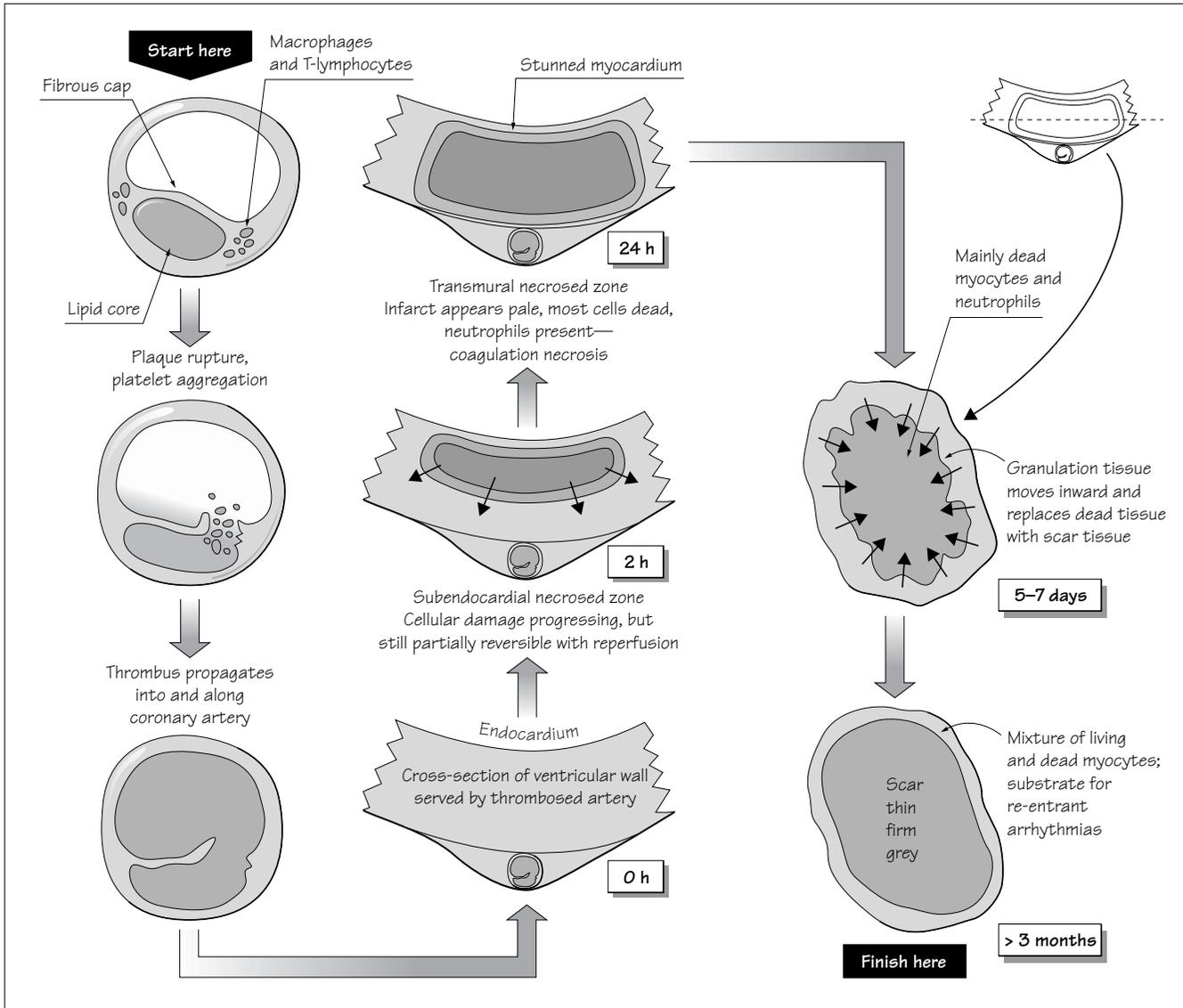


41 Pathophysiology of acute myocardial infarction



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Infarction is tissue death caused by ischaemia. Acute **myocardial infarction** (MI) occurs when localized myocardial ischaemia causes the development of a defined region of **necrosis**. MI is most often caused by rupture of an atherosclerotic lesion in a coronary artery. This causes the formation of a thrombus that plugs the artery, stopping it from supplying blood to the region of the heart that it supplies.

Role of thrombosis in MI

Pivotal studies by DeWood and colleagues showed that *coronary thrombosis* is the critical event resulting in MI. Of patients presenting within 4 h of symptom onset with ECG evidence of transmural MI, coronary angiography showed that 87% had

complete thrombotic occlusion of the infarct-related artery. The incidence of total occlusion fell to 65% 12–24 h after symptom onset due to spontaneous fibrinolysis. Fresh thrombi on top of ruptured plaques have also been demonstrated in the infarct-related arteries in patients dying of MI.

Mechanisms and consequences of plaque rupture

Coronary plaques which are prone to rupture are typically small and nonobstructive, with a large lipid-rich core covered by a thin fibrous cap. Activated **macrophages** and **T-lymphocytes** localized at the site of plaque rupture are thought to release **metalloproteases** and **cytokines** which weaken the fibrous cap, rendering it liable to tear or erode due to the shear stress exerted by the bloodflow.

