Soon after the onset of cardiogenic shock, compensatory mechanisms are activated. In mammals, a primary objective of the regulatory system of the circulation is to maintain arterial pressure (7–10) to preserve perfusion to the vital organs such as the brain and the heart. This is accomplished by activation of neurohumoral systems, not dissimilar from the responses observed during hemorrhagic shock and exercise. In particular, there are withdrawal of the parasympathetic system and activation of the sympathetic, renin–angiotensin–aldosterone and vasopressin systems, culminating in arterial and venous vasoconstriction, salt and fluid retention, positive chronotropy, and inotropy. Although beneficial in hemorrhagic shock and severe exercise, these compensatory mechanisms may be detrimental in cardiogenic shock. For instance, venoconstriction and salt and fluid retention would increase the preload and arterial vasoconstriction would increase the afterload, thereby overloading the already failing ventricles. Increased heart rate and myocardial contractility would increase the demands in the face of limited supply of oxygenated blood to at-risk myocardial regions (ischemic territories and the subendocardium). The skill of immediate management is therefore to curb the excesses of the compensatory mechanisms without negating some of their potential beneficial effects.

As the shock state persists, hypoperfusion of both the myocardium and peripheral tissues will induce anaerobic metabolism in these tissues and may result in lactic acidosis. An earlier study has shown that the serum lactate level is an important prognostic factor in cardiogenic shock (11). Uncorrected, the accumulation of lactic acid may cause mitochondrial swelling and degeneration, inducing glycogen depletion, which, in turn, impair myocardial function and inhibit glycolysis, leading to irreversible ischemic damage (12). Unfavorable effects on other organ functions follow. The shock state in patients with an acute myocardial infarction leads to a vicious cycle that causes a downward spiral of worsening ischemia: As cardiac output falls, arterial pressure falls and coronary perfusion is lowered, thus exacerbating the low output state. This eventually leads to further ischemia and extension of necrosis in the left ventricle. Several compensatory mechanisms occur during this chain of events that, if left untreated, lead to cardiac pump failure and, ultimately, death.

Compensatory Sympathetic Nervous System Activation

When myocardial function is depressed, several compensatory mechanisms occur. However, the compensatory mechanisms may become maladaptive and actually worsen myocardial ischemia. Initially, as cardiac pump function declines, there is a redistribution of blood flow, in order to ensure adequate perfusion of the heart and

brain. Activation of the sympathetic nervous system occurs, resulting in arterial constriction, increased myocardial contractility, and an increase in heart rate.

Systemic vasoconstriction occurs in an attempt to increase blood pressure. This causes the systemic pressure to increase in the aorta during diastole, which initially minimizes the decrease in coronary perfusion. However, this vasoconstriction increases afterload, causing further impairment of cardiac performance and increasing myocardial oxygen demand (13).

α -Mediated adrenergic arteriolar constriction accounts for a reduction in muscular, cutaneous, splanchnic, and renal blood flow, which may induce ischemic injury in these organs (14). This flow mismatch may be further increased by the administration of inotropic or vasodilator agents. α -Adrenergic responses also lead to a postcapillary venular constriction. The combined effect of both arteriolar and venular constriction leads to an increase in capillary hydrostatic pressure causing an egress of fluid from the capillaries, decreasing intravascular volume and causing hemoconcentration. Intravascular volume is also regulated by renal blood flow. As vasoconstriction causes renal blood flow to decrease, the renin–angiotensin–aldosterone system is activated in an attempt to restore intravascular volume to normal and to increase preload.

A reflex increase in heart rate occurs, which further exacerbates myocardial oxygen demand and worsens ischemia. As the sympathetic system is activated further, ventricular extrasystoles become more frequent and cardiac dysrhythmias occur, which decrease cardiac pumping capacity and cardiac output.

CARDIAC DYSFUNCTION IN CARDIOGENIC SHOCK

Hemodynamic Profiling During Cardiogenic Shock

The earliest hemodynamic studies in cardiogenic shock were conducted in the 1950s (15–17). With accumulation of such objective data, concepts of pathophysiology and therapeutic options evolved in the ensuing decades (13,18–25). It is now well established that hemodynamic evaluation is a vital element in the management of patients with cardiogenic shock (26–28).

Gilbert and colleagues were the first to measure cardiac outputs in patients with cardiogenic shock (15). Freis and Smith and their colleagues confirmed decreases in arterial pressure and cardiac output but found systemic vascular resistance rather variable (16,17). Subsequent investigators concentrated on responses to vasoconstrictors as an attempt to raise blood pressure in cardiogenic shock (13,18–20).

Gunnar and colleagues compared post-myocardial-infarction patients with and without shock and found that shock patients had lower mean aortic pressure (mean \pm SD: 53 ± 12 mm Hg vs 92 ± 23 mm Hg) and lower cardiac output (measured with indocyanine green dilution method: 2.2 ± 0.9 vs 3.8 ± 1.5 L/min) (21). One of their patients with a cardiac output of 0.61/min died before any treatment could be given. Four patients were unable to increase mean aortic pressure above 80 mm Hg in response to norepinephrine infusion, and all of them died within 8 h of the onset of shock. These early hemodynamic data suggested that those with the most compromised cardiac function and least able to respond to inotropic stimulation had the least favorable prognosis.

Smith and colleagues compared the effects of metaraminol (a vasoconstrictor) and isoproterenol on patients in cardiogenic shock who had hypotension, low cardiac output, raised venous pressure, and a systemic vascular resistance index ranging from

1600 to 4500 dyn s cm⁵ m² (22). They found that metaraminol elevated arterial and venous pressures and systemic vascular resistance at the expense of some reduction in cardiac output. Isoproterenol was found to increase cardiac output and decrease venous pressure and systemic vascular resistance, but in most cases the arterial pressure was also increased (Fig. 1B).

Objectives of Hemodynamic Evaluation

The primary objectives of hemodynamic evaluation in cardiogenic shock are to guide the treatment of this precarious condition (29) and to provide prognostic information (26,27). One of the earliest attempts to use hemodynamic evaluation to determine prognosis and to guide therapy was by Ratshin and colleagues (23). All of their cardiogenic shock patients who had left ventricular filling pressure of >15 mm Hg and cardiac index of <2.3 L/min died despite medical therapy. Attempts were also made to assess the reserve function of the failing hearts using dextran infusion, intravenous digoxin, epinephrine, norepinephrine, and isoproterenol, but the results were too varied to draw any useful conclusions.

Swan and colleagues were the first to recognize cardiogenic shock as the extreme manifestation of cardiac power failure (24). Comparing the basal hemodynamics of two cohorts of patients, one with and one without cardiogenic shock post-acute myocardial infarction, the parameter most distinguishing the two cohorts was left ventricular stroke work (26 ± 10 g-m/beat with shock and 81 ± 36 g-m/beat without shock, $p < 0.005$). However, there was significant overlap of the individual basal unstimulated values between survivors and nonsurvivors of shock (Fig. 3). These observations were confirmed by Scheidt and colleagues, who also showed that although various hemodynamic variables are statistically significantly different between the survivors and nonsurvivors of acute myocardial infarction, individual values showed significant overlaps between the two cohorts (25).

If death is the end point to prevent, identifying individual patients who are most likely to die will require an accurate and reliable predictive hemodynamic indicator. Using a logistic regression modeling technique, the GUSTO-I investigators showed that “cardiac output measurements were of greatest prognostic significance” even when demographic and clinical variables were included in the analysis (27). This is consistent with the concept that in the absence of life-threatening arrhythmia the most important determinant of mortality is cardiac pump function, because it is the inadequacy of this that leads to circulatory collapse and cardiogenic shock.

