Clinical implications of energetic problems in cardiovascular disease

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Abstract

Cardiac energy metabolism can be altered in many forms of heart disease, including ischemic heart disease, cardiac hypertrophy, heart failure, and cardiac arrhythmias. Some of these energy metabolic changes are beneficial and help the heart adapt to the presence of the underlying cardiac pathology. However, some of the changes can also be maladaptive and actually contribute to the severity of cardiovascular disease. Because of the importance of energy metabolism in mediating cardiovascular disease, optimization of cardiac energetics has recently emerged as a novel approach to treat cardiovascular disease. This includes increasing the efficiency of oxygen utilization by the heart, which can be achieved by shifting cardiac metabolism to favor the use of carbohydrates rather than fatty acids as a metabolic fuel. This can be attained by reducing the circulating concentrations of fatty acids to which the heart is exposed, by inhibiting the uptake of fatty acids into the mitochondria, by directly inhibiting the enzymes of fatty acid oxidation, or by directly stimulating glucose metabolism. Clinical studies using these approaches have shown promise in treating various cardiovascular diseases, including ischemic heart disease, acute myocardial infarction, cardiac surgery, and heart failure. One agent that uses this approach is trimetazidine, which directly inhibits cardiac fatty acid oxidation and has been shown to be clinically effective in treating ischemic heart disease and heart failure. The paper will review those alterations in energy metabolism that occur in ischemic heart disease and heart failure, and the promising clinical approach of switching energy metabolism from fatty acid to glucose oxidation as a therapy in heart disease.
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Introduction

Cardiovascular disease is a major health problem worldwide, and by 2010 could be the leading cause of death worldwide [1]. It is therefore important to develop new therapeutic approaches to lessen the burden of this major health problem. One such approach is to optimize energy metabolism in the heart. The heart has a very high energy demand, and most forms of cardiovascular disease are accompanied by alterations in cardiac energy metabolism. An obvious example of this is ischemic heart disease, in which the myocardium is deprived of the necessary oxygen and energy needed to sustain contractile function. However, independent of ischemia, cardiac energy metabolism can also be altered in other forms of heart disease, including cardiac hypertrophy, heart failure, and cardiac arrhythmias.

Some of the metabolic changes that occur in heart disease are beneficial, and help the heart adapt to the presence of the underlying cardiac pathology. However, it is also clear that some of the energy metabolic changes can be maladaptive, and can contribute to the severity of cardiovascular disease (this subject has

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been reviewed elsewhere [2–5]). Mutations in genes involved in energy metabolism can also be the actual precipitating cause of the heart disease [2]. Because of the importance of energy metabolism in cardiovascular disease, it is reasonable to expect that optimization of cardiac energetics may be a suitable therapeutic approach to the management of cardiovascular disease. One such approach involves shifting cardiac metabolism to favor the use of carbohydrates rather than fatty acids as a metabolic fuel, thereby allowing the heart to use oxygen and produce energy more efficiently [2–5].

The aim of this review will be to discuss the potential clinical implications for optimizing cardiac metabolism in heart disease. It will examine the clinical trials aimed at optimizing cardiac metabolism for the treatment of angina, acute myocardial infarction, cardiac surgery, and heart failure. This will be preceded by a brief discussion of how cardiac metabolism is regulated and what alterations occur in various forms of cardiovascular disease.

Cardiac energy metabolism

In order to meet the high energy demands of contraction and ionic homeostasis, the heart must produce an abundant supply of ATP [6]. In the normal healthy heart, almost all (>95%) ATP generated in the heart comes from mitochondrial oxidative phosphorylation, with the remainder derived from glycolysis [2,6]. The contribution of fatty acids and carbohydrates to oxidative generation of ATP in the heart is influenced by a number of conditions, which include alterations in hormonal control, workload, energy substrate supply, and oxygen supply to the heart. Mitochondrial metabolism of fatty acids accounts for approximately 60–90% of total energy production (in the form of ATP), with carbohydrates contributing the remaining 10–40%. However, despite producing more ATP than carbohydrates, fatty acids are not as oxygen-efficient, requiring approximately 10% more oxygen to produce an equivalent amount of ATP [6]. This is of particular importance when oxygen becomes a limiting factor for oxidative metabolism.

