Metabolic therapy for heart failure including diastolic heart failure

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Abstract

Cardiac energetic impairment is a feature of systolic heart failure irrespective of the underlying etiology, and the magnitude of this impairment is predictive of subsequent mortality. It is also a feature of other forms of heart muscle diseases including hypertrophic cardiomyopathy and heart failure with normal ejection fraction. While the adult heart normally uses predominantly free fatty acids to generate energy, this consumes more oxygen than the use of carbohydrate to generate energy. In the context of heart muscle disease the reduction in efficiency of fatty acid versus carbohydrate utilization may be substantial. This provides the rationale for the use of drugs that inhibit fatty acid utilization and increase carbohydrate utilization. These agents either prevent the uptake of long chain fatty acids into the mitochondria (eg, perhexiline) or inhibit fatty acid β-oxidation (eg, trimetazidine). Studies in patients with systolic heart failure have shown encouraging results with increased cardiac performance and exercise capacity with these agents.

Keywords: Cardiac energetics; cardiac metabolism; cardiomyopathy; heart failure; metabolic therapy

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Introduction

The heart cycles approximately 6 kg of ATP each day [1] required to drive the actin–myosin interaction in myofibrils, and for other vital functions including the activity of ion channels. It is perhaps not surprising that cardiac pathology is associated with an impairment of cardiac energy production and/or utilization, as originally described by Herrman and Decherd [2]. Studies in animal models of systolic heart failure have confirmed this initial observation, and in the rapid pacing model of heart failure, cardiac energetic impairment begins before the appearance of overt left ventricular systolic dysfunction or heart failure [3]. In patients with systolic heart failure ^{31}P cardiac magnetic resonance spectroscopy shows a reduced ratio of phosphocreatine (PCr)/ATP, the magnitude of which predicts mortality [4]. These observations support the concept that energy impairment is both a consequence of the cardiomyopathic process and a contributor to its progression.

Cardiac substrate use and energy production in health and disease

The heart is a metabolic omnivore, able to use different substrates (fatty acids, carbohydrates, lactate, ketones, amino acids) in varying amounts in different circumstances. In fetal life

carbohydrates form the primary substrate, but soon after birth there is a metabolic shift and in the adult in the fasting state fatty acid utilization accounts for approximately 70% of ATP generation and even more during conditions of increased work [5]. With adequate oxygen availability and normal underlying cardiac biochemical function, fatty acid oxidation provides an extremely efficient source of energy, generating more ATP per gram of substrate than carbohydrate oxidation. However, it costs more oxygen per unit of ATP generated than carbohydrate oxidation, theoretically approximately 12%, but when plasma free fatty acids (FFA) are markedly raised there is a substantial "oxygen wasting" effect (approximately 40–50%) [6]. The mechanism responsible has not been proved but is likely to be related to increased mitochondrial "uncoupling", and to futile metabolic cycles. Fatty acids increase the expression of uncoupling proteins (by peroxisome proliferator activated receptor alpha activation), and lipid peroxides derived from oxidative conversion of lipids in the mitochondrial matrix increase uncoupling protein activity. They dissipate the electrochemical gradient across the inner mitochondrial membrane that drives the phosphorylation of ADP to ATP. Plasma FFA are increased by high plasma catecholamines (by activation of lipoprotein lipase), and consequently high FFA levels are typically observed in acute myocardial infarction and in heart failure; thus uncoupling protein expression was increased in the hearts of patients with left ventricular systolic dysfunction and expression was correlated with plasma FFA [7]. Furthermore, the accumulation of acetyl coenzyme A (CoA) and NADH from high levels of fatty acid oxidation inhibits the enzyme pyruvate dehydrogenase (PDH) that catalyses the conversion of pyruvate to acetyl CoA. This results in pyruvate accumulation and its conversion to lactate leading to harmful proton accumulation particularly in the context of myocardial ischaemia, which can be lessened using partial inhibitors of fatty acid β-oxidation, reducing ischaemic left ventricular dysfunction [8].