Which Hemodynamic Variables to Measure?

The heart is a complex organ with many components. Various measurements have been developed in the past to evaluate aspects of cardiac function. Many of the variables are interrelated and concordant, but quite often they are contradictory. For instance, in gross mitral regurgitation, the left ventricular ejection fraction is exaggerated and overestimates cardiac function, whereas in tight aortic stenosis, it provides an underestimate. In cardiogenic shock, being the severest form of cardiac impairment, there is very little room for misinterpretation in the management of patients. Therefore, it is vitally important to conduct the correct measurements and interpret the results appropriately.

The crucial steps involved in evaluating cardiogenic shock are as follows: (1) to establish whether the heart is responsible for the shock (see previous section), (2) to

Table 1
Normal Hemodynamic Values at Rest (for a Healthy Average-Sized Adult Man)^a

<i>Variables</i>	<i>Values</i>	<i>Comments</i>
Heart rate (min ⁻¹)	71 (53–89)	May be as low as 30 in elite athletes
Pressures (mm Hg) (1 kPa = 7.5 mm Hg)		
Right atrium	5 (0–9)	Congestive if > 10
Right ventricle, systolic	22 (16–28)	
Right ventricle, end diastolic	5 (0–9)	
Pulmonary artery, S/D	16–28/4–16	PHT if S > 40
Pulmonary artery, mean	15 (6–17)	
Pulmonary artery wedge, mean	8 (2–12)	Congestive if > 15
Left atrium, mean	8 (2–12)	Congestive if > 15
Left ventricle, systolic	100–140	
Left ventricle, end diastolic	8 (2–12)	Congestive if > 15
Aorta, systolic	122 (105–140)	Hypotensive if < 90
Aorta, diastolic	73 (65–90)	
Aorta, mean	93 (80–110)	Hypotensive if < 60
Cardiac flow generation		
Cardiac output (L/min)	6.5 (3.6–9.4)	Cardiogenic shock if < 3.5
Cardiac index (L/min/m ²)	3.6 (2.0–5.2)	Cardiogenic shock if < 2.0
Stroke volume (mL)	93 (53–133)	
LV end-diastolic volume (mL)	75–200	Dependent on method of measurement
LV ejection fraction (%)	55–70	Dependent on method of measurement
Vascular resistances (dyn s/cm ⁵) (1 mmHg/L min = 80 dyn s/cm ⁵ = 8 kPa/L ⁻¹ s)		
Systemic	1070 (660–1480)	Usually > 1500 in cardiogenic shock
Total pulmonary	70 (20–120)	PHT if > 200
Cardiac work		
LV stroke work index (J/m ²)	0.4–0.7	With normal preload
Baseline cardiac power output (W)	0.8–1.3	Very severe cardiogenic shock if < 0.4

Source: Modified from refs. 55 and 113.

^a Abbreviations: D, diastolic; dyn, dynes; J, joules; LV, left ventricle; PHT, pulmonary hypertension; S, systolic; SHT, systemic hypertension; W, watts.

assess which component part(s) of the heart is (are) responsible for the circulatory failure, and (3) to measure the extent of the overall organ dysfunction. A readily available imaging technique (usually echocardiography) often fulfills the function of identifying whether the heart is responsible for the shock (step 1) and which components are malfunctioning (step 2). However, it provides only qualitative information about the extent of overall cardiac dysfunction (step 3) and, therefore, invasive hemodynamic measurements and monitoring are required to determine prognosis and provide a quantitative indication of responses to treatment.

Over 100 hemodynamic parameters have been proposed through the ages (Table 1), and each group of investigators advocates its own parameter as the ideal (30,31). When managing critically ill patients in cardiogenic shock, clinicians do not have the luxury of academic uncertainties, but must rely on clarity of thought and prompt actions. With this aim, readers are encouraged to study other chapters in this volume.

Briefly, there are parameters that reflect systolic versus diastolic ventricular function, determinants of cardiac performance such as preload, afterload, chronotropy, and inotropy. Conceptually, for a long time, the holy grail had been the search for an ideal index of myocardial contractility, in the belief that “contractility” is the most accurate representation of how good the heart is, independent of peripheral influences through loading conditions of the ventricle and rate-related phenomena. This concept has been shown to be flawed because indices of contractility obtained from whole ventricular chamber dynamics are at best a summation of the necrotic, ischemic, stunned, hibernating, and normally functioning myocardium, and, at molecular levels, the inotropic aspects of the sliding filaments are inextricably linked to the loading conditions of the myofilaments. Thus, a conceptual paradigm shift away from muscle mechanics toward whole-organ dynamics and functional assessments is more helpful for clinicians in order to select which parameters should be adopted during the management of cardiogenic shock (32,33). To achieve this, it is helpful to return to basics and revisit first principles.

Central Hemodynamics: Concepts and Definitions

By definition, the hallmark of cardiogenic shock is severe primary cardiac pump failure. In true cardiogenic shock, circulatory collapse persists even after optimization of peripheral factors. Understanding the hemodynamic concepts of primary pump failure in cardiogenic shock is vital to correct diagnosis, interpretation of hemodynamic data, and management.

The definition of primary cardiac pump failure hinges on an understanding of the physiological role of the heart in maintaining the circulation. The milestone definition of the function of the heart must be attributed to William Harvey, the discoverer of the circulation, who in 1628 stated “...that the movement of the blood is constantly in a circle, and is brought about by the beat of the heart ... for the sake of nourishment...” When the heart stops beating, forces opposing blood flow in the vessels halt the circulation. To restart and maintain the motion, energy is required, which is provided by the cardiac pump.

The primary function of the heart, expressed in modern physiological terms, is to convert biochemical energy into hydraulic energy at rates sufficient to maintain an adequate circulation under normal physiological conditions. In three-dimensional space, the power (work per unit time) of moving a volume of fluid is the product of pressure and flow rate. Thus, the ability of the heart to generate energy and perform external work encompasses not only its ability to generate flow but also its ability to generate pressure. Pressure generation is essential, unless the impedance to flow in the circulation is zero (an impossibility). Adopting the definition of cardiac function as stated here, the definition of primary cardiac pump failure can be simply stated as the failure of the heart, under physiological loading conditions, to produce sufficient hydraulic power output to maintain an adequate circulation at rest and during normal physiological stress.

Components of Pump Failure

It follows that primary cardiac pump failure is the end result of summated effects of the defects in cardiac structures and functions. The defects may include systolic and diastolic dysfunction, dyssynchronous contractile dysfunction, conduction defects and arrhythmias, valvular diseases, and other structural defects, including septal defects.

These may be intrinsic to the heart or extrinsic, such as induced by drugs, malfunctioning devices (e.g., pacemaker-induced tachyarrhythmia), or abnormal neurohumoral controls. Systolic and diastolic dysfunction includes all causes of cardiomyopathies (ischemic, dilated, hypertrophic, restrictive), myopericarditis, transplant rejection, constrictive pericarditis, and pericardial effusion. Correct identification of component defects and their hemodynamic consequences is important to institute appropriate treatment. For instance, cardiogenic shock in a patient with severe obstructive hypertrophic cardiomyopathy is worsened when treated with standard cardiogenic shock therapy such as using positive inotropic agents, diuretics, and vasodilators.

Each cardiac lesion may precipitate hemodynamic compromise in a number of ways. After a massive myocardial infarction, for example, there may be a combination of component dysfunction such as systolic and diastolic dysfunction, papillary muscle rupture and mitral regurgitation, acquired ventricular septal defects, conduction defects (partial bundle branch block or heart blocks), arrhythmias, and pericardial tamponade.