The rates of flux through the various metabolic pathways are controlled by both the degree of expression of key metabolic proteins (enzymes and transporters) and the complex pathway regulation including both allosteric regulation of enzymes and substrate–product relationships. As will be discussed, one of the main clinical approaches used to optimize cardiac energetics involves manipulating a number of these enzymes/transporters to inhibit the oxidation of fatty acids, or to increase the oxidation of carbohydrates, thereby making oxygen utilization and energy production more efficient.

Carbohydrate metabolism

Glucose and lactate are the primary carbohydrates metabolized by the heart. The majority of glucose that the heart metabolizes is derived from the blood, with its uptake being facilitated by glucose transporters (GLUT) (*Figure 1*). GLUT 1 is responsible for maintaining basal glucose uptake, whereas GLUT 4 translocates from an intracellular pool to the sarcolemmal membrane in response to insulin, increased work demand, or ischemia [7,8].

Alternatively, the mobilization of endogenous glycogen stores can generate glucose-6-phosphate, which is the first intermediate in the metabolic pathway of glucose. Subsequent glucose metabolism can be separated into two major components: glycolysis and glucose oxidation (*Figure 1*). Glycolysis results in the production of pyruvate and accounts for less than 10% of the total ATP produced by the non ischemic heart [6]. If glycolysis is coupled to glucose oxidation, the pyruvate generated from glycolysis will be converted to acetyl coenzyme A (CoA) (which can be subsequently oxidized in the tricarboxylic acid cycle) by the enzymatic action of the multienzyme complex, pyruvate dehydrogenase (PDH). The other major source of pyruvate for PDH is lactate, which, after uptake by the heart, is converted to pyruvate by lactate dehydrogenase.

The PDH complex itself is under tight regulation by an upstream kinase, PDH kinase, which acts to phosphorylate and inhibit the activity of the PDH complex [9]. This PDH kinase is positively regulated by acetyl CoA and NADH. Because the oxidation of fatty acids generates acetyl CoA and NADH, the oxidation of fatty acids is a potent inhibitor of PDH and glucose oxidation. This can ''uncouple'' glycolysis from glucose oxidation, resulting in the production of lactate and protons [2,10]. The oxidation of fat uses approximately 10% more oxygen than carbohydrates, but the uncoupling of glycolysis from glucose oxidation can also cause a substantial decrease in cardiac efficiency. The decreased coupling of glycolysis to glucose oxidation caused by increased fatty acid oxidation can cause myocardial tissue acidosis from the hydrolysis of glycolytic ATP and build-up of lactate and protons [10]. Accumulation of protons can lead to the accumulation of sodium and calcium, requiring the use of ATP to maintain ion homeostasis. This redirection of ATP from contractile function to ion homeostasis can dramatically decrease cardiac efficiency [2,10]. Thus a number of drugs designed for the optimization of cardiac energetics either inhibit fatty acid oxidation to give indirect improvement in the coupling of glycolysis to glucose oxidation, or

