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Metabolic aspects of cardiovascular pathophysiology and therapy. The clinician's perspective

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Abstract

The heart is a metabolically active organ that converts chemical energy stored in fatty acids and glucose into the mechanical energy necessary to sustain its contractile function.

Alterations in myocardial energy substrate metabolism contribute significantly to ischemic heart disease. The evidence of the role of altered cardiac metabolism in heart failure is increasingly robust.

Targeting cellular energy metabolism optimizes myocardial substrate utilization and improves cardiac efficiency. Therefore, agents acting in this way are likely to complement the established therapy and offer the possibility of clinical benefit in a range of cardiovascular diseases. In this article, we discuss the clinical potential of metabolically acting agents such as trimetazidine, ranolazine, perhexiline, etomoxir, oxfenicine, and dichloroacetate.

Keywords: cardiovascular pathophysiology, metabolic, alterations, heart failure, therapy/

Introduction

Despite many advances in medical therapy, cardiovascular disease remains a major health problem worldwide and by 2010 could even become the leading cause of death worldwide [*NHLBI, 2004*].

The heart has a very high-energy demand, and disease states that result in an insult to the heart can seriously perturb energetic balance, which can contribute to myocardial damage. An example of this is ischemic heart disease, which dramatically alters both the rate of energy production and the source of energy supply. Also, it appears that the energetic reserve is compromised in heart failure [*Ingwall J.S., Weiss R.G., 2004*].

Traditional pharmacological treatments for myocardial ischemia have been aimed at increasing oxygen supply (i.e. calcium antagonists) and/or decreasing oxygen demand (i.e. nitrates, beta-adrenergic receptor antagonists).

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Because of the major involvement of energy metabolism in cardiovascular disease, it is rational to expect that optimization of cardiac energetics may also be a suitable therapeutic approach to the management of cardiovascular disease. Furthermore, agents acting in this way could provide benefits complementary to those of the established therapy and offer the possibility of clinical improvement in a range of cardiovascular diseases.

The aim of this review will be to discuss metabolic aspects of cardiovascular pathophysiology and to review the clinical implications of different metabolic agents in various forms of heart disease.

Cardiac energy metabolism in normal conditions. It has been recognized for over half a century that the heart is a metabolically active organ, which generates approximately 30 *kg* (30-50 times its own weight) of adenosine triphosphate (ATP) per day, which is necessary to sustain its contractile function and basal metabolism [*Bing R.J., 1954*]. To acquire its energy, the heart converts chemical energy stored in fatty acids and glucose into the mechanical energy of the myofibrils.

In normal conditions, free fatty acids are the

major source of energy for the heart and account for 60% to 90% of total energy production (in the form of ATP), while the remaining 10% to 40% is provided mainly by carbohydrate oxidation (glucose oxidation and lactate oxidation), and also, at a very low percentage, by glycolysis and the oxidation of ketone bodies [*Stanley W.C., et al, 1997*].

Glucose is transported into the heart via the glucose transporter and is either stored as glycogen or broken down by glycolysis to pyruvate in the cytosol. Energy production from the metabolism of glucose can be separated into two main components, glycolysis and glucose oxidation. Glycolysis is the initial sequence of reactions involved in the breakdown of glucose to pyruvate, and contributes to small yields of ATP (less than 2% of total ATP produced by the aerobic heart). Glucose oxidation is the second part of the glucose metabolic pathway, where the pyruvate generated from glycolysis, and to a lesser extent from lactate, is further metabolized within the mitochondria to produce the main amount of carbohydrate-derived ATP. The conversion of pyruvate in the mitochondria to acetyl-coenzyme A is catalyzed by the enzymes in the pyruvate dehydrogenase (PDH) complex. PDH activity is influenced by concentrations of substrate (pyruvate) and product (acetyl CoA) and also by the active enzyme present in the tissue. In the tricarboxylic (TCA) cycle or Krebs cycle, acetyl CoA undergoes further metabolism, with the resultant production of ATP by the process of oxidative phosphorylation.

