Partial inhibition of fatty acid β-oxidation with trimetazidine – a novel approach to the treatment of ischemic heart disease

Jagdip S. Jaswal, Gary D. Lopaschuk

Departments of Pediatrics and Pharmacology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, T6G 2S2, Canada

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Corresponding author:
Dr. Gary D. Lopaschuk
4-23 Heritage Medical Research Centre
University of Alberta
Edmonton, Alberta, Canada
T6G 2S2
E-mail:
gary.lopaschuk@ualberta.ca

Abstract

Optimizing myocardial energy substrate metabolism represents a novel therapeutic intervention in the treatment of ischemic heart disease that can be a useful adjunct to traditional hemodynamic therapies. Specifically, the partial inhibition of fatty acid β-oxidation, and the concomitant, reciprocal increase in glucose oxidation, improves cardiac efficiency, and limits the deleterious effects of ischemia on cardiac function. Trimetazidine is a reversible inhibitor of 3-ketoacyl-CoA thiolase, the terminal enzyme of fatty acid β-oxidation. The anti-ischemic effects of trimetazidine are related to its ability to partially inhibit fatty acid β-oxidation, while indirectly stimulating glucose oxidation. These anti-ischemic effects of trimetazidine have been demonstrated in numerous experimental and clinical studies in diverse forms of ischemic heart disease ranging from angina to acute myocardial infarction, and heart failure. Thus the partial inhibition of fatty acid β-oxidation is a novel and viable therapeutic intervention to limit the deleterious effects of ischemic heart disease.

Key words: glucose oxidation, 3-ketoacyl-CoA thiolase, pyruvate dehydrogenase.

Introduction

Myocardial ischemia occurs when coronary blood flow is inadequate, and hence oxygen (O_2) supply to the myocardium is not sufficient to meet O_2 demand. The manifestations of myocardial ischemia are dependent upon the nature and the severity of the ischemic episode, as well as the subsequent re-establishment of flow (reperfusion). Consequences of ischemia include changes in cardiac ultrastructure, functional deficits, and metabolic alterations.

In Western Society there has been marked decline in the number of deaths due to myocardial ischemia, which have been attributed predominantly to improved therapies (e.g. evidence based pharmacological therapy, thrombolysis, and advancements in revascularization) and to reductions in the prevalence of major cardiovascular risk factors (e.g. hypertension, hypercholesterolemia, and the prevalence of smoking) [1]. Despite these improved survival rates, ischemic heart disease remains the major contributor to overall morbidity and mortality, as well as the major economic burden of cardiovascular disease [1, 2].

Classically the treatment of ischemic heart disease has focused on restoring the balance between O_2 supply and demand, such that O_2 supply is sufficient to meet O_2 demand. This can be achieved via pharmacological agents that alter systemic and cardiac hemodynamics, or that alter cardiac contractility. Pharmacological mainstays in the treatment of ischemic heart disease include angiotensin converting enzyme (ACE) inhibitors, L-type Ca^{2+} channel blockers, nitrates, and β-adrenoceptor antagonists. While ACE inhibitors, L-type Ca^{2+} channel blockers, and nitrates improve the hemodynamic profile by decreasing both preload and systemic vascular resistance to increase O_2 supply and decrease O_2 demand, β-adrenoceptor antagonists exert their anti-ischemic effects via negative chronotropic and inotropic actions, thereby reducing O_2 demand. Evidence suggests that β-adrenoceptor antagonists can also alter energy metabolism; specifically they appear to shift substrate preference from free fatty acid (FFAs) towards glucose utilization [3].

An emerging and novel intervention to treat ischemic heart disease is the manipulation of myocardial energy metabolism, such that the efficiency of converting the hydrolysis of adenosine triphosphate (ATP) into contractile work is maximized, and O_2 use is reduced. Recently several pharmacological agents classified as partial fatty acid β-oxidation inhibitors, including trimetazidine, have received renewed interest as anti-ischemic agents. Trimetazidine acts by mechanisms independent of alterations in systemic hemodynamics and cardiac contractility, and as such represents a useful adjunct to classical therapeutic modalities for the treatment of ischemic heart disease. Specifically, trimetazidine exerts its anti-ischemic effects via mechanisms related to its ability to induce a shift in energy substrate metabolism from fatty acids towards glucose, which may lead to O_2 sparing effects, as well as reduced intracellular acidosis and Ca^{2+} overload [4]. This article will review cardiac energy substrate metabolism and present the rational basis for the use of trimetazidine in the treatment of ischemic heart disease.

