# The effect of initial reperfusion temperature on myocardial function and preservation in patients undergoing mitral valve replacement

Thesis

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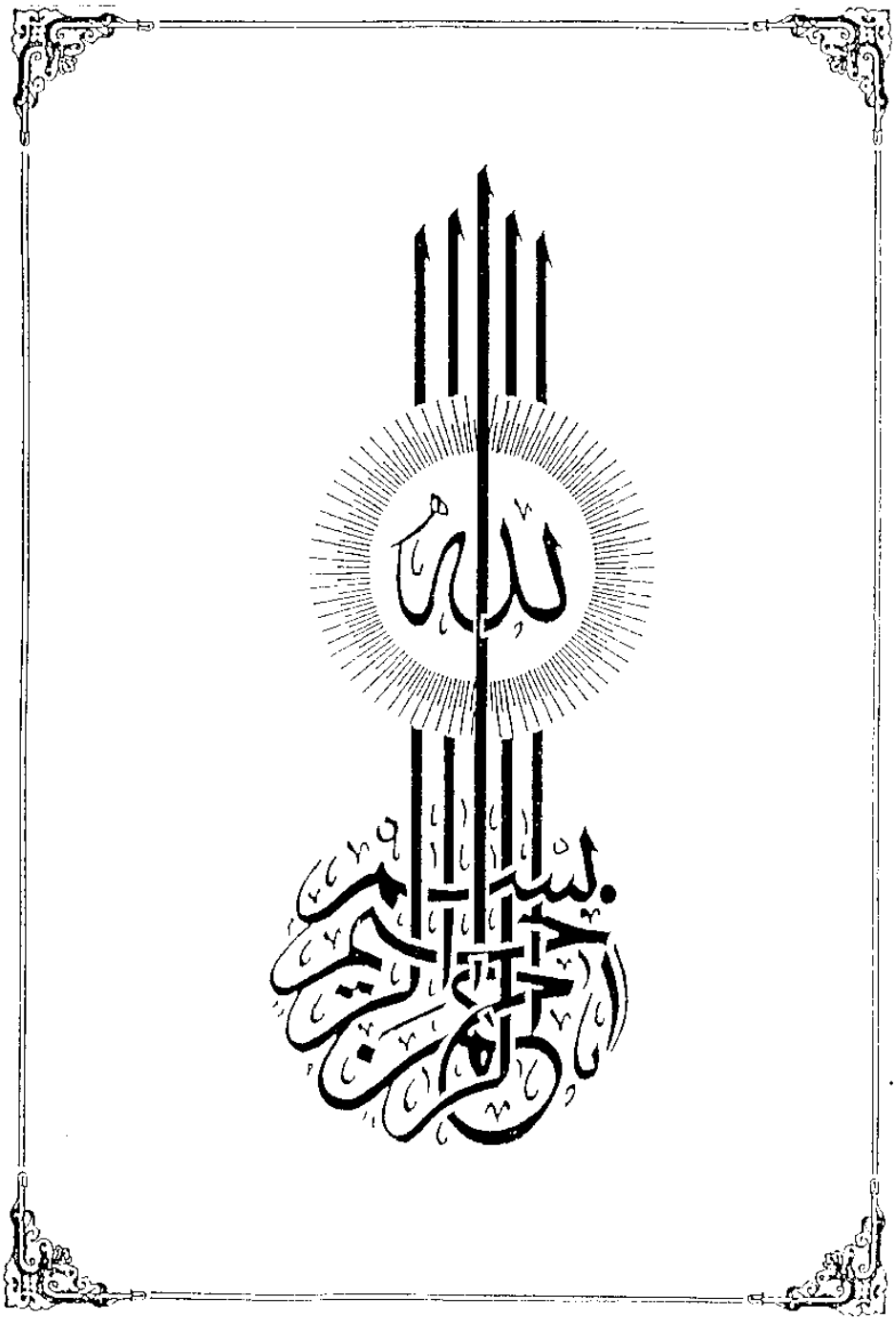

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# REVIEW OF LITERATURE

# INTRODUCTION

Surgeons and anesthesiologists have always been perplexed by the observation that a "technically successful" cardiac operation could result in a low cardiac output and death. Early failures were referrred to in vague terms of unavoidable "stress" of anesthesia, cardiopulmonary bypass and direct manipulation of the diseased heart (William et al, 1965).

