ABSTRACT

Although the healthy heart predominantly derives energy from the oxidation of circulating free fatty acids, when oxygen is limited as in ischemic heart disease, the provision of fatty acids becomes harmful. By contrast, glycolysis and glucose oxidation become protective by synthesis of glycolytic adenosine triphosphate, independently of the oxygen supply, to sustain the activity of membrane-related events such as the sarcolemmal sodium pump. The ischemic tissue is not totally deprived of blood and hence has residual oxidative metabolism. Fatty acids compete better than glucose for this residual oxygen, so that reduction of fatty acid oxidation increases glucose oxidation, hence enhancing the rate of glycolysis by removing the adverse end products including protons. Glycolysis and glucose oxidation are increased by several therapeutic procedures of which the forerunner is glucose-insulin-potassium. The insulin component also decreases the levels of the harmful circulating fatty acids that potentially increase ischemia. Furthermore, insulin promotes intracellular protective paths. Similar protective metabolic effects are obtained by insulin-glucose infusions or infusion of glucagon-like peptide, the latter releasing insulin from the pancreas. In the management of coronary heart disease, 2 partial fatty acid oxidation inhibitors, ie, trimetazidine and ranolazine, are being tested in large-scale clinical studies. Both of these metabolically active agents, which favor glucose oxidation by mitochondria, have demonstrated efficacy and safety in patients with chronic stable angina either as monotherapy or when added to background traditional hemodynamically active antianginal treatment. These and other interventions that directly or indirectly stimulate glucose metabolism and glycolysis offer novel treatment alternatives for the treatment of ischemic heart disease, a common and life-threatening condition. (Adv Stud Med. 2004;4(10B):S808-S815)

Cardiac energy metabolism is vital for the maintenance of normal cardiac contractility. Cardiac mechanical function requires incredibly large amounts of adenosine triphosphate (ATP), between 3.5 and 5 kg per day, to maintain sarcomeric and ionic function. This ATP utilization is necessarily coupled to a correspondingly high rate of ATP production in mitochondria. The important role that fatty acids play as a fuel for the animal heart was initially reported more than 6 decades ago. Later, Bing et al found that in the fasting state about two thirds of the oxygen taken up by the human heart could be accounted for by the uptake of fatty acids, if fully oxidized, with one third accounted for by carbohydrate uptake. Furthermore, free fatty acids could inhibit the oxidation of glucose by the perfused heart thus being better able to compete for the available oxygen. However, these patterns are dependent on the nutritional-hormonal status, with fatty acids dominating oxidative metabolism in the fasting state and...
glucose after a carbohydrate meal or after administration of insulin.5

When fatty acids and glucose are taken up into the heart cells, these fuels are broken down by the pathways of intermediary metabolism to the 2-carbon fragment acetyl-coenzyme A (acetyl-CoA), which enters the citrate cycle in the mitochondria (Figure 1).1,6 The reducing equivalents formed are processed by the electron transfer chain to generate ATP. The amount of ATP produced is greater per mole of fatty acids than glucose catabolized. In contrast, during high rates of fatty acid oxidation, mechanical efficiency of the heart, the work performed in relation to the uptake of oxygen, is less with fatty acids than with glucose. The reason for this change is still not clear, but is probably multifactorial, including the “oxygen-wasting” effects of fatty acids. Substrate partitioning is probably never absolute, and both major substrates are utilized to varying degrees in the heart and even during normal function the heart is dependent upon glycolysis and pyruvate oxidation to maintain optimal function. During ischemia, there is impairment in aerobic formation of ATP in the mitochondria and this results in activation of nonoxidative anaerobic glycolysis and a change from myocardial uptake of lactate to production of lactate.7 This increase in glycolysis is unable to produce enough energy for the normally contracting heart. Even maximal rates of glycolysis can only account for about 5% of the normally contracting heart’s energy needs. However, glycolytically produced ATP is thought to be specifically membrane protective when the oxygen supply is limited (Table).