Fatty acid metabolism and utilization

Fatty acid uptake and β-oxidation

In cardiac and skeletal muscle intracellular triacylglycerol represents a significant source of non-esterified free fatty acids for energy production. Fatty acids can also be liberated from circulating chylomicrons and very low density lipoprotein (VLDL), which can act as a significant source of fatty acids for cardiac mitochondrial β-oxidation. The uptake of circulating fatty acids is governed by the fatty acid concentration gradient across the sarcolemmal membrane. Following dissociation from plasma albumin, fatty acids can either directly enter the cell by the process of passive diffusion, or indirectly following binding to plasma membrane fatty acid binding protein (FABPpm). Conversely, fatty acids can enter cells by the process of facilitated transport being translocated either directly following dissociation from albumin by fatty acid tranlsocase proteins (FATPs) or FAT/CD36, or following binding to FABPpm and subsequent translocation by FAT/CD36 [5].

Once fatty acids have gained entry to the cytoplasm, they require activation prior to further metabolism. Fatty acids are activated through the formation of fatty acyl-CoA moieties through an ATP and coenzyme-A (CoA) dependent process catalyzed by a family of acyl-CoA synthetases. In the cytosol fatty acyl-CoA moieties are bound to acyl-CoA binding protein (ACBP), and can be utilized for a variety of purposes including phospholipid and triacylglycerol synthesis, signal transduction, or β-oxidation for ATP generation.

As the inner mitochondrial membrane is impermeable to fatty acyl-CoA molecules, the entry of fatty acyl-CoAs into the mitochondrial matrix is regulated by a complex of proteins using carnitine as a shuttle mechanism. Carnitine palmitoyl transferase I (CPT-I), localized to the outer mitochondrial membrane converts the fatty acyl-CoA into an acyl-carnitine [6], which is subsequently translocated into the mitochondrial matrix by carnitine translocase, and re-converted to a fatty acyl-CoA moiety by carnitine palmitoyl transferase II (CPT-II) located on the internal leaflet of the inner mitochondrial membrane [7, 8].

The catabolism of fatty acyl-CoA molecules proceeds through the β-oxidation spiral catalyzed by the enzymes acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-L-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase in the mitochondrial matrix (Figure 1). β-oxidation progressively shortens fatty acyl-CoA molecules by liberating acetyl-CoA (2 carbon units) for further metabolism by the tricarboxylic acid (TCA) cycle, and producing reducing equivalents in the form of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) for subsequent oxidation by the electron transport chain [7, 8].

Regulation of fatty acid β-oxidation

Important factors regulating the rate of fatty acid oxidation are the level of circulating free fatty acids in the plasma and the intracellular level of malonyl-CoA [9]. The concentration of fatty acids in the plasma is determined by both prandial and hormonal state. Plasma free fatty acid concentrations increase with fasting, and decrease in the fed state due in part to the anabolic and anti-lipolytic effects of insulin [10].