In a review published in 1966 by Rosky and Rodman, early postoperative low cardiac output was discussed extensively, but no mention was made of myocardial necrosis as a complication of the surgery or as a cause of low cardiac output. Taber and colleagues (1967) described scattered small areas of myocardial necrosis, estimated to involve about 30% of the left ventricular myocardium, in a group of patients dying early after cardiac operations, and implicated this as the etiology of the patients' low cardiac output. Najafi and colleagues showed in 1967 that acute diffuse subendocardial myocardial infarction was found frequently in patients dying early after valve replacement and suggested that this was related to methods of intraoperative management of the myocardium. They discussed the possibility that disturbances of the myocardial oxygen

supply - demand ratios might be implicated and that proper perfusion ratios might be implicated and that proper perfusion particular problem during cardio pulmanory bypass.

In 1973, in a consecutive series of patients with normal coronary arteries who underwent various open cardiac operations, Hultgren and colleagues documented a 7 % incidence of acute transmural myocardial infarction. Autopsy studies have confirmed that acute transmural myocardial infarction as well as scattered myocardial necrosis and confluent subendocardial necrosis can occur after cardiac surgery despite the presence of normal coronary arteries.

In recent years, imp roved methods of identifying myocardial necrosis during life have been developed. The electrocardiographic criteria for diagnosing transmural myocardial infarction and ischaemic changes have been clarified and applied to postoperative patients. The appearance of cardiac - specific enzymes in plasma has been shown to correlate well with other evidence of myocardial necrosis and their concentration has been shown to correlate directly with the amount of muscle that has become necrotic (Gray et al, 1978).

Kirklin (1985) demonstrated that the early postoperative cardiac index was inversely proportional to the extent of myocardial necrosis as determined by serial analysis of CK-MB isoenzyme activity. The amount of damage correlated not only

with the early postoperative condition, but also with the probability of survival.

## Physiology of myocardial perfusion:

The myocardium is perfused by blood via the left and right coronary arteries. The flow is determined by the coronary perfusing pressure (aortic pressure), tension in various layers of the myocardium (related in part to ventricular wall thickness and size) and coronary vascular resistance. In normal hearts with intact circulation, the ratio between the flow to the inner one-fourth of the myocardium (the subendocardial layer) to the outer one fourth (the subepicardial layer) is about one or a little more. The left ventricular subendocardial muscle is the most susceptible region to ischemia because it can receive its blood supply only during diastole (Hoffman et al, 1976). Intramyocardial vessels are squeezed shut during systole. When subendocardial vessels dilate maximally (in response to increased oxygen need, reduced blood pressure or lowered oxygen content), blood supply becomes determined by the diastolic coronary driving presssure (aortic pressure minus left ventricular diastolic pressure) and the duration of diastole.

The subendocardial muscle is in greatest jeopardy in patients with ventricular hypertrophy or coronary arterial

disease. This is true because both conditions cause resting coronary vasodilatation and substantial reduction in the capacity of the subendocardial vessels to dilate more so as to regul te flow proportionate to changing oxygen needs. Myocardial ischaemia can develop, therefore, because of minor imbalances between oxygen supply and demand in these patients even before extra-corporeal circulation is started.

## Pathophysiology of myocardial ischemia:

Myocardial ischaemia results in the heart's reversion from aerobic oxidation of substrates (glucose, lactate and free fatty acids) by krebs cycle and oxidative phosphorylation (yielding 36 mol. ATP / mol. glucose ) to anaerobic glycolysis (yielding only 2 mol ATP / mol glucose) for energy production. Aortic cross- clamping results in almost complete cessation of coronary blood flow and oxygen delivery. Myocardial oxygen tension declines rapidly despite the presence of variable amounts of oxgyenated non - coronary collateral flow. Oxidative phosphorylation ceases when the tissue partial pressure of oxygen falls below 5-10 mm Hg (Kubler, 1970).

During aortic cross-clamping, the main sources of high - energy phosphate are creatine phosphate and anaerobic glycolysis. The amount of ATP produced by transfer of energy from creatine phosphate to adenosine diphosphate (ADP) is limited initially by substrate availability and

subsequently by lactate inhibition. Anaerobic metabolism is both inefficient and self - limited because accumulated metabolites such as lactate, pyruvate and hydrogen ions eventually inhibit essential enzyme systems.

