Evolution of the metabolic approach to heart disease

Vaninder K. Sidhu and Gary D. Lopaschuk
Cardiovascular Research Centre, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada

Correspondence: Dr Gary Lopaschuk, 423 Heritage Medical Research Center, University of Alberta, Edmonton, Canada T6G 2S2.
Tel: +1 (780) 492 2170; fax: +1 (780) 492-9753; e-mail: gary.lopaschuk@ualberta.ca
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Abstract
Cardiovascular disease is a broad term that describes a host of conditions affecting both the heart and the vasculature, ischemic heart disease being the most prevalent. Ischemic heart disease is often accompanied by a drastic change in myocardial energy metabolism that favors fatty acid oxidation at the expense of glucose oxidation. This form of energy production is both inefficient and detrimental to the myocardium. However, both the glucose and fatty acid oxidative pathways can be targeted to improve cardiac efficiency. In particular, decreasing fatty acid oxidation and increasing glucose metabolism can improve cardiac efficiency in the ischemic heart. Optimizing energy metabolism in the diseased heart is an exciting approach, with tremendous therapeutic potential. Although the concept of modulating cardiac metabolism has existed for decades, it has only recently gained momentum with the introduction of new and effective pharmacological agents targeting key components in the metabolic pathways. This review will examine the use of metabolic therapies in heart disease and provide an update on current research and potential new therapies.

Keywords: Cardiac efficiency, fatty acid oxidation, glucose oxidation, ischemic heart disease

Introduction
Ischemic heart disease is the most common form of cardiovascular disease (CVD) and is often the underlying cause of angina, acute myocardial infarction (AMI) and heart failure [1–3]. Traditionally, ischemic heart disease is treated by pharmacological or mechanical means that act primarily either to increase oxygen supply to the heart or to decrease oxygen demand of the heart muscle [1]. Recently, a number of studies of cardiac metabolism have suggested that an additional approach to treating ischemic heart disease is by means of metabolic modulation, whereby optimizing energetics in the myocardium can improve cardiac efficiency of the heart muscle (ie, increase the contractile work achieved per molecule of oxygen consumed). This emerging approach holds the promise of providing added benefit when used alongside existing therapies.

Energy metabolism in the diseased heart
The relative contribution of glucose and fatty acid oxidation to myocardial energy production dictates cardiac function in addition to efficiency. Therefore, any disruption to the metabolic homeostasis can adversely affect the heart and contribute to cardiac pathologies. In the ischemic myocardium, fatty acid oxidation dominates as the residual source of oxidative phosphorylation as a result both of an increase in fatty acid concentrations in the coronary circulation...
and of subcellular changes that result in a dysregulation of fatty acid oxidation [4,5]. This increased dependence on fatty acids is both inefficient and undesirable at a time of oxygen shortage [1]. Furthermore, high rates of fatty acid oxidation inhibit glucose oxidation via the Randle Cycle phenomenon, thereby uncoupling glucose oxidation from glycolysis [1,6]. This uncoupling eventually leads to proton overload and intracellular acidosis that not only further decreases cardiac efficiency, but also increases the risk for ischemic injury while compromising cardiac contractility [5].

Metabolic approach to heart disease

The premise for a metabolic intervention is to switch the energy substrate preference from fatty acid oxidation to glucose oxidation. By increasing glucose oxidation, the ischemic heart will produce less lactate and protons, thereby increasing cardiac efficiency. The energetics of the heart can be altered to favor this shift by the direct inhibition of fatty acid β-oxidation (which results in a secondary increase in glucose oxidation) or by the direct stimulation of glucose oxidation (Figure 1) [7]. A number of pharmacological agents have been developed that act at different levels in the fatty acid and glucose metabolic pathways (Table I). These agents modulate fatty acid metabolism by decreasing the supply of fatty acids to the heart, inhibiting fatty acid uptake and β-oxidation, or stimulating glucose oxidation.