In animal models of systolic heart failure developing in the context of left ventricular hypertrophy, the expression of fatty acid β-oxidation enzymes is consistently downregulated. There is a shift towards increased glucose uptake but because of the reduced activity of PDH, there is reduced carbohydrate oxidation only partly compensated by anaplerotic reactions. Accordingly, the heart is unable to utilize fully either major substrate and this contributes importantly to its energy starvation [9]. Furthermore, the combination of increased plasma FFA together with a reduced capacity to oxidize them sets the scene for increased expression and activity of the uncoupling proteins, probably further reducing the efficiency of energy generation. In other animal models of heart failure different findings have been reported. For example, in the canine rapid pacing model substrate utilization was relatively normal in the early stages but in advanced heart failure fatty acid utilization was markedly reduced [10].

Studies in patients with systolic heart failure have been conflicting, potentially explained by factors including etiology, stage of heart failure and technique employed (for example positron emission tomography (PET) with [18F]fluorodeoxyglucose gives information about glucose uptake but does not provide information about pyruvate oxidation, which is likely to be impaired as noted above even if glucose uptake is preserved or increased). In explanted hearts from patients with advanced heart failure there is downregulation of the expression of fatty acid oxidation enzymes compared to donor hearts [11]. Funada and colleagues [12] demonstrated preserved FFA uptake in compensated heart failure using an assessment of cross-heart uptake of stable isotopes. Using cross-heart indirect calorimetry and stable isotope infusion, fasting glucose uptake was shown to be impaired and fatty acid utilization increased in patients with heart failure of moderate severity [13]. Using PET-based assessment Taylor and colleagues [14] reported increased fatty acid uptake and lower glucose uptake in the hearts of patients with severe left ventricular systolic dysfunction and stable heart failure symptoms, whereas Davila-Roman et al [15] reported reduced fatty acid uptake and increased glucose uptake.

"Metabolic modulation" as a therapy for heart failure

The observation that FFA are increased in heart failure and that high FFA levels reduce the efficiency of energy generation has led to the concept that reducing FFA utilization and increasing carbohydrate utilization may increase the efficiency of energy generation in heart failure, improving cardiac function and functional status.

The concept that increased carbohydrate oxidation may be beneficial is underscored by a study in which

dicholoacetate was infused in patients with severe heart failure. Dicholoroacetate is an activator of PDH that is used in the treatment of lactic acidosis. A 30-minute infusion increased left ventricular stroke work at a lower oxygen cost [16]. However, its short half-life necessitates continuous infusion, and as a sodium salt this involves a high sodium load making its long-term use in heart failure impractical. However, as fatty acid utilization generates NADH and acetyl CoA, which are both potent inhibitors of PDH, inhibition of fatty acid oxidation should theoretically increase PDH activity and therefore simultaneously reduce fatty acid utilization and increase carbohydrate oxidation. Three major strategies could potentially facilitate this (Fig. 1):

1. Reduction in plasma FFA by the inhibition of lipoprotein lipase activity using nicotinic acid derivatives. Acute treatment with acipimox in patients with heart failure due to dilated cardiomyopathy reduced plasma FFA, reduced myocardial fatty acid oxidation and increased glucose uptake (assessed by PET) but left ventricular stroke work and cardiac efficiency fell [17]. The reason for this could be that the increase in glucose uptake was insufficient to compensate for the loss of the fatty acid substrate, or more likely that despite increased glucose uptake the reduced PDH activity was not acutely reversed so that the loss of fatty acid oxidation was not matched by an increase in carbohydrate oxidation. However, a 28-day placebo controlled trial of acipimox in patients with ischemic left ventricular dysfunction did not demonstrate any improvement in left ventricular performance despite reducing plasma FFA [18].
2. Blockade of the uptake of long chain fatty acids into the mitochondria. Long chain FFA are first converted to long chain acyl CoA (by fatty acid acyl CoA synthase), which can only cross the mitochondrial membrane as a result of the addition of a carnitine molecule by the enzyme carnitine palmitoyl transferase (CPT) 1. On the other side of the mitochondrial membrane the carnitine is cleaved off by the enzyme CPT2 and the long chain acyl CoA then undergoes β-oxidation. This is the rate-limiting step in fatty acid metabolism, and the activity of the CPT enzymes is potently regulated by malonyl CoA, formed by acetyl CoA carboxylase and degraded by malonyl CoA decarboxylase. A number of malonyl CoA decarboxylase inhibitors are available. In a pig cardiac ischemia model one of these inhibitors reduced fatty acid utilization and increased carbohydrate oxidation [19].

