LIMITATION OF THE SIZE
OF ACUTE CARDIAC INFARCTION

A REVIEW ARTICLE

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BY

HASSAN FAROUK MOHAMED AGGAG

Supervised By

Prof. ALI RAMZY

Professor of Cardiology

Ain Shams University

Dr. MOHAMED AWAD TAHER

Lecturer of Cardiology

Ain Shams University

Faculty of Medicine

Ain Shams University

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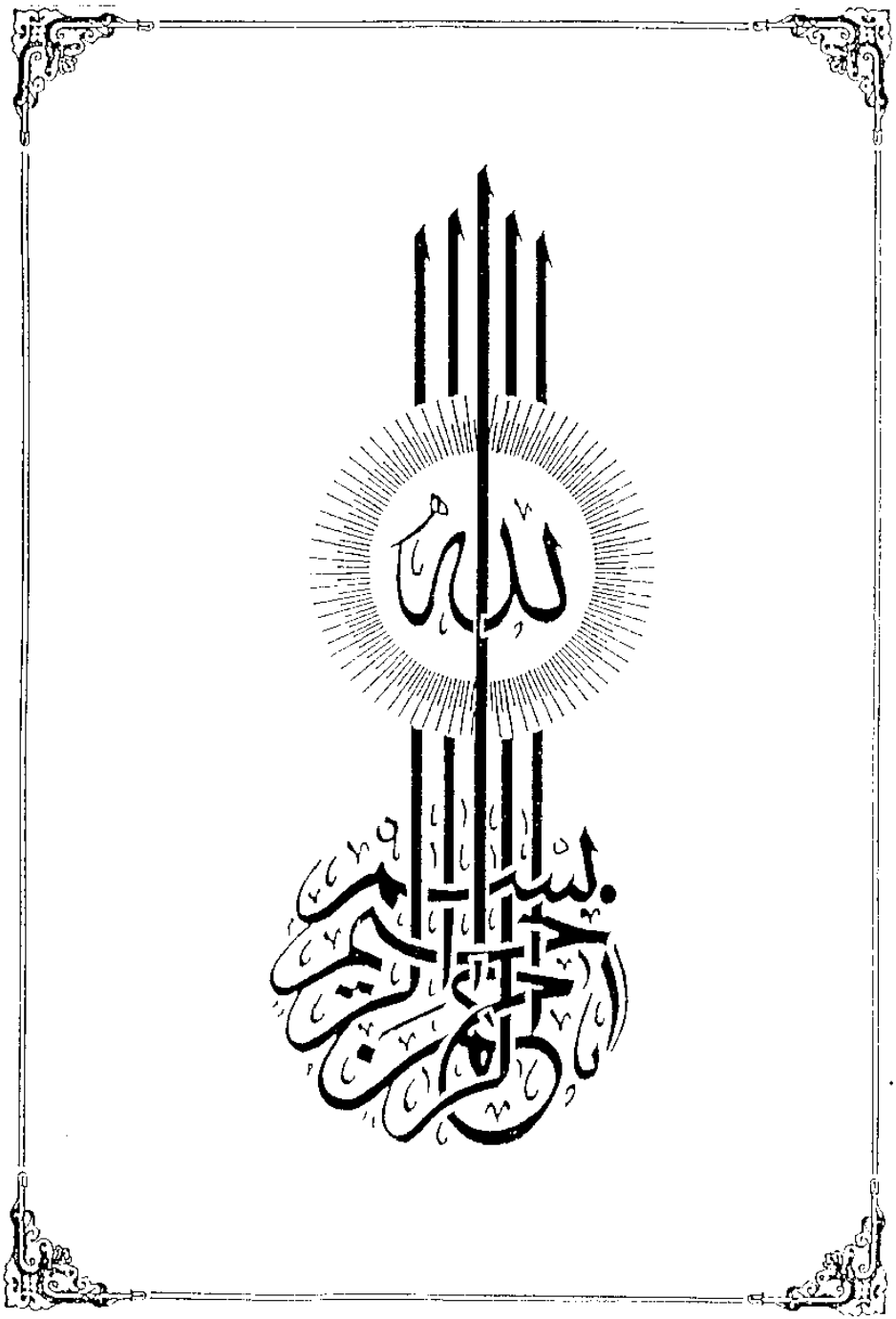