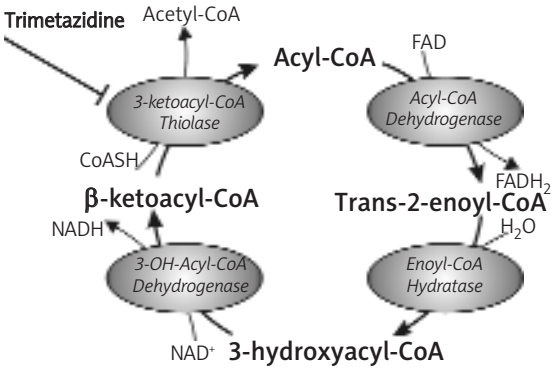

Figure 1. Schematic illustration of mitochondrial fatty acid β-oxidation. The catabolism of fatty acyl-CoA molecules occurs via the β-oxidation spiral by the enzymes acyl-CoA dehydrogenase, 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase in succession. Each turn of the β-oxidation spiral progressively shortens the fatty acyl-CoA chain by 2 carbon units, resulting in the formation of 1 molecule of acetyl-CoA, 1 molecule of $FADH_2$, and 1 molecule of NADH. The complete oxidation of palmitoyl-CoA (a C-16 fatty acyl-CoA moiety) for example would require 7 turns of the β-oxidation spiral, and generate 8 molecules of acetyl-CoA, and 7 molecules each of $FADH_2$, and NADH. The $FADH_2$ and NADH generated by fatty acid β-oxidation are subsequently used for the generation of ATP via the electron transport chain by the process of oxidative-phosphorylation. The acetyl-CoA generated by fatty acid β-oxidation is subsequently oxidized by the tricarboxylic acid cycle to generate additional NADH and $FADH_2$ for use in ATP generation via oxidative phosphorylation. Trimetazidine competitively inhibits the activity of 3-ketoacyl-CoA thiolase, thereby decreasing the formation of acetyl-CoA from the β-oxidation of fatty acids

An increase in catecholamine discharge, (e.g. during ischemic or surgical stress) also increases circulating free fatty acid concentration by increasing lipolysis [10, 11]. An increase in the delivery of fatty acids to the site of utilization can increase the rate of fatty acid β-oxidation.

In addition to being regulated by the fatty acid uptake, the rate of fatty acid β-oxidation is also regulated by the activities of the enzymes involved in mitochondrial fatty acid β-oxidation [12, 13]. There are specific enzymes for long, medium, and short chain fatty acyl-CoA intermediates for each reaction of the β-oxidation spiral [14]. Of particular importance to this review is long-chain 3-ketoacyl-CoA thiolase, the terminal enzyme of fatty acid β-oxidation.

Glucose metabolism and utilization

The cellular uptake of glucose is a complex process coupled to the rate of glucose delivery to the interstitial space, the rate of glucose transport into cells, and the rate at which glucose is phosphorylated [15]. Glucose enters the cell via facilitative transport, mediated by glucose transporters (GLUTs) [16-18], of which GLUT 1 and GLUT 4 are important in the heart. Following transport, glucose is phosphorylated by hexokinase I and/or hexokinase II forming glucose-6-phosphate (G-6-P), which is a substrate for one of either two metabolic fates, storage in the form of glycogen (reviewed elsewhere [19]) or catabolism by glycolysis.

Glycolysis is the process where by glucose is converted to lactate or pyruvate in the absence or presence of O_2, respectively [10]. The metabolism of glucose by the glycolytic pathway occurs in the cytosol, where the enzymes involved in glycolysis are located (Figure 2) [20]. There is a net production of 2 moles (mol) ATP/1 mol of exogenous glucose that passes through glycolysis. The first enzyme of the ATP generating stage of glycolysis, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is involved in the oxidation and phosphorylation of glyceraldehyde phosphate coupled to the production of NADH from NAD^+ [21]. Thus to ensure flux through GAPDH is not restricted, NADH must be continually reoxidized to NAD^+. This is accomplished by one of two routes. In anaerobic conditions in the absence of O_2, NADH is reoxidized by the enzyme lactate dehydrogenase (LDH) [21]. In the presence of O_2, under aerobic conditions, NADH is reoxidized by the mitochondrial electron transport chain [20].