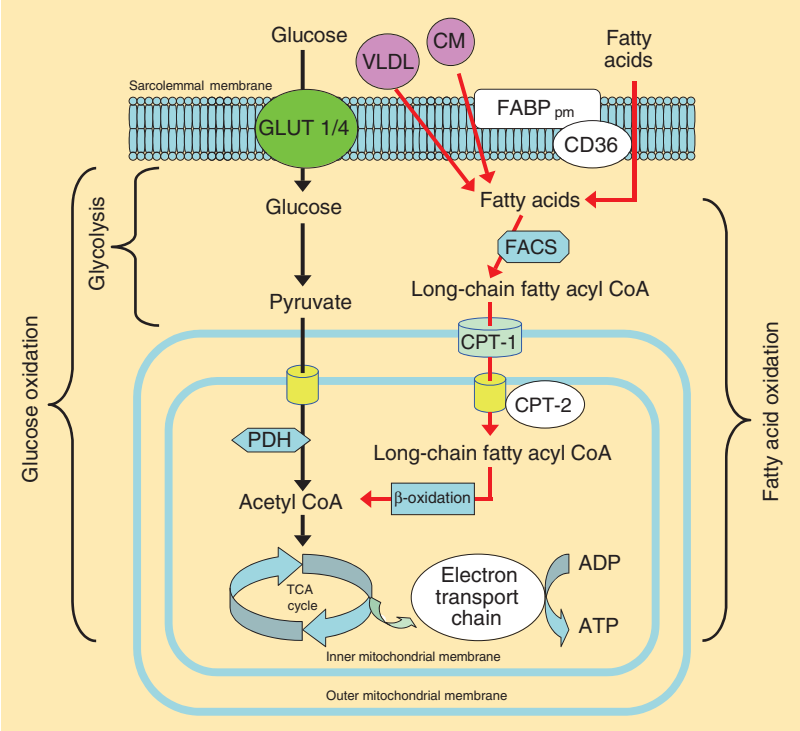

Figure 1. Glucose and fatty acid metabolism. Glucose enters the cardiomyocyte through glucose transporter (GLUT) 1 or 4 and undergoes the first phase of glucose metabolism, glycolysis. The end product of glycolysis, pyruvate, can be further oxidized in the mitochondria to acetyl coenzyme A (CoA) by the actions of pyruvate dehydrogenase. Acetyl CoA then enters the tricarboxylic acid (TCA) cycle to generate reducing equivalents for the production of ATP in the electron transport chain. Fatty acids enter the cardiomyocyte by either passive diffusion or protein-mediated transport through the sarcolemma via plasma membrane fatty acid binding protein ($FABP_{pm}$) or CD36/fatty acid translocase. The fatty acids are then esterified by the actions of fatty acyl CoA synthase (FACS) and subsequently taken up via carnitine palmityl transferase (CPT)-1 into the mitochondria, where they can be oxidized to generate acetyl CoA for the TCA cycle. CM, chylomicron; PDH, pyruvate dehydrogenase; VLDL, very low density lipoprotein.

increase glucose oxidation, giving direct improvement in its coupling to glycolysis.

Fatty acid metabolism

Long-chain fatty acids are supplied to the heart either as triglycerides in chylomicrons and very low density lipoproteins, or as fatty acids in the non esterified form bound to albumin [2]. The rate of fatty acid uptake by the heart is primarily determined by the concentration of fatty acids in the blood, which can vary over a 4-fold range in healthy humans during the course of a day (from about 0.2 to 0.8 mmol/L) [3,6,11]. Under conditions of metabolic stress such as ischemia, diabetes, or starvation, plasma free fatty acid concentrations can increase to much greater values (>1.0 mmol/L) [2,12].

Fatty acids enter the cardiomyocyte by either passive diffusion or protein-mediated transport across the sarcolemma (*Figure 1*) [13]. Once transported across the sarcolemma, the fatty acids are subsequently activated by esterification to fatty acyl CoA by fatty acyl CoA synthase. This acyl CoA can either be esterified to intracellular lipids or converted to long-chain fatty acyl carnitine by carnitine palmityltransferase (CPT)-1 [2]. Studies have demonstrated in humans that 70–90% of fatty acids taken up by the heart are immediately oxidized, and the remaining 10–30% probably become part of the intracardiac triglyceride pool [11].

Fatty acid β-oxidation (*Figure 1*) occurs predominantly in the mitochondria [14]. Before mitochondrial β-oxidation of fatty acids can begin, the cytoplasmic long-chain fatty acyl CoA must first be transported into the mitochondrial matrix. A key enzyme in this process is CPT-1 [15]. As will be discussed later in this review, one way to optimize cardiac energetics in the patient with heart disease is to inhibit CPT-1 (*Figure 2*). This indirectly leads to decreased cardiac mitochondrial β-oxidation of fatty acids by preventing the uptake of fatty acids into the mitochondria, which indirectly increases glucose oxidation and improves its coupling to glycolysis, thereby reducing proton production. Thus benefit is provided, not only by making ATP production more fuel-efficient, but also by reducing myocardial tissue acidosis.