Direct pharmacological inhibitors of the CPT enzymes are available. Oxfenicine slowed the development of heart failure in the rapid pacing canine model [20], but is not available for human use. Etomoxir is a potent irreversible inhibitor of the CPT enzymes. It did not reverse the development of heart failure in the rat aortic banding model [21]. An initial open label (uncontrolled) study in 10 patients with heart failure reported an increase in left ventricular ejection fraction (LVEF), and an improvement in exercise hemodynamics [22], but a subsequent randomized controlled trial was abandoned at an early stage of recruitment because four patients in the etomoxir group had unacceptably elevated liver transaminase levels [23]. Perhexiline is a drug that was used in the 1970s and 1980s to treat angina, for which it was highly effective. At the time it was not clear exactly how it worked. A small proportion of patients developed liver toxicity and neuropathy that were found to be caused by phospholipid accumulation, and the drug was voluntarily withdrawn by the manufacturers. Subsequent work in isolated mitochondria showed that perhexiline reversibly inhibits cardiac (and hepatic) CPT1 and CPT2 [24]. Furthermore, the toxicity was shown to be caused by long-term exposure to high plasma concentrations of the drug that is predominantly metabolised by P450 2D6, which is subject to substantial genetic variations in activity. Dose titration according to plasma levels avoids long-term toxicity [25], and this has led to a resurgence in the use of the drug in some parts of the world – particularly Australia and New Zealand. We evaluated the effects of perhexiline in a randomized double blind placebo controlled trial of 56 patients with stable chronic heart failure who were on optimally tolerated conventional medical therapy and who were treated for 2 months. There was a substantial improvement in peak oxygen consumption (the primary endpoint) and also in the predefined secondary endpoints of LVEF, and quality of life assessment [26]. These encouraging data have yet to be evaluated further in a large multicenter study with "hard" endpoints. Perhexiline has pleotropic effects potentially relevant to its beneficial effects in heart

