Metabolic Response during Impending Myocardial Infarction

II. Clinical Implications

By M. F. Oliver, M.D.

SUMMARY

The immediate local metabolic response of the myocardium to acute regional ischemia is determined by an interaction of various influences. These include: (1) the extent of and the variability in reduction of blood flow; (2) the degree and persistence of hypoxia; and (3) the effects of local release of catecholamines, particularly in relation to loss of intracellular potassium.

The subsequent metabolic response of the myocardium is partly dependent on the degree of impairment locally of normal myocardial metabolism and partly on the systemic reaction to increased catecholamine activity and hence on: (1) adipose tissue lipolysis; (2) hepatic and muscle glycogenolysis; (3) insulin suppression; and (4) growth hormone and cortisol activity. These determine the extent of the uptake from blood of FFA and glucose by the ischemic myocardium.

There is increasing evidence that high arterial concentrations of FFA can depress myocardial performance by leading to ventricular arrhythmias and decreased contractility. This effect probably depends on a critical interaction between the local concentration of FFA, catecholamines, and hypoxia.

Metabolic intervention in the management of heart attacks should accordingly be directed toward reducing mobilization of adipose tissue FFA and increasing myocardial glycolytic activity.

The immediate myocardial and systemic metabolic responses to a "heart attack" result from acute myocardial ischemia rather than from myocardial infarction. The essential difference between these conditions is that ischemia can disappear spontaneously and is potentially reversible therapeutically. There are difficulties in studying the immediate consequences of myocardial ischemia in man, since many episodes probably occur without recognizable symptoms and many patients die before they can summon medical aid. Indeed, the median time of death after the onset of symptoms of impending infarction is about 2 hours, and well before the morphologic characteristics of myocardial infarction can be identified. It is just for this reason that understanding of the metabolic and electrophysiologic consequences of acute myocardial ischemia is so vital. The problem is compounded by the fact that most studies of experimentally-induced myocardial ischemia have little analogy with ischemia occurring spontaneously in the aging and extensively arteriosclerotic human heart. Further, angina induced by exercise, pacing, or hypoxia does not lead to the same degree of systemic disturbance as prolonged ischemia due to acute coronary occlusion.

The purpose of this paper is to review, in the context of acute heart attacks in man, the probable immediate local metabolic response in the myocardium, the general systemic metabolic response, and the effect of each on myocardial rhythmicity and contractility.

Immediate Local Metabolic Response

This is primarily determined by acute myocardial ischemia and secondarily by local catecholamine release.

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Ischemia

In the acutely ischemic and infarcted myocardium, there is likely to be hypoxia of varying degrees rather than extensive anoxia. The myocardium beyond the site of coronary artery occlusion probably undergoes rapid changes with collateral vessels opening and closing as thrombi occur locally, with some areas of poor perfusion recovering as intravascular pressure improves and with others becoming temporarily or permanently starved as flow ceases altogether. There can be little static in the myocardium during the first hour after occlusion, and this is emphasized by the heterogeneity of pathologic change after experimental coronary artery occlusion.\(^2\) Perfusion of viable myocardial tissue depends on the interaction of many influences and the balance obtained between opposing forces. For example, the immediate decrease in local pressure in the arteries distal to the area of partial or complete block will directly reduce perfusion and stimulate inflow from collateral vessels. Again, metabolic changes (see below) can cause vasodilatation through release of adenosine, and catecholamines can cause vasodilatation and vasoconstriction. Spreading thrombus formation in arteries under low pressure, a decrease in stroke output, and raised left ventricular systolic and diastolic pressure can all impair local perfusion.

The high oxygen content of venous blood leaving the ischemic area and the reasonably well-maintained epicardial (but not endocardial) oxygen tension emphasize that it is hypoxia rather than anoxia that determines the immediate local metabolic response. In addition, it is regional hypoxia compounded by reduction and not cessation in coronary flow—in other words, regional myocardial ischemia in a heart where flow to other areas is not impaired. The persistence of myocardial ischemia, the degree of adaptation to it, and the critical nature of certain affected sites (Purkinje tissue) may all be more important than its extent in relation to the subsequent onset of ventricular arrhythmias and acute failure.