Plaque rupture reveals subendothelial collagen, which serves as a site of platelet adhesion, activation and aggregation. This results in:

- 1 The release of substances such as *thromboxane A₂* (TXA₂), *fibrinogen*, *5-hydroxytryptamine (5-HT)*, *platelet activating factor* and *ADP*, which further promote platelet aggregation.
- 2 Activation of the clotting cascade, leading to fibrin formation and propagation and stabilization of the occlusive thrombus.

The endothelium is often damaged around areas of coronary artery disease. The resulting deficit of antithrombotic factors such as *thrombomodulin* and *prostacyclin* enhances thrombus formation. In addition, the tendency of several platelet-derived factors (e.g. TXA₂, 5-HT) to cause vasoconstriction is increased in the absence of endothelial-derived relaxing factors. This may promote the development of local vasospasm, which worsens coronary occlusion.

Sudden death and acute coronary syndrome onset show a **circadian variation** (daily cycle), peaking at around 9 a.m. with a trough at around 11 p.m. Levels of catecholamines peak about an hour after awakening in the morning, resulting in maximal levels of platelet aggregability, vascular tone, heart rate and blood pressure, which may trigger plaque rupture and thrombosis. Increased physical and mental stress can also cause MI and sudden death, supporting a role for increases in catecholamines in MI pathophysiology. Furthermore, chronic β -adrenergic receptor blockade abolishes the circadian rhythm of MI.

Autopsies of young subjects killed in road accidents often show small plaque ruptures in susceptible arteries, suggesting that plaque rupture does not always have pathological consequences. The degree of coronary occlusion and myocardial damage caused by plaque rupture probably depends on systemic catecholamine levels, as well as local factors such as plaque location and morphology, the depth of plaque rupture, and the extent to which coronary vasoconstriction occurs.

Severe and prolonged ischaemia produces a region of necrosis spanning the entire thickness of the myocardial wall. Such a *transmural* infarct usually causes ST segment elevation (i.e. STEMI, see Chapter 38). Less severe and protracted ischaemia can arise when:

- 1 Coronary occlusion is followed by spontaneous reperfusion.
- 2 The infarct-related artery is not completely occluded.
- 3 Occlusion is complete, but an existing collateral blood supply prevents complete ischaemia.
- 4 The oxygen demand in the affected zone of myocardium is smaller.

Under these conditions, the necrotic zone may be mainly limited to the subendocardium, typically causing non-ST segment elevation MI.

The classification of acute MI according to the presence or absence of ST segment elevation is designed to allow rapid decision-making concerning whether thrombolysis should be initiated (see Chapter 42). This classification replaces the previous one, based on the presence or absence of Q waves on the ECG, which was less useful for guiding immediate therapy.

Evolution of the infarct

Both infarcted and unaffected myocardial regions undergo progressive changes over the hours, days and weeks following coronary thrombosis. This process of postinfarct myocardial evolution leads to the occurrence of characteristic complications at predictable times after the initial event (see Chapter 42).

Ischaemia causes an immediate loss of contractility in the affected myocardium, a condition termed **hypokineses**. Necrosis starts to develop in the subendocardium (which is most prone to ischaemia; see Chapter 37), about 15–30 min after coronary occlusion. The necrotic region grows outward towards the epicardium over the next 3–6 h, eventually spanning the entire ventricular wall. In some areas (generally at the edges of the infarct) the myocardium is **stunned** (reversibly damaged) and will eventually recover if bloodflow is restored. Contractility in the remaining viable myocardium increases, a process termed **hyperkineses**.

A progression of cellular, histological and gross changes develop within the infarct. Although alterations in the gross appearance of infarcted tissue are not apparent for at least 6 h after the onset of cell death, cell biochemistry and ultrastructure begin to show abnormalities within 20 min. Cell damage is progressive, becoming increasingly irreversible over about 12 h. This period therefore provides a window of opportunity during which thrombolysis and reperfusion may salvage some of the infarct (see Chapter 43).

Between 4 and 12 h after cell death starts, the infarcted myocardium begins to undergo **coagulation necrosis**, a process characterized by cell swelling, organelle breakdown and protein denaturation. After about 18 h, **neutrophils** (phagocytic lymphocytes) enter the infarct. Their numbers reach a peak after about 5 days, and then decline. After 3–4 days, **granulation tissue** appears at the edges of the infarct zone. This consists of **macrophages**, **fibroblasts**, which lay down scar tissue, and **new capillaries**. The infarcted myocardium is especially soft between 4 and 7 days, and is therefore maximally prone to **rupturing**. This event is usually fatal, may occur at any time during the first 2 weeks and is responsible for about 10% of MI mortality. As the granulation tissue migrates inward toward the centre of the infarct over several weeks, the necrotic tissue is engulfed and digested by the macrophages. The granulation tissue then progressively matures, with an increase in connective (scar) tissue and loss of capillaries. After 2–3 months, the infarct has healed, leaving a noncontracting region of the ventricular wall that is thinned, firm and pale grey.

Infarct expansion, the stretching and thinning of the infarcted wall, may occur within the first day or so after a MI, especially if the infarction is large or transmural, or has an anterior location. Over the course of several months, there is progressive dilatation, not only of the infarct zone, but also of healthy myocardium. This process of **ventricular remodelling** is caused by an increase in end-diastolic wall stress. Infarct expansion puts patients at a substantial risk for the development of congestive heart failure, ventricular arrhythmias, and free wall rupture.