In the Western world, the commonest cause of primary pump failure leading to cardiogenic shock is extensive myocardial infarction (27,34). At autopsy, more than two-thirds of patients with cardiogenic shock demonstrate stenosis of 75% or more of the luminal diameter of all three major coronary vessels, usually including the left anterior descending coronary artery (35). Others have found that patients with cardiogenic shock had lost at least 40% of the left ventricular myocardium (36–38), although smaller infarctions or mere ischemia may also precipitate shock (39). Size estimates of regional infarction need to be adjusted for diffuse cardiomyocyte loss as a result of biological attrition of cardiomyocytes over time (40) or as a result of other causes such as subclinical cardiomyopathies. During ischemia, myocardial metabolism is severely deranged and cellular energy stores are depleted. It is important to recognize that large areas of nonfunctional but viable myocardium (stunned and hibernating myocardium) can contribute to the development of the syndrome. Cardiogenic shock resulting from or contributed by ongoing ischemic (as opposed to infarcted), stunned, or hibernating myocardium is likely to have a better prognosis if these factors can be reversed in time.

Baseline Versus Reserve Cardiac Function

It is a truism that how good a heart is, is gaged by how well it maintains the circulation, not at baseline resting states but during the most severe stress. This concept is even more applicable in cardiogenic shock, because, by definition, the failure of the cardiac pump to provide an adequate circulation to ensure appropriate tissue perfusion is responsible for the shock state. This implies that the cardiac pump is fully stimulated by the cardiovascular regulatory system, but this may not be the case in all circumstances. In cases when the cardiac pump is functioning at its maximum and circulatory collapse still persists, alternative modes of circulatory support are required. In other cases, the cardiac pump may underperform for several reasons (e.g., under the influence of cardiodepressant drugs, marked vagal tone, in the presence of extensive stunned or hibernating myocardium), and the reserve function of the heart has not been exhausted.

In cardiogenic shock, therefore, a more important feature than the cardiac function at baseline resting states is the reserve pumping capability of the failing heart (i.e., the ability to increase pumping capacity during stress). Availability of this mechanistic information alone would help clinicians to select individual patients who should go

forward for invasive therapy (28). This information may be taken in conjunction with the more probabilistic information contained in the risk factors derived from multivariate analyses of other patient cohorts.

Evaluating the Overall Pump Failure in Shock

The most natural form of stimulating cardiac performance is physiological, through maximal exercise. However, it is impracticable and undesirable to ask patients in cardiogenic shock to perform any form of exercise. An alternative is to use pharmacological means of stressing the heart. In current cardiological practice, the commonest agent used is dobutamine, which can be supplemented with a phosphodiesterase inhibitor (such as milrinone or enoximone), although in intensive care practice, adrenaline is often used instead. Using dobutamine stimulation, Tan and Littler investigated the predictive power of hemodynamic variables measured at baseline and during peak stimulation in consecutive patients admitted to a coronary care unit with cardiogenic shock (26). They found that the presence or absence of reserve function of the failing heart is strongly predictive of prognosis, in contrast to baseline unstimulated states in which there were significant overlaps in all hemodynamic parameters between the survivors and nonsurvivors. When plotted against pulmonary arterial occlusion pressure at baseline unstimulated states, there was a tendency for those with higher cardiac output or left ventricular stroke work and lower left ventricular filling pressure to survive, but there were significant overlaps between the two groups (Fig. 1). When the values during maximal dobutamine stimulation were plotted, the separation between the two groups became more obvious (Fig. 2).

These investigators also tested the hypothesis that the likelihood of prolonged survival is low if patients in cardiogenic shock were unable to exceed the normal resting cardiac power output of 1 W during maximal dobutamine stimulation (41). The results (Fig. 3) showed that at baseline unstimulated states, all patients had cardiac power output values of less than 1 W and there was significant overlap of the values between the survivors and nonsurvivors. Patients with particularly depressed cardiac performance, power output <0.4 W (after optimizing filling pressures), all died. The rest of the cohort showed a diverging response to dobutamine response, with those able to exceed 1 W of power output surviving the 1 yr of follow-up; the nonsurvivors had limited increments in power output (26).

Hemodynamics of Peripheral Factors

VENOUS AND PRELOAD EFFECTS

Hypovolemia, caused by, for example, severe dehydration or hemorrhage, can precipitate shock through underfilling of the ventricles despite normal cardiac function. The threshold for shock is lower if cardiac function is also impaired. In right ventricular infarction leading to predominantly right ventricular failure, the right atrial pressure is elevated relative to the left atrial pressure. To maintain an adequate circulation, the central venous pressure is necessarily elevated to ensure adequate left atrial pressure and left ventricular filling. Maintaining the central venous pressure within the normal range may result in *relative* hypovolemia, manifesting as significant underfilling of the left ventricle, thereby further compromising cardiac function. In the presence of right ventricular infarction and the possibility of relative hypovolemia (shown by raised right atrial pressure and low pulmonary wedge pressure), fluid challenge to

