

CHAPTER 1

Pathophysiology of acute coronary syndromes

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Introduction

Acute coronary syndromes (ACS) comprise a spectrum of clinical conditions, initiated by rupture of an atherosclerotic coronary plaque with overlying acute thrombosis. The consequences of thrombosis include direct obstruction of blood flow to the coronary beds, as well as distal embolization of the platelet-rich thrombus. Both of these processes may lead to myocardial ischemia and may progress to myocyte necrosis and myocardial infarction. The coronary thrombus may be completely occlusive, as is frequently seen in ST-segment-elevation myocardial infarction (STEMI), or nonocclusive, as can be observed in unstable angina or non-ST-elevation myocardial infarction (UA/NSTEMI). The latter two entities are also known collectively as non-ST-elevation acute coronary syndromes (NSTEMI). This chapter discusses the basic pathophysiology underlying ACS.

Braunwald has described five processes contributing to development of ACS, or any atherothrombotic event (Figure 1.1). These processes include: (1) thrombus on preexisting plaque, (2) dynamic obstruction from coronary spasm or Prinzmetal's angina, (3) progressive mechanical obstruction, (4) inflammation and/or infection, and (5) secondary unstable angina due to global myocardial oxygen supply and demand mismatch.

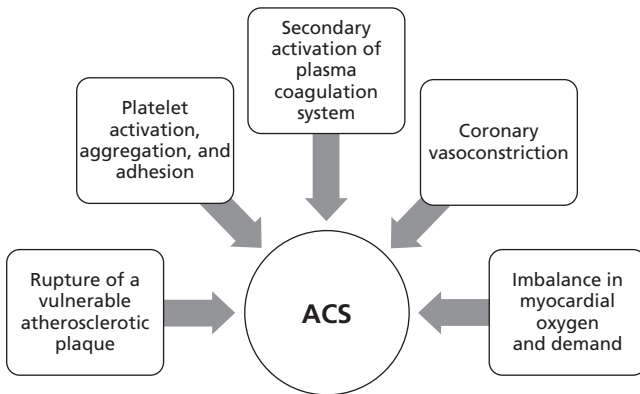


Figure 1.1 Processes contributing to the development of ACS.

Formation of atherosclerotic plaque

Complex plaques of mature atherosclerosis are the end-result of a long pathophysiologic process, which typically begins in early adulthood. Endothelial dysfunction appears to play an initial role in atherosclerosis. Injury to the endothelium results in establishment of the cycle of inflammatory cell migration and proliferation, tissue damage, and repair, and ultimately leads to plaque growth. These mechanisms are outlined in Table 1.1 and are further illustrated in Figure 1.2 (see color plate for a full-color version).

On histological specimens, early precursors of complex plaques include intimal thickening, isolated lipid-containing macrophage foam cells, and pools of extracellular lipids. These are visible on gross specimens as fatty streaks, and

Table 1.1 Primary components of atherosclerotic plaque formation, initiated by endothelial dysfunction (data from Ross¹)