Traditional hemodynamic-based agents treat stable angina by reducing the need for ATP by decreasing heart rate, cardiac contractility, and/or afterload or by increasing the aerobic formation of ATP by increasing coronary blood flow.8 Due to our growing understanding of cardiac metabolism, novel metabolic agents that exert their mechanism of action via effects on cardiac metabolism have come to the forefront (Table). The multiple mechanisms whereby glycolysis and glucose oxidation are more protective to the ischemic myocardium than fatty acids raise the possibility of multiple sites of intervention by metabolic maneuvers and pharmacological agents.8,11 Thus, whenever the metabolism of the heart is shifted to promote glycolysis and glucose oxidation or to lessen fatty acid oxidation, protection from ischemia can be expected. This paper will provide an overview of such strategies aimed at optimizing cardiac metabolism during ischemia.

**INCREASED GLYCOLYSIS-DERIVED ATP**

Suboptimal oxygenation accelerates glycolysis and increases the production of lactate.6 Such oxygen-independent anaerobic glycolysis serves as a defensive system allowing sufficient production of oxygen-independent energy to help to sustain the noncontractile ischemic myocardium.12 Biochemically speaking, the factors controlling the uptake and utilization of glucose and glycolysis have been studied extensively and are well understood. During hypoxia and mild-to-moderate ischemia, the activities of several key enzymes that regulate the rate of glycolysis are increased, thereby promoting anaerobic glycolysis and the synthesis of glycolytic ATP. Glycolysis provides an immediate source of cytosolic ATP during ischemia.

**Figure 1. Major Myocardial Fuels**

![Figure 1. Major Myocardial Fuels](image-url)
Glycolysis-derived ATP appears to be a preferential and important source of ATP for membrane ion transport processes. However, even high rates of anaerobic production of ATP cannot meet the energy demands of the heart unless contraction is arrested by a high extracellular potassium level.

**Biochemical Control Points**

Whereas mild ischemia results in stimulation of glycolysis and provides oxygen-independent ATP, more severe ischemia inhibits glycolysis by decreasing the delivery of glucose to the ischemic cells, by glycogen depletion and enzyme inhibition.

In severely ischemic tissue, flow through glycolysis is strongly inhibited by the end products of anaerobic glycolysis (lactate, protons, and nicotinamide adenine dinucleotide). Thus, one way of increasing the metabolic flow through glycolysis is by lessening the severity of ischemia by increasing the blood flow to the ischemic tissue (Figure 2).

**Provision of Glucose as Glucose-Insulin-Potassium**

Metabolic modulation with glucose-insulin-potassium (GIK) was the first metabolically active therapy proposed for acute myocardial infarction by Sodi-Pallares. Proof of benefit has been slow to come, basically because many early trials were flawed. More recently, the Estudios Cardiológicos Latinoamérica (ECLA) study, a randomized, open-label, multicenter pilot study conducted in 407 patients presenting within the first few hours of an acute myocardial infarction (MI), was conducted. GIK infusion was feasible and associated with few side effects. In the subgroup of reperfused patients, GIK reduced morbidity and mortality. Both an increase in myocardial glucose uptake and glycolysis, and a decrease in circulating fatty acids due to insulin’s inhibitory effect on adipocytes free fatty acid release, are postulated to be responsible for the beneficial effects observed. It should be noted that high-dose GIK was used in ECLA while low-dose GIK gave no benefit in another study (reviewed by Apstein et al in 1999). The promising results

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**Table. Contrasting Effects of Benefits of Glucose Metabolism and Detrimental Effects of Free Fatty Acids in Moderately Ischemic Myocardium**

<table>
<thead>
<tr>
<th>Site of Metabolic Action</th>
<th>Provision of Glucose/Glycolysis</th>
<th>Provision of Free Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse membrane effects</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Synthesis of protective glycolytic ATP</td>
<td>In proportion to rate of glycolysis</td>
<td>None</td>
</tr>
<tr>
<td>Competition for limited oxygen</td>
<td>Poor when compared with fatty acids</td>
<td>Good, “steals” oxygen from glucose</td>
</tr>
<tr>
<td>Synthesis of oxidative ATP</td>
<td>Good if FAO inhibited</td>
<td>Impaired mitochondrial function, uncoupling, “oxygen wastage”</td>
</tr>
<tr>
<td>Efficacy of mechanical work (in relation to oxygen uptake)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Agents promoting benefit of glucose/glycolysis or harm of fatty acids</td>
<td>Insulin, inhibitors of FAO (trimetazidine, ranolazine, perhexiline, etomoxir), increased PDH activity (dichloroacetate, carnitine inhibitors of FAO), reperfusion</td>
<td>High blood fatty acids; low blood insulin levels; regional myocardial ischemia</td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; FAO = fatty acid oxidation; PDH = pyruvate dehydrogenase.

**Figure 2. Sites of Therapeutic Interventions Aimed at Increasing Glycolytic Flow**

INS = insulin; ATP = adenosine triphosphate; FFA = free fatty acids; CPT-1 = carnitine palmitoyl transferase-1; FAO = fatty acid oxidation.

Reprinted with permission from Opie et al. Metabolic plasticity and the promotion of cardiac protection in ischemia and ischemic preconditioning. J Mol Cell Cardiol. 2002;34(9):1077-1089.
of ECLA led to a large multinational study, currently nearing completion and designed to confirm the efficacy and convenience of GIK administration as routine care for acute MI patients. In a much smaller trial, GIK given as adjunctive therapy to angioplasty in acute MI reduced mortality but only in those without heart failure. The chronic use of GIK for effort angina is not clinically practical; however, a better understanding of the mechanisms behind the benefits of GIK has driven the development of novel agents that can be administered on a chronic basis.

**INSULIN-GLUCOSE INFUSIONS**

Insulin is a “metabolically independent” component of GIK. Animal data suggest that insulin has independent cardioprotective effects during ischemia and reperfusion. In a blood-perfused rat heart model, insulin and glucose increased production of both glycolytic and total ATP, the latter perhaps by suppressing adverse mitochondrial fatty acid beta-oxidation. Insulin attenuates apoptotic (programmed cell death) processes and therefore provides cardioprotection during reperfusion when there is active apoptosis. When given to patients with acute MI undergoing thrombolytic therapy, glucose-insulin infusions have anti-inflammatory and profibrinolytic effects.

Insulin treatment in diabetic patients following MI improves the short- and long-term prognosis of this patient population. The Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study demonstrated that an infusion of insulin-glucose followed by multidose insulin therapy reduced 1-year mortality in diabetic patients with acute MI. These effects were more dramatic in non–insulin-dependent diabetes patients who had not received previous insulin treatment.

**GLUCAGON-LIKE PEPTIDE**

A member of the proglucagon incretin family that has been implicated in the control of satiety and appetite, glucagon-like peptide-1 (GLP-1 [7-36] amide) is a naturally occurring substance with both insulinomimetic and insulinotropic activity. Unlike GIK infusions, GLP-1 stimulates glucose uptake without promoting hypoglycemia.

A single-center, nonrandomized pilot study evaluated the efficacy and safety of GLP-1 infusion in 10 high-risk patients with acute MI and left ventricular systolic dysfunction after successful reperfusion with primary angioplasty. In addition to background therapy, GLP-1 was infused over 72 hours (1.5 pmol/kg/min). Eleven medically comparable patients who did not receive GLP-1 served as a control group. Regional and global left ventricular function improved independently from hemodynamic effects. GLP-1 was well tolerated and side effects were reversible. Beneficial effects of GLP-1 were also observed in diabetic patients.

**STIMULATION OF PYRUVATE DEHYDROGENASE**

A limit even to insulin-stimulated glycolytic ATP production can be set by the accumulation of end products such as lactate and protons. Logically, a simple way to remove these would be by increased oxidation of pyruvate, the product of glycolysis that must enter the mitochondria via pyruvate dehydrogenase to enter the citrate cycle of Krebs (Figure 2). If glycolysis is thus linked (or “coupled”) to glucose oxidation several beneficial consequences follow: (1) increased production of protective glycolytic ATP; (2) a reduction in proton production and an improvement in tissue pH; and (3) adverse fatty acid oxidation is reduced. Consonant experimental data are that stimulation of glucose oxidation during and after ischemia is associated with benefit for the ischemic heart. The normal metabolic pathway for glucose and fatty acids is shown in Figure 1. The oxidation of glucose can be increased directly by stimulating the rate-limiting enzyme for pyruvate oxidation, pyruvate dehydrogenase, or indirectly by decreasing intramitochondrial acetyl-CoA/CoA ratios.