Long-chain fatty acids are the other major source of acetyl CoA for the TCA cycle, and the oxidative production of ATP produced by the heart. Fatty acid oxidation produces more ATP per molecule oxidized than does glucose oxidation, but this is at expense of greater oxygen consumption. Thus, fatty acid oxidation is less efficient than glucose oxidation with regards to ATP production per molecule of oxygen consumed.

Fatty acids enter the cardiomyocyte by either passive diffusion or protein-mediated transport across the sarcolemma. The fatty acids are then etherified and subsequently taken up into the mitochondria via a process of active transport involving a carnitine-dependent shuttle. A key enzyme in the regulation of fatty acid oxidation is carnitine palmitoyl transferase 1 (CPT-1).

Once fatty acids are taken up by the mitochondria, they undergo b-oxidation, a four-step process that repeatedly cleaves off two carbon acetyl-CoA units to generate acetyl CoA, which then enters the TCA cycle. This process involves specific enzymes for each of these four steps: acyl-CoA dehydrogenase, 2-enoyl-CoA hydratase, 3-hydroxyacyl CoA dehydrogenase, and 3-ketoacyl CoA thiolase (3-KAT).

The acetyl CoA produced by fatty acid β-oxidation competes with acetyl CoA from glucose oxidation. A consequence of this is that if heart is exposed to elevated levels of fatty acids, fatty acid oxidation is increased (as in physical exercise, fasting, myocardial ischemia, heart failure), and glucose oxidation is decreased.

Alteration in energy metabolism in various forms of cardiovascular disease

I. ***Metabolic alterations in the context of chronic ischemic heart disease.*** The reduction in oxygen supply that occurs during myocardial ischemia results in a concomitant decline in energy production of the heart. Mitochondrial oxidative metabolism decreases during ischemia, to an extent dependent on the degree of oxygen deprivation to the heart, which in turn depends on the severity of ischemia [*Neely J.R., Morgan H.E., 1974*]. During an ischemic episode, such as occurs in an angina attack, fatty acid oxidation and glucose oxidation both diminish and, on balance, glycolysis becomes a significant source of energy because it is the only one to produce ATP in the absence of oxygen.

Furthermore, during ischemia, activation of the sympathetic nervous system and norepinephrine release increases triglyceride breakdown and thus plasma free fatty acid concentrations and further augments the rate of fatty acid oxidation to the detriment of glucose oxidation. As previously discussed, PDH is consequently inhibited by the high rate of fatty acid oxidation, which in turn

leads to reduced oxidation of pyruvate and increased conversion to lactate and a rise in a tissue lactate content. Cell homeostasis is dramatically disrupted: there is an accumulation of lactate and protons and a fall in intracellular pH. This also impairs the ability of myocardium to maintain calcium homeostasis and contributes to calcium overload. Consequently, more ATP is required to re-establish ionic homeostasis, "the chemical work", and less ATP is used for contractile work, "the mechanical work" of the heart.

II. ***Metabolic alterations in the context of heart failure.*** The chronic heart failure is multifactorial, although available evidence suggests that it represents a state of cardiac energy starvation, "an engine out of fuel" [*Neubauer S., 2007*]. Also, it appears that the energetic reserve is compromised in heart failure, as the consequence of impaired mitochondrial function [*Stanley W.C. et al., 2005*]. 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, the rates of fatty acid oxidation are normal or increased, whereas rates of glucose oxidation are low. In late-stage heart failure, the 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 cardiac 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.

As knowledge on cardiac energy metabolism increases, the potential application of metabolic modulation to the treatment of cardiovascular disease has become the subject of extensive research and the clinical evidence to support this concept will be discussed in the following section.