In the ischaemic working heart, the concentration of lactic acid rises and intracellular pH falls rapidly. In contrast, in the anoxic heart, perfusion washes out the acid products of glycolysis, thereby retarding the rate of development of intracellular acidosis. Thus in the ischaemic heart, the glycolylic rate is about one- fourth that of the anoxic heart in a steady state. Pretreatment of rat myocardium to an alkaline pH of 7.9 maintains tension during a subsequent period of hypoxia (Regan et al, 1976).

Under normal aerobic conditions, the myocardium extracts lactate from the arterial blood with an extraction fraction of 20 %. When myocardial ischaemia is present, lactate extraction declines or even is replaced by net lactate production.

## Fat metabolism in ischemia:

Under normal aerobic conditions, 60 - 90 % of myocardial energy requirements are met by oxidation of free fatty acids which are trapped in cells in the form of fatty (acyl) esters containing coemzyme A. Oxidation predominates since the products formed (two carbon moities called acetyl groups) are readily incorporated as intermediates in krebs

cycle and oxidized to $CO_2$ and water. Oxidation of fatty acids inhibits glucose uptake, glycolytic flux and glycogenolysis.

In ischemia, oxidation of fatty acids is inhibited because of inhibition or loss of long- chain acyl- carnitine transferase enzyme activity, necessary for the transport of cytosolic acyl - CoA to the mitochondria before oxidation (wood et al, 1973).

## Protein metabolism in ischemia:

Under physiological conditions, the myocardium extracts glutamine from arterial blood and produces ammonia and glutamic acid, which appear in coronary extracts glutamine from arterial blood and produces ammonia and glutamic acid, which appear in coronary sinus effluent. When ischaemia occurs, ammonia derived from amino acids that can not be incorporated into protein under these conditions, is incorporated into alanine and glutamine with a subsequent increase in their concentration in coronary sinus effluent. The increased production of alanine is taken to be analogous to increased production of lactate; both are markers of ischaemia. In case of alanine, transamination of pyruvate serves as a sink for ammonia that would otherwise accumlate. In case of lactate, pyrurate serves as a sink for hydrogen ions.

## Calcium in ischemia:

$Ca^{++}$ is mainly an extracellular cation. Precise changes in cytosolic calcium are required to initiate, modulate and terminate the conversion of myocardial chemical energy from the form of high - enregy phosphate into mechanical energy in the form of developed tension. Calcium enters the myocyte by its electrical and corcentration gradients. The magnitude of calcium entry is determined by voltage and high - energy phosphate dependant gating mechanisms. The influx of extra - cellular calcium during the plateau phase of membrane action potential triggers the release of calcium from the sarcoplasmic reticulum. The more calcium released, the greater the force of contraction and energy consumption. Additional high erergy phosphate utilization occurs during relaxation when calcium is actively returned to the sarcoplasmic reticulum. Although reuptake acutely lowers the concentration of intracellular ionized calcium, long - term homeostasis necessitates calcium efflux against its concentration gradient. A sodium - calcium exchange mechanism is primarily responsible for the prevention of intracellular calcium accumlation. The maintenance of a high extracellular to intracellular sodium ratio favourable to calcium efflux is ultimately energy dependant (Mullins, 1979).

When ATP stores are reduced by ischaemia, trans-sarcolemmal $Na^+$- $K^+$ exchange is impaired. Elevated intracellular $Na^+$ raises intracellular $Ca^{++}$ through an enhanced $Na^+$ - $Ca^{++}$ exchange. Lowered ATP stores also reduce $Ca^{++}$ uptake by the sarco-plasmic reticulum and reduce $Ca^{++}$ extrusion from the cells. The resultant augmented intracellular $Ca^{++}$ causes mitochondrial $Ca^{++}$ overload, which depresses ATP production further. Activation of intracellular $Ca^{++}$ ATP ases activates sarcolemmal phospholipases, which release membrane phospholipid degradation products whose detergent properties impair the integrity of the cell membrane (Sedlis et al, 1983).

Henry and associates (1977) found that during one hour of severe ischaemia, the left ventricle undergoes progressive ischemic contracture, With the development of an elevated ventricular diastolic pressure and a fourfold increase in mitochondrial $Ca^{++}$. With subsequent reperfusion, both myocardial systolic and diastolic functions remain abnormal and a further marked increase in $Ca^{++}$ accumlation occurs. Adminstration of nifedipine prevents ischemic contracture and permits recovery of systolic contractile function and of myocardiol relaxation. These favourable hemodynamic changes are accomparnied by a marked reduction in the accumulation of $Ca^{++}$ in the mitochondria.