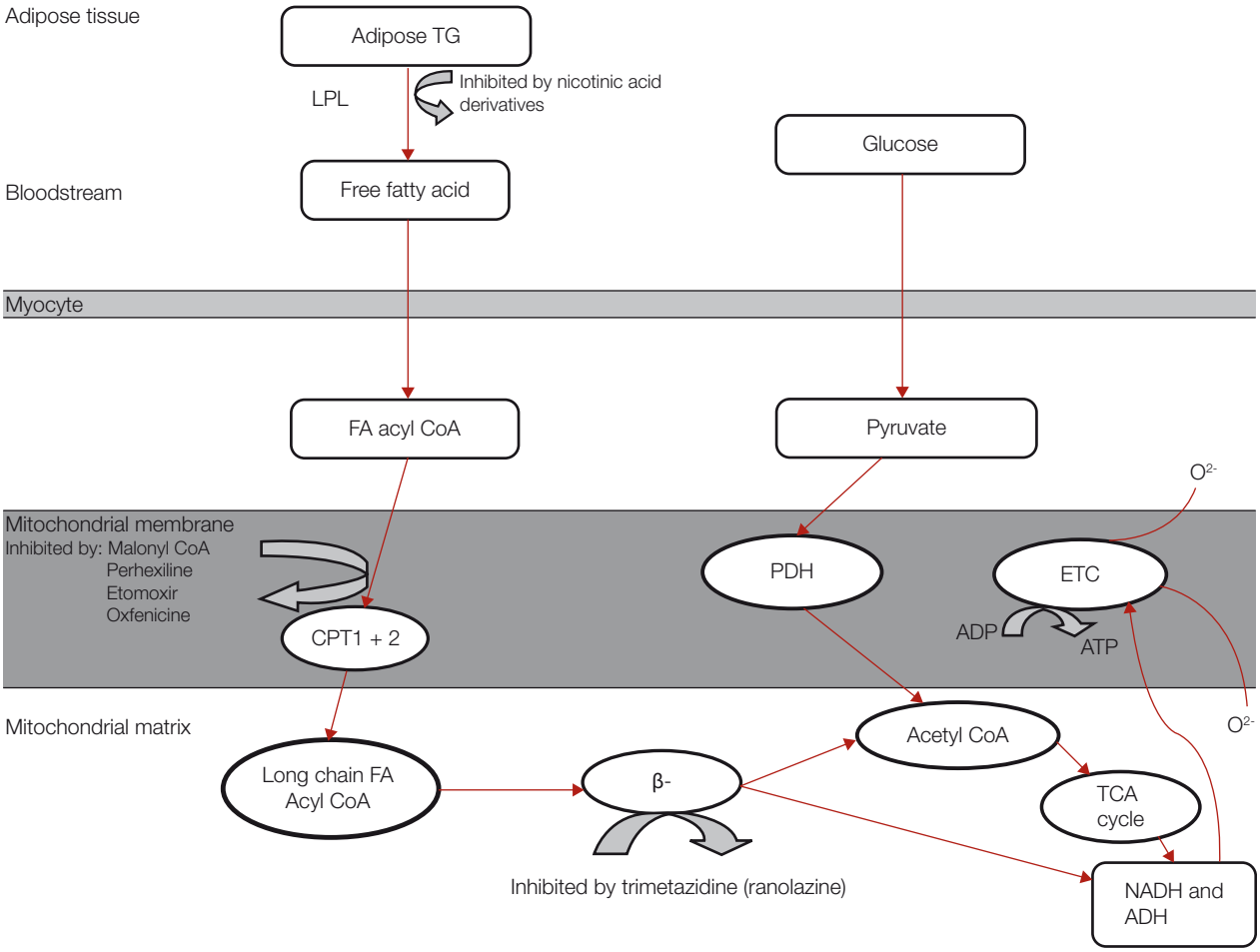

Fig. 1 *CoA = coenzyme A, CPT = carnitine palmitoyl transferase, ETC = electron transport chain, FA = fatty acid, LPL = lipoprotein lipase, PDH = pyruvate dehydrogenase, TCA = tricarboxylic acid, TG = triglyceride.*

muscle diseases. Indeed, a study in the working rat heart model raises the possibility that at least some of the beneficial effects on cardiac performance are not mediated by CPT1 inhibition. While 48 hour pretreatment was associated with an increase in cardiac mechanical efficiency and reduced palmitate uptake, increased efficiency was also seen with 24 hour pretreatment without any change in palmitate uptake [27]. These pleotropic mechanisms include:

i) Altered redox status – perhexiline reduces superoxide generation by the phagocytic form of NADPH oxidase 2 [28], and was recently shown to reduce cardiac expression of thioredoxin interacting protein (a potent inhibitor of thioredoxin) in patients pretreated with perhexiline versus placebo before coronary artery bypass grafting [29].

ii) Altered cell survival mechanisms. Perhexiline reversibly inhibits the mammalian target of complex 1 (mTORC1) and therefore stimulates cell autophagy, which may be an important cell survival mechanism [30].

Interestingly, β-blockers that have been shown to improve outcome markedly in patients with heart failure may also work in part by a similar mechanism. Metoprolol reduced CPT1 activity in a microembolization canine model [31], and using PET, Wallhaus et al [32] showed that carvedilol treatment reduced fatty acid uptake and increased glucose uptake in patients with heart failure.

3. Partial inhibition of fatty acid β-oxidation enzymes. Trimetazidine inhibited fatty acid oxidation in isolated cardiac myocytes, conferring protection from hypoxia [33], and in the working rat heart model clinically relevant concentrations of trimetazidine reduced fatty acid oxidation, increased glucose oxidation, and inhibited long chain 3 ketoacyl CoA thiolase, a key fatty acid β-oxidation enzyme [34]. It is noteworthy that the study also demonstrated that in hearts

subjected to low-flow ischemia, trimetazidine resulted in a 210% increase in glucose oxidation rates.

Trimetazidine is an effective anti-anginal agent. It has also been evaluated in a series of studies in patients with heart failure. Cardiac and systemic metabolism was evaluated using PET in a randomized placebo controlled trial of 19 patients with dilated cardiomyopathy. Trimetazidine significantly increased LVEF, modestly decreased cardiac FFA oxidation, and did not change the myocardial oxidative rate, implying increased oxidation of glucose and increased insulin sensitivity [35]. In a recent study in obese humans trimetazidine inhibited oxidation of endogenous intramyocardial lipids and increased cardiac mechanical efficiency [36]. In another study, improvements in symptomatic status and LVEF were accompanied by a 33% increase in the cardiac PCr/ATP ratio, indicating an improvement in the myocardial high-energy phosphate levels [37]. Two recent meta-analyses have assessed the benefits of trimetazidine as add-on therapy in patients with congestive heart failure [38, 39]. The last one, published in 2012 in the *Journal of the American College of Cardiology* [39], showed that the addition of trimetazidine significantly increases LVEF by 6.46%, which is consistent with the improvement of LVEF by 7.5% obtained in the other meta-analysis reporting data on nearly 1000 patients with heart failure and published in the journal *Heart* in 2011 [38].