In an accompanying paper, Opie\(^3\) has described the metabolism of glucose and free fatty acids (FFA) in the normally oxygenated heart and the adjustments that probably occur in ischemia. The evidence for accelerated glycolysis and anaerobic energy production is reviewed. One of the difficulties we have at present is understanding exactly how these intracellular metabolic events trigger off an arrhythmia or lead to acute heart failure. Two resultant acute changes which require emphasis are reduction in extracellular \(pH\)\(^4\) and release of myocardial catecholamine stores. Reduction of \(pH\) is probably due mostly to release of hydrogen ions during hydrolysis of ATP at a greater rate than it is synthesized and perhaps from accumulation of hydrogen ions associated with lactate release and accumulation of FFA. Very little is known about changes in intracellular \(pH\) but reduction could occur very locally and lead to local cellular damage. Acidosis has been shown to suppress pacemaker and contractile performance in the anoxic isolated rat heart.\(^2\) Release of myocardial catecholamines may be the most important of all the adverse influences and responsible for many of the local metabolic changes.

Local Catecholamine Release

Experimentally it has been shown that activation of sympathetic receptors in the myocardium can occur immediately as a result of myocardial ischemia or of an increase in coronary artery pressure: a very rapid spinal reflex, abolished by sectioning of different fibers to the stellate ganglia, takes place with stimulation of different sympathetic fibers to the myocardium.\(^6\) Release occurs of epinephrine and norepinephrine, stored in granules on the preterminal sympathetic fibers. Catecholamines are released within minutes into the circulation in most dogs after coronary artery ligation.\(^7\) \(^8\) Depletion of catecholamines from ischemic and infarcted areas of the myocardium was first reported in man from histochemical studies,\(^9\) and this has been observed experimentally as soon as half an hour after ligation of a coronary artery.\(^10\) The view that local catecholamine activity can lead to early myocardial damage seems reasonable in consideration of the many reports of

*Circulation, Volume XLI. February 1972*
morphologic changes following the administration of catecholamines.\textsuperscript{11, 12} Catecholamine stimulation of phosphorylase activity is well described\textsuperscript{a} and can occur within 1 min of producing total myocardial ischemia.\textsuperscript{13} Together with a rise in orthophosphate, this is probably the immediate and initial stimulus to glycogenolysis. Catecholamine stimulation also leads to an increase in succinic and lactic dehydrogenase activity in the ischemic area of the myocardium with efflux into the coronary sinus. Histochemical or morphologic changes do not occur when coronary artery ligation is not associated with catecholamine release.\textsuperscript{14}

Certain local metabolic changes could result from local catecholamine activity. These include glycogenolysis and glycolysis. Hydrolysis of stored triglyceride can occur since catecholamines activate a myocardial lipase.\textsuperscript{15} This local effect of catecholamines may be particularly important in humans, since there is much more triglyceride stored in our hearts compared with that in most animals.\textsuperscript{16} In the presence of severe hypoxia, an increase in the intracellular concentration of FFA could result. Any decrease in carrier protein would exaggerate the effects of intracellular FFA accumulation. Weakly bound FFA could combine with acyl-CoA and also form cation salts. It has been hypothesized that these could harm cell and mitochondrial membranes as a result of detergent action.\textsuperscript{17} Increased concentrations of FFA can also depress mitochondrial oxidative metabolism.\textsuperscript{18}