Therapies targeting fatty acid and glucose supplies to the heart

One of the earliest strategies to modulate fatty acid metabolism was regulation of the supply of fatty acids and glucose to the heart. Introduced in the 1960s for treating acute myocardial infarctions, glucose–insulin–potassium (GIK) solution was one of the first pharmacological agents used to improve the efficiency of cardiac energy production [8]. Initially, the cardioprotective effects of GIK were attributed to its ability to increase glucose uptake and stimulate glycolysis while reducing the concentrations of free fatty acids (by suppressing lipolysis) and their subsequent oxidation [8,9]. Indeed, early studies in animal models of myocardial infarction demonstrated a favorable switch in energy substrate, in addition to a reduction in infarct size and improved post-ischemic recovery after an infusion of GIK [10,11]. However, there is considerable discrepancy among the findings of recent clinical studies, in which GIK therapy has failed to improve ischemic recovery and mortality. Although both the Estudios Cardiológicos

Figure 1. Summary of myocardial energy metabolism and therapeutic targets. ACC, acetyl coenzyme A carboxylase; CoA, coenzyme A; CPT-1, CPT-2, carnitine palmitoyl transferases-1 and -2; 3-KAT, 3-ketoacyl CoA thiolase; MCD, malonyl CoA decarboxylase; P, inorganic phosphate; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase.

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Latinoamerica (ECLA) and the Dutch Glucose–Insulin–Potassium Study 1 (GIPS 1) studies found that GIK treatment significantly reduced mortality with reperfusion, the GIPS 2 study did not demonstrate a benefit in terms of mortality or infarct size [8,12]. Even the largest study to assess the effect of GIK on mortality in patients with acute ST-segment elevation myocardial infarction, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiología Latinoamerica (CREATE-ECLA), produced findings leading the investigators to conclude that such treatment afforded no benefit [13]. Furthermore, a combined analysis of the Organization for the Assessment of Strategies for Ischemic Syndromes-6 (OASIS-6) and CREATE-ECLA found a greater mortality in the GIK group after early treatment [14].

The lack of identified benefit, or even adverse effects, of GIK may possibly be related to a situation in which glycolysis becomes uncoupled from glucose oxidation, leading to intracellular acidosis and ischemic injury [15]. Hyperglycemia is another potential untoward effect of GIK therapy, whereby a glucose overload can exacerbate ischemic injury [8,12]. Differences in patient populations studied, in addition to the dose and timing of GIK therapy, could also account for some of the ambiguity in these clinical studies. Thus further studies are warranted to validate the use of GIK in heart disease, especially for altering myocardial fatty acid oxidation to minimize ischemic injury.

β-Blockers and nicotinic acid are drugs that are commonly prescribed in heart disease. β-Blockers are used to reduce cardiac workload and improve contractility [12,15], whereas nicotinic acid is used mainly for its antiatherogenic effects [16]. However, both have the added benefit of decreasing circulating concentrations of fatty acids. They exert their anti-ischemic effects by decreasing lipolysis, and therefore indirectly reduce myocardial fatty acid oxidation and promote glucose utilization [16–18]. In clinical studies, both agents have been shown to improve cardiac function without increasing oxygen consumption [19–21], an effect desirable for patients with ischemic heart disease or heart failure, or both.

### Therapies targeting the import of fatty acids

In addition to regulation of the supply of substrates to the heart, a more direct approach to the modulation of fatty acid metabolism is to regulate the import of fatty acids into the mitochondria. Carnitine palmitoyltransferase-1 (CPT-1) catalyzes the rate-limiting step in the mitochondrial uptake of long-chain fatty acids [7]. This enzyme has become the target of several pharmacological agents known as CPT-1 inhibitors, including etomoxir, oxfenicine, and perhexiline [3,12]. All three decrease CPT-1 activity and thus limit fatty acid oxidation while favoring glucose oxidation (via the Randle Cycle) [3]. In animal studies, etomoxir has demonstrated favorable outcomes. Lopaschuk et al [22] showed that etomoxir improved glucose oxidation and cardiac function while protecting the heart from injury after ischemia-reperfusion.

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**Table 1. Metabolic modulators.**