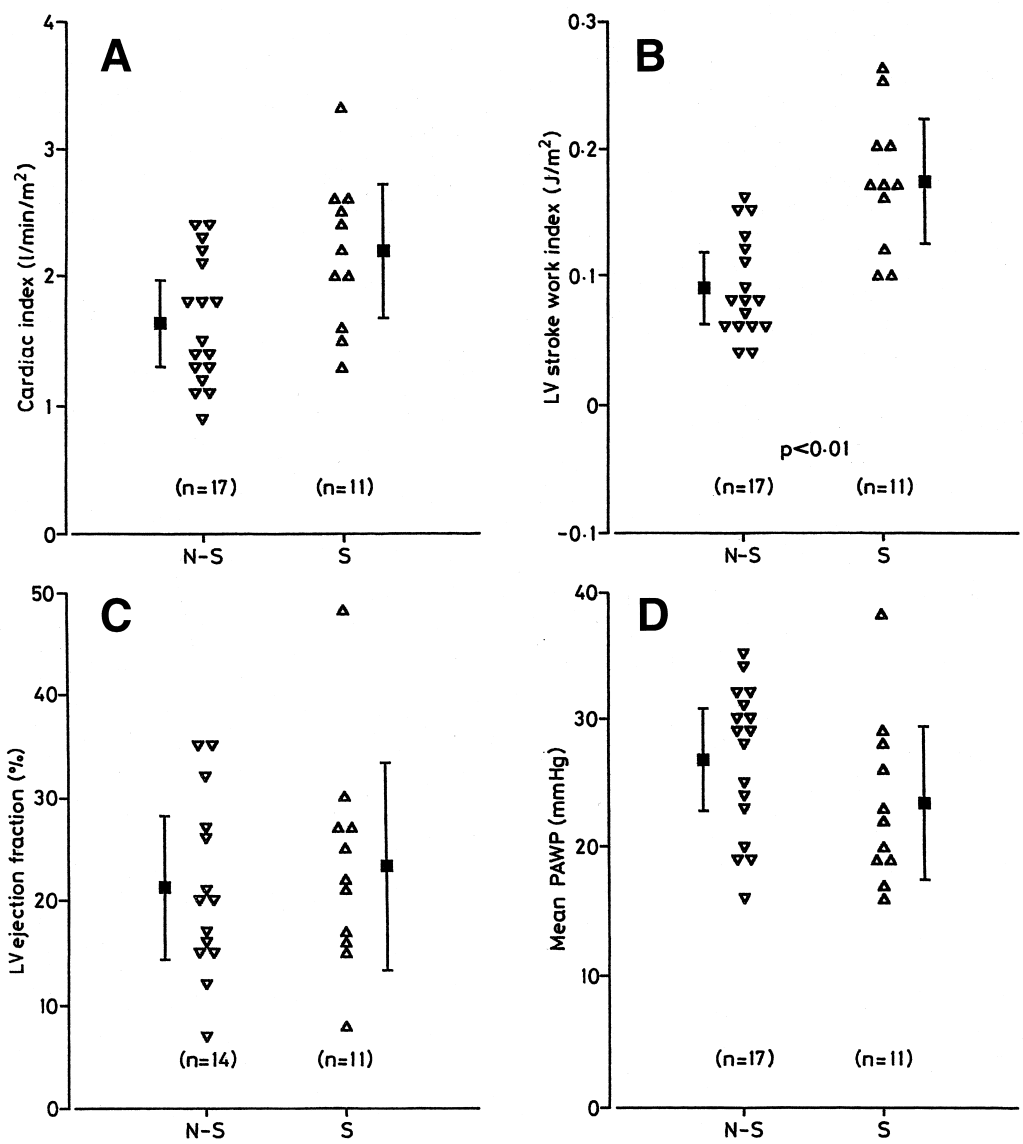


Fig. 1. Baseline resting hemodynamic data of survivors (S) and nonsurvivors (N-S) from consecutive patients admitted to a coronary care unit presenting with cardiogenic shock: **(A)** cardiac index, **(B)** left ventricular stroke work index, **(C)** left ventricular ejection fraction, **(D)** mean pulmonary artery occlusion pressure, **(E)** cardiac index versus pulmonary artery occluded pressure, and **(F)** left ventricular stroke work index versus pulmonary artery occluded pressure. Although the mean values favored the survivors, there were significant overlaps of the individual values between survivors and nonsurvivors. Reprinted with permission from ref. 26.

raise the pulmonary wedge pressure to >18 mm Hg should be made before diagnosing cardiogenic shock.

On the other hand, overdilation of the left ventricle may precipitate or exacerbate functional mitral regurgitation, effectively resulting in the ventricle functioning in the

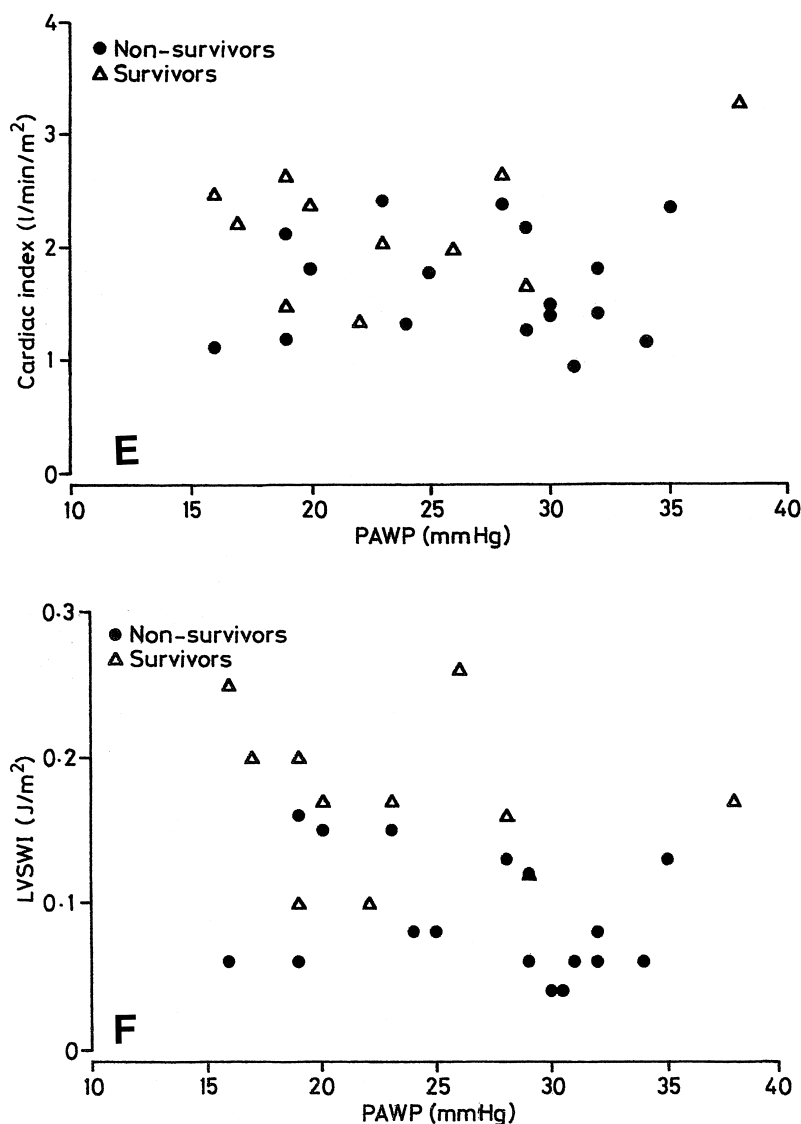


Fig. 1. (Continued).

descending limb of Starling's curve. Fluid challenge blindly without hemodynamic monitoring may aggravate this situation. Instead, judicious use of diuretics, venodilation, or even hemofiltration or ultrafiltration may be beneficial.

ARTERIAL AND AFTERLOAD EFFECTS

Any peripheral factors that result in excessive demands on the cardiac pump performance are liable to precipitate or exacerbate cardiogenic shock. In a normal circulation, there is an impedance matching of the cardiac pump and the arterial system such that the hydraulic power output of the heart is maximal (42). Disturbance of this matching would render cardiac function suboptimal. An example is the excessive vasodilatation

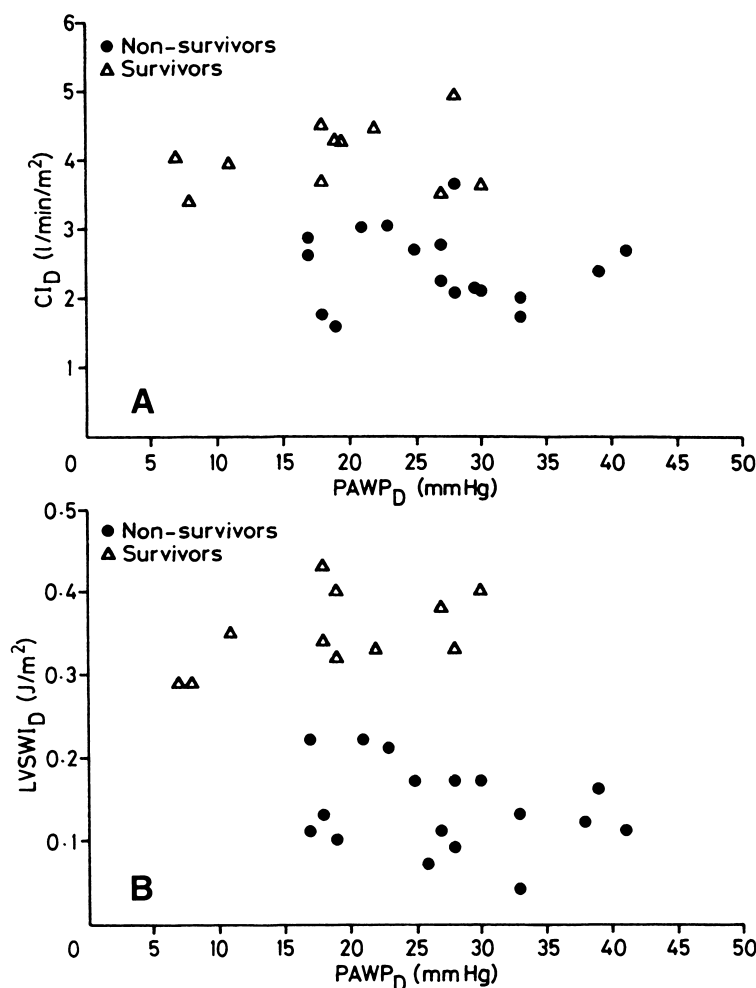


Fig. 2. Hemodynamic data during peak dobutamine stimulation in the same cohort of patients as in Fig. 4, showing clear demarcation of the values of survivors (open triangles) from those of nonsurvivors (filled circles). Reprinted with permission from ref. 26.

via the nitric oxide pathways, especially of the splanchnic vasculature via the release of endotoxins in septicemic shock (43–45). The threshold for the onset of shock is lower if the cardiac function itself is also impaired (a combination of septicemic and cardiogenic shock). Excessive vasodilatation (through therapeutic use of nitrates or other antianginal agents, morphine or diamorphine) may also exacerbate cardiogenic shock. Similarly, in high-output states (e.g., Paget’s disease, arteriovenous malformation, anemia, thyrotoxicosis), shock occurs at lower levels of compromise of cardiac function.