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- Increased endothelial adhesiveness
 - Increased endothelial permeability
 - Migration and proliferation of smooth muscle cells and macrophages
 - Release of hydrolytic enzymes, cytokines, and growth factors
 - Focal vessel wall necrosis
 - Tissue repair with fibrosis
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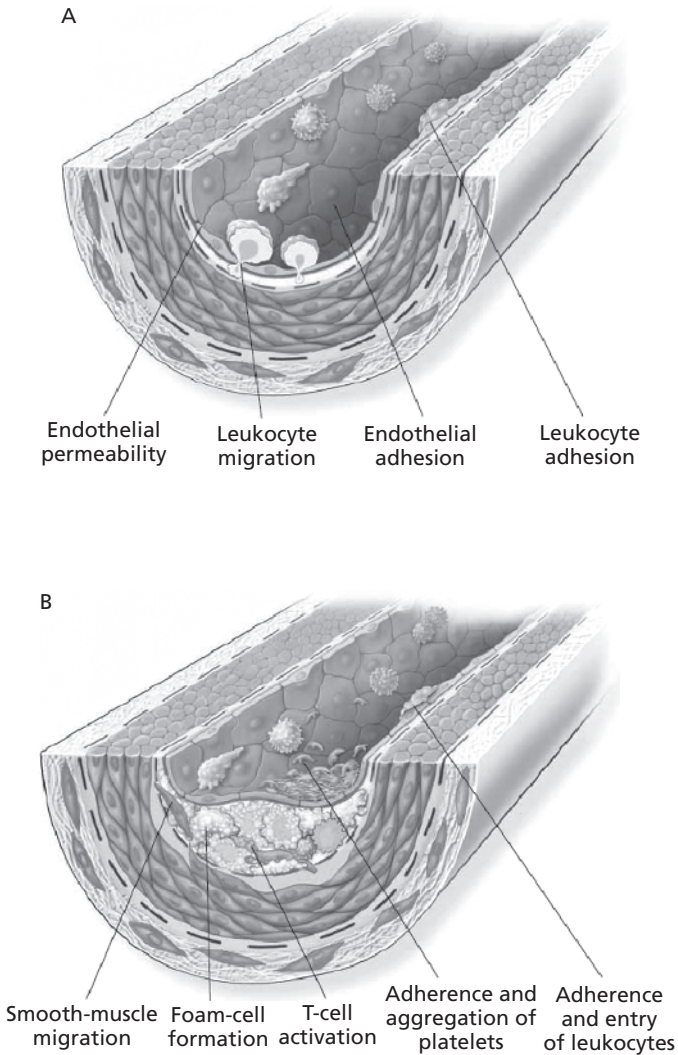


Figure 1.2 The mechanism of atherosclerotic plaque formation (reproduced from Ross *N Engl J Med* 1999; 340: 115–26). (A) Early endothelial dysfunction in atherosclerosis; (B) fatty streak formation; (C) formation of advanced complex lesion of atherosclerosis; (D) formation of an unstable fibrous plaque. A full-color version of this figure appears in the plate section.

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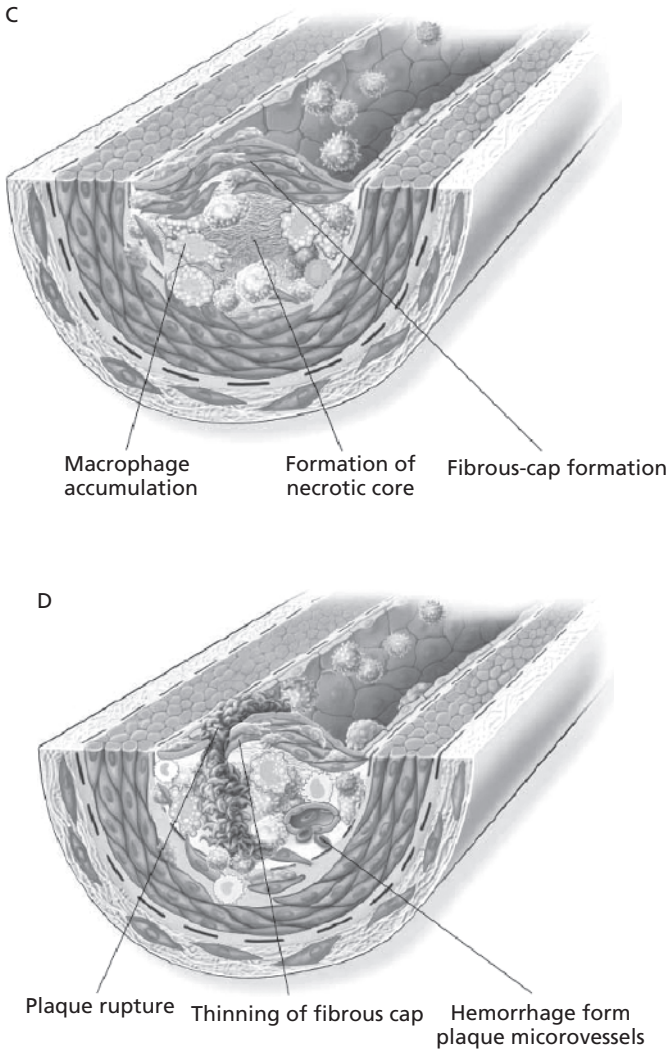


Figure 1.2 Continued.

are present in a substantial proportion of young adults who live in the developed world. Eventually, a reactive fibrotic cap and a large lipid core are formed, the lesion may become neovascularized, and calcium is deposited within the plaque (Figure 1.2).

Plaque instability and the development of ACS

If given enough time, most atherosclerotic plaques gradually progress, although their architecture generally remains stable. Symptoms occur when luminal stenosis reaches 70–80%. In contrast, the inciting event in the majority of ACS cases is plaque rupture, and most of such plaques occupy <50% of the luminal diameter prior to becoming unstable.³ Why some plaques rupture and others remain stable for years is incompletely understood, but studies have demonstrated that a large lipid core, a thin fibrous cap, and inflammation within the plaques all predispose to rupture (Figure 1.3 – see color

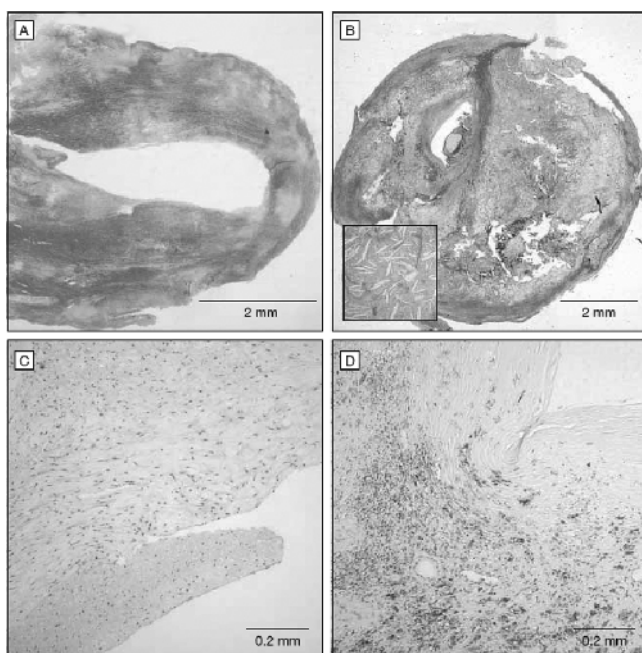


Figure 1.3 A representative histology of atherosclerotic plaque (reprinted, with permission, from Hellings *et al. Jama* 2008; 299: 547–54²). Collagen staining at low magnification showing fibrous plaque with (A) no lipid core (<10% of the plaque area) and (B) a significant lipid core (>40% of the plaque area) with visible cholesterol crystals (inset). Staining for a macrophage marker CD-68 at higher magnification, demonstrating plaques with (C) minor macrophage infiltration and (D) heavy macrophage infiltration (see color plate section for a full-color version).

plate section for full-color version).⁴ Inflammation is thought to play a central role in actual plaque disruption.¹ Indeed, a high macrophage content identifies plaques prone to rupture,⁵ and unstable, symptomatic plaques can be identified with molecular imaging targeting inflammation.⁶ C-reactive protein, a marker of inflammation, is a significant, independent predictor of myocardial infarction, stroke, and peripheral arterial disease.⁷

Exposure of thrombogenic plaque material to flowing blood initiates the endogenous thrombotic response. Actual plaque rupture may precede the clinical syndrome of ACS by several days or even weeks, as evidenced by findings of both fresh and old thrombus in samples of coronary aspirate.⁸ It seems likely that most plaque erosions and ruptures are healed with small “sealing” surface thrombi, and major occlusive thrombosis occurs relatively rarely. In these latter cases, however, progressive *in situ*

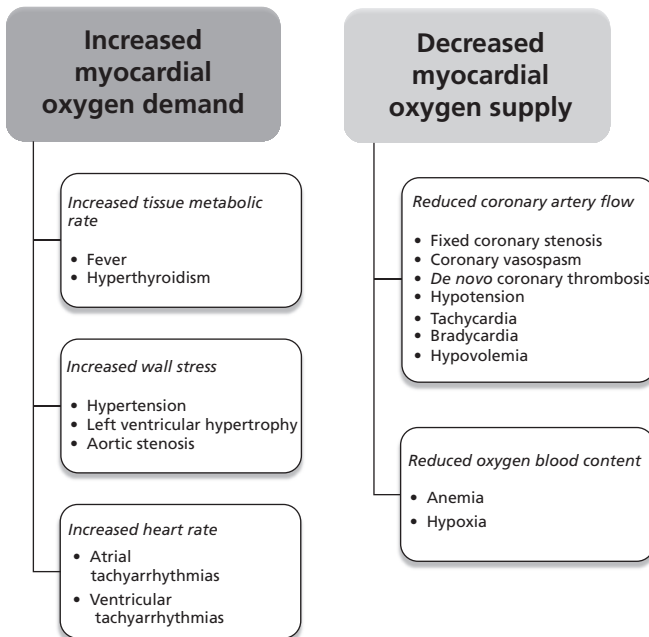


Figure 1.4 Determinants of myocardial oxygen balance and related pathophysiologic factors that contribute to acute coronary syndrome.

thrombosis, together with plaque and thrombus fragment embolization to the distal coronary microcirculation, and the overlying vasospastic response, create conditions for myocardial ischemia.

Myocardial ischemia

Myocardial ischemia occurs when the oxygen demand of the myocardium is greater than its oxygen supply (Figure 1.4). An acute thrombotic coronary occlusion in a previously patent vessel abruptly decreases myocardial oxygen supply. Alternatively, in a patient with a stable intracoronary plaque, elevated heart rate may cause myocardial ischemia by increasing myocardial oxygen demand without having the ability to increase supply. Although most cases of ACS are caused by decreased myocardial oxygen demand, a thorough understanding the components of myocardial oxygen demand and supply is crucial to an understanding of the pathophysiology of myocardial ischemia.

Thrombus formation

Acute coronary syndrome is largely caused by thrombus formation on preexisting plaque. This has been shown through both autopsies and coronary angiography.^{9,10} Platelets and the plasma coagulation system are the two major mechanisms through which a thrombus is formed (Figure 1.5).

Platelets

Platelets play a major role in primary hemostasis and in thrombus formation. This occurs in three stages: platelet adhesion, platelet activation, and platelet aggregation (Figure 1.5).¹²

Platelet adhesion

- 1 Plaque rupture exposes collagen and tissue factor to the bloodstream.
- 2 GP Ib receptor on platelets interacts with von Willabrand Factor (vWF) to adhere to the damaged endothelial surface.

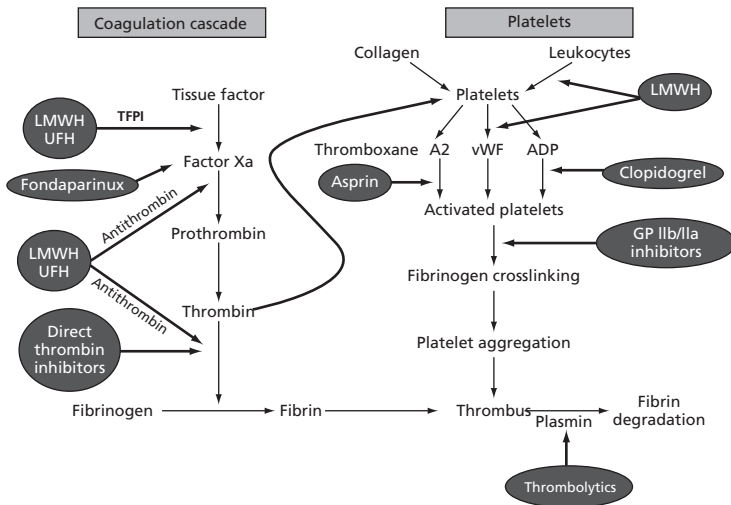


Figure 1.5 An abbreviated schema of thrombus formation and pharmacologic agents targeting thrombosis pathways (adapted, with permission, from Selwyn *Am J Cardiol* 2003; 91: 3H–11H¹¹).

Platelet activation

- 1 Platelet degranulation releases thromboxane A2 (TxA2), adenosine diphosphate (ADP), and other chemoattractants that mediate platelet aggregation. Thrombin and tissue factors also stimulate platelet aggregation.
- 2 Platelets undergo a conformational change, from a smooth shape to an irregular shape with a larger surface area.
- 3 Platelets express the GPIIb/IIIa receptor.

Platelet aggregation

- 1 GPIIb/IIIa receptors on the surface of the activated platelets interact with circulating fibrinogen.
- 2 Fibrinogen acts as a bridge between GPIIb/IIIa receptors on multiple activated platelets, causing the formation of a platelet plug.