<table>
<thead>
<tr>
<th>Metabolic agent</th>
<th>Metabolic action</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose–insulin–potassium (GIK)</td>
<td>↓ Glucose uptake, glycolysis</td>
<td>Conflicting reports of reduced mortality post-perfusion or of no benefit with GIK; further study required</td>
</tr>
<tr>
<td>solution</td>
<td>↓ Circulating fatty acids</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>↓ Circulating fatty acids</td>
<td>Well established benefit in acute coronary syndromes; improved survival</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ Circulating fatty acids</td>
<td>Limited to patients with heart failure; antianginal properties not evaluated. Not under further clinical development, because of toxicity</td>
</tr>
<tr>
<td>Etomoxir</td>
<td>CPT-1 inhibitor ↓ Fatty acid oxidation</td>
<td>Antianginal agent since 1970s. Limited clinical use</td>
</tr>
<tr>
<td>Perhexiline</td>
<td>CPT-1 inhibitor ↓ Fatty acid oxidation</td>
<td>Approved as antianginal agent in more than 80 countries. Most commonly prescribed metabolic agent for ischemic heart disease</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>3-KAT inhibitor ↓ Fatty acid oxidation</td>
<td>Approved in 2006 for angina (USA). Mechanism of action controversial</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Partial inhibitor of fatty acid oxidation inhibits late sodium current (mechanism under study)</td>
<td></td>
</tr>
<tr>
<td>Dichlororacetate</td>
<td>PDK inhibitor ↓ Glucose oxidation</td>
<td>Currently in clinical trial. Pharmacokinetics limit use to acute treatment</td>
</tr>
<tr>
<td>CMB-301940</td>
<td>MCD inhibitor ↓ Fatty acid oxidation</td>
<td>Experimental use only. No clinical data available</td>
</tr>
</tbody>
</table>

CPT-1, carnitine palmitoyl transferase-1; 3-KAT, 3-ketoacyl coenzyme A thiolase; MCD, malonyl coenzyme A decarboxylase; PDK, pyruvate dehydrogenase kinase.
In a separate study, etomoxir was found to reduce myocardial oxygen consumption while sustaining contractile function in ischemic rat hearts [12,23]. Although studies using etomoxir in animals are extensive, epidemiological studies have been limited to a few clinical trials. In one open-label and uncontrolled study, etomoxir was found to improve left ventricular ejection fraction, cardiac output at peak exercise, and clinical status in patients with New York Heart Association Class II–III heart failure [12,24], but the Etomoxir for the Recovery of Glucose Oxidation (ERGO) study was terminated prematurely because of toxicities resulting from irreversible effects on fatty acid oxidation [25]. Although etomoxir has been investigated as a treatment for heart failure, its antianginal properties remain to be evaluated. In contrast, perhexiline was introduced in the 1970s as an antianginal agent effective in improving anginal symptoms and increasing exercise tolerance [3,26]. Furthermore, the findings of recent studies have supported its suitability for the treatment of angina pectoris and heart failure, in addition to short-term therapy for ischemia [12]. A randomized control trial consisting of 56 patients with heart failure receiving 8 weeks of treatment led to the conclusion that perhexiline was associated with an improved left ventricular ejection fraction and peak oxygen uptake (VO₂max) [27]. Although perhexiline may have clinical benefit, its use in treating CVD is limited.

Another approach to inhibiting CPT-1 and decreasing mitochondrial fatty acid uptake is via inhibition of malonyl coenzyme A (CoA) decarboxylase (MCD). MCD is responsible for degrading malonyl CoA, a potent endogenous reversible inhibitor of CPT-1 [7]. Several experimental studies have found that pharmacological MCD inhibitors increase malonyl CoA concentrations in the heart, thereby indirectly inhibiting CPT-1 and decreasing fatty acid oxidation [28,29]. Stanley et al [30] reported that inhibition of MCD by CBM-301940 was associated with a 4-fold increase in malonyl CoA concentration, an 87% decrease in the rate of fatty acid oxidation, and a 50% decrease in lactate production. In a study by Dyck et al [28], MCD knockout mice demonstrated a lower rate of fatty acid oxidation, greater glucose oxidation, and overall improved cardiac function during and after ischemia. These findings suggest that the inhibition of MCD may be a feasible approach to optimizing energy metabolism and have potential in the treatment of heart disease. However, clinical studies using this approach have yet to be performed.

**Therapies targeting fatty acid β-oxidation**

Direct inhibition of fatty acid oxidation can be achieved by targeting enzymes in the β-oxidative pathway, particularly long-chain 3-ketoacyl CoA thiolase (3-KAT). Trimetazidine is a 3-KAT inhibitor that reduces fatty acid oxidation while promoting glucose oxidation via the Randle Cycle [31]. The Trimetazidine in Angina Combination Therapy (TACT) study showed that trimetazidine, in conjunction with either long-acting nitrates or β-blockers, improved exercise test duration and anginal symptoms [32]. Recently, the Cochrane Collaboration conducted a review of randomized studies comparing trimetazidine with placebo or other antiangina drugs in adults with stable angina [33]. This meta-analysis led to the conclusion that trimetazidine is effective in the treatment of stable angina when compared with placebo, alone or combined with conventional antianginal agents, and that trimetazidine may result in fewer failures to continue treatment as a result of adverse events. Furthermore, in the Second Trimetazidine in Poland (TRIMPOL II) study, trimetazidine improved workload, time to 1 mm ST-segment depression, and anginal symptoms in patients already receiving metoprolol, and was beneficial even after percutaneous coronary intervention [34]. A number of studies have shown that trimetazidine can also improve the symptoms of heart failure (for review see [35]). Currently, trimetazidine is the metabolic agent most commonly prescribed worldwide to treat CVD, and is available in Europe and more than 80 countries worldwide [15].

Ranolazine is an antianginal agent recently approved in the USA for treating chronic stable angina [3]. It is structurally similar to trimetazidine and, although substantially less potent than trimetazidine, at clinically relevant concentrations ranolazine partially inhibits fatty acid oxidation while stimulating glucose oxidation, under normoxic and ischemic conditions [36]. Although the mechanism of action remains under investigation, the therapeutic effect of ranolazine on metabolism may be mediated via inhibition of 3-KAT [12]. However, the findings of recent studies suggest that its cardioprotective effects may also be attributable to inhibition of the late sodium current, thereby preventing the sodium-dependent calcium overload that is characteristic of ischemic injury [37]. Support for a metabolic mechanism of action comes from a recent study in which it was shown that ranolazine significantly improved glycated hemoglobin A (HbA₁c) concentrations and recurrent ischemia in patients with diabetes mellitus, and reduced the incidence of increased HbA₁c in those without evidence of previous hyperglycemia [38].

The anti-ischemic effects of ranolazine have been established in numerous experimental studies [39,40]. In an animal model of heart failure, for example, ranolazine increased both ejection fraction and mechanical function without increasing oxygen consumption [41]. In clinical settings, ranolazine has
demonstrated favorable cardiac outcomes in patients with angina. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study revealed a significant increase in exercise duration and time to 1 mm ST-segment depression with ranolazine [42]. The Efficacy of Ranolazine in Chronic Angina (ERICA) trial also found that, compared with placebo, ranolazine significantly reduced the frequency of angina episodes and consumption of glyceryl trinitrate in patients already receiving the maximum recommended dose of amlodipine [43]. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes (MERLIN-TIMI) trial, ranolazine was effective in reducing recurrent ischemic episodes and angina, but not AMI and death, in patients with ischemic heart disease [44]. Ranolazine is an effective antianginal agent, yet it remains to be clarified whether its cardioprotective effects against ischemia are mediated by metabolic or electrophysiological changes, or both.

**Therapies targeting glucose oxidation**

Glucose oxidation can be directly stimulated with dichloroacetate by inhibiting pyruvate dehydrogenase kinase (PDK), an enzyme that inactivates mitochondrial pyruvate dehydrogenase (PDH) [1,45]. Numerous in-vitro and in-vivo studies have documented that activation of PDH increases glucose oxidation, shifting the energy metabolism to an efficient fuel source. Furthermore, it improves coupling between glycolysis and glucose oxidation, minimizing intracellular acidosis and contractile dysfunction [1,45,46]. In a small clinical study, dichloroacetate increased myocardial efficiency, left ventricular stroke volume, and lactate disposal; however, its use is limited by a short half-life and need for high doses and intravenous administration [47]. Novel PDK inhibitors are currently being investigated.

**Summary**

Over the past decade, considerable progress has been made in the development of new treatments to combat cardiovascular disease. The metabolic approach to treating heart disease has evolved from a broad concept of minimizing circulating plasma fatty acid concentrations to a more refined approach focusing on the enzymatic machinery in the metabolic pathway. Recent advances have led to the development of pharmacological agents targeting specific enzymes such as CPT-1, MCD, 3-KAT, and PDK. Currently, several metabolic therapies are used as adjunct treatments in heart disease, and the findings of recent studies suggest that metabolic modulation could become a mainstay in the treatment of cardiovascular disease.

**REFERENCES**


31. Vaninder K. Sidhu and Gary D. Lopaschuk