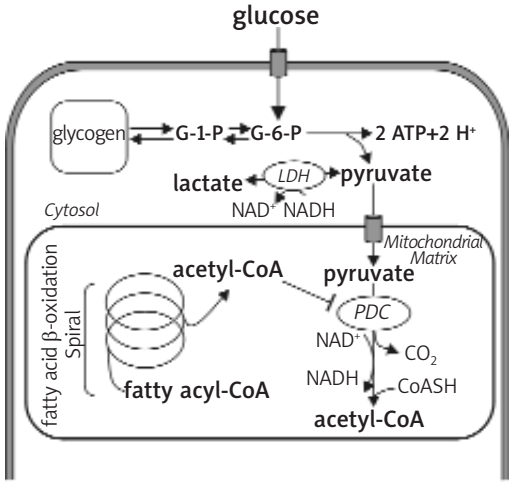

Figure 2. Schematic illustration of glucose metabolism. Following facilitative transport and subsequent phosphorylation by hexokinase, glucose is either stored as glycogen or subject to catabolism by glycolysis, generating ATP. The end product of aerobic glycolysis is pyruvate, which itself is oxidized in the mitochondria generating NADH and acetyl-CoA. The end product of anaerobic glycolysis is lactate, which is formed from pyruvate in order to regenerate NAD^+ in the absence of oxygen. The hydrolysis of glycolytically derived ATP results in the production of H^+, which are normally consumed by the tricaboxylic acid cycle; however, during ischemia (the absence of blood flow and oxygen delivery) H^+ can accumulate in the cytoplasm resulting in intracellular acidosis

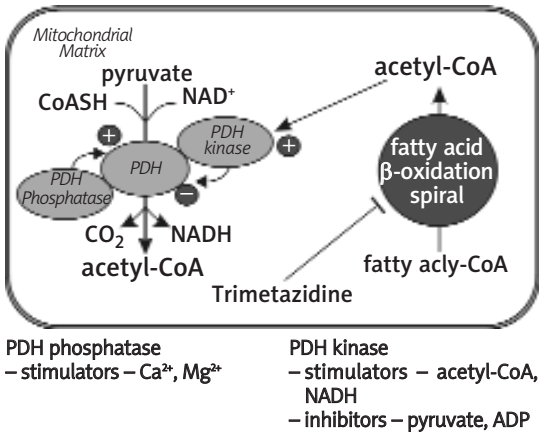

Figure 3. Schematic illustration describing the regulation of the aerobic disposal of pyruvate (glucose oxidation). The pyruvate dehydrogenase complex consists of the enzymes PDH, PDH kinase, and PDH phosphatase. PDH is sensitive to product inhibition exerted by both acetyl-CoA and NADH. PDH is also regulated by covalent modification. PDH kinase phosphorylates and inhibits PDH, while PDH phosphatase dephosphorylates and stimulates PDH. Trimetazidine, by partially inhibiting fatty acid β-oxidation decreases acetyl-CoA-induced stimulation of pyruvate dehydrogenase kinase and hence leads indirectly to a stimulation of glucose oxidation

Under aerobic conditions pyruvate is the end product of glycolysis. The aerobic disposal of pyruvate (glucose oxidation) requires that it be transported into mitochondria via a monocarboxylate carrier [22]. Once in the mitochondrial matrix, the majority of pyruvate undergoes oxidative decarboxylation by the pyruvate dehydrogenase complex (PDC) to yield acetyl-CoA, which is then fed into the TCA cycle, where the acetyl groups undergo complete oxidation liberating carbon dioxide (CO_2) (Figure 2) [23].

Regulation of glucose oxidation

PDC is a mitochondrial multi-enzyme complex consisting of pyruvate dehydrogenase (PDH), PDH kinase, and PDH phosphatase, the complex is regulated by its substrates and products, as well as by covalent modification [24, 25]. Normally only a small portion (~20%) of PDH is in the active form, this percentage is increased in response to an increase in glycolytic flux and hence an increased generation of pyruvate, in the face of an increase in workload or in the presence of catecholamines [26]. PDH is also sensitive to inhibition by its products as increased ratios of NADH/NAD^+ and acetyl-CoA/CoA decrease the rate of pyruvate decarboxylation [26]. With regards to covalent modification, PDH phosphatase dephosphorylates and activates PDH, whereas PDH kinase, in response to acetyl-CoA and NADH (produced primarily from fatty acid β-oxidation) phosphorylates and inhibits PDH, and thus restricts the oxidation of carbon units derived from glycolysis (Figure 3) [24, 25].

Interaction between cardiac fatty acid and glucose oxidation

The competition for oxidative metabolism between fatty acids and glucose was originally described by Randle et al. in 1963 [27]. Under normal, physiological conditions the metabolic fuels involved in sustaining cardiac function are fatty acids and carbohydrates (mainly glucose and lactate). Fatty acids provide the major source of oxidative substrate for cardiac energy metabolism, accounting for 60-80% of O_2 consumption, with a much lesser contribution from glucose and lactate [9]. This preference is likely due to the higher ATP yield obtained from the oxidation of fatty acids compared to the oxidation of glucose (e.g. 105 ATP/palmitate molecule vs. 30 ATP/glucose molecule). However, preference for fatty acids as an oxidative fuel, at the expense of glucose also carries disadvantages, attributed to the greater amount of O_2 required per mole of ATP produced.