Once fatty acids are taken up by the mitochondria, they undergo β-oxidation, a process that repeatedly cleaves off two carbon acetyl CoA units, generating

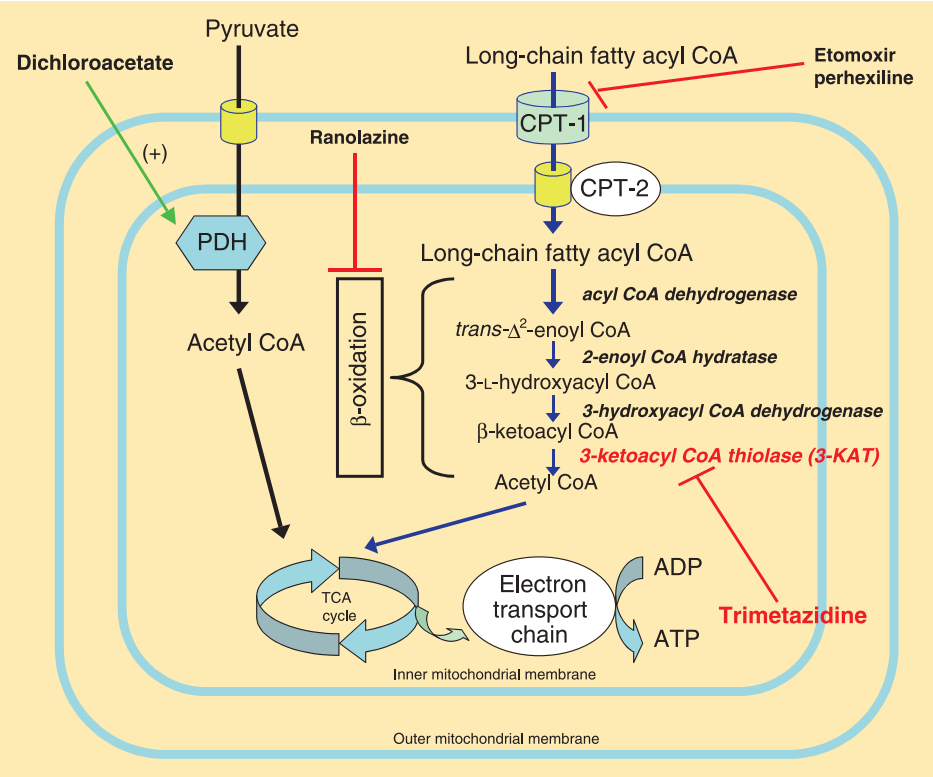

Figure 2. Targets for optimization of cardiac energetics. Before fatty acids can be oxidized, they must first be taken up into the mitochondria via carnitine palmityl transferase (CPT-1). Therefore, inhibition of CPT-1 with etomoxir or perhexiline will optimize cardiac energetics by indirectly inhibiting the oxidation of fatty acids, which thereby increases glucose oxidation and its coupling to glycolysis. Direct inhibition of fatty acid oxidation represents another approach to optimizing cardiac energetics. This can be achieved with trimetazidine, which inhibits 3-ketoacyl CoA thiolase (3-KAT), or ranolazine, a partial inhibitor of fatty acid oxidation. One other approach to optimize cardiac energetics is to increase glucose oxidation and its coupling to glycolysis. This can be achieved directly with dichloroacetate, which inhibits pyruvate dehydrogenase kinase (PDH) kinase to stimulate PDH, resulting in increased oxidation of pyruvate to acetyl CoA. TCA, tricarboxylic acid.

NADH and reduced flavine adenine dinucleotide in the process. The β-oxidation process involves four enzymatically catalyzed reactions, starting with acyl CoA dehydrogenase, followed by 2-enyl CoA hydratase, and then 3-hydroxyacyl CoA dehydrogenase. The last reaction is catalyzed by 3-ketoacyl CoA thiolase (3-KAT), which regenerates acyl CoA for another round of β-oxidation and releases acetyl CoA for the citric acid cycle. As mentioned earlier, the oxidation of a fatty acids generates acetyl CoA, which inhibits PDH and glucose oxidation. Therefore, potential targets for optimizing cardiac energetics in heart disease include the enzymes of the β-oxidation pathway. Targeting such enzymes (*Figure 2*) can directly inhibit fatty acid oxidation, leading to a secondary increase in glucose oxidation. Examples of agents that do this include the 3-KAT inhibitor, trimetazidine.