In heart failure, including cardiogenic shock, resulting from activation of the sympathetic and renin–angiotensin–aldosterone systems, there is a tendency for vasoconstriction, which can be excessive for the failing heart and render its function suboptimal (42). Extra elevation of afterload through such mechanisms as treatment with norepinephrine or dopamine (sometimes used in cardiogenic shock), chronic hypertension, aortic steno-

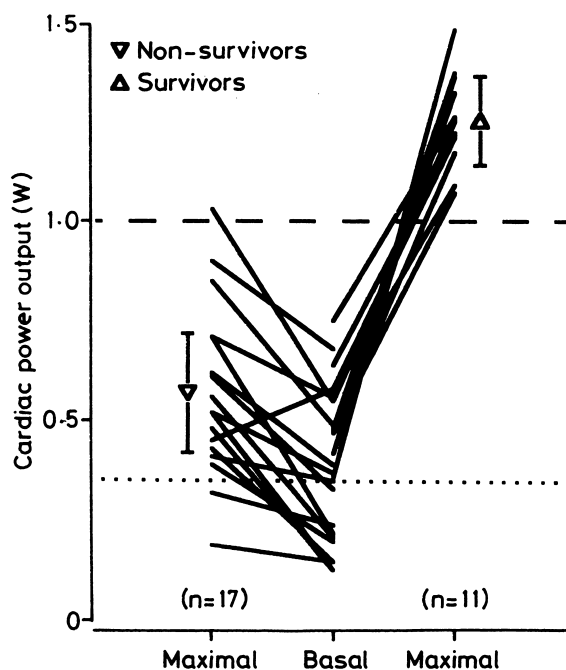


Fig. 3. Cardiac power output at baseline resting states and during peak dobutamine stimulation in the same cohort of patients as in Fig. 4, showing that (1) patients with baseline power output of < 0.4 W all perished, (2) the baseline power outputs of survivors and nonsurvivors were indistinguishable, and (3) patients with peak cardiac power output of > 1 W tended to survive on medical therapy alone. Reprinted with permission from ref. 26.

sis, or coarctation of the aorta would further exacerbate the mismatch in impedance. In poorly controlled chronic hypertension, there is a further complication in that the autoregulatory levels for blood flow into vital organs are readjusted upward such that higher pressures are required to produce the same blood flow as in normotensives (46–48). In these subjects, the onset of cardiogenic shock (tissue hypoperfusion) can, therefore, occur at higher arterial pressures (e.g., systolic blood pressure > 110 mm Hg).

Practical Issues: Monitoring and Interpreting Central Hemodynamics

Because the initiating and primary defect in cardiogenic shock is failure of cardiac function, close monitoring of central hemodynamics is an essential component of managing patients. The objective is to optimize the performance of the heart, to maintain an adequate circulation without stressing the heart unduly. The Schumacker concept of treating septicemic shock by maximizing cardiac output should be avoided in the management of cardiogenic shock (44).

Meticulous management of cardiogenic shock requires invasive measurements via a fluid-filled flotation pulmonary artery catheter and, ideally, invasive monitoring of intra-arterial pressure, in order to assess several important variables that fully reflect cardiac function. Previous concerns about the use of such invasive monitoring are not generally applicable because there were only very few cases of cardiogenic shock

included in that study (49). All invasive procedures in seriously ill patients carry some risks and should be conducted by well-trained, experienced personnel.

The parameters that indicate the hemodynamic status of the patient with cardiogenic shock are as follows: (1) cardiac output (determined by heart rate and rhythm and stroke volume), reflecting the blood flow output of the heart; (2) right atrial pressure (RAP) and central venous pressure (CVP), which reflect the right ventricular filling pressure; (3) pulmonary artery wedge pressure (PAWP) and left atrial pressure (LAP), which reflect the left ventricular end-diastolic (filling) pressure; and (4) arterial blood pressure (systolic and diastolic), which reflects the pressure generating capacity of the heart and systemic vasomotor tone. Using these variables, left ventricular stroke work and cardiac power output, which is an indicator of overall cardiac function and incorporates both the pressure- and flow-generating abilities of the heart, can be calculated (41). Cardiac power output is the product of cardiac output \times mean arterial pressure $\times k$, a conversion factor (2.22×10^{-3}) and is expressed in watts (W). It has been shown to be a powerful prognostic indicator in patients with cardiogenic shock and heart failure (26,41,50,51).

Because nonsurvivors (who had inadequate cardiac reserve at the time of evaluation) and survivors (with adequate reserve) have clear differences between their hemodynamic parameters (26,27), it is possible to triage patients according to their cardiac functional reserve status. Patients with poor reserve are the ones who will not do well with medical therapy alone and need to be considered for aggressive interventions if death is to be avoided. If the peak cardiac power output (CPO) is >1 W, medical therapy—including the use of inotropic agents to maintain adequate pressure and flow—is usually sufficient, unless there is a risk of progression of myocardial damage. If the peak CPO is <1 W (or simple bedside observation of peak attainable systolic blood pressure [BP] of <80 mm Hg despite maximal dobutamine stimulation), then urgent and definitive treatment of primary defects (urgent coronary angioplasty, bypass surgery, other curative operation, or cardiac transplantation) should be sought.

BIOCHEMICAL CONCEPTS

Energetics of the Normal Myocardium

Viewed in terms of energetics, the prime function of the heart is to convert the stored biochemical energy in available substrates and transduce it into mechanical energy, via cardiomyocyte contraction (in a synchronized fashion) to allow the ventricles to deliver hydraulic energy into the systemic and pulmonary vasculature beds (52). Because under normal physiological conditions, cardiac metabolism is oxidative and oxygen is not stored, the most crucial substrate to be supplied for myocardial metabolism is therefore oxygen. The major substrates oxidized in the normal myocardium are fatty acids (67%), glucose (18%), and lactate, although amino acids, ketones, and pyruvate are also used (53–55) (Fig. 4). In a normally oxygenated heart, high cellular levels of adenosine triphosphate (ATP) and citrate inhibit glycolysis (56). The energy equivalent of 1 mL of oxygen has been estimated to provide 20.15 J of energy (57,58).

