

Pathophysiology

This chapter reviews the key elements in the pathophysiology and natural history of atherosclerosis. The interaction between the coagulation cascade and platelet physiology will also be discussed. Our understanding of the complex pathophysiology of atherosclerosis, the coagulation cascade, and platelet physiology is important in order to optimize pharmaceutical and device therapy.

Atherosclerosis

The development of atherosclerosis is influenced by an individual's risk factors: hypertension, hyperlipidemia, diabetes, and smoking. Atherosclerosis progresses over many decades until it is clinically detected [1]. Intimal thickening is present early in life; however, this is not felt to be pathologic. In the second to third decade of life, monocytes infiltrate the subintima. Once in the subintima, monocytes become macrophages, which become foam cells upon the ingestion of cholesterol. This is called a fatty streak or fatty dot and occurs early in the atherosclerotic disease process, although it progresses to an advanced plaque as a necrotic core develops. Expansion of this lipid content into a necrotic core occurs along with degradation of the extracellular matrix by matrix metalloproteinases and other inflammatory cytokines. Hemorrhage from the vasa vasorum may also contribute to the enlargement of the necrotic core. This process is more likely to occur at arterial branch points, which are areas of low shear stress. At this point, a vulnerable plaque may be present, characterized by a large necrotic lipid core underlying a thin fibrous cap. This is also referred to as a thin cap fibroatheroma and it is prone to rupture at its shoulder. The thin fibrous cap is composed of macrophages, lymphocytes, type I collagen, and relatively few smooth muscle cells [2].

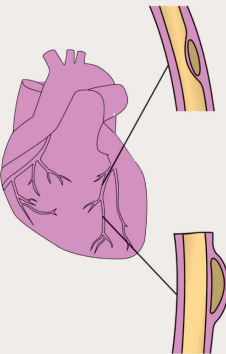
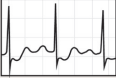

Plaque rupture

Plaque rupture is responsible for most causes of sudden death and acute coronary syndromes [3]. Microscopically, plaques that rupture have decreased smooth muscle cells and increased macrophages and inflammatory cells. Macroscopically, vulnerable plaques are usually characterized by expansion of the external elastic media, referred to as positive remodeling,

which preserves the luminal area. This is in contrast to patients with stable coronary artery disease who usually display negative remodeling or luminal narrowing. A rupture that leads to coronary occlusion is termed a ST-elevation myocardial infarction, while partial occlusion is a non-ST-elevation acute coronary syndrome (*see* Figure 2.1) [4]. Plaque rupture is more common in older individuals.

Recently, it has been discovered that vulnerable plaques can undergo frequent asymptomatic rupture with healing. Healing is characterized by

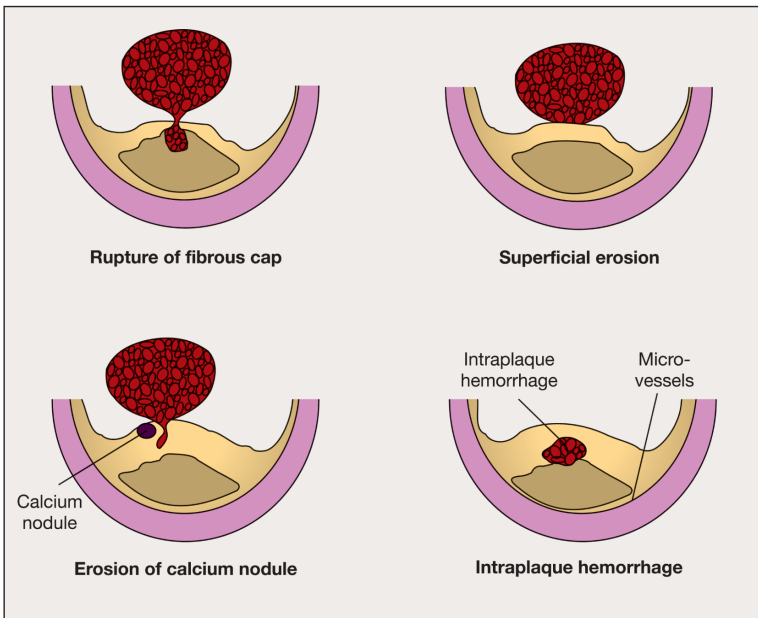
Figure 2.1 Stenotic versus nonstenotic lesions

	Type of lesion	Clinical manifestation	Management
	Stenotic <ul style="list-style-type: none">• Few inflammatory cells• Fibrinotic• Thick cap• Less compensatory enlargement	 Ischemia <ul style="list-style-type: none">• Angina pectoris• Positive exercise test• Perfusion defect	Local therapy/ revascularization <ul style="list-style-type: none">• PTCA• Stent• CABG
	Nonstenotic <ul style="list-style-type: none">• Many inflammatory cells• Lipid-rich• Thin cap• Compensatory enlargement	 Infarction	Systemic therapy <ul style="list-style-type: none">• Lifestyle modification• Drug therapy

Stenotic lesions tend to be associated with thick fibrous caps and produce stable angina, while vulnerable plaques have a large lipid cores with thin caps and produce unstable coronary events. CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty, Reprinted with permission from Libby & Theroux [4].

progressive thickening of the fibrous cap. While it is possible that each rupture can be subclinical, over time this process may result in luminal narrowing and cause stable angina [5]. An important finding is that most unstable coronary events originate from nonflow-limiting lesions (e.g., less than 70% stenosis) [6]. The implication is that revascularization of a severe coronary stenosis is usually done with the intent of symptom relief, rather than reduction in myocardial infarction or death. The next most common cause of unstable coronary events is plaque erosion, characterized by increased smooth muscle cells and decreased macrophages. Plaque erosion is frequently seen in younger individuals. The least common cause of an unstable coronary event is a calcified nodule (*see* Figure 2.2) [4].

Figure 2.2 Causes of unstable coronary events



The most common cause of an unstable coronary event is rupture into a vulnerable plaque, although other mechanisms are possible. Reprinted with permission from Libby & Theroux [4].

The coagulation cascade

The coagulation cascade is accelerated on the surface of platelets. This process can be initiated from multiple points; however, binding of the platelet glycoprotein VI receptor to subendothelial collagen is one of the important steps after plaque rupture. This results in platelet adhesion to the subendothelium followed by platelet activation. Fibrinogen mediates the aggregation of activated platelets through the cross-linking of the glycoprotein IIb/IIIa receptor. This is called the final common pathway of platelet aggregation. Glycoprotein IIb/IIIa inhibitors act by preventing the binding of fibrinogen to this receptor. Aspirin blocks cyclooxygenase, which prevents the conversion of arachidonic acid to prostaglandin G₂ and thromboxane A₂. These two agents cause potent platelet aggregation and vasoconstriction. Thienopyridines (e.g., clopidogrel) prevent platelet activation and aggregation by blocking the platelet adenosine diphosphate receptor. Aggregated platelets combine with fibrin to form thrombus. A platelet-rich thrombus forms at areas of high shear stress and is called a white thrombus, while a fibrin-rich thrombus is called a red thrombus. A red thrombus forms at areas of relative hemostasis, and can therefore trap red blood cells within the fibrin mesh. Fibrin is the final product of the coagulation cascade, which is the meeting point of the extrinsic and intrinsic pathways. Exposure of tissue factor after plaque rupture initiates the process that converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin. Tissue factor is the main stimulus for thrombin generation after plaque disruption.

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