There is much evidence linking increased catecholamine activity with serious arrhythmias in experimental animals\textsuperscript{19–22} and in man, and measures designed to reduce the action of catecholamines on the myocardium such as cardiac denervation\textsuperscript{23} or \(\beta\)-adrenergic blockade\textsuperscript{24} decrease the arrhythmogenic tendency. The mechanisms through which these changes trigger an arrhythmia are not clear. During myocardial ischemia, potassium and phosphate loss occurs\textsuperscript{24} but this loss of ions is enhanced by large concentrations of norepinephrine although reversed by low concentrations of norepinephrine.\textsuperscript{25} Presumably there is irregularity of potassium loss, and marked difference in the gradients of cation concentration across cell membranes may well exaggerate the temporal discrepancy in recovery of excitability known to exist between Purkinje tissue and ventricular muscle and to the initiation of arrhythmias.\textsuperscript{26} A further factor of importance is the movement of extracellular fluid into the ischemic cell causing swelling and further reduction of intracellular potassium concentration.\textsuperscript{27}

**Systemic Metabolic Response**

This is mainly determined by increased plasma catecholamine concentrations (fig. 1). When acute coronary artery occlusion leads to symptoms, and this is not always the case, there is stimulation of postganglionic sympathetic nerve endings with release of norepinephrine, and of the adrenal medulla with release of epinephrine. Both catecholamines are present in high concentrations in plasma\textsuperscript{28} and urine\textsuperscript{29} during the first 24–48 hours after the onset of symptoms. The concentrations of these catecholamines in plasma reach high levels within the first few hours after the onset of symptoms and later appear to be related to the severity of the infarct. Norepinephrine acts through \(\beta\)-adrenergic receptors to activate the adenylcyclase system in adipose tissue causing conversion of ATP to cyclic AMP, and cyclic AMP activates a lipolytic system leading to hydrolysis of stored triglycerides to diglycerides, FFA, and also glycerol. While some reesterification of FFA occurs, the net effect is release of FFA and glycerol into the circulation.\textsuperscript{30} In acute myocardial infarction, plasma FFA concentrations are elevated within 4 hours of the onset of symptoms.\textsuperscript{31} The highest values are found on the first day, and by the sixth day normal values are usually reached.\textsuperscript{32} Glycerol levels are also elevated.\textsuperscript{33} There is a close relationship between blood catecholamine and FFA values in myocardial infarction.\textsuperscript{34}

Epinephrine has a weak effect on adipose tissue lipolysis but its main action at this time is to stimulate glycogenolysis in liver and muscle with elevation of blood glucose levels. Epinephrine also suppresses \(\beta\)-cell activity in
OLIVER

Acute myocardial ischemia

Pain and "stress"

Activation of sympathetic system

ACTH

Adrenal medulla

Postganglionic sympathetic nerves

Epinephrine

Suppression of insulin secretion

Hepatic and muscle glycogenolysis

Plasma glucose +

Gluconeogenesis

Cortisol

Norepinephrine

Growth hormone

Adipose tissue lipolysis

Plasma free fatty acids +

Plasma glycerol +

Figure 1

Schematic diagram illustrating some of the systemic metabolic responses which occur during impending myocardial infarction. Many of these interact, and the diagram is deliberately simplified.

the pancreas with a decrease in insulin secretion leading to further elevation of blood glucose. Thus, hyperglycemia occurs after acute myocardial infarction, and more than half of these patients have an abnormal glucose tolerance test during the first 72 hours of the attack. Reduction of insulin secretion has been demonstrated in patients after acute myocardial infarction following an intravenous glucose load and an intravenous tolbutamide test. The degree of failure in these responses has been positively correlated with the severity of the illness and with the presence of cardiogenic shock. Cortisol secretion and plasma growth-hormone levels are increased during the first 24 hours after the onset of acute myocardial infarction. As the clinical condition improves, the degree of glucose intolerance diminishes and insulin secretion increases. In the second week plasma insulin levels are above normal, and at this stage the anabolic effect of insulin in enhancing the transport of amino acids into cells and their incorporation into protein is important for repair of the injured myocardium. Cortisol stimulates the breakdown of protein for gluconeogenic purposes and also the key gluconeogenic enzymes, but it is doubtful whether these actions operate until the acute period has passed.