Alterations in energy metabolism in cardiovascular disease

Mitochondrial oxidative metabolism is critically dependent on oxygen supply to the heart, and any decrease in oxygen supply to the myocardium results in a decrease in the production of mitochondrial ATP. An initial adaptive response is to increase glycolysis, because glycolysis can produce ATP in the absence of oxygen [6]. However, during myocardial ischemia there are a number of additional subcellular changes occurring that alter cardiac metabolism, which can further exacerbate the deleterious effects of an imbalance between oxygen supply and demand (reviewed in [16]). In particular, the heart is exposed to high concentrations of fatty acids [2,12], and alterations in the subcellular control of fatty acid oxidation result in fatty acid oxidation becoming the main residual source of mitochondrial oxidative metabolism. This results in low rates of glucose oxidation during ischemia. The high glycolysis coupled to low glucose oxidation results in the production of lactate and protons [10], which in turn leads to a decrease in cardiac efficiency. Clinical therapy that improves this coupling of glycolysis to glucose oxidation can reduce myocardial tissue acidosis and the build-up of lactate.

If the myocardium is reperfused after ischemia (such as during thrombolysis, angioplasty, or reperfusion after cardiac bypass surgery), mitochondrial oxidative metabolism recovers as oxygen is reintroduced to the heart [2]. However, during reperfusion, fatty acid

oxidation dominates as a source of ATP production, primarily as a result of the high circulating concentrations of fatty acids to which the heart is exposed, but also as a result of decreased subcellular control of fatty acid oxidation (reviewed in [2]). This results in low rates of glucose oxidation, and a continued coupling of glycolysis to glucose oxidation. Consequently, the continued production of lactate and protons contributes to a decrease in cardiac efficiency [10]. Promising experimental and clinical studies, however, have shown that inhibiting fatty acid oxidation or stimulating glucose oxidation, or both, can increase cardiac efficiency during this critical period of reperfusion (as discussed in the next section).

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood [17]. Despite the growing incidence of heart failure in our society, there is not a consensus as to the effects of heart failure on myocardial energy metabolism and fuel selection (reviewed in [15,16]). In general, it appears that energetic reserve is compromised in heart failure, as the consequence of an impaired mitochondrial function (reviewed in [18]). This results in a compensatory increase in glycolysis, similar to the adaptive increase in glycolysis seen in the ischemic heart. It appears that, in the early stages of heart failure, rates of fatty acid oxidation are normal or increased, whereas rates of glucose oxidation are low [18]. In late-stage heart failure, overall mitochondrial oxidative metabolism can be markedly impaired (with both fatty acid and glucose oxidation being decreased), while glycolysis becomes a more important source of energy. The increase in glycolysis in relation to glucose oxidation can result in an uncoupling of glycolysis from glucose oxidation similar to that observed in the ischemic heart. This can cause a decrease in efficiency as a result of lactate and proton production, and suggests that switching mitochondrial oxidative metabolism from fatty acid to glucose oxidation may also be a valid approach to the treatment of heart failure. The clinical evidence to support this concept will be discussed in the following section.

Optimization of cardiac energetics for the treatment of heart disease

Treatment of angina pectoris

Inhibition of fatty acid oxidation and stimulation of glucose oxidation can improve cardiac efficiency and cardiac function in the ischemic heart. Trimetazidine, a piperazine derivative that inhibits 3-KAT in the β-oxidation pathway [19], offers one such approach to switching the heart from fatty acid to glucose oxidation. Trimetazidine is available in more than 80 countries for the treatment of angina pectoris, and has been the subject of a large number of clinical studies in patients with angina (reviewed in [16]). A meta-analysis of human clinical trials of trimetazidine was recently undertaken by the Cochrane Collaboration [20], to determine its efficacy and tolerability in patients with stable angina. A total of 23 studies encompassing 1378 patients were analyzed, and it was concluded that trimetazidine is an effective treatment for stable when angina compared with placebo (approximately 40% reduction in mean number of angina attacks per week), alone or combined with conventional antianginal agents. The authors of the meta-analysis also concluded that the use of trimetazidine may result in fewer patients withdrawing from trials as a result of adverse events. It has also been pointed out that, although there are insufficient data to permit analysis of the effect of trimetazidine on mortality or major adverse cardiovascular events, the intensity of anginal symptoms consistently predicts total mortality among outpatients with ischemic heart disease [21], and their quality of life [22]. Overall mortality has never served as a primary endpoint in a trial assessing the effects of a drug on stable angina. Time to onset of angina, exercise duration, and time to 1 mm ST-segment depression are often the primary/secondary endpoints analyzed in trials in stable angina, as they are determinants of quality of life. A patient who experiences improvements in these endpoints is likely to enjoy a better quality of life and it would, therefore, be safe to conclude that trimetazidine represents an exciting novel treatment for ischemic heart disease.