Moreover, these meta-analyses showed significant improvements in New York Heart Association status and exercise time, a reduction in hospitalization due to heart failure and a trend towards reduced mortality. Aside from its primarily metabolic effects, trimetazidine has been shown to lower plasma C-reactive protein [40]. Generally well tolerated, it rarely induces a Parkinsonian syndrome [41].

Ranolazine is a widely used anti-anginal agent. In the Langendorff perfused normoxic rat heart it reduced fatty acid oxidation and increased PDH activity [42]. It appears to be a partial inhibitor of fatty acid β-oxidation but the concentrations achieved clinically are considerably lower than those that substantially inhibit fatty acid β-oxidation, and more recently its therapeutic action has been attributed primarily to blockade of the slow inward sodium current [43]. Ranolazine increased left ventricular power and mechanical efficiency in the canine rapid pacing heart failure model [44], and in a recent placebo controlled study in patients with diastolic heart failure, acute intravenous ranolazine reduced left ventricular end-diastolic pressure, and 14 days of oral therapy reduced the minute ventilation/carbon dioxide production slope on exercise [45].

"Metabolic therapy" for other heart muscle diseases including HCM and heart failure with preserved LVEF?

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disease usually caused by mutations of one of several genes encoding sarcomere proteins. Cardiac energetic impairment is an almost universal finding, irrespective of the gene responsible, precedes the development of left ventricular hypertrophy [46], and is caused by an energy wasting effect from increased crossbridge turnover associated with increased sarcomeric calcium sensitivity [47]. We recently conducted a double blind placebo controlled trial in 46 patients with symptomatic non obstructive HCM of (mean) 4.6 months duration [48]. Perhexiline significantly improved exercise capacity – measured as peak oxygen consumption – the primary endpoint, and improved the quality of life score. The cardiac PCr/ATP ratio was substantially increased by perhexiline. We also measured the effect of therapy on cardiac diastolic function at rest and during exercise using radionuclide ventriculography. The time to peak filling (TTPF), measured from the time activity curve is an indirect marker of the rate of left ventricular active relaxation. Sympathetic activation causes an increase in the rate of left ventricular active relaxation during exercise by protein kinase A (PKA)-mediated phosphorylation of key proteins including troponin I, SERCA and titin, which are highly energy dependent processes. Even after correcting the TTPF for the RR interval (to produce a normalized TTPF) there was a slight shortening of this from rest to peak exercise in an age-matched control group permitting adequate left ventricular filling during the shortened diastolic filling period occurring at high heart rates on exercise. In contrast, normalized TTPF became markedly longer on exercise in the patients with HCM. Perhexiline nearly normalized the response of corrected TTPF during exercise, almost certainly due to the marked associated improvement in cardiac energetic status. While systolic heart failure is typically associated with elevated plasma FFA, providing a rationale for the beneficial effect of metabolic modulators, this is not usually so in HCM. One

study reported PET evaluation of eight patients with HCM due to alpha tropomysosin gene mutations. There was increased FFA metabolism in those patients with mild hypertrophy, but not in those with severe hypertrophy [49]. It is not known whether increased fatty acid metabolism is common in HCM, and/or whether the beneficial effects of perhexiline on energetics in HCM might be due to an alternative pleotropic effect.

Up to 50% of patients with the clinical features of heart failure have normal LVEF and are usually said to have heart failure with normal ejection fraction (HFnEF). While many patients have impairment of left ventricular active relaxation and/or increased passive left ventricular stiffness at rest, this is not universal. Increased passive stiffness is attributable to myocyte hypertrophy and interstitial fibrosis, a consequence of the hypertension that commonly predisposes to the disorder, and to a shift of expression of the giant sarcomere protein titin to the shorter stiffer form, and/or impairment of titin phosphorylation [50]. We recently demonstrated that the exercise pathophysiology of HFnEF may share some features in common with that of HCM. The cardiac PCr/ATP ratio was substantially lower than in a group of age-matched controls. These patients typically have stiff large arteries, and accordingly have increased arterial elastance (a measