usually relieved by rest (decreasing demand) or administering vasodilators, such as nitroglycerin and calcium channel blockers (increasing perfusion).

- *Prinzmetal variant angina is an uncommon form of episodic myocardial ischemia; it is caused by coronary artery spasm.* Although individuals with Prinzmetal variant angina may well have significant coronary atherosclerosis, the anginal attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to vasodilators.
- *Unstable or crescendo angina* refers to *a pattern of increasingly frequent, prolonged (>20 min), or severe angina or chest discomfort that is described as frank pain, precipitated by progressively lower levels of physical activity or even occurring at rest.* In most patients, unstable angina is caused by the disruption of an atherosclerotic plaque with superimposed partial thrombosis and possibly embolization or vasospasm (or both). Approximately one-half of patients with unstable angina have evidence of myocardial necrosis; for others, acute MI may be imminent.

Myocardial Infarction

Myocardial infarction, also commonly referred to as "heart attack," is the death of cardiac muscle due to prolonged severe ischemia. Roughly 1.5 million individuals in the United States suffer an MI annually.

Incidence and Risk Factors. MI can occur at virtually any age; nearly 10% of myocardial infarcts occur in people younger than age 40, and 45% occur in people younger than age 65. Nevertheless, MI frequency rises progressively with increasing age. The incidence of MI also strongly correlates with genetic and behavioral predispositions to atherosclerosis. Blacks and whites are equally affected. Through middle age, male gender increases the relative risk of MI; indeed, women are generally protected against MI during their reproductive years. However, postmenopausal decline in estrogen production is usually associated with accelerated CAD, and IHD is the most common cause of death in older women. Unfortunately, postmenopausal hormonal replacement therapy has not been shown to be protective, and in fact, in some cases, may be detrimental.

Pathogenesis

Coronary Arterial Occlusion. The following sequence of events likely underlies most MIs (see Chapter 11 for additional details):

- A coronary artery atheromatous plaque undergoes an acute change consisting of intraplaque hemorrhage, erosion or ulceration, or rupture or fissuring.
- When exposed to subendothelial collagen and necrotic plaque contents, platelets adhere, become activated, release their granule contents, and aggregate to form microthrombi.
- Vasospasm is stimulated by mediators released from platelets.
- Tissue factor activates the coagulation pathway, adding to the bulk of the thrombus.
- Within minutes, the thrombus can expand to completely occlude the vessel lumen.

Compelling evidence for this sequence derives from (1) autopsy studies of patients dying of acute MI; (2) angiographic studies demonstrating a high frequency of thrombotic occlusion early after MI; (3) the high success rate of coronary revascularization following MI (i.e., thrombolysis, angioplasty, stent placement, and surgery); and (4) the demonstration of residual disrupted atherosclerotic lesions by angiography after thrombolysis. Coronary angiography performed within 4 hours of MI onset shows coronary thrombosis in almost 90% of cases. However, angiography after 12 to 24 hours reveals thrombosis only about 60% of the time, suggesting resolution due to fibrinolysis, relaxation of spasm, or both.

In approximately 10% of cases, transmural MI occurs in the absence of the typical coronary atherothrombosis. In such situations, other mechanisms may be responsible for the reduced coronary blood flow, including:

- *Vasospasm* with or without coronary atherosclerosis, perhaps in association with platelet aggregation or due to drug ingestion (e.g., cocaine or ephedrine)
- *Emboli* from the left atrium in association with atrial fibrillation, a left-sided mural thrombus, vegetations of infective endocarditis, intracardiac prosthetic material; or *paradoxical emboli* from the right side of the heart or the peripheral veins, traversing a patent foramen ovale and into the coronary arteries
- *Ischemia without detectable or significant coronary atherosclerosis and thrombosis* may be caused by disorders of small intramural coronary vessels (e.g., vasculitis), hematologic abnormalities (e.g., sickle cell disease), amyloid deposition in vascular walls, vascular dissection, marked hypertrophy (e.g., aortic stenosis), lowered systemic blood pressure (e.g., shock), or inadequate myocardial "protection" during cardiac surgery.

Myocardial Response. **Coronary arterial obstruction diminishes blood flow to a region of myocardium (Fig. 12-9), causing ischemia, rapid myocardial dysfunction, and eventually—with prolonged vascular compromise—myocyte death.** The anatomic region supplied by that artery is referred to as the *area at risk*. The outcome depends predominantly on the severity and duration of flow deprivation (Fig. 12-10).

The early biochemical consequence of myocardial ischemia is the cessation of aerobic metabolism within seconds, leading to inadequate production of high-energy phosphates (e.g., creatine phosphate and adenosine triphosphate) and accumulation of potentially noxious metabolites (e.g., lactic acid) (Fig. 12-10*A*). Because of the exquisite dependence of myocardial function on oxygen and nutrients, myocardial contractility ceases within a minute or so of the onset of severe ischemia. Such loss of function actually precipitates heart failure long before myocyte death occurs.

As detailed in Chapter 2, ultrastructural changes (including myofibrillar relaxation, glycogen depletion, cell and mitochondrial swelling) also develop within a few minutes of the onset of ischemia. Nevertheless, these early manifestations of ischemic injury are potentially reversible. Indeed, experimental and clinical evidence shows that only severe ischemia (blood flow 10% or less of normal) lasting 20 to 30 minutes or longer leads to irreversible damage (necrosis) of cardiac myocytes. This delay in the onset of