Metabolic Response during Impending Myocardial Infarction

I. Relevance of Studies of Glucose and Fatty Acid Metabolism in Animals

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SUMMARY
Both glucose and free fatty acids (FFA) are major fuels for the normally oxygenated heart with the dominant contribution being derived from glucose in the resting, fed state and FFA in the resting, fasted state. In anoxia, all energy must be produced anaerobically from glycogen or glucose. Anoxia by itself accelerates glycolysis, but further increases may follow an increased circulating glucose concentration and the addition of insulin. Even maximal rates of anaerobic glycolysis, achieved at high coronary flow rates, can only sustain the energy needs of the K⁺-arrested heart but not of the working heart. FFA cannot be utilized for energy in anoxia and may accumulate intracellularly as triglyceride or FFA. From these and other animal data have grown the concepts that glucose is "good" for the survival of the ischemic heart, and that FFA is "bad." However, glucose-fatty acid interaction has not been well studied in the infarcting, ischemic myocardium. While a "toxic" effect of FFA has been shown in many experimental models, there are other reports of increased FFA concentrations having no harmful effect or even a beneficial effect on the infarcting myocardium. The possible benefits of administration of glucose (with insulin) to patients with acute myocardial infarction could only be assessed by a controlled therapeutic trial.

Additional Indexing Words:
Anoxia  Anaerobic glycolysis  Ischemia  FFA toxicity  Glucose therapy

ON THE BASIS of animal studies, recent reviews have suggested that factors promoting glucose utilization may have a beneficial effect on the ischemic myocardium.¹ ² Conversely, factors promoting free fatty acid (FFA) uptake may be harmful to the survival of the ischemic myocardium according to other workers.³ ⁴ Such suggestions are of much potential importance to clinical cardiologists, because of the possibility of manipulating circulating glucose and FFA concentrations in patients with myocardial infarction,⁵ with possible consequent benefit to myocardial metabolism and performance.

Glucose and FFA Metabolism in the Normal Heart
In the normally oxygenated heart, glucose and free fatty acid are both major sources of energy.⁶ In the fed state, the blood glucose and insulin concentrations are relatively high, the blood FFA concentration is low, and glucose is probably the major fuel of the myocardium (fig. 1). During the fasted state, the blood FFA concentration is high, blood glucose and insulin concentrations are relatively low, and FFA is the major fuel of the myocardium (fig. 2). FFA is known to inhibit myocardial glucose uptake, glycolysis, and glucose oxidation.⁷ ⁸ During the fed state, the very low rate of FFA uptake by the heart presumably removes the above inhibitions on glycolysis and, at the same time, the high

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circulating glucose and insulin concentrations promote glucose uptake and glycolysis. This "seesaw" concept of the role of glucose and FFA is a further development of the glucose-fatty acid cycle of Randle and co-workers, which stresses chiefly the inhibition on glucose metabolism by exogenous, circulating FFA which is high in the fasted state. In addition, glucose could and probably does make a major contribution to oxidative metabolism in the fed state.

Most of the studies on control of glycolysis, both in normoxia and in anoxia, have been carried out on the isolated perfused rat heart, and it is therefore pertinent first to ask how the patterns of metabolism in rat and human heart compare. The metabolic patterns in the isolated working rat heart and in the intact human heart are to some extent rather similar when allowance is made for the much higher heart rate, oxygen uptake, and cardiac output in the rat heart. However, when the rat heart is perfused with glucose and/or FFA, lactate may be put out into the perfusion medium, whereas the heart in situ usually takes up lactate. This difference may well be due to the initial absence of lactate from the perfusion medium of the rat heart. Recent work on humans by Carlson's group shows that when high circulating-FFA values are reduced by the administration of nicotinic acid, the glucose uptake by the heart increases; thus, the patterns of glucose-fatty acid interaction described in the rat heart appear to be applicable to man.

**Anoxia with Unimpaired Coronary Flow**

Both glucose and glycogen are converted to glucose 6-phosphate before further conversion by glycolysis to pyruvate; the normal end product of this process of glycolysis in the aerobic heart is entry of pyruvate into the citrate cycle. During total oxygen lack, glycolysis is accelerated, and the end product becomes lactate (anaerobic glycolysis). At the same time, FFA cannot be utilized for energy purposes in anoxia, and FFA uptake is diminished.