The metabolic relationship between fatty acid and glucose metabolism is reciprocal [28]. The molecular mechanisms underlying this reciprocal relationship are manifest at multiple levels of the pathways involved in the catabolism of glucose. Acetyl-CoA produced from the β-oxidation of fatty acids inhibits PDH, which in turn can lead to an inhibition of phosphofructokinase-1 (PFK-1, the rate limiting enzyme of glycolysis) and of hexokinase [28]. The reciprocal regulation of glucose metabolism by fatty acid oxidation occurs in a hierarchical manner, with glucose oxidation being inhibited to the largest extent, followed by a lesser effect on glycolysis and glucose uptake. The effects of fatty acid β-oxidation-induced inhibition of glucose metabolism are manifest primarily as an uncoupling between glycolysis and glucose oxidation. Thus H^+ produced from the hydrolysis of glycolytically derived ATP are not consumed by the TCA cycle and the mitochondrial electron transport chain, and so have the potential to produce intracellular acidosis, especially during periods of ischemia when blood flow is insufficient to remove metabolic by-products.

Myocardial energy substrate metabolism during ischemia and reperfusion

The rate of ATP turnover in the heart is very rapid, with the myocardial ATP pool turning over approximately every 12 seconds due to a high ATP demand required to maintain contractile function (60% of total ATP demand) and ionic homeostasis (40% of ATP demand) [29]. As the major effect of myocardial ischemia is the inhibition of oxidative ATP production, both contractile function and ionic homeostasis can be compromised as a result of ischemia.

Due to its ability to generate ATP in the absence of O_2, glycolysis becomes increasingly important during periods of ischemia. During periods of mild

to moderate ischemia, flux through glycolysis is stimulated/or leads to an increase in glucose uptake and increased glycogen mobilization [30]. Although glycolysis can provide ATP in order to correct and maintain ionic homeostasis during ischemia, the hydrolysis of glycolytically derived ATP in the absence of subsequent pyruvate oxidation leads to an accumulation of lactate and H^+, which can further aggravate ionic disturbances brought about by ischemia. Thus during periods of ischemia, when glycolysis is accelerated, a greater proportion of ATP hydrolysis must be diverted towards performing chemical work (re-establishing ionic homeostasis) than contractile work [31]. This problem is exacerbated if any residual oxidative metabolism is derived from fatty acid oxidation, as opposed to glucose oxidation. In situations of severe ischemia the metabolic by-products of anaerobic glycolysis are not removed, and flux through the pathway is eventually inhibited by the effects of acidosis [21, 30].

In the post-ischemic period during reperfusion, the rates of oxidative fatty acid metabolism recover rapidly to pre-ischemic values at the expense of glucose oxidation, while contractile function remains depressed [32, 33]. This rapid recovery of fatty acid oxidation can contribute to an ongoing uncoupling of glucose metabolism thus aggravating intracellular acidosis, and impairing the recovery of cardiac function and efficiency despite the restoration of flow [34]. Intracellular acidosis impairs the response of the contractile filaments to Ca^{2+}, thereby contributing the impaired recovery of function during reperfusion. Furthermore, as extracellular pH quickly normalizes upon reperfusion, there is large pH gradient across the sarcolemmal membrane that promotes Na^+/H^+ exchange, increasing intracellular Na+, which in turn promotes Na^+/Ca^{2+} exchange, and the sequelae associated with intracellular Ca^{2+} overload, including contracture, mitochondrial dysfunction, the activation of Ca^{2+} dependent proteases, and cardiac myocyte cell death [35].

Optimizing energy metabolism to treat ischemic heart disease

Optimizing energy substrate metabolism in the ischemic and reperfused myocardium represents a novel mechanism to enhance the preservation of mechanical function and efficiency, whether the ischemia is the result of some underlying pathophysiology or due to elective surgical procedures. Pharmacological agents that shift the balance between fatty acid and glucose metabolism towards glucose utilization have recently received considerable attention. In particular, pharmacological agents that improve the coupling between glycolysis and glucose oxidation, either by inhibiting fatty acid β-oxidation and/or by stimulating glucose oxidation are promising anti-ischemic interventions.

Anti-ischemic effects of trimetazidine

Trimetazidine protects the heart during and following ischemia

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) is a clinically effective anti-anginal agent that is currently used throughout Europe, and more than ninety countries worldwide [36, 37]. The compound was originally described as a cytoprotective agent, devoid of effects on cardiac contractility and heart rate, as well as coronary flow. The cytoprotective effects of trimetazidine are evident in cardiac myocytes where it reduces the release of lactate dehydrogenase during both hypoxia and reoxygenation, an effect that is also associated with a potent inhibition of palmitoyl-carnitine (a C-16 fatty-acyl-CoA moiety) oxidation [38]. In addition, the protective effects of trimetazidine are transferable to experimental models of ischemia-reperfusion. Trimetazidine effectively reduces ischemic contracture and lessens the increase in diastolic pressure during reperfusion following ischemia [39], as well as inhibiting cardiac myocyte apoptosis to preserve cardiac function during reperfusion following ischemia [40]. With regards to its novel, anti-ischemic mechanism of action, trimetazidine also protects hearts from the deleterious effects of fatty acids on the recovery of cardiac function [41].

Trimetazidine partially inhibits fatty acid β-oxidation

Trimetazidine is "metabolic modulator" that optimizes cardiac energy substrate metabolism. Trimetazidine partially inhibits myocardial fatty acid β-oxidation via the selective, reversible/competitive inhibition of long-chain 3-ketoacyl-CoA thiolase, the terminal enzyme of mitochondrial fatty acid β-oxidation [42, 43]. Furthermore, trimetazidine indirectly increases myocardial glucose β-oxidation by relieving inhibition of PDH induced by acetyl-CoA and NADH derived from fatty acid β-oxidation [42, 43].

The reciprocal increase in glucose oxidation improves its coupling to glycolysis, and as such, decreases the rate of H^+ production attributable to the hydrolysis of glycolytically derived ATP. The improvement in the coupling between glycolysis and glucose oxidation lessens the potential for the activation of the Na^+/H^+ exchanger, and thus decreases intracellular Na^+ overload, which itself reduces the potential for reverse mode Na^+/Ca^{2+} exchange, and therefore can reduce intracellular Ca^{2+} overload [35, 44, 45]. The metabolic effects of trimetazidine thus increase cardiac efficiency and therefore decrease O_2 utilization by allowing ATP hydrolysis to be more efficiently converted to contractile work in hearts where the rate of fatty acid β-oxidation is reduced. This may be related to a lesser amount of ATP hydrolysis required to

correct deleterious alterations in ionic homeostasis. The effects of trimetazidine on myocardial fatty acid β-oxidation indeed translate into meaningful cardioprotection, as it improves the recovery of function during reperfusion following both global- and low-flow ischemia [42, 43, 46-48], which is similar to the clinical phenomenon of angina.

Trimetazidine – clinical experience

The efficacy and tolerability of trimetazidine in the treatment of ischemic heart disease has been consistently and reproducibly demonstrated in numerous clinical trials as both monotherapy and as an adjunct to conventional antianginal therapy. As such, trimetazidine may be useful as an alternative first-line agent, or as an add-on to standard hemodynamic therpies, which lack further benefit when combined [49]. With regards to the treatment of chronic stable angina, the major beneficial effects of trimetazidine are an increased exercise time to 1 mm ST segment depression, a reduction in the number of weekly angina attacks, as well as a reduction in weekly nitrate consumption in non-revascularized patients [50-52] and patients revascularized via percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) procedures [53]. Furthermore, trimetazidine also reduces cardiac troponin I release and left ventricular (LV) wall motion abnormalities that can arise following elective PCI [54, 55]. The anti-ischemic efficacy of trimetazidine in angina is also extended to patients with underlying type 2 diabetes mellitus [50, 56], a hallmark of which is an increased, almost exclusive reliance on fatty acid β-oxidation to meet myocardial energy requirements [57]. Trimetazidine may be particularly effective in diabetic patients with ischemic heart disease as it may serve to shift the pre-existing reliance on fatty acids as an oxidative fuel towards glucose.