Ranolazine is another piperazine derivative that acts as a partial inhibitor of fatty acid β-oxidation [22]. This drug has recently been proposed to act as a slow sodium channel modifier, but the concentrations known to inhibit fatty acid oxidation [22] are also consistent with the plasma concentrations observed in clinical trials that demonstrated its efficacy in angina pectoris [23,24]. Like trimetazidine, ranolazine has the potential to provide benefit during ischemia by making ATP production more fuel-efficient, although ranolazine is substantially less potent then trimetazidine. Ranolazine may also benefit the patient with ischemic heart disease by decreasing myocardial tissue acidosis, because it improves coupling of glycolysis to glucose oxidation by indirectly stimulating PDH [25]. It was recently introduced into the US market for the treatment of angina, and can be used either as monotherapy or in combination with other antianginal agents [23,24].

Treatment of acute myocardial infarction

Despite promising experimental evidence that optimizing energy metabolism can be beneficial after

severe ischemia (reviewed in [16]), few clinical studies have addressed the potential of altering energy metabolism as an approach to treating acute myocardial infarction. Some studies have addressed the concept of improving metabolism with infusions of glucose–potassium–insulin (GIK): the exogenous insulin suppresses circulating concentrations and myocardial uptake of free fatty acids, and the high-dose glucose can make glucose the preferred fuel for the heart. The actions of both result in improved overall efficiency of energy production by the heart. A meta-analysis of GIK trials, published in 1997 [26], covered the findings of nine trials with a total of 1932 patients; its authors concluded that GIK treatment may have an important role in reducing in-hospital mortality after acute myocardial infarction (154 deaths among 956 patients in the GIK groups [16.1%], compared with 205 deaths among 976 patients in the placebo group [21%]). A more recent analysis [27] also demonstrated that mortality was reduced by 18% with GIK therapy. In line with similar findings in another meta-analysis that examined 13 studies involving 4992 patients [28], benefit with GIK appeared to be greatest when a high-dose infusion of GIK was administered.

Recently, the results from the merged Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) and Estudios Cardiologicas LatinoAmerica (ECLA) Study Group 2 GIK Full Scale Trial were published [29]. A total of 20 201 patients were allocated randomly to groups to receive either usual care alone (10 110 patients) or an infusion of GIK plus usual care (10 091 patients). Unfortunately, the results of this trial demonstrated equal mortality rates between the two groups, and the authors ultimately concluded that infusion of GIK in patients with acute myocardial infarction has no impact on mortality, and is unlikely to be of any real value in these patients.

As mentioned earlier, a key physiological change that takes place during reperfusion of previously ischemic myocardium is an increase in the concentration of circulating fatty acids, which is one of the primary causes of the enhanced rates of fatty acid oxidation observed during reperfusion. Such an observation suggests that an infusion of GIK for the treatment of acute myocardial infarction should take place immediately at the onset of reperfusion with either thrombolytic therapy or primary percutaneous coronary intervention (PCI). This would provide the best therapeutic window in which to allow insulin to block the myocardial uptake of fatty acids. In the CREATE–ECLA trial, patients received an infusion of GIK immediately after random allocation to groups. However, the median time from onset of symptoms to reperfusion therapy (in patients receiving thrombolysis or primary PCI) was 3.9 h in the GIK infusion group, and the median time from onset of symptoms to allocation to groups was 4.7 h. Moreover, GIK infusion was started within 1 h of the allocation to groups in more than 90% of patients. Hence, the majority of patients receiving the GIK infusion were receiving it at least 1 h after they received reperfusion therapy. Because the optimal therapeutic window for the actions of insulin is within the first few minutes immediately after the onset of reperfusion, the authors' negative conclusions on the use of GIK infusions for treating acute myocardial infarction are misleading.