These increases in plasma FFA and glucose usually allow ischemic myocardial cells to be perfused with sufficient concentrations of substrates to ensure the survival of many. However, an excessive response, which may no longer be optimal, can occur in some patients. Plasma FFA can be elevated beyond the concentration when they are carried by the two principal binding sites on albumin—a 2:1 molar ratio is exceeded when plasma FFA levels are greater than 1200 µEq/liter, and occasionally levels in the

Circulation, Volume XLV, February 1972
region of 2000 μEq/liter have been recorded. When the FFA/albumin ratio increases, fatty acids are progressively more weakly bound to albumin, and there is an exponential relationship between increases in FFA/albumin ratio and FFA entry into the cell. In dogs during extensive myocardial ischemia, there is a proportionately greater myocardial uptake of FFA when compared with that of glucose and pyruvate and with myocardial oxygen consumption despite reduced coronary flow. This relatively larger uptake of FFA is reflected in an increase in the oxygen-extraction ratio for FFA from 77% in the control period to 101% during ischemia and a decrease in the oxygen-extraction ratio for glucose from 33 to 25%. In patients with a severe systemic response to acute myocardial infarction, insulin suppression can be almost complete, and this will reduce the availability of glucose to myocardial cells in spite of the rise which occurs in plasma glucose levels. In addition, there is recent evidence that glucose uptake by the myocardium in normal resting man is inversely related to FFA levels and perhaps less dependent on insulin than was previously thought. Thus, ischemic myocardial cells may in some patients be exposed to an unusually high FFA/glucose ratio as a result of a marked systemic metabolic response.

Effect of Local and Systemic Metabolic Response on Myocardial Performance

The two chief complications of myocardial ischemia or infarction are serious ventricular arrhythmias and pump failure. The former occur soon after the onset of symptoms and the latter may either occur early as so-called cardiogenic shock when it is associated with a poorly understood set of vascular reflexes or later as left or progressive right ventricular failure. In this section, consideration will be given to the relationship of the local and general metabolic changes on the development of arrhythmias and on myocardial contractility.

Arrhythmias

Reference has already been made to the relationship between increased catecholamine activity and arrhythmias, and in recent years the possibility has arisen that high plasma FFA levels may have an independent arrhythmogenic action. This is a potentially important concept and is based on the following evidence. In patients with acute myocardial infarction, a positive relationship has been reported between the incidence of serious ventricular arrhythmias and of early deaths with plasma FFA levels above 1200 μEq/liter, although this has not been observed by all investigators. In similar patients, a positive correlation between plasma glycerol levels and arrhythmias has also been observed. FFA can cause arrhythmias in other species without changes in catecholamine activity. In the normal dog, intravenous infusions of FFA as their sodium salts can cause conduction defects although not ventricular arrhythmias; in geese, elevation of FFA by glucagon produced ventricular arrhythmias and myocardial necrosis; and, in isolated perfused rat-heart preparations, octanoate produced arrhythmias.

Investigations had been made of the effects on cardiac rhythm of increased arterial FFA, elevated by heparin induction of plasma lipolysis independently of catecholamine activity, in dogs in which myocardial infarction was produced experimentally. In studies in which occlusion of the circumflex coronary artery was produced in a closed-chest preparation with subsequent infarction of the lateral wall of the left ventricle, marked elevation of plasma FFA was usually associated with the development of frequent ventricular ectopic systoles and sometimes with ventricular tachycardia or even ventricular fibrillation. In a comparable set of studies, however, conducted in dogs in which an apical branch of the anterior descending artery was ligated with consequent production of a small infarct at the apex of the left ventricle, marked elevation of plasma FFA by use of the same system for inducing plasma lipolysis was not associated with any increase in the incidence of serious ventricular arrhythmias. An explanation for these apparently contradictory results is not immediately forthcoming. It is important to
recognize that there were marked differences in the experimental models and systems of study. These are illustrated in Table 1. Differences of potential importance are that Opie and colleagues\(^5\) may have conducted their experiments in conditions of reduced sensitivity to the induction of arrhythmias, as a result of pericardectomy which reduces contractile force,\(^5\) of reduced local catecholamine concentration due to interruption of the sympathetic supply during ligation of the artery, and of the higher heart rate which could prevent complete manifestation of a parasystolic focus originating in an accelerated “automatic” cell in the Purkinje system.