Thus, there is a switch from usage of both glucose and FFA for energy provision in
metabolic changes in the infarcting myocardium of the dog. We occluded small branches of the main coronary arteries so that left ventricular failure was not likely to occur. Glucose uptake was increased relative to that of FFA, while lactate was put out by the ischemic tissue in contrast to lactate uptake by the nonischemic tissue. Glycogen was partly broken down. Thus there was a switch toward the pattern found in anaerobic glycolysis and away from FFA metabolism, but the switch was not complete. FFA was still taken up by the ischemic tissue; there was still some but diminished oxidation, and more \(^{14}C\)-labeled-FFA was recovered in the mitochondrial fraction of tissue lipids (Riemersma R, Opie LH: Unpublished data). A significant part of the glucose uptake was oxidized even after 2 hours of ischemia. Thus the patterns of metabolism correspond to those of partial but not total oxygen lack in the ischemic myocardium.

**MYOCARDIAL METABOLISM: POSSIBLE EFFECTS OF ANOXIA**

**Figure 3**

In a totally anoxic but well-perfused localized area of the heart, there would be increased glucose uptake, glycogen breakdown, and lactate discharge instead of the normal uptake; the FFA taken up would not be oxidized but stored within the cell. The rate of conversion of glycogen or glucose to lactate (anaerobic glycolysis) could help regulate the survival of the anoxic area. Therefore, administration of glucose (plus insulin) could be expected to promote survival of the anoxic tissue ("glucose hypothesis"). Conversely, intracellular accumulation of FFA may be toxic ("fatty acid hypothesis"). The problem of the clinician is to know the extent to which these hypotheses are applicable to patients with acute myocardial infarction.

Glucose and Fatty Acid Metabolism in the Infarcting Myocardium

If a localized area of total anoxia but with adequate perfusion could be achieved in the human heart, then that area would show the patterns of metabolism delineated in the anoxic perfused isolated rat heart. There would be increased glucose uptake, glycogen breakdown, and lactate output; FFA would still be taken up (although in lesser amounts) and would be stored rather than be oxidized (fig. 3). These possible patterns are supported by the findings in experimental underperfusion of the dog left ventricle. To what extent are similar metabolic changes found in the infarcting myocardium?

My colleagues and I have been interested in aerobic metabolism to total reliance on glycolysis in anaerobiosis. Once cardiac glycogen has been broken down, all glycolysis must depend on the provision of glucose in the extracellular fluid. The rate of such glucose uptake is accelerated in anaerobiosis and further promoted by the addition of insulin to the perfusion fluid. Nevertheless, rate of anaerobic energy production is so low that adequate energy cannot be provided for the needs of working heart muscle. Anaerobic glycolysis from glucose can only provide sufficient energy to keep a Langendorf-perfused heart feebly beating, but there is accelerated recovery of such a heart when it is subsequently reexposed to oxygen. The lower the ATP demand of the heart, and the greater the rate of anaerobic energy production, the greater the possibility of anaerobic energy supply covering the demands of the heart. Thus maximal rates of anaerobic glycolysis achieved in ideal conditions could just cover the energy needs of the K+-arrested isolated rat heart.

At the same time, the uptake of FFA by the anoxic heart falls markedly and there is intracellular accumulation of FFA, which may promote triglyceride formation. It has been postulated that such accumulation of FFA and/or triglyceride may be toxic in some way, but the evidence of such "lipid toxicity" is by no means settled.

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Thus biochemically demonstrated features of mixed aerobic and anaerobic metabolism probably correspond to a mixed cell population, with some cells dying more rapidly than others.

Is Increased Glucose Utilization Beneficial to the Ischemic or Infarcting Myocardium?

It is attractive to suppose that increased circulating glucose concentrations might benefit the infarcting myocardium by promoting anaerobic glycolysis and ATP production. However, the circulating glucose concentration in many patients with acute myocardial infarction is high even without glucose administration. An increase of glucose concentration in the range of 90 to 150 mg% is unlikely by itself greatly to promote anaerobic glycolysis even in the perfused rat heart with high coronary flow rates. Glucose utilization by the heart, both ischemic and nonischemic, might be diminished by the poor insulin secretion found in some patients with myocardial infarction, especially those with shock.

The addition of insulin to the anoxic perfused heart further increases the glucose uptake and the rate of anaerobic glycolysis, but it should be emphasized that anoxia by itself considerably accelerates glycolysis in the heart; this holds even for the severely diabetic heart in the absence of added insulin.

Very approximate calculations show that maximal rates of glycolysis likely to be achieved in the infarcting myocardium during glucose and insulin administration could contribute significantly to the energy needs of the ischemic tissue, provided that one third of the usual oxygen supply is still delivered by collateral circulation and ATP demand is reduced to half by half-normal contractility. In the presence of lower rates of collateral flow, even if only to localized areas, a substantial ATP deficit would arise. Hence measures to promote glucose utilization would be expected chiefly to benefit tissue still receiving some collateral flow. Furthermore, administration of glucose to improve energy production in oxygen-limited tissue would clearly have to be done as soon as possible after the

Figure 4

Schematic diagram, indicating that loss of potassium and phosphate ions from the myocardial cell appear to reflect intracellular hypoxia. The mechanism of loss and also of ATP conservation are at present only speculative. Discharge of lactate (fig. 3), potassium, and phosphate into coronary venous blood may indicate intracellular hypoxia, which may in turn be caused by extracellular ischemia.

There was also loss of both potassium and phosphate ion into the coronary venous blood, the cause of which was presumed to be breakdown of intracellular high-energy phosphate stores (ATP and phosphocreatine) as shown schematically in figure 4. At the same time, diminished contractility of the ischemic zone probably resulted in some decrease of ATP demand. Thus ischemia, essentially an extracellular event, caused intracellular hypoxia, which in turn resulted in extracellular metabolic changes. Lactate discharge into coronary venous blood was evidence of a switch to anaerobic glycolysis, while potassium and phosphate discharge indicated the inability of residual rates of oxidative metabolism and of anaerobic glycolysis to satisfy the ATP demand of the ischemic tissue.

Studies with arteriovenous differences essentially assume that the ischemic, infarcting myocardium is biochemically homogeneous. In fact the myocardial oxygen tension in endocardium and epicardium is different during coronary occlusion and different ischemic areas may be more hypoxic and infarcting at a greater rate than other areas.
onset of the patient's pain and before irreversible tissue changes have set in.

Additional reasons for administration of glucose (and insulin) are as follows:
(1) Glucose will help maintain the nutrition of the whole body.
(2) Glucose may decrease potassium loss from the ischemic area and possibly decrease the development of arrhythmias. The mechanism of action is complex and may involve extracellular-volume changes.
(3) Glucose may help maintain the action potential in anoxia, if the extracellular concentration is increased by about four times. The relevance of such studies on anoxic papillary muscle to the infarcting myocardium needs verification.
(4) Glucose may benefit cardiac function in patients with acute myocardial infarction.
(5) Glucose may decrease circulating-FFA concentrations in patients with acute myocardial infarction. The possible benefit of this action is considered in the next section.

Could FFA Be Toxic to the Infarcting Myocardium?

Substantial arguments exist to show that high concentrations of FFA could be detrimental to the function and rhythm of the heart in special experimental circumstances. The question arises whether such a detrimental effect could exist in acute human myocardial infarction.

Circumstances in which FFA "toxicity" has been shown include the following:
(1) Injection of unbound long-chain FFA directly into venous blood of animals caused cardiac arrest. Later experiments suggested that similar injections could cause rhythm disturbances (atrioventricular conduction defects). Similarly unbound medium-chain FFA (octanoate) caused atrioventricular block in the isolated rat heart.
(2) Administration of glucagon to geese led to elevation of circulating FFA and abnormalities of heart rhythm.
(3) In the isolated rat heart, with limited coronary flow and contracting on an isovolumic balloon, linoleate at high concentration (nearly 2000 µEq/liter, bound to albumin 2 g/100 ml) depressed cardiac function but not the oxygen uptake.
(4) In isolated hypoxic rat papillary muscle, FFA depressed the contractility relative to the effect of glucose.
(5) In the isolated rat heart, perfused with FFA-albumin alone, there was a small increase in O2 uptake associated with FFA utilization.
(6) In the intact, anesthetized dog, balloon distension of the circumflex artery followed by administration of Intralipid (a triglyceride emulsion) with heparin raised the blood FFA considerably and apparently caused increased ectopic beats, ventricular tachycardia, and fibrillation.

The above evidence from animal experiments certainly suggests that FFA could be harmful to the infarcting myocardium. Nevertheless, hesitation seems advisable in extrapolating to the situation in human acute myocardial infarction without more careful consideration of experimental details.

The first and major hesitation is that several of these studies refer to blood FFA-albumin ratios that exceed those usually found in man. The higher the FFA-albumin ratio, the greater the tendency for FFA to be unbound, and the easier it is for tissues such as the heart to take up FFA from the blood. The affinity of albumin for palmitate and oleate, the two major long-chain FFAs in the blood of patients with myocardial infarction, is greater than the affinity for linoleate used in the studies of Henderson et al. Furthermore, the albumin concentration used by these workers was only about half normal. Hence, their FFA-albumin ratios were decidedly higher than those thought to exist in patients with myocardial infarction.