Given that thrombus formation in coronary arteries is the major pathologic process causing ACS, many of the important pharmacologic agents used to treat ACS target platelet function.

Medications that act by interfering with primary hemostasis

- 1 **Aspirin** inhibits the production of TxA₂ by inhibiting cyclooxygenase, an enzyme in the pathway that converts arachadonic acid to TxA₂ and other prostaglandins.
- 2 **Thienopyridines (ticlopidine, clopidogrel, prasugrel)** block the ADP receptor on the platelet, which inhibits platelet aggregation and binding of fibrinogen to the GIIb/IIIa receptor on activated platelets.
- 3 **GPIIb/IIIa receptor antagonists** directly bind to the receptors that mediate platelet aggregation.

Secondary hemostasis

Secondary hemostasis (the **coagulation cascade**) is activated concurrently with the platelet-mediated primary hemostatic mechanisms described above (Figure 1.5). Plaque rupture exposes tissue factor to the bloodstream, which both has a role in platelet adhesion and in activation of the extrinsic system of the clotting cascade.

The production of thrombin

- 1 Plaque rupture exposes collagen and tissue factor to the bloodstream.
- 2 Tissue factor converts factor X to Xa.
- 3 Factor Xa converts prothrombin to thrombin.

The role of thrombin in thrombosis

- 1 Thrombin converts fibrinogen to fibrin, which is the final step in clot formation.
- 2 It activates factor XIII, which causes crosslinking of fibrin and stabilization of the clot.
- 3 It stimulates platelet aggregation (as part of primary hemostasis).

Some medications that act by interfering with the coagulation cascade

- 1 **Unfractionated heparin** activates antithrombin II (ATII), which inactivates factor Xa and thrombin.
- 2 **Low molecular weight heparin (LMWH)** also activates antithrombin, which inactivates factor Xa. However, LMWH has a much lesser effect on thrombin than does unfractionated heparin.

- 3 **Direct thrombin inhibitors (bivalirudin, argatroban)** inhibit thrombin and therefore prevent the conversion of fibrin to fibrinogen.
- 4 **Factor Xa inhibitor (fondaparinux)** inactivates factor Xa, which then prevents the conversion of prothrombin to thrombin.

In the setting of ACS, the normal balance between thrombosis and endogenous fibrinolysis is disrupted in favor of thrombosis. In addition to medications aimed at inhibiting formation of a platelet plug (aspirin, clopidogrel, GIIb/IIIa receptor antagonists), anticoagulants such as unfractionated heparin, LMWH, direct thrombin inhibitors, and factor Xa inhibitors are beneficial in the treatment of ACS (this is discussed further in Chapters 3 and 4).

Dynamic obstruction

Dynamic obstruction can occur with epicardial coronary vasospasm or be limited to the microcirculation. Symptomatic epicardial vasospasm (Prinzmetal's angina) can occur either at the site of a preexisting nonobstructive atherosclerotic plaque or in a normal portion of the vessel.¹³ Nonfocal coronary vasospasm can occur in the setting of cocaine use, cold immersion, or emotional stress.^{14,15} Angiographic evidence of epicardial coronary obstruction may be absent if the study is performed at a later time, but recurrent spasm may be demonstrated by asking the patient to hyperventilate on the angiography table. Microcirculatory angina can occur with vasoconstriction in small intramural arteries.

Progressive mechanical obstruction

Progressive mechanical obstruction is an unusual cause of ACS. It is most frequently seen when progressive in-stent restenosis causes decreasing myocardial oxygen supply over the course of months. Gradual-onset exertional angina, not ACS, is a more typical outcome of progressive mechanical obstruction.

Inflammation

As discussed above, inflammation appears to play a major role in initiation and progression of atherosclerosis, as well as in the transition from a stable to an unstable plaque and the onset of acute atherothrombosis.

Secondary unstable angina

Secondary unstable angina is myocardial ischemia/infarction caused by a process other than plaque rupture with thrombus formation. Anemia, bradycardia and severe hypotension are common causes of reduced oxygen supply, whereas tachycardia, fever, and hyperthyroidism frequently increase myocardial oxygen demand. Secondary angina is further discussed in Chapter 5.

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