The protective effects of optimizing myocardial metabolism with trimetazidine are not limited to angina. Trimetazidine has been shown to elicit anti-ischemic effects during elective revascularization procedures. In patients undergoing CABG, pre-treatment with trimetazidine was protective as evinced by decreased release of troponin T [58]. Trimetazidine also decreases ischemic severity in PCI procedures as assessed by attenuation of ST segment elevation during angioplasty balloon inflation [59]. The clinical utility of optimizing myocardial metabolism with trimetazidine also has additional beneficial effects transferable to the settings of acute myocardial infarction (AMI). The use of trimetazidine as an adjunct to thrombolysis decreases arrhythmic risk during AMI [60], and reperfusion arrhythmias associated with PCI [61]. As an adjunct to primary angioplasty, trimetazidine also leads to earlier resolution of ST segment elevation [62], and improved exercise duration in patients post MI [63].

Improved survival following AMI has unfortunately increased the incidence of ischemic cardiomyopathy and heart failure characterized by left ventricular dysfunction [1, 2]. As alterations in energy substrate metabolism contribute to the progression of ischemic cardiomyopathy [64], rationale for the use of trimetazidine is indicated. Indeed, clinical trails have demonstrated significant benefits of adding trimetazidine to standard hemodynamic therapy. In patients with ischemic cardiomyopathy trimetazidine provides symptomatic improvements in the symptoms of angina [65], improvement in New York Heart Association (NYHA) functional class [66, 67], as well as reductions in weekly nitroglycerin consumption [68, 69]. Furthermore, in patients with heart failure, the addition of trimetazidine to conventional therapy improves New York Heart Association (NYHA) functional class, left ventricular (LV) end-systolic volume, ejection fraction, as well as quality of life [68, 70, 71]. Thus, the partial inhibition of fatty acid β-oxidation with trimetazidine is an effective therapeutic intervention in the treatment of diverse forms of ischemic heart disease (summarized in Table I).

In conlusions the rapid recovery of fatty acid β-oxidation during reperfusion following myocardial ischemia uncouples glycolysis and glucose

Table I. Beneficial effects of trimetazidine in the treatment of ischemic heart disease

Ischemic heart disease	Clinical parameters	Ergometric parameters
Angina [52]	i) decrease in weekly angina attacks ii) decease weekly nitroglycerin consumption	i) increase time to 1 mm ST segment depression
AMI [60-63]	i) decrease arrhythmic risk and reperfusion arrhythmias ii) earlier resolution of ST segment elevation	i) increase exercise duration post MI
Ischemic cardiomyopathy/heart failure [65-71]	i) decrease symptoms of angina ii) decrease weekly nitroglycerin consumption iii) decrease plasma levels of cardiac troponin T	i) improve exercise tolerance

Summary of the beneficial effects of trimetazidine in the treatment of ischemic heart disease including angina, acute myocardial infarction, and ischemic cardiomyopathy and heart failure

oxidation, and so increases H^+ production, which via increased Na^+/H^+ exchange can contribute to increased intracellular Ca^{2+} via Na^+/Ca^{2+} exchange. The partial inhibition of fatty acid β-oxidation with trimetazidine reciprocally increases glucose oxidation, decreases H^+ production, and so increases the efficiency of ATP generation. These effects of trimetazidine have the potential to ameliorate the deleterious alterations in ionic homeostasis that can occur both during and following ischemia, and can improve overall myocardial energetics, as greater proportion of ATP hydrolysis is left available to drive contractile work. Trimetazidine is a novel therapeutic strategy for the treatment of ischemic heart disease that has been successfully combined with classical hemodynamic therapy. The utility of trimetazidine in the treatment of ischemic heart disease has been confirmed in various experimental models, as well as in numerous clinical trials demonstrating its beneficial effects in the treatment of angina, AMI, and heart failure. Thus modulating and optimizing myocardial energy substrate metabolism via the partial inhibition of fatty acid β-oxidation is a viable approach to limit the deleterious consequences of ischemic heart disease.

Acknowledgments

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