**L-CARNITINE**

L-carnitine plays an important role in cardiac metabolism because the oxidation of fatty acids requires the translocation of fatty acids into the inner mitochondrial space via transport mediated by L-carnitine. In addition, L-carnitine assists in the regulation of pyruvate oxidation. The administration of L-carnitine or propionyl L-carnitine, an L-carnitine analog, results in an increase in the oxidation of glucose. Preclinical and clinical studies have demonstrated the anti-ischemic cardioprotective benefits of L-carnitine and propionyl L-carnitine. In small studies involving patients with coronary artery disease, both agents have demonstrated a reduction in ST-segment depression and left ventricular end-diastolic pressure during stress testing.
ADVERSE EFFECTS OF HIGH LEVELS OF FREE FATTY ACIDS

The adverse effects of high levels of free fatty acids are multiple and in the normal heart include (1) a dramatic inhibition of glucose oxidation and decreased glycolysis; (2) increased delivery of activated fatty acids to mitochondria with increased fatty acid oxidation; and (3) “oxygen wastage” with a marked decrease, up to 50%, in the efficiency of the heart (work output in relation to the oxygen uptake).27 The mechanisms are not fully understood but include mitochondrial uncoupling of ATP production from oxygen uptake, stimulation of the enzymes breaking down ATP in the mitochondria, and increased ATP—requiring futile cycling of fatty acids in and out of the triglyceride pool.28 In the acutely ischemic isolated heart, enzyme release is greatly and rapidly increased, probably because high fatty acid levels damage the cell membranes.

Therefore, one therapeutic approach to treating ischemic heart disease is to decrease circulating fatty acid levels. A relatively simple way of doing this is by administration of insulin, covered by glucose, or as part of GIK, or to increase insulin release from the pancreas by GLP. To better appreciate the effects of decreasing levels of circulating fatty acids available for the oxidative production of ATP, a brief overview of mechanisms involved in the regulation of fatty acid concentration is provided.

LEVELS OF FATTY ACIDS FOLLOWING ISCHEMIC EVENTS

The levels of circulating free fatty acids increase in the ischemic state.29-33 Fatty acids are hydrophobic and depend upon complex processes for transport of the activated fatty acid (fatty acyl CoA) from the cytosol across the mitochondrial membrane.29,33 There are 2 important regulators of the enzyme (carnitine palmitoyl transferase-1 [CPT-1]) that governs transfer of the activated fatty acid into mitochondria, namely carnitine and malonyl CoA.1,29,34 In ischemia, the synthesis of inhibitory malonyl CoA is decreased, and mitochondrial fatty acid uptake is increased. Within the mitochondria, fatty acid derivatives cause respiratory uncoupling and “oxygen wastage,” as well as limiting the oxidation of glucose and hence inhibiting glycolysis. Furthermore, fatty acids continue to be oxidized in preference to glucose thereby “stealing” the already limited residual oxygen supply from glucose.6

INHIBITION OF FATTY ACID OXIDATION: RANOLAZINE AND TRIMETAZIDINE

The inhibition of fatty acid oxidation indirectly increases glucose oxidation and improves cardiac efficiency. Trimetazidine and ranolazine are 2 direct fatty acid beta-oxidation inhibitors that demonstrate anti-ischemic and antianginal effects without altering hemodynamics or baseline contractile parameters.26 Both of these agents are novel piperazine derivatives that inhibit 3-ketoacyl-coenzyme A thiolase and are classified as partial fatty acid oxidation inhibitors.23,26 Trimetazidine is widely used outside of North America and the United Kingdom, while ranolazine is currently under evaluation by the US Food and Drug Administration.

TRIMETAZIDINE

Trimetazidine shifts cardiac energy metabolism from fatty acid to glucose oxidation.36 In addition, there appears to be mitochondrial-protective effects.37 This explains beneficial effects on the recovery of mechanical function and cardiac efficiency during reperfusion of the ischemic heart. Double-blind, placebo-controlled trials in chronic stable angina show that trimetazidine monotherapy (20 mg 3 times per day) reduces the frequency of angina episodes, with less need for nitroglycerin, and improved exercise time to onset of angina or time to 1-mm ST-segment depression.38-43 Different from traditional antianginal therapy such as the beta blocker propranolol, trimetazidine’s beneficial effects on exercise time and frequency of anginal episodes are not associated with blood pressure changes or bradycardia. Due to metabolic effects on the myocardium, trimetazidine demonstrates additional benefit when added to either beta-adrenergic antagonists or calcium channel antagonists. Trimetazidine also improves the contractile response of chronically dysfunctional myocardium to dobutamine in patients with ischemic cardiomyopathy, independently of hemodynamic effects.44