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PATHOGENESIS

PATHOGENESIS OF ISCHEMIC MYOCARDIAL INJURY

Myocardial ischemia is the result of imbalance between oxygen supply to the myocardium and its demand, i.e., when the arterial flow available to the heart or to a portion of the heart is inadequate to provide enough oxygen to support aerobic metabolism. As a result of the oxygen deficiency, myocardial energy metabolism promptly shifts to anaerobic glycolysis. The myocardial ischemia is characterized by low arterial flow, low oxygen tension, and the presence of anaerobic glycolysis. At or about the time the ischemic myocytes die, anaerobic glycolysis ceases and only degradative processes, hypoxia, and the depression in arterial flow remain as the local signs of ischemia (Kirk and Jennings, 1982).

In the open-chest anesthetized dog, proximal occlusion of a coronary artery is followed within 5 to 15 seconds by the appearance of hypoxia; the affected myocardium becomes cyanotic, electrocardiographic changes appear, and myocardium begins to convert to anaerobic metabolism, during the first few seconds after occlusion, there is sufficient oxygen trapped in the tissue as oxyhemoglobin and oxymyoglobin to provide for some aerobic metabolism, however, within a few seconds, the only oxygen available is that provided by the collateral arterial flow. Once oxygen is no longer available to accept the hydrogen or electrons removed from substrates, all parts of the terminal electron transport system of the mitochondria, including flavine adenine dinucleotide (FAD), nicotine adenine dinucleotide (NAD), and the cytochromes, become reduced with a simultaneous reduction or cessation of all forms of metabolism dependent on oxygen. Mitochondrial oxidative metabolism essentially stops, shortly, most cellular functions dependent upon a significant supply of high energy phosphate (HEP), such as contraction, are depressed or cease. Anaerobic glycolytic metabolites such as lactate, accumulate along with a concomitant decrease in cellular glycogen (Kirk and Jennings, 1982).

The local area of severe ischemia show that lactate accumulation develops 15 to 30 seconds after experimental coronary occlusion. Lactate levels essentially triple during this interval. The lactate accumulates both because it can not be metabolized further by ischemic cells and because washout is greatly impeded by the depressed flow, thus, after only 15 to 30 seconds of ischemia, enough lactate has accumulated to show that anaerobic glycolysis is very active and that it probably has become the predominant form of energy production by the myocardium (Braasch et al., 1968). The transition to anaerobic metabolism is accompanied by the utilization of the reserve HEP of the cell. Creatine phosphate (CP) decreases from 8 to 4 μmol/g between 15 to 30 seconds, and thereafter continues to decrease. This decrease is accompanied by an increase inn cellular creatine and maintenance of adenosine triphosphate (ATP) levels via creatine Kinase (CK). Once the CP supplies become markedly reduced, the ATP of the cell also begins to decrease (Kirk and Jennings, 1982).

Anaerobic glycolysis generates lactate at a high rate during the first minute of ischemia, but the rate then quickly slows. The phase of the high rate yields enough HEP in high flow anoxia in isolated rat hearts perfused with glucose to maintain significant mechanical function and to prevent degradation of the adenine nucleotide pool. However the slowing is an important feature of ischemic injury because it is unable to provide enough HEP to prevent degradation of the adenine nucleotide pool (Kirk and Jenning, 1982). The slowing of the initial high rate of glycolysis may be due to inhibition of glyceraldehyde-3-phosphate dehydrogenase by high levels of reduced nicotine adenine dinucleotide (NADH) and lactate. In addition, the acid PH of the ischemic cell may contribute to the slowing by inhibiting phosphofructokinase (Neely et al., 1976).

Since in total ischemia, the slow rate remains relatively constant until glycolysis stops, it seems certain that the factors which slow the rate of glycolysis develop promptly and persist without increasing in severity (Kirk and Jennings, 1982). Glycolysis continues to produce lactate and HEP at a relatively slow rate until injury becomes irreversible (Jennings and Reimer, 1981).