A few trials have also investigated the effect of trimetazidine in the treatment of acute myocardial infarction. A small study of 81 patients [30] demonstrated that pretreatment with trimetazidine before thrombolytic therapy reduces reperfusion damage, or infarct size, or both, in patients with anterior acute myocardial infarction. In addition, another small study involving 94 patients demonstrated that treatment with trimetazidine before primary PCI on the infarct vessel was safe and led to earlier resolution of ST-segment elevation in the patients [31]. A larger multicenter trial has also been performed [32], involving 17 169 patients in whom the effects of trimetazidine (in conjunction with or without thrombolysis) on acute myocardial infarction mortality were investigated. As with the findings of the CREATE–ECLA trial, the multicenter trial showed no significant reduction in mortality with trimetazidine. Interestingly, there was a non significant trend to increased short- and long-term mortality with trimetazidine in patients receiving thrombolysis; a significant short-term decrease in mortality in patients not receiving thrombolysis was also observed. Perhaps the beneficial effects of trimetazidine in conjunction with thrombolysis were masked by reperfusion being established at so late a time that the myocardial area at risk could no longer be salvaged. This may also explain why there was a significant trend to decreased mortality in patients not receiving thrombolysis, as these patients probably have improved collateral circulation, and thus a longer therapeutic window for myocardial salvage. It could also simply be that trimetazidine is not beneficial in conjunction with thrombolysis, and may be more suited as a therapy in conjunction with primary PCI. A previous small trial demonstrated that trimetazidine delivered intracoronarily during percutaneous transluminal coronary angioplasty (PTCA) at 10% of the dose used in the large acute myocardial infarction trial had direct anti-ischemic effects in man [33]. The results of this small trial by no means imply that trimetazidine is beneficial in conjunction with primary PCI for treating acute myocardial infarction, but suggests that trimetazidine does warrant further investigation for use in this setting.

Primary cardiac surgery techniques to reperfuse the heart involve coronary artery bypass grafting (CABG) surgery and PTCA. Because circulating concentrations of fatty acids increase during reperfusion [12], the optimization of cardiac energetics during CABG and PTCA has been explored to future enhance cardiac recovery further. In a small trial of 19 patients, pretreatment for 3 weeks with trimetazidine and the addition of trimetazidine to the cardioplegic solution were shown to have cardioprotective effects in patients undergoing CABG surgery [34]. Furthermore, trimetazidine has also been shown to have cardioprotective effects during PTCA [33]. More recent PTCA trials have demonstrated an earlier resolution of ST-segment elevation in patients treated with trimetazidine during recanalization of the infarct vessel [35], and that pretreatment with trimetazidine results in a shorter time to pain relief [36]. Larger trials are necessary to determine whether the optimization of cardiac energetics during cardiac surgery should be implemented in routine practice.

Treatment of heart failure

Although clinical data are limited, the findings of a number of small clinical trials suggest that inhibiting fatty acid oxidation and stimulating glucose oxidation may also improve heart function and increase cardiac efficiency in heart failure. Bersin and co-workers [36,37] observed improved contractile function in 10 patients with heart failure (New York Heart Association [NYHA] classes III and IV) treated with intravenous dichloroacetate. Dichloroacetate inhibits PDH kinase to activate PDH, thereby increasing pyruvate oxidation and the coupling of glycolysis to glucose oxidation [38], and reducing myocardial tissue acidosis and making ATP production more fuel-efficient. Consistent with a stimulation of PDH, during treatment with dichloroacetate there was a significant increase in stroke volume and stroke work, and an increase in left ventricular mechanical efficiency from 15.2 to 20.6%. These results suggest that dichloroacetate increases pyruvate oxidation and mechanical efficiency by switching the preference of the heart to the more efficient fuel. However, caution should be taken when interpreting these results, as the study lacked a vehicle-treated control group, and because rates of glucose and free fatty acid uptake and oxidation were not measured.