Although "metabolic agents" have undergone clinical evaluation principally for the treatment of ischemic heart disease, both experimental and available clinical data point towards a potential therapeutic role for this class of drugs in patients with heart failure. Moreover, because the optimization of cardiac energetics could be effective in the early stages of heart failure, the chronic inhibition of myocardial fatty acid oxidation may slow down the progression of the heart failure and improve cardiac function.

Optimization of cardiac energetics for the treatment of heart disease. The cellular pathways of substrate use present several avenues for cardioprotective intervention with metabolic agents. The optimization of cardiac energetics involves switching the fuel preference of the heart from fatty-acid-dependent to carbohydrate-dependent.

The main clinical approaches used to optimize cardiac energetics involve manipulating substrates or 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 may be directly increased with agents such as dichloroacetate that directly activate pyruvate dehydrogenase and thus increase oxidation of pyruvate. Alternatively, the rate of fatty acid oxidation may be decreased by inhibiting the mitochondrial uptake of fatty acids via suppression of CPT I or II activity or by directly inhibiting the enzymes that participate in fatty acid oxidation.

To evaluate these hypotheses, a number of agents including trimetazidine, ranolazine, perhexiline, etomoxir, oxfenicine, and dichloroacetate have been investigated in experimental and clinical studies.

Trimetazidine. As a key enzyme in fatty acid oxidation, 3-KAT has emerged as a target for modifying fatty acid oxidation. Trimetazidine is the first of a class of partial fatty acid oxidation inhibitors that selectively inhibit the terminal enzyme of fatty acid oxidation—long-chain 3-ketoacyl CoA thiolase [*Kantor P.F. et al., 2000*]. By inhibiting fatty acid oxidation, trimetazidine stimulates glucose oxidation and thus

improves the coupling between glycolysis and glucose oxidation, thereby decreasing the rate of lactate and proton production attributable to the hydrolysis of glycolytically derived ATP.

These effects of trimetazidine on the pathways of fatty acid and glucose metabolism can prevent deleterious alterations in intracellular ionic homeostasis by diminishing the potential for intracellular acidosis during ischemia, and reducing the ATP needed to correct ionic homeostasis, thus increasing the amount of ATP hydrolysis available to drive meaningful contractile work.

Trimetazidine is available in more than 90 countries worldwide for the treatment of angina pectoris. Numerous clinical trials have demonstrated its efficacy in various forms of ischemic heart disease, ranging from angina pectoris to ischemic cardiomyopathy, and heart failure. The therapeutic effect of trimetazidine in stable angina patients has been extensively investigated in monotherapy and in association with a beta-blocker, calcium antagonist, or nitrates [*Sellier P., 1990; Detry J.M. et al., 1994; Lévy S., 1995; Manchada S.C., Krischnaswami S., 1997; Szwed H. et al., 2001*]. The therapeutic benefits include fewer anginal attacks, increased exercise capacity, and prolonged ischemic threshold and time to 1-mm ST-segment depression. Recently, a large meta-analysis of clinical trials of trimetazidine was undertaken by the Cochrane Collaboration [*Ciapponi A., 2005*] 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, compared with placebo, trimetazidine significantly reduced the weekly angina attack rate by 40% (mean difference −1.44; 95% confidence interval [CI], −2.10 to −0.79; P<0.0001) and nitrate consumption (−0.73; 95% CI −1.47 to −2.20; P<0.0001). Objectively, trimetazidine improved exercise time to 1-mm ST-segment depression (P=0.0002). Trimetazidine was efficient in monotherapy as well as in combination. The tolerability was excellent.

Trimetazidine also represents a therapy aimed at reversing some of the metabolic abnormalities of heart failure and at improving left ventricular function. There are both experimental studies and clinical studies in man [*Brottier L. et al., 1990; Belardinelli R, Purcaro A., 2001. El-Kady E, et al., 2005; Fragasso G., et al., 2006*] supporting such an approach.