For the entire organ, it is technically quite difficult to measure all of the substrates used, whereas oxygen consumption is relatively easier to measure. Because of this technical limitation, the energy *input* to the heart has traditionally been represented by myocardial oxygen consumption (MVO_2). A more direct measure of energy input into the myocardial contractile elements is the ATP consumption, which can be measured by nuclear magnetic

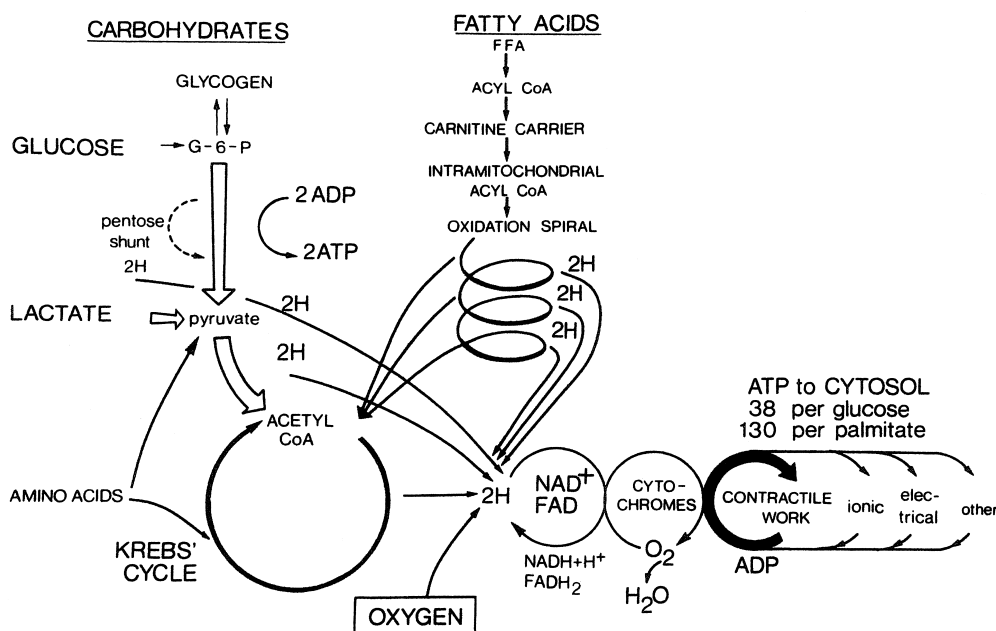
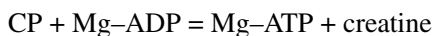


Fig. 4. Free fatty acids, glucose, and lactate are the major substrates of normal myocardium, and their oxidation and final interaction with the cytochrome chain produce the ATP that is the primary fuel for transduction into mechanical energy of myofilament contraction. Reprinted with permission (109).

resonance (NMR) spectroscopy (59,60). Rates of ATP synthesis estimated from magnetization transfer were similar to values calculated from oxygen consumption (60).

The breakdown of ATP to adenosine diphosphate (ADP) (and P_i + free energy) is the direct source of energy for myofilament contraction, the maintenance of ionic gradients, and other vital cellular functions (61) (Fig. 5). ADP is reconverted to ATP via oxidative phosphorylation in the mitochondria. In normal myocardium, ATP is maintained relatively constant, despite variations in cardiac performance, through matched changes in the rates of ATP synthesis to its utilization. This is achieved through the buffering mechanism of creatine phosphate (CP) that is present in high concentration in normal myocardium. The transfer of the phosphoryl group from CP to ADP is catalyzed by creatine phosphokinase (CPK or CK) in the following reaction:



which favors the formation of ATP by about 50 times. In vivo, the turnover of the phosphoryl group by CK, measured directly by ³¹P magnetization transfer, is an order of magnitude faster than net ATP synthesis estimated from oxygen consumption.

The useful energy output of the heart is the hydraulic energy imparted into the circulation. The rest of the energy is dissipated as wasted heat. The ratio of the useful energy output to energy input is the efficiency of the cardiac transduction process. In certain pathological states, such as severe aortic stenosis, the efficiency may be seriously compromised, especially when coupled with modest limitations of oxygen supply (e.g., noncritical coronary artery stenosis), and this may result in an unstable state of cardiogenic shock. How efficiency is affected in cardiac pathophysiological

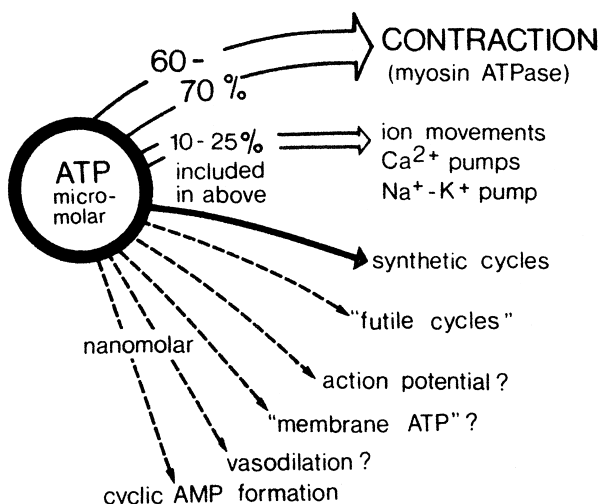


Fig. 5. Cellular functions of ATP in cardiomyocytes. Reprinted with permission (110).

states depends on the relative proportions of the determinants of myocardial oxygen consumption.

The determinants of MVO_2 in terms of the whole organ are as follows: (1) useful external work (62,63), (2) development of wall tension (64,65), (3) noncontractile basal cellular metabolism (64), (4) depolarization and activation (66), (5) heart-rate-related energy expenditure (67), and (6) contractility or inotropy-related energy expenditure (58,64,68). Under different conditions, the three major determinants of myocardial oxygen consumption are systolic wall tension, contractility, and heart rate (62,63,66,68–72), although what proportion of these are wasted as heat and which are converted into useful external work is difficult to ascertain. During normal physiological contractions, probably the highest cost in terms of energy consumption is in the development of left ventricular wall tension (64,65). Wall tension development unaccompanied by forward stroke volume (e.g., during a nonejecting extrasystolic beat) is a wasteful consumption of energy. Similarly, a dilated ventricle requires more energy to develop a much higher wall tension to generate the same intraventricular pressures according to the Law of LaPlace [wall stress = (pressure \times radius)/(2 \times wall thickness)] (73). MVO_2 is also influenced by the supply of substrates to the heart. The use of free fatty acids increases MVO_2 , and catecholamines sensitize the heart to the oxygen-wasting effect of free fatty acids (63). Alteration of myocardial metabolism from mainly free fatty acid to carbohydrate oxidation reduces the extent of myocardial ischemic injury (74).

Energetics and Metabolism of Hypoperfused Myocardium

As a result of circulatory shock and hypoperfusion of the myocardium, aerobic cellular metabolism cannot be maintained. The regeneration of high-energy phosphate compounds, CP and ATP, is impaired and intracellular high-energy reserves therefore decline. When oxygen delivery to the cardiomyocytes is inadequate, oxidative metabolism ceases, cellular citrate and ATP levels fall, and the cell switches to glycolytic anaerobic metabolism to produce a limited amount of ATP. The rate of glucose uptake

is accelerated and available glycogen is rapidly depleted (75,76), resulting in lactate production instead of lactate uptake by the myocardium (77–80). The energy made available from anaerobic glycolysis is only about 6% of that obtainable from oxidative metabolism (81). A rough estimate of the efficiencies of glucose metabolism in the production of ATP is as follows (82): aerobic oxidation of 1 mol of glucose (free energy of 686 kcal) can produce 36 mol of ATP (7.3 kcal each), giving a conversion efficiency of 38%. Anaerobic metabolism of 1 mol of glucose produces 2 mol of ATP, giving a conversion efficiency of 2.2%. Anaerobic glycolysis is therefore a poor means of compensating for inadequate supply of oxygen (77), albeit it may be sufficient to maintain viability of the jeopardized myocytes.