Hermann et al [38,39] evaluated the effects of an acute intracoronary infusion of sodium pyruvate on left ventricular function in patients with NYHA class III heart failure with dilated cardiomyopathy (ejection fraction <25%). Infusion of pyruvate resulted in rapid increases in left ventricular peak d*P*/d*t*, ejection fraction, and cardiac output that immediately reversed upon cessation of the infusion [38,39]. Unfortunately, from a practical standpoint, it would not be feasible to infuse sodium pyruvate intravenously to attain high arterial pyruvate concentrations, because of the high sodium load that accompanies infusion of the sodium salt.

Because the optimization of cardiac energetics could be effective in the early stages of heart failure, chronic inhibition of myocardial fatty acid oxidation may slow down the progression of the heart failure and improve cardiac function. This has been investigated in a few trials with trimetazidine [40–42]. One of these [40] demonstrated that, compared with placebo, 2 months of treatment with trimetazidine resulted in a significant improvement in left ventricular ejection fraction at rest and enhanced left ventricular wall motion during a dobutamine stress test in patients with NYHA class II/III heart failure. Furthermore, two small clinical trials [41,42] demonstrated that, compared with placebo, treatment with trimetazidine improved systolic left ventricular function in patients with diabetes and ischemic cardiomyopathy. More recently, another trial involving 200 patients with ischemic cardiomyopathy demonstrated that patients treated with trimetazidine experienced a reduction in the insult from of an ischemic attack as determined by gated single photon emission computed tomography [43]. This finding was not accompanied by changes in hemodynamics. In addition, trimetazidine was able to improve functional NYHA heart failure class and left ventricular function in a double-blind, crossover study involving 12 patients [44]. To date, trimetazidine has not been evaluated in patients with heart failure from other than an ischemic origin, and no large-scale clinical trials have been conducted to investigate clinically relevant outcomes such as overall mortality.

As mentioned earlier, another approach to optimizing cardiac energetics is to prevent the uptake of fatty acids into the mitochondria through CPT-1. Such an approach provides benefit by making ATP production in the heart more fuel-efficient, and also reduces myocardial tissue acidosis by improving the coupling of glycolysis to glucose oxidation. Etomoxir is one agent that acts in this way by inhibiting CPT-1 [45], and in an open-label pilot study in patients with NYHA class II/III heart failure was shown to improve left ventricular function and exercise performance after 3 months of treatment. The first controlled trial of a CPT-1 inhibitor for treating heart failure was recently published; perhexiline was the agent used [46]. The authors demonstrated improved maximal oxygen consumption, left ventricular ejection fraction, resting and peak stress myocardial function, and skeletal muscle energetics, in patients with NYHA class II/III heart failure. They concluded that perhexiline may represent a novel treatment for heart failure,

provided that the dosage is adjusted according to plasma concentrations.

Long-term β-adrenergic receptor antagonists reduce mortality and improve left ventricular function in patients with heart failure [47,48]. Interestingly, in clinical studies, this improvement has been associated with a switch in myocardial metabolism away from fatty acid uptake and oxidation towards more glucose uptake and carbohydrate oxidation [49,50], and greater lactate uptake [51]. However, the mechanisms for these effects are not known, and they have not been demonstrated in large-scale clinical trials.

Overall, the optimization of cardiac energetics for the treatment of heart failure does show promise in the small pilot studies and trials that have been completed to date. Larger, long-term multicenter trials looking at clinically relevant outcomes such as overall mortality are both warranted and needed.

Conclusions

The optimization of cardiac energetics represents an exciting new approach to the treatment of heart disease. This form of optimization involves switching the fuel preference of the heart to become carbohydrate-dependent rather than fatty-acid-dependent. This can be achieved with agents that (i) directly inhibit mitochondrial fatty acid oxidation (trimetazidine and ranolazine), (ii) prevent the mitochondrial uptake of fatty acids (etomoxir), (iii) reduce the circulating concentrations of free fatty acids (GIK infusion), or (iv) directly stimulate glucose oxidation and improve its coupling to glycolysis (dichloroacetate). The initial results of trials investigating the optimization of cardiac energetics to treat angina, acute myocardial infarction, cardiac surgery, or heart failure have demonstrated more exciting promise than negative findings. However, larger long-term studies evaluating this form of treatment against first-line treatments, while assessing other clinically relevant outcomes such as overall mortality, are necessary to establish a role for the optimization of cardiac energetics in routine clinical practice. ■

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