The onset of irreversible injury is associated with both ATP depletion and with cessation of glycolysis (Jennings et al., 1981). The terminal slowing and final cessation of anaerobic glycolysis occurs when the ATP of the tissue decreases to less than 1 μmol per gram of dry weight, ATP is required to phosphorylate fructose-6-phosphate (Jennings et al., 1981). Additional factors may include the presence of inhibitors of glycolysis such as increased ionic Ca^{++} within the cell, depletion of glycogen from the tissue, loss of cofactors required for the enzymatic reactions of glycolysis such as Mg^{++}, K^{+} and NAD (Jennings and Reimer, 1983).

The demand of tissue for HEP exceeds the capacity of anaerobic glycolysis to generate it, and reserve supplies of HEP are consumed, the reserve supplies of HEP comprise some 20 to 22 μmol, of which 8 to 10 μmol are CP. This is utilized almost completely in 2 to 3 minutes, and ATP levels decline continuously there after because the anaerobic glycolytic rate in ischemic tissue is inadequate to meet the rate of utilization of HEP, after 15 minutes of severe regional ischemia in the dog heart, more than 65% of the ATP of the tissue is gone and the adenine nucleotide pool is depleted by 55%, by the time 40 minutes of severe ischemia has passed, only 8% of the ATP remains, adenosine diphosphate (ADP) also decreases, but adenosine monophosphate (AMP) increases (Jennings and Reimer, 1981).

The loss of the adenine nucleotide pool is due to the degradation of adenine nucleotides to adenosine, inosine, hypoxanthine, and xanthine (Jennings et al., 1981).

Another consequence of ATP depletion is the appearance of cardiac contracture rigor, stiffening of the myocardium in vivo or in vitro occurs in dog heart at ATP levels of 2 μmol per gram of dry weight or less, although changes in sarcoplasmic calcium concentration may contribute to the initial contracture, the rigor is an indicator of the presence of irreversible injury (Kirk and Jennings, 1982).

Pathogenesis of Irreversible Ischemic Injury

Myocyte death occurs in zones of severe ischemia when the tissue ATP is at a very low level and when anaerobic glycolysis has virtually ceased, at this time, electron microscopy reveals the striking mitochondrial, nuclear, and sarcolemmal alterations which are diagnostic of ischemic cell death (Jennings and Ganote, 1974).

After the death of the myocytes, the later phases of phagocytosis and repair, the funeral events, occur at a much slower pace and may require 30 to 40 days for completion (Kirk and Jennings, 1982).

The characteristic features at the onset of the irreversible phase is associated with slowing of anaerobic glycolysis, depletion of HEP, ATP content is 2 μmol per gram dry (8% of control or less), ADP is only 50% of control, and tissue AMP is increased. Ultrastructural analysis shows breaks in the plasmalemma and amorphous matrix densities in swollen mitochondria. The changes noted 24 hours after the onset of low-flow ischemia, i.e., the time at which necrosis is obvious by light microscopy, are virtually identical to those found early in the irreversible phase. The membrane defects enlarge; soluble cell constituents leak to the extracellular fluid and diffuse to the systemic circulation; and the intracellular and extracellular fluid come to equilibrium (Jennings and Reimer, 1981).

Numerous hypotheses, which often are interrelated, have been proposed to explain the cause of lethality (Jennings and Reimer, 1981); at present, the most popular ideas focus on membrane damage as the lethal event. Disruption of the sarcolemma and perhaps other membrane systems of the cell are considered to cause irreversibility; accordingly, the approximate cause of myocyte death will be the sequence of events that leads to functional and structural disruption of the membranes. The two major consequences of damage to the sarcolemma are:

(1) The entry of excess Ca^{2+} into the myocyte from the extracellular space with resultant disruption of much of the internal metabolic machinery of the cell, and

(2) The loss of critical intracellular components such as enzymes and cofactors through a leaky membrane to the extracellular space (Kirk and Jennings, 1982).

The causes of membrane disruption are unknown. Those proposed include activation of endogenous phospholipases of sarcolemma as a consequence of either increased intracellular calcium or depressed phosphorylation of membrane proteins by the reduced sarcoplasmic ATP of the ischemic cell, alternatively, membranes could be damaged because of the action of phospholipases released from lysosomes, the detergent action of acylcarnitine and acyl COA which accumulate in ischemia, free radical effects such as lipoperoxidation, and/or failure to resynthesize membranes lost through pinocytosis or other processes (Kirk and Jennings, 1982).

Defective mitochondrial function and structure are additional striking features of the early irreversible phase (Jennings and Ganote, 1976). Some workers consider mitochondrial defects to be the real cause for the transition to irreversibility. Since mitochondrial function is inhibited in the absence of oxygen, it seems unlikely that mitochondrial damage would be of any added consequence to the tissue as long as it remains ischemic (Kirk and Jennings, 1982).

The best current hypothesis is that cell death occurs when HEP principally ATP, is depleted to levels insufficient to retain the structural integrity of the ischemic cell (Jennings and Reimer, 1981). It seems certain that the ATP deficit must be present for a period of minutes before cell death can be detected, this has been termed a "metabolite deficit period" in hepatic D-galactosamine poisoning and appears to exist in ischemic heart as well. Because HEP, in the form of ATP, is required for a large number of synthetic and degradative reactions within the cell, the premise that ATP is required to keep a cell functional and alive is generally accepted, however, the converse hypothesis, that the absence of HEP is the proximate cause of cell death, is difficult to prove without identification of reactions requiring ATP, the absence of which causes myocyte death (Kirk and Jennings, 1982).

PATHOGENESIS OF REPERFUSION

Myocardial ischemia initially causes reversible cellular injury in the sense that reperfusion prevents myocyte death. With longer periods of ischemia, cellular injury becomes irreversible; necrosis occurs even if arterial flow is restored. The transition from reversible to irreversible injury does not occur simultaneously in all cells, but occurs first in the subendocardial region (starting within 20 minutes) and progressively involves more cells in a transmural wave front of cell death until the infarct reaches its maximum size 3-6 hours after occlusion. Vascular injury also becomes more widespread with increasing duration of ischemia, but more slowly than myocyte damage (Jennings and Reimer, 1983).

In experimental coronary occlusion in the dog, and probably in man as well the duration of cellular viability and the final transmural extent of an infarct depend chiefly on the amount of collateral arterial blood flow. Both collateral flow and the duration of myocyte survival are lowest in the subendocardial and highest in the subepicardial region of the myocardium (Jennings and Reimer, 1983).

Reperfusion of ischemic myocardium has several effects:

(1) It accelerates the disintegration of irreversibly injured cells. Such cells swell explosively and exhibit a disrupted sarcolemma, loss of cell volume regulation, contraction band necrosis and calcium loading of mitochondria. These changes are associated with an accelerated washout, of creatine Kinase in the initial phase of reperfusion.

(2) If the vasculature has been compromised, reperfusion may not occur. Potential causes of this no-reflow phenomenon include endothelial damage, endothelial or myocyte swelling, development of contracture-rigor, and perhaps plugging of capillaries by granulocytes. Also, vascular damage may result in

hemorrhage into parts of the irreversibly injured tissue. Available evidence suggests that hemorrhage is a secondary event that does not contribute to myocyte necrosis.

(3) If reperfusion is instituted at a time when viable ischemic myocytes are present in the tissue, it limits infarct size. In experimental ischemic injury, most of the ischemic myocardium that can be salvaged is in the subepicardial region of relatively mild ischemia. In effect, the severely ischemic myocardium dies quickly; the moderately ischemic subepicardium dies more slowly and can be salvaged by later reperfusion. Thus, successful reperfusion converts a potentially transmural infarct into a subendocardial infarct. In both the open-chest and awake dog models, the period within which reperfusion can limit infarct size is about 3 hours.