Small doses of norepinephrine, which elevated FFA but did not lead to any hemodynamic changes, reduced the incidence of ventricular ectopic activity and enhanced contractility in dogs with extensive myocardial infarction.\(^2\) Whether this can be regarded as evidence against the arrhythmogenic activity of FFA is not clear, since the egress of potassium ions that usually occurs in acute ischemia was reduced in the same experiments. Recently, it has been shown that infusions of FFA/albumin complex to dogs with experimental myocardial infarction will raise arterial FFA to levels comparable to those seen in patients and lead to serious ventricular arrhythmias.\(^2\) Positive findings have been recorded in a majority of dogs. No arrhythmias occurred in dogs with myocardial infarction given plasma infusions under comparable conditions without elevation of FFA. In these studies, no heparin, catecholamine, or lipid emulsion was used. The raised arterial FFA decreased exponentially with time and appear to be utilized physiologically. If further studies confirm these preliminary findings, the case is strong for regarding elevated plasma FFA as arrhythmogenic in the presence of myocardial ischemia.

Final interpretation of the various experiments described is not yet possible and should certainly take into account the type of preparation studied, the degree of ischemia (the absolute level of oxygen is crucial to the metabolism of FFA), the extracellular concentrations of FFA, glucose, and insulin, and the chain length of the fatty acids. Metabolically, the conducting system is like white muscle.

**Table 1**

*Main Differences in Experimental Design between Edinburgh and London in Relation to Induction of Arrhythmias by Elevation of Arterial FFA and through Administration of Intralipid and Heparin*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Edinburgh</th>
<th>London</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA levels ((\mu\text{Eq/liter}))</td>
<td>2000–6000</td>
<td>2000–6000</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Yes</td>
<td>Greyhounds (different life history, exercise, habits, physiologic hypertrophy of heart, and perhaps different feeding)</td>
</tr>
<tr>
<td>Subjects</td>
<td>Mongrels (sometimes undernourished)</td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Closed-chest preparation</td>
<td>Open-chest and pericardectomy</td>
</tr>
<tr>
<td>Artery</td>
<td>Main circumflex</td>
<td>Branch of anterior descending</td>
</tr>
<tr>
<td>Treatment</td>
<td>Occlusion of artery with balloon catheter</td>
<td>Ligation of artery</td>
</tr>
<tr>
<td></td>
<td>?Stimulation of arterial sympathetic nerves by stretching</td>
<td>Interruption of arterial sympathetic nerves</td>
</tr>
<tr>
<td>Local catecholamine concentration</td>
<td>?Increase</td>
<td>?Decrease</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>120–150</td>
<td>160–180</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>3.2–3.7</td>
<td>3.6–4.0</td>
</tr>
<tr>
<td>Serum albumin (g/liter)</td>
<td>2–3</td>
<td>4–4.5</td>
</tr>
</tbody>
</table>

\(\text{Circulation, Volume XLV}, \text{February 1972}\)
and has a lower capacity to metabolize fatty acids, and more are likely to accumulate there when compared with the rest of the myocardium. This accumulation of FFA in myocardial cells might be exaggerated if there is much leakage and sequestration of albumin in extracellular tissue. Increase in arterial FFA and increased uptake by the ischemic myocardium may be followed by triglyceride deposition if oxidation is incomplete and if there is glucose 3-phosphate available for esterification to take place. Fatty infiltration of the ischemic and infarcted myocardium has been described years ago, and experimental evidence is now available of a positive relationship between the degree of elevation of arterial FFA and triglyceride deposition in the ischemic myocardium.