The effect of trimetazidine on left ventricular function was first assessed in 1990 [*Brottier L. et al., 1990*] in a small double-blind study, which included 20 patients with severe ischemic cardiomyopathy (NYHA class III-IV and ejection fraction [EF]<30%) randomized to trimetazidine or placebo and followed up for 6 months. At the end of this period, not only did the patients have fewer episodes of angina and improved dyspnea, but EF was increased by 9.3% in the trimetazidine group, while it decreased by 15.6% in the placebo group (P<0.018). Furthermore, another trial [*Belardinelli R, Purcaro A., 2001*] demonstrated that, compared with placebo, 2 months of treatment with trimetazidine resulted in a significant improvement in left ventricular EF at rest and enhanced left ventricular wall motion during a dobutamine stress test in patients with NYHA class II/III heart failure. More recently, a study involving 200 patients with ischemic cardiomyopathy demonstrated trimetazidine treatment reduced damage following an ischemic attack and significantly increased EF, as determined by gated single-photon emission computed tomography [*El-Kady E., et al., 2005*].

G. Fragasso and co-authors randomized in an open-label fashion 55 patients with heart failure to conventional treatment alone or to conventional treatment plus trimetazidine [*Fragasso G, et al., 2006*]. Mean follow-up was 13±3 months. The patients were also already optimally treated for chronic heart failure with conventional agents such as angiotensin-converting enzyme inhibitors, beta-blockers, long-acting nitrates, digoxin, diuretics, and antiplatelet agents, as required. Trimetazidine treatment significantly decreased left ventricular volume and increased EF from 36±7% to 43±10%. In the conventional treatment group, left ventricular end-diastolic and systolic volumes increased and EF decreased from 38±7% to 34±8%.

In addition, the beneficial effects of trimetazidine in patients with ischemic cardiomyopathy are also evident in long-term follow-up. The 18-month study reported that treatment with trimetazidine was able to improve functional NYHA heart failure class and left ventricular function in 61 patients with severe ischemic cardiomyopathy, while in the control group they were decreased following the natural course of the disease [*Di Napoli P., 2005*].

Ranolazine. Although the exact molecular mechanism for its antianginal action is still not elucidated, it appears that ranolazine acts as a partial inhibitor of fatty acid β-oxidation. More recently, this drug has been proposed as an inhibitor of the late sodium current contributing to a reduction in intracellular sodium and calcium overload and therefore reducing ischemic injury [*Antzelevitch C., 2004*].

A number of clinical trials have demonstrated that ranolazine increases exercise tolerance, decreases weekly anginal episodes, and decreases sublingual nitroglycerin consumption for breakthrough angina [*Chaitman B.R. et al., 2004a;c*].

In canine models of heart failure, ranolazine improves ejection fraction and stroke volume without increasing oxygen consumption and hence increases myocardial efficiency [*Chandler M.P., 2003*].

Given that ranolazine prolongs the QT interval [*Chaitman B.R. et. al., 2004b*], caution is advised in patients taking other drugs that may prolong the QT interval or influence the metabolism of ranolazine.

CPT inhibitors. Oxfenicine and etomoxir inhibit CPT-I, the key regulator of fatty acid uptake by mitochondria. Inhibition of CPT-I leads to reduced fatty oxidation rates, increased glucose oxidation, and improved myocardial energy efficiency [*Lopaschuk G.D. et al., 1989; Chandler M.P. et al., 2003*]. Oxfenicine has been found to increase the time to onset of angina in patients in response to pacing stress [*Bergman G. et al., 1980*]. Although etomoxir has been investigated as a treatment for heart failure [*Schmidt-Schweda S., Holubarsch C., 2000*], it has not yet been studied as an antianginal agent. Further clinical development has not been reported with these two agents.

Perhexiline was introduced in the 1970s as an antianginal agent, but has only recently been proposed to exert its clinical effects through inhibition of CPT I and to lesser degree CPT II. A recently published first controlled trial of perhexiline in heart failure patients demonstrated improved maximal oxygen consumption, left ventricular EF, resting and peak stress myocardial function. Despite potentially favorable effects, clinical interest in the chronic administration of perhexiline has been diminished by an association with infrequent, but serious hepatotoxicity and neuropathy that necessitates regular monitoring of plasma levels and is a relative contraindication to perhexiline in patients with hepatic or renal dysfunction [*Morrow D.A., 2005*]. The mechanism for toxicity appears to be due to phospholipid accumulation, which is a direct consequence of CPT-1 inhibition and so this is a potential side-effect of any drug that acts similarly [*Kennedy J.A. et al., 1996*].

Dichloroacetate. Most knowledge on the activation of glucose oxidation refers to stimulation of the activity of the mitochondrial pyruvate dehydrogenase enzyme complex by dichloroacetate. Dichloroacetate inhibits PDH kinase-mediated activation of PDH, thereby increasing pyruvate oxidation and also the coupling of glycolysis to glucose oxidation [*Bersin R.M., Stacpool P.W., 1997*].

However, clinical experience with dichloroacetate is limited since it has a short half-life and so intravenous perfusion is the only route of administration.

In the setting of heart failure in a small clinical trial, dichloroacetate increased left ventricular stroke volume and myocardial efficiency. The metabolic effects of dichloroacetate remain to be assessed in angina pectoris.

Conclusions

The modulation of myocardial energy substrate metabolism, particularly by shifting energy substrate preference from the use of fatty acids to the use of glucose as an oxidative fuel, is an established therapeutic option for stable

angina, but it is also a promising approach for other manifestations of ischemic heart diseases such as ischemic cardiomyopathy and heart failure.

Such effects can be attained by regulating the rates of flux through the pathways of fatty acid oxidation and glucose oxidation, both by manipulating the activities of key enzymes and by altering the availability of circulating substrates. Among agents that act in this way, trimetazidine is used extensively as metabolic treatment of stable angina that has proven effective in preserving cardiac function in the setting of ischemic heart disease.

References:

1. *Antzelevitch C., Belardinelli L., Zygmunt A.C., et al.* Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004; 110: 904-910.
2. *Belardinelli R., Purcaro A.* Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamide in ischaemic cardiomyopathy. Eur. Heart J. 2001; 22: 2164-2170.
3. *Bergman G., Atkinson L., Metcalfe J., Jackson N., Jewitt D.E.* Beneficial effect of enhanced myocardial carbohydrate utilization after oxfenicine (L-hydroxyphenylglycine) in angina pectoris. Eur. Heart J. 1980; 1: 247-253.
4. *Bersin R.M., Stacpool P.W.* Dichloroacetate as metabolic therapy for myocardial ischemia and failure. Am. Heart J. 1997; 134: 841-845.
5. *Bing, R.J.* The metabolism of the heart. Harvey Lect. 1954; 50: 27-70.
6. *Brottier L., Barat J.L., Combe C., Boussens B., Bonnet J., Bricaud H.* Therapeutic value of cardioprotective agent in patients with severe ischemic cardiomyopathy. Eur. Heart J. 1990; 11: 209-212.
7. *Chaitman B.R., Pepine C.J., Parker J.O. et al.,* the Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA. 2004a; 291: 309-316.
8. *Chaitman B.R., Skettino S.L., Parker J.O. et al.* Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J. Am. Coll. Cardiol. 2004; 43: 1375–1382.
9. *Chaitman B.R., Skettino S.L., Parker J.O. et al.*, the MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J. Am. Coll. Cardiol. 2004c; 43:1375-1382.
10. *Chandler M.P., Chavez P.N., McElfresh T.A., Huang H., Harmon C.S., Stanley W.C.* Partial inhibition of fatty acid oxidation increases regional contractile power and efficiency during demand-induced ischemia. Cardiovasc. Res. 2003; 59: 143-151.
11. *Ciapponi A., Pizarro R., Harrison J. Ciapponi A..* Trimetazidine for stable angina. Cochrane Database Syst. Rev. 2005; (4): CD003614
12. *Detry J.M., Sellier P., Pennaforte S., Cokkinos D., Dargie H., Mathes P.* Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Br. J. Clin. Pharmacol. 1994; 37: 279-288.
13. *Di Napoli P., Taccardi A.A., Barsotti A.* Long-term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. Heart 2005; 91: 161-165.

14. *El-Kady E., El-Sabban K., Gabaly M., Sabry A., Aldel-Hady S.* Effects of trimetazidine on myocardial perfusion and the contractile response of chronically dysfunctional myocardium in ischemic cardiomyopathy. A 24-Month Study. Am. J. Cardiovasc. Drugs 2005; 5 (4): 271-278.

15. *Fragasso G., Palloshi A., Puccetti P., Silipigni C., et al.* A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in heart failure patients. J. Am. Coll. Cardiol. 2006; 48: 992-998.

16. *Ingwall J.S., Weiss R.G.* Is the failing heart energy starved? On using chemical energy to support cardiac function. Circ. Res. 2004; 95: 135-145.

17. *Kantor P.F., Lucien A., Kozak R., Lopaschuk G.D.* The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ. Res. 2000, 86: 580-588.

18. *Kennedy J.A., Unger S.A., Horowitz J.D.* Inhibition of carnitine palmitoyltransferase-1 in rat heart and liver by perhexiline and amiodarone. Biochem. Pharmacol. 1996; 52: 273-280.

19. *Lévy S.* Combination therapy of trimetazidine with diltiazem in patients with coronary artery disease. Am. J. Cardiol. 1995; 76: 12B-16B.

20. Lopaschuk G.D., McNeil G.F., McVeigh J.J. Glucose oxidation is stimulated in reperfused ischemic hearts with the carnitine palmitoyltransferase 1 inhibitor. Etomoxir. Mol. Cell. Biochem. 1989; 88: 175-179.

21. *Manchada S.C.,* Krischnaswami S. Combination treatment with trimetazidine and diltiazem in stable effort angina. Heart 1997; 78: 353-357.

22. *Morrow D.A.* Modulation of Myocardial Energetics: Emerging Evidence for a Therapeutic Target in Cardiovascular Disease Circulation 2005; 112: 3218-3221.

23. *Neely J.R., Morgan H.E.* Relationship between carbohydrate metabolism and energy balance of heart muscle. Ann. Rev. Physiol. 1974; 36: 413-459.

24. *Neubauer S.* The Failing Heart—An Engine Out of Fuel. N. Engl. J. Med. 2007; 356: 1140-1151.

25. NHLBI Morbidity and Mortality Chart-Book. Bethesda, MD: National Heart, Lung, and Blood Institute; 2004.

26. *Schmidt-Schweda S., Holubarsch C.* First clinical trial with etomoxir in patients with chronic congestive heart failure. Clin. Sci. (Lond) 2000; 99: 27-35.

27. *Sellier P.* Chronic effects of trimetazidine on ergometric parameters in effort angina. Cardiovasc. Drugs Ther. 1990; 4: 822-823.

28. *Stanley W.C., Lopaschuk G.D., Hall J.L. et al.* Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions. Potential for pharmacological interventions. Cardiovasc. Res. 1997; 33: 243-257.

29. *Stanley W.C., Recchia F.A., Lopaschuk G.D.* Myocardial substrate metabolism in the normal and failing heart. Physiol.Rev.. 2005; 85: 1093-1129.

30. *Szwed H., Sadowski Z., Elikowski W. et al.* Combination treatment in stable effort angina using trimetazidine and metoprolol. Results of a randomized, double-blind, multicentre study (TRIMPOL II). Eur. Heart J. 2001; 22: 2267-2274.