A second objection is that some of the above studies were conducted with FFA as the sole substrate for the heart. The effect of FFA in increasing oxygen uptake has not been shown in the presence of normal "mixed" substrates.

Thirdly, in the case of dog-heart experiments on arrhythmias following coronary
artery occlusion, there are substantial differences in both results and methods between two groups of workers in Edinburgh\textsuperscript{36} and in London;\textsuperscript{38} in particular the difference between open- and closed-chest animals has been emphasized.\textsuperscript{39} However, Regan et al. used a closed-chest dog preparation with anterior descending artery thrombosis and found that a subpressor infusion of catecholamine increased circulating-FFA concentration to over 2200 μEq/liter.\textsuperscript{40} There was increased FFA and decreased glucose uptake by the ischemic myocardium. Arrhythmias were not provoked but, on the contrary, the authors noted an apparent improvement of myocardial function and fewer rhythm disturbances.

FFA need not be harmful to the ischemic myocardium and may even be beneficial.\textsuperscript{40} The latter possibility is supported by the studies in which FFA (as palmitate, at a low concentration of 400 μEq/liter) increased aortic output in the oxygen-deficient isolated working rat heart.\textsuperscript{41}

Regan's studies differ from those of Owen et al.,\textsuperscript{18} who showed increased glucose uptake relative to that of FFA by the ischemic heart. A major difference appears to be the far greater size of the ischemic area and the much higher blood-FFA concentrations in the study of Regan et al.\textsuperscript{40} It would follow that glucose-FFA interaction in the infarcting dog myocardium may be regulated by the circulating-FFA concentrations and by possibly other factors altering glucose uptake such as blood insulin, blood glucose, and the degree of anaerobiosis in the infarcting myocardium.

Further Reservations

First, in studies on arrhythmias it is perhaps the metabolism of the conduction tissue that needs greatest attention. Glucose-fatty acid interaction in this tissue has not been well studied. Secondly, studies on myocardial infarction in dogs may not be directly applicable to man. Our recent studies with subhuman primates show that coronary artery ligation is followed almost at once by the development of a very well-circumscribed cyanotic area, with marked epicardial S-T-segment elevation and frequent ventricular fibrillation even in small lesions. Thus the consequences of arterial occlusion appear to be more severe and rapid in onset in the baboon than the dog. Such a species difference may be of major importance in applying the results of animal experiments to man.

Conclusions

Animal studies have yielded two complementary hypotheses: (1) glucose is "good" for the ischemic myocardium; and (2) FFA is "bad" for the ischemic myocardium. It follows that administration of glucose and insulin, which would tend to promote glucose utilization and to decrease FFA uptake by the heart, would be desirable as would agents such as nicotinic acid acting solely by reduction of blood FFA concentrations. However, the above hypotheses are almost certainly too simplistic because they are based on extreme experimental situations.

In the case of FFA, the "toxic" hypothesis has suffered by contrary suggestions that FFA may be harmless or even beneficial to the infarcting myocardium. Further studies may help define more clearly whether the FFA concentrations reached in patients are ever likely to be "toxic" or not. In the case of glucose, there is no present evidence for any expected harmful consequences of its administration to patients with acute myocardial infarction. The sum total of animal observations favor a beneficial effect of glucose and insulin, if given early enough. However, the extent to which glucose (and insulin) administration could in reality benefit patients with acute myocardial infarction would only be shown by a controlled clinical trial. It should be noted that the Multicentre Medical Research Council trial,\textsuperscript{42} testing the efficacy of therapy with glucose, potassium, and insulin in patients with acute myocardial infarction, was aligned toward reversal of potassium loss from the myocardium rather than toward increased myocardial glucose utilization.

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References
2. Taylor SH, Majid PA: Insulin and the heart. J Molec Cell Cardiol 2: 293, 1971
6. Opie LH: Metabolism of the heart in health and disease: II. Amer Heart J 77: 100, 1969
15. Brachfeld N, Scheuer J: Metabolism of glucose by the ischemic dog heart. Amer J Physiol 212: 603, 1967
16. Scheuer J, Brachfeld N: Myocardial uptake and fractional distribution of palmitate-1-C14 by the ischemic dog heart. Metabolism 15: .945, 1966
27. Burke WM, Asokan SK, Moschos CB, Oldewurtel HA, Regan TJ: Effects of glucose and nonglucose infusions on myocardial potassium ion transfers and arrhythmias during ischemia. Amer J Cardiol 24: 713, 1969
35. Challoner DR, Steinberg D: The effect of free fatty acid on the oxygen consumption of the perfused rat heart. Amer J Physiol 210: 280, 1966

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