PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION - OVERVIEW

Jagdish L Kakadiya, Dr. Nehal J Shah

**Department of Pharmacology, Dharmaj degree Pharmacy College,
Petlad-khambhat road, Dharmaj,
Dist: Anand, Gujarat, India.**

ADDRESS FOR CORRESPONDENCE

Mr. Jagdish L. Kakadiya
Dharmaj degree pharmacy college,
Amrapali Township, Petlad-khambhat road,
Dharmaj, Dist: Anand-388430,
Gujarat, India.
jagdishkakadiya@yahoo.co.in

1. INTRODUCTION

Myocardial infarction (MI) is the rapid development of myocardial necrosis caused by a critical imbalance between oxygen supply and demand of the myocardium. This usually results from plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium.

Myocardial ischemia due to coronary occlusion for as little as 60 seconds causes ischemic zone changes from a state of active systolic shortening to one of passive systolic lengthening (1). Occlusions for less than 20 minutes usually cause reversible cellular damage and depressed function with subsequent myocardial stunning. Furthermore, reperfusion of the infarct leads to variable amounts of salvageable myocardium. After 40 minutes of ischemia followed by reperfusion, 60% to 70% of the ultimate infarct is salvageable, but this decrease dramatically to 10% after 3 hours of ischemia (2, 3) Animal model evidence has also demonstrated that 6 hours of regional ischemia produces extensive transmural necrosis (4). The exact timing in humans is even more difficult to analyze because of collateral flow, which is a major determinant of myocardial necrosis in the area at risk in humans (3). The collateral blood supply is extremely variable, especially in patients with long-standing coronary disease. However, collateral flow is jeopardized with arrhythmias, hypotension, or the rise of left ventricular end-diastolic pressure above tissue capillary pressure (2). Thus loss of collateral flow to the infarct area may lead to the cellular death of salvageable myocardium. Control of blood pressure and prevention of arrhythmias are vital during this immediate time after infarction.

Myocardial infarction ("heart attack") is the irreversible damage of myocardial tissue caused by prolonged ischemia and hypoxia. This most commonly occurs when a coronary artery becomes occluded following the rupture of an atherosclerotic plaque, which then leads to the formation of a blood clot (coronary thrombosis). This event can also trigger coronary vasospasm. If a vessel becomes completely occluded, the myocardium normally supplied by that vessel will become ischemic and hypoxic. Without sufficient oxygen, the tissue dies. The damaged tissue is initially comprised of a necrotic core surrounded by a marginal (or border) zone that can either recover normal function or become irreversibly damaged. The hypoxic tissue within the border zone may become a site for generating arrhythmias. Collateral blood flow is an important determinant of infarct size and whether or not the border zone becomes irreversibly damaged.

Infarcted tissue does not contribute to tension generation during systole, and therefore can alter ventricular systolic and diastolic function and disrupt electrical activity within the heart. After several weeks, the infarcted tissue forms a fibrotic scar. Long-term consequences include ventricular remodeling of the remaining myocardium (e.g., development of compensatory hypertrophy or dilation), ventricular failure, arrhythmias and sudden death.

Myocardial infarctions produce clinical symptoms that include intense chest pain that may radiate into the neck, jaw or arms (i.e., referred pain), a sense of substernal heaviness, squeezing or pressure, shortness of breath (dyspnea), fatigue, fainting (syncope), nausea, sweating (diaphoresis), anxiety, sleeplessness, hypertension or hypotension (depending in part on the extent of cardiac damage), tachycardia and arrhythmias. Recent clinical research indicates that the symptoms may be very different between men and women. Chest pain is less common in women. Instead, their most common symptoms are weakness, fatigue and dyspnea.

Many clinical trials have shown the beneficial effects of early reperfusion within (5) hours after acute myocardial infarction (6). Although benefits of late reperfusion beyond hours, particularly in asymptomatic patients, have yet to be shown in large clinical studies, advocates for aggressive management believe that reperfusion is warranted to preserve the border areas that may be underperfused during the early days after an infraction. While some of these patients may develop objective evidence of ischemia, the clinical assumption that a hypotensive patient with a suddenly dilated and pressure-overloaded ventricle is prone to losing more muscle mass in border zones of the infarct is reasonable. This is true even in patients who have had complete revascularization. Conservative measures, such as nitroglycerin and intra-aortic balloon pumps, have demonstrated their efficacy in this population of patients without clearly salvageable myocardium by improving coronary blood supply and reducing the work demand of the left ventricle. More radical approaches such as insertion of a left ventricular assist device (LVAD) have been advocated as well (7, 8).

Anatomically, the location of the coronary obstructive lesion and additional diseased vessels and the presence of collateral flow will determine the extent of early injury, especially for borderline areas. However, ventricular remodeling of the infarct has important consequences influencing ventricular function after myocardial infarction (9). Thus appropriate and aggressive invasive therapies such as PTCA, IABP, CABG, controlled reperfusion, and LVAD insertion can

mitigate myocardial injury and salvage borderline areas. However, since last two decades it has been noticed that the beneficial effects of restoration of blood supply comes with consequences leading to injury known as reperfusion injury.

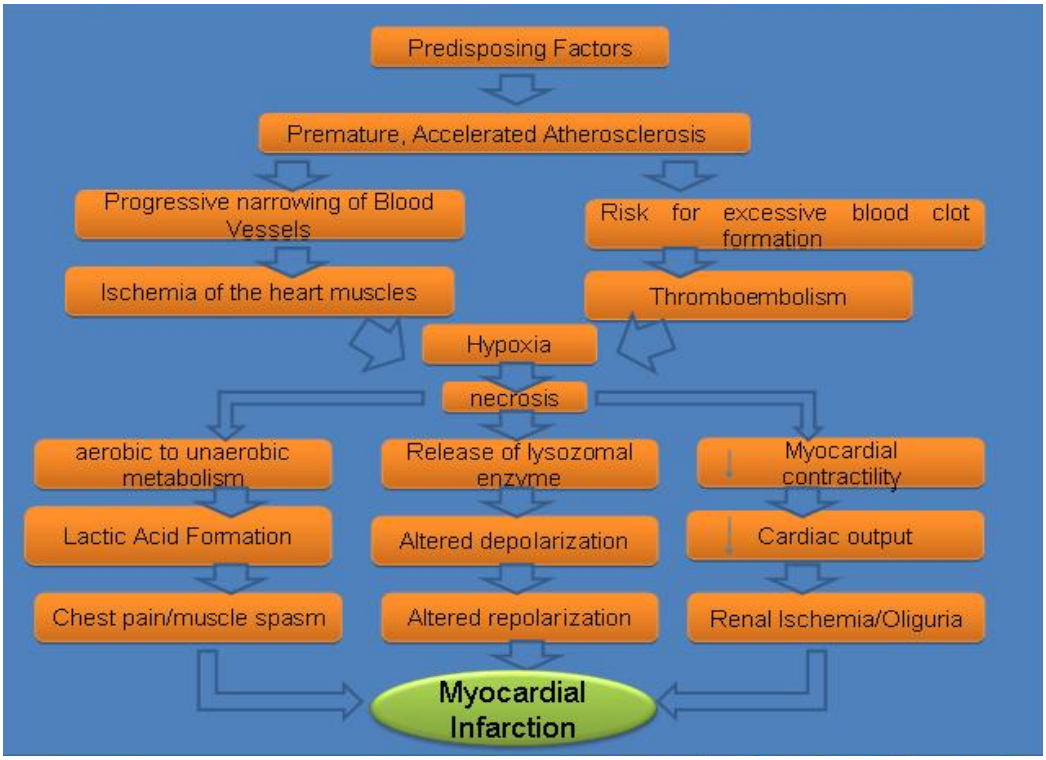

Figure 1: Pathophysiology of myocardial infarction

2. REPERFUSION INJURY

It is major contributor to myocardial damage as free oxygen radicals are released and destroy endothelial cells and produce interstitial edema. The timing and management of reperfusion effects on myocardial damage may have an impact on both survival and functional recovery of individuals following acute myocardial infarction (10). Some centers have argued convincingly that controlled reperfusion with specially designed perfusate and a decompressed, energy-conserving ventricle resting on cardiopulmonary bypass is the best means to preserve muscle mass.

3. CARDIOGENIC SHOCK

Cardiogenic shock is defined clinically as a systolic blood pressure below 80 mm Hg in the absence of hypovolemia, peripheral vasoconstriction with cold extremities, changes in mental

status, and urine output of less than 20 mL/h. Hemodynamic parameters for cardiogenic shock include cardiac index less than 1.8 L/min/m^2, stroke volume index less than 20 mL/m^2, mean pulmonary capillary wedge pressure greater than 18 mm Hg, tachycardia, and a systemic vascular resistance of over 2400 dyn·sec/cm^5. These patients are defined as type IV by the Killip classification, a widely used system to classify myocardial infarctions (11).

4. PREVALENCE

Shock is the most common cause of in-hospital mortality following myocardial infarction. The in-hospital mortality associated with cardiogenic shock has remained unchanged at approximately 80% despite the development of new treatment modalities (12). Cardiogenic shock occurs in 2.4% to 12.0% of patients with acute myocardial infarction (13). Since 1975, the incidence of cardiogenic shock complicating acute myocardial infarctions has remained constant at 7.5%, ranging between 5% and 15% (12). One reason these figures may have remained constant is the increasing efficiency of emergency medical systems in resuscitating patients in the community and bringing them to the hospital. Previously, these patients would have died before reaching the hospital. Similarly, there has been a decrease in the incidence of out-of-hospital deaths due to coronary disease between 1975 and 1988 (12). The key to success in patients in shock is early intervention and revascularization. In a prospective randomized study, Hochman et al showed that revascularization within 6 hours of diagnosis of cardiogenic shock confers survival benefits, particularly in those patients under 75 years of age (14, 15). Use of mechanical circulatory support also may play a role by resting stunned myocardium to allow its recovery and to prevent the irreversible end-organ injury that may result from prolonged shock (16).

5. INFARCT SIZE AND SHOCK

Shock is directly related to the extent of the myocardium involved. Myocardial infarctions resulting in loss of at least 40% of the left ventricle have been shown to result in cardiogenic shock (17-19). Autopsy findings also revealed marginal extension of the recent infarct and focal areas of necrosis in patients with cardiogenic shock (17). Extensive three-vessel disease is usually found in individuals with cardiogenic shock, and extension of the infarct is an important determinant in those individuals (17-19). Limiting the size of the infarct and its extension is the key to therapeutic interventions in patients with myocardial infarction. By following creatinine phosphate kinase (CPK) levels, and showed that the progression/extension

of myocardial damage results in cardiogenic shock. Patients who develop shock have higher peak values (20).

6. STATES OF IMPAIRED MYOCARDIUM

Coronary insufficiency can result in three states of impaired myocardium: infarcted, hibernating, and stunned. Each state requires separate clinical interventions and carries different prognostic implications. Infarcted myocardium is irreversible myocardial cell death due to prolonged ischemia. Hibernating myocardium is a state of impaired myocardial and left ventricular function at rest due to reduced coronary blood flow that can be restored to normal if a normal myocardial oxygen supply-demand relationship is reestablished (21, 22). Hibernating myocardium is defined as contractility-depressed myocardial function secondary to severe chronic ischemia that improves clinically immediately following myocardial revascularization. Stunned myocardium is left ventricular dysfunction without cell death that occurs following restoration of blood flow after an ischemic episode. If a patient survives the insult resulting from a temporary period of ischemia followed by reperfusion, the previously ischemic areas of cardiac muscle eventually demonstrate improved contractility.

7. HIBERNATING MYOCARDIUM

Hibernation may be acute or chronic. Angina after myocardial infarction commonly occurs at a distance from the area of infarction. In fact, mortality is significantly higher in patients with ischemia at a distance (72%) compared with ischemia adjacent to the infarct zone (33%) (23). It is the hibernating myocardium that may be in jeopardy and salvageable, although its presence is usually incidental to the occurrence of the acute infarction. By distinguishing between hibernating myocardium and irreversibly injured myocardium, a more aggressive approach to restoring or improving blood flow to the area at risk is reasonable. Function often improves immediately after revascularization of appropriately selected regions.

8. STUNNED MYOCARDIUM

In the 1970s it was observed that after brief episodes of severe ischemia, prolonged dysfunction with gradual return of contractile activity occurred. Stunning is a fully reversible process despite the severity and duration of the insult if the cells remain viable. However, myocardial dysfunction, biochemical alterations, and ultrastructural abnormalities continue to

persist after return of blood flow. Within 60 seconds of coronary occlusion, the ischemic zone changes from a state of active shortening to one of passive shortening (24). Coronary occlusion lasting less than 20 minutes is the classic model reproducing the stunning phenomenon (25, 26).

The most likely mechanisms of myocardial stunning are calcium overload, generation of oxygen-derived free radicals, excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction, or a combination thereof. Other mechanisms that may contribute to the stunning phenomenon include insufficient energy production, impaired energy use by myofibrils, impaired sympathetic neural responsiveness, impaired myocardial perfusion, damaged extracellular collagen matrix, and decreased sensitivity of myofilaments to calcium (27, 28).

Stunned myocardium can occur adjacent to necrotic tissue after prolonged coronary occlusion and can be associated with demand-induced ischemia, coronary spasm, and cardioplegia-induced cardiac arrest during cardiopulmonary bypass. Clinically these regions are edematous and even hemorrhagic. They also have a propensity for arrhythmias, which can lead to more extensive ventricular stunning and hypotension with subsequent infarction of these regions.

9. ATHEROSCLEROSIS

Acute myocardial infarction refers to two subtypes of acute coronary syndrome, namely non-ST-elevated myocardial infarction and ST-elevated myocardial infarction, which are most frequently (but not always) a manifestation of coronary artery disease. The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade, sometimes resulting in total occlusion of the artery.

Atherosclerosis is the gradual buildup of cholesterol and fibrous tissue in plaques in the wall of arteries (in this case, the coronary arteries), typically over decades. Blood stream column irregularities visible on angiography reflect artery lumen narrowing as a result of decades of advancing atherosclerosis. Plaques can become unstable, rupture, and additionally promote a thrombus (blood clot) that occludes the artery; this can occur in minutes. When a severe enough plaque rupture occurs in the coronary vasculature, it leads to myocardial infarction (necrosis of downstream myocardium).

If impaired blood flow to the heart lasts long enough, it triggers a process called the ischemic cascade; the heart cells in the territory of the occluded coronary artery die (chiefly

through necrosis) and do not grow back. A collagen scar forms in its place. Recent studies indicate that another form of cell death called apoptosis also plays a role in the process of tissue damage subsequent to myocardial infarction (29).

Injured heart tissue conducts electrical impulses more slowly than normal heart tissue. The difference in conduction velocity between injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be the cause of many lethal arrhythmias. The most serious of these arrhythmias is ventricular fibrillation (V-Fib/VF), an extremely fast and chaotic heart rhythm that is the leading cause of sudden cardiac death. Another life threatening arrhythmia is ventricular tachycardia (V-Tach/VT), which may or may not cause sudden cardiac death. However, ventricular tachycardia usually results in rapid heart rates that prevent the heart from pumping blood effectively. Cardiac output and blood pressure may fall to dangerous levels, which can lead to further coronary ischemia and extension of the infarct.

The cardiac defibrillator is a device that was specifically designed to terminate these potentially fatal arrhythmias. The device works by delivering an electrical shock to the patient in order to depolarize a critical mass of the heart muscle, in effect "rebooting" the heart. This therapy is time dependent, and the odds of successful defibrillation decline rapidly after the onset of cardiopulmonary arrest.

In summary, infarcted myocardium is nonviable myocardium, while hibernating myocardium is viable myocardium that is chronically dysfunctional due to impaired blood supply. Stunned myocardium is viable myocardium that is acutely dysfunctional after adequate blood supply has been restored.

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