RANOLAZINE

Similar to trimetazidine, ranolazine stimulates glucose oxidation in the animal model.45 This beneficial metabolic effect of ranolazine was observed under a variety of conditions (normoxic conditions, ischemic conditions, or in reperfusion after global ischemia). Phase 3 antianginal trials have been conducted with sustained-release ranolazine and have established the
efficacy and tolerability of the agent when used as monotherapy or when combined with other antianginal drugs.46,47

In a randomized, double-blind, placebo-controlled study (Monotherapy Assessment of Ranolazine In Stable Angina [MARISA]), 191 anginal patients were randomized to ranolazine (500, 1000, and 1500 mg) and placebo for 1 week each with a crossover design of the 4 treatments.46 Monotherapy with ranolazine was associated with an improvement in symptom-limited exercise performance and ST-segment depression independent of any direct hemodynamic effects. In addition, treatment with ranolazine was found to be well tolerated and safe in diabetic and elderly patients.

Ranolazine improved exercise capacity and gave additional relief from angina compared with placebo when used in combination with standard antianginal therapy in the Combination Assessment of Ranolazine In Stable Angina (CARISA) study.47 Chronic stable angina patients (n = 823) were randomized to receive twice-daily administration of ranolazine 750 mg, 1000 mg, or placebo in addition to background therapy (atenolol, diltiazem, or amlodipine). Over the 12 weeks of treatment, exercise testing was performed at both peak and trough plasma levels. At endpoint, both doses of ranolazine were associated with a significant increase in total exercise duration and exercise time to onset of angina, an effect that was observed at both peak and trough concentrations (Figure 3). Beneficial effects of ranolazine were observed regardless of background antianginal therapy.

**Electrophysiological Effects of Ranolazine**

The electrophysiological effects of ranolazine in myocytes has been studied in several animal models.48-51 At concentrations ranging from 2 µM to 6 µM, ranolazine has been shown to suppress early afterdepolarizations and inhibit the following ion current channels: $I_{Kr}$ and late $I_{Na}$.48 These data provide theoretical evidence that ranolazine may be beneficial as an antiarrhythmic agent as late sodium current is increased in conditions such as ischemia, heart failure, and variants of long-QT syndrome; however, these potential benefits need to be explored with further clinical evaluation. Such an effect is a pleiotropic effect of ranolazine that is most likely not directly mediated via metabolic modulation.

**Effects of Trimetazidine and Ranolazine in Heart Failure**

In a double-blind, placebo-controlled, crossover study, 16 white male patients with diabetes and hypokinetic cardiomyopathy secondary to ischemic heart disease were treated with trimetazidine (20 mg 3 times per day) for 15 days as short-term therapy and for 6 months as long-term therapy.52 Trimetazidine improved left ventricular function, symptoms, glucose metabolism, and endothelial function. There are no prospective clinical trials to assess the effects of ranolazine on heart failure. However, in subgroup analysis, MARISA participants with New York Heart Association Class I or II heart failure experienced a greater improvement in total exercise duration with ranolazine than those without heart failure.

**Perhexiline**

Perhexiline is a potent inhibitor of the enzyme that regulates transport of activated fatty acid from the cytoplasm into the mitochondria (CPT-1),53 and clinically is a very effective antianginal agent. However, long-term administration is associated with neurotoxicity and cardiac hypertrophy.26 Thus, it is only registered for clinical
use in certain countries such as Australia where doses are carefully regulated by blood levels.

CONCLUSIONS

Experimental ischemic damage can be limited by decreasing the metabolism of fatty acids increasing that of glucose. The clinical counterpart is that the anginal symptoms associated with coronary heart disease can be countered by drugs that optimize the energy metabolism of the heart.

REFERENCES

47. Chairman BR, Pepine CJ, Parker JO, et al, for the Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amiodarone, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA. 2004;291(3):309-316.