During the first 15 minutes, the entire ischemic region was salvageable (reversibly injured), since no necrosis developed: by 40 minutes, 60-70% of the ultimate infarct was still salvageable, but by 3-6 hours only about 10% of the final infarct was salvageable. In some animals, small amounts of salvageable myocardium may persist beyond 3 hours, but limitation of infarct size has not been demonstrated experimentally beyond 5-6 hours.

(4) Reperfusion of reversibly injured myocytes is followed by recovery of contractile function and of the high-energy phosphate and adenine nucleotide pool. However, this recovery process may require several days (*Jennings and Reimer, 1983*).

Effect of Reperfusion during the Phase of Reversible Ischemic Injury

Reperfusion of reversibly injured tissue is followed by resumption of aerobic metabolism. The various metabolites that have accumulated either are reused or are washed to the systemic circulation. Electrocardiographic changes disappear. *Furthermore, the reversibly injured tissue manifests no permanent structural defects* and electrolytes and water content are restored (Whalen et al., 1974), however, the

preservation of cellular viability by reperfusion does not necessarily imply immediate recovery of regional contractile function or metabolism. A number of studies have shown prolonged depression of regional contractile function following even brief episodes of ischemia associated with reversible cell injury (Wood et al., 1979). The cause of the prolonged contractile dysfunction has not been established, but could be related to the depressed adenine nucleotide pool (Jennings and Reimer, 1983).

In the ischemic region, the ATP content increased slightly after 20 minutes of reperfusion, but no further increase was detected even at 24 hours. By 4 days, the ATP content was nearly lack to control but was still significantly less than control ATP levels. The early recovery of ATP is probably due to the recharging of the ADP and AMP by resumption of aerobic metabolism in the ischemic myocytes. Further repletion of ATP requires net resynthesis of adenine nucleotides either by salvage or de novo pathways, these pathways are known to be slow in myocardium (Zimmer et al., 1973).

Recent experimental studies have shown that both metabolic and functional recovery occur gradually over 1-4 days after reperfusion (Jennings and Reimer, 1983).

Effect of Early Reperfusion on Irreversibly Injured Myocytes

Reperfusion of irreversibly injured myocytes early in the phase of irreversible injury results in rapid and very striking changes (Kloner et al., 1974). Sarcomeres become supercontracted and form prominent contraction bands. Large subsarcolemmal blebs of fluid develop. The sarcolemma itself is severely damaged in focal areas, especially in the blebs. Often, vesicles of plasma membrane are the only remnants of plasmalemma still attached to the glycocalyx. The severe membrane damage is associated with massive calcium overload (Whalen et al., 1974). Mitochondria

accumulate some of the excess calcium, which is deposited as intramitochondrial crystalline densities. This accelerated cellular disintegration may explain, in addition to reperfusion per se, why rapid washout of creatine kinase is characteristic of successful reperfusion of irreversibly injured myocytes (Jennings and Reimer, 1983).

The total tissue water content of the irreversibly injured cell remained unchanged from control during the early phase of reversible injury, but increased by 21% after reperfusion for only 2 minutes (Whalen et al., 1974). This explosive swelling is chiefly due to intracellular edema, the ultrastructural appearance of which includes intracellular vacuoles, mitochondrial swelling, and the appearance of large subsarcolemmal blebs of fluid (Kloner et al., 1974).

The Ca^{++} that accumulates in the mitochondria originates from the arterial blood reperfusing the tissue (Shen et al., 1972). When marked, it results in grossly visible dystrophic calcification. The mitochondrial Ca^{++} accumulation is an active process that requires energy and inorganic phosphate anion as well as Ca^{++} (Lehninger, 1974). Thus, calcification does not develop in myocytes that have been severely ischemic for a long period of time (Kloner et al., 1974). Reperfusion of irreversibly injured cells induces contraction band necrosis, striking cell swelling and calcium accumulation, also, it is associated with a washout of protons, adenosine, inosine, lactate, and a variety of soluble enzymes such as creatine kinase. This response is considered to be secondary to cellular damage that developed while the cells were ischemic and not to be an effect of reperfusion itself (Jennings and Reimer, 1983).