**Myocardial Contractility**

Myocardial oxygen consumption (MV,ω) is determined by a number of factors including intramyocardial tension, the contractile state of the heart, heart rate, the external work performed by the heart, the energy required to activate contraction, and the metabolic status of the myocardium. All of these can be changed sharply by increased catecholamine activity, thus increasing MV,ω. Any marked increase in MV,ω could be deleterious to certain critically ischemic areas of myocardium. High levels of FFA can also increase MV,ω. This has been shown in the isolated perfused heart and in intact dogs through studies of the effect of high concentrations of arterial FFA produced by plasma lipolysis; local metabolic rate in the left ventricular wall is also increased by elevated arterial FFA.

The effects of FFA and dextrose on contractility have been compared by studying rat papillary muscle. Contractility under well-oxygenated conditions was not altered by equivalent concentrations of FFA or dextrose, but under hypoxic conditions contractility was depressed by concentrations of FFA in the region of 2:1 albumin molar ratio and increased by dextrose. Similarly, dextrose improved mechanical performance in isolated perfused hearts when hypoxic, although not when adequately oxygenated. High concentrations of FFA in the region of 6:1 FFA/albumin molar ratio depressed myocardial contractility in perfused isovolumic heart preparations. In addition, diastolic pressure increased. A comparable synergism on myocardial contractility has been shown between FFA, using octanoate, and glucose in isolated perfused rat hearts. From studies using a nonmetabolized FFA (pent-4-enoic acid), this depression of contractility appears to be mediated directly by FFA or acyl-CoA derivatives rather than their metabolic products.

High arterial levels of FFA may therefore induce arrhythmias and depress myocardial contractility during acute myocardial ischemia, particularly if there is a relatively small increase in glucose uptake by the myocardium and marked hypoxia. Additionally, high concentration of FFA can decrease coronary blood flow and cause platelet aggregation.

**Metabolic Intervention**

Control of the extent of the metabolic response might contribute to the management of cardiac arrhythmias and of acute pump failure in myocardial ischemia. The aim should be to reduce elevated plasma FFA levels and to increase intracellular plasma FFA concentrations.

One therapeutic approach, not fully explored in man, is to reduce arterial concentrations of FFA. This might be achieved by drugs which reduce adipose tissue lipolysis. β-Adrenergic blockade is unlikely to be a satisfactory means of controlling the metabolic response since the inotropic and chronotropic effects of catecholamines can be critically important in the early stages of acute myocardial infarction. A β-blocker which has a specific effect in preventing catecholamine activation of adipose tissue lipolysis would however be of interest. Nicotinic acid also has such an effect, but it is usually associated with flushing. The effects of nicotinic acid analogs require to be studied, and one has been shown to have an antiarrhythmic action.

An alternative approach is to increase the uptake of glucose by the myocardium. The intravenous use of glucose, insulin, and
potassium to improve uptake of glucose and prevent depletion of potassium is superficially attractive. However, hypervolemia can occur and the results of clinical trials are not impressive. This may be due to the fact that these trials have been conducted in unselected groups of patients with acute myocardial infarction. The patients who would be expected to respond optimally are those with a high plasma FFA/glucose ratio. Further, the concentrations of glucose, insulin, and potassium which have been used have been lower than those theoretically and experimentally desirable. Increased glucose uptake might also be achieved by the use of glucagon. This substance has been shown to have a positive inotropic action in the management of cardiac failure and following acute myocardial infarction. This effect might be due to increased uptake of glucose by myocardial cells or to increased myocardial calcium stores. Potassium and magnesium salts of dl-aspartic acid increase glucose utilization and potassium aspartate and tris-aspartate have been reported to lower heparin-induced elevation of plasma FFA. This might be another approach worthy of study.

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