When ischemia is severe, the products of glycolysis accumulate. Anaerobic glycolysis yields lactic acid, which results in cellular acidosis that, in turn, inhibits glycolysis and ATP generation ceases. The relative lack of ATP means failure of energy-dependent ion transport pumps, impairing cation transport, with an efflux of potassium and intracellular accumulation of sodium and calcium (83). This causes myocyte swelling (see above) and decreasing ventricular compliance. As the ischemia becomes severe, myocardial cell injury becomes irreversible with necrosis; mitochondrial swelling; accumulation of denatured proteins and chromatin in the cytoplasm; lysosomal breakdown; and fracture of the mitochondria, nuclear envelope, and plasma membrane (83). Apoptosis may also be responsible for some of the myocyte loss occurring as a result of ischemia; evidence of apoptosis has been found in the border zone of the myocardium during infarction and also sporadically in areas remote from the ischemia (40,84). Apoptotic pathways may be activated by inflammatory cascades, oxidative stress, or stretching of myocytes (84). The ratio of apoptotic cell death to myocyte necrosis during myocardial ischemia is currently unknown. In these situations, the earliest restoration of oxygenated blood flow is the most rewarding practical solution, provided the jeopardized myocardium is still viable.

In the presence of limited oxygen supply, secondary to coronary artery stenosis or occlusion, considerations about the efficiency of energy transduction also become of paramount importance. In animal experiments following coronary occlusion, interventions that increase myocardial energy expenditure appear to increase the size of the infarction, whereas those that decrease myocardial oxygen consumption reduce the size of the infarction. Reduction of myocardial oxygen demands produced by slowing the heart rate and counteracting the augmentation of sympathetic influences may reduce oxygen demands and thereby the size of the infarction (68). However, excessive bradycardia may result in ventricular dilatation that, in turn, will negate or even exceed the energy-saving attempt through reducing the heart rate, resulting in a net increase in myocardial oxygen consumption. The situation becomes very complex in the presence of cardiogenic shock.

Once heart failure is established, recent evidence from NMR spectroscopy studies using myocardium obtained from heart failure patients suggests that the capacity for ATP resynthesis via the CK system is compromised in the failing myocardium (85,86). CK activity and ATP, ADP, CP, and free creatine are decreased in failing myocardium. The decrease in the content of the energy reservoir compound, CP, is greater than that for ATP. Phosphoryl transfer via the CK decreases from being 10-fold greater than the rate of ATP synthesis via oxidative phosphorylation in the normal heart to only about threefold greater (assuming no change in the rate of oxidative phosphorylation) in the failing heart. Decreased energy reserve via the CK system for the severely failing heart

is likely to reduce the contractile reserve of the heart. It may also contribute to decreased baseline contractile performance (87).

Metabolic Treatment by the Glucose–Insulin–Potassium Infusion

As we have seen previously, several metabolic changes occur during cardiogenic shock, related to the lack of ATP available for cellular energy. ATP is produced from two main sources: glucose and free fatty acids (FFA). When oxygen is abundant during normal perfusion conditions, it is more efficient for the cell to use FFA, as it yields a larger amount of ATP (88). However, during ischemic conditions, the cell switches to glucose metabolism and this causes an accumulation of FFA. Also, sympathetic activation and high catecholamine levels seen during cardiogenic shock lead to increased circulating FFA levels. Myocardial accumulation of FFA leads to depression of myocardial function, membrane instability, and arrhythmias (89) and an increase in myocardial oxygen consumption without a parallel increase in myocardial work: the “oxygen-wasting effect of FFA” (74,90).

Although metabolic agents have been routinely used for a number of years as protection against ischemic–reperfusion injury during cardiac surgery (91,92), investigators have only recently adopted a strategy of metabolic alterations as a therapeutic option in the treatment of acute ischemia. There is increasing experimental and clinical evidence of the possible benefit of metabolic treatment of ischemia, which may prevent the development of cardiogenic shock (93). Administration of the polarizing substance, glucose–insulin–potassium (GIK), was first used as a treatment for ischemia in acute myocardial infarction in 1962 by Sodi-Pallares and colleagues (94). GIK is thought to have several possible mechanisms of action in the treatment of ischemia, ranging from its importance in providing a metabolic substrate for an increased energy source, through to its anti-FFA actions (95). All responsible mechanisms may lead to an improvement in contractile performance in ischemic ventricular dysfunction. (See Chapter 5 for a further discussion of GIK.)

Clinical Evidence for GIK Use in Acute Ischemia

A retrospective meta-analysis performed in 1997, involving 1932 patients from nine clinical trials performed during the prethrombolytic era, found GIK to significantly reduce in-hospital mortality versus placebo (16% vs 21%, $p = 0.004$) (96). In a subgroup of four studies using high-dose GIK, in-hospital mortality was reduced by 48%, which is comparable to the mortality reduction seen with reperfusion therapy several years later, suggesting that metabolic protection of the ischemic myocardium may be as important as reperfusion therapy *per se*. However, the results of this meta-analysis must be interpreted with caution, as it suffers from all the drawbacks of the meta-analysis techniques.

Two randomized trials have looked at GIK in the treatment of acute myocardial infarction in the thrombolytic era. The Diabetes Insulin–Glucose in Acute Myocardial Infarction (DIGAMI) trial included 620 diabetic patients with an acute myocardial infarction, all treated with thrombolysis (97). A significant reduction in mortality at 1 yr was seen in the group who received an intensive insulin regimen (insulin–glucose infusion for 24 h, followed by subcutaneous insulin every day for 3 mo or more) versus standard therapy (29% relative reduction [$p = 0.027$]). The results need to be interpreted with caution, however, as the mortality benefit may merely reflect better diabetic control.

The ECLA (Estudios Cardiológicos Latinoamérica) trial involved 407 patients with an acute myocardial infarction, randomized to receive either (1) high-dose GIK (25% glucose, 50 IU insulin, 80 meq potassium/L at 1.5 mL/kg/h), (2) low-dose GIK (10% glucose, 20 IU insulin, 40 meq potassium/L at 1 mL/kg/h), or (3) placebo, in addition to standard therapy (62% of patients were treated with reperfusion therapy [95% thrombolysis, 5% primary percutaneous transluminal coronary angioplasty (PTCA)]) (98). Overall, GIK therapy was associated with a nonsignificant reduction in in-hospital mortality and major and minor in-hospital events. In the subgroup who received reperfusion, the reduction in in-hospital mortality was significant in the GIK-treated group (5.2% vs 15.2%, $p = 0.01$). At 1 yr, there was a trend toward lower mortality in the overall and reperfused groups, although the subgroup of patients who were reperfused and received high-dose GIK had a significant reduction in mortality versus placebo. The results of the ECLA study suggest that high-dose GIK may be more beneficial than either a low-dose regimen or placebo, which is consistent with the findings of the previous meta-analysis (96). This may be due to the fact that the high dose that was used had previously been found to achieve maximal suppression of arterial FFA levels as well as maximal increases in myocardial uptake of glucose in previous experimental studies (99). The finding that there was significant mortality reduction with GIK only in the reperfused group needs to be interpreted with caution, because of the small sample size and conflicting findings from the more statistically robust meta-analysis.

Use of GIK in Cardiogenic Shock

There has been a small amount of work looking at the effects of GIK on patients with severe left ventricular dysfunction immediately following cardiac surgery. This syndrome represents a particular form of cardiogenic shock, and marked metabolic abnormalities such as high concentrations of FFA, hypoxemia, and lactic acidosis are frequently seen. An early small controlled trial consisting of 22 patients saw GIK to significantly decrease plasma FFA levels and increase cardiac index (by up to 40%) after 12 hs of therapy versus a control group treated with standard therapy (inotropic support and intra-aortic balloon pumping, $p < 0.005$) (100,101). Svedjeholm and colleagues showed GIK to enhance the inotropic effect of dobutamine, decrease circulating FFA levels and myocardial FFA uptake, and increase mechanical efficiency (102). Following on from this work, the same group showed GIK to improve hemodynamic function in a group of 16 patients who had signs of cardiac failure after surgery (102). The largest trial performed involved 322 consecutive patients with postoperative heart failure (103). GIK significantly reduced hospital mortality by 35% ($p < 0.02$) and reduced the length of stay in intensive care (compared with a standard control group).

Further randomized trials with larger patient numbers are needed to investigate the effects of GIK further and find out whether adoption of a metabolic strategy prevents the development of, or reverses the changes seen in, cardiogenic shock in the setting of an acute myocardial infarction.

EFFECTS OF SHOCK ON OTHER ORGANS

As the cardiac pump fails, systemic tissue perfusion becomes markedly reduced. This leads to changes and adaptations in several other organs.

Renal Failure

Renal failure is a major complication of circulatory shock, developing within 36–72 h after the onset of the condition. Renal blood flow can be reduced to as low as 10% of normal. α -Adrenergic action and renal nerve sympathetic activity cause vasoconstriction, which diminishes blood flow to the cortical areas leading to renal tubular injury. This progresses to cellular necrosis and tubular obstruction, with accumulation of proteinaceous and cellular debris in the tubular lumen. Back-diffusion and leakage of the glomerular filtrate may cause tubular collapse (104). Initially, there is an increase in sodium and water resorption resulting from the secretion of antidiuretic hormone (ADH) and aldosterone in response to low blood flow—this also enhances back-diffusion. Eventually, the system fails to respond to increases in aldosterone and ADH. Both sodium and urea concentration in the medulla are reduced so that the hypertonic gradient for resorption of water is disabled, leading to loss of the capability of the kidneys to concentrate solute (105).

Pulmonary Function

Early changes include increases in ventilation resulting in an increased ventilation–perfusion mismatch and an increased physiological dead space and alveolar capillary gradient for oxygen. Initially, pulmonary vascular resistance is only mildly elevated, but this increases as hypoxia worsens. Adult respiratory distress syndrome (ARDS) may eventually develop as a result of circulatory collapse and progressive pulmonary injury (106). Primary pulmonary failure is relatively uncommon in patients with cardiogenic shock. Significant lactic acidosis would induce Kussmaul breathing.

Changes in Skeletal Muscle

The resting transmembrane potential declines as a result of decreased blood supply, resulting in impaired membrane transport. The most important muscle affected is the diaphragm, which accounts for decreased efficiency of ventilation and increases oxygen requirements for breathing (107). When oxygen delivery is severely decreased, the increased work requirements may reduce the patient's ability to breathe, resulting in alveolar hypoventilation with hypercarbia and hypoxemia (108), which may require mechanically assisted ventilation. Prolonged hypoperfusion may also result in increasing production of lactate, thus exacerbating respiratory acidosis by metabolic acidosis.

Gastrointestinal System

Massive hepatic necrosis and overt liver failure are uncommon in patients with cardiogenic shock. Nonspecific increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are commonly seen (109). Hepatic congestion renders the liver less able to metabolize lactate, thereby compounding lactic acidosis. Intestinal ischemia leading to submucosal bleeding is relatively uncommon, although it is seen more frequently in elderly patients with preceding atherosclerotic disease of the arteries supplying the intestine. Blood flow to the pancreas is markedly reduced and necrosis is infrequently seen (110).

Blood

With slowing of blood flow, there is intravascular aggregation and clumping of red cells, white cells, and platelets, causing sludging. This process itself may elevate vas-

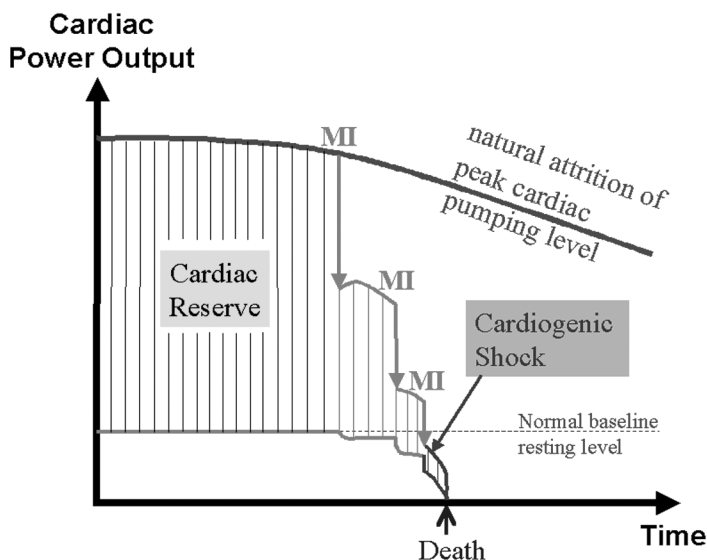


Fig. 6. A conceptual schematic diagram representing progressive deterioration of cardiac pumping capability and reserve with time. Two mechanisms of cardiomyocyte losses are depicted: (1) through natural attrition of myocytes with age and (2) through discrete myocardial infarctions (MI), which cause stepwise reductions in cardiac pumping reserve. After cumulative MIs, when the peak cardiac pumping level falls below the normal baseline resting level, the prognosis is very poor, with a high probability of death unless viable function can be restored without delay through interventions.

cular resistance. Severe shock may result in disseminated intravascular coagulation (DIC). Typical laboratory findings include thrombocytopenia, prolongation of prothrombin time and partial thromboplastin time, decreased levels of factor V and VIII, and an increased concentration of fibrin monomers and fibrin split products.

Brain

Autoregulation maintains constancy of cerebral blood flow protecting the cerebral circulation, but when perfusion pressure falls below the autoregulatory range, the resulting hypoperfusion leads to mental obtundation, drowsiness, and occasional confusional states. It is, however, unusual to see lasting cerebral insult unless there is intrinsic cerebrovascular disease (111).

SUMMARY

The pathophysiological concept of the cumulative effects of myocardial infarctions on cardiac pump function culminating in the onset of cardiogenic shock is depicted in Fig. 6. In the absence of cardiac disease, Olivetti and colleagues (112) have shown that the number of cardiac myocytes decreases with age, and compensatory remodeling could not ameliorate the progressive loss of function. When discrete masses of cardiac myocytes are damaged through infarction, stepwise losses of cardiac function occur. When the cardiac reserve function is so compromised that the failing heart becomes barely able to maintain the baseline circulation at rest, cardiogenic shock ensues. Aggressive medical

and interventional measures are required to prevent or regain the loss of cardiac functional reserve, through preserving or restoring the viability of cardiomyocyte function.

The pathophysiology of cardiogenic shock involves a vicious downward spiral: myocardial hypoperfusion causing myocardial dysfunction, which, in turn, worsens the hypoperfusion. The key to a good outcome is a prompt recognition of the preshock state in order to initiate therapy early to prevent the onset of cardiogenic shock. Once the state of shock has been reached, therapeutic success depends largely on a systematic approach to diagnosis, clear conceptual understanding of the pathophysiological processes involved, careful hemodynamic monitoring of cardiac performance, and responses to treatment; the immediate goal is sensible priority setting of management plans and adjustment of appropriate therapy. Recent work has suggested that metabolic changes may be just as important as coronary revascularization and this exciting clinical area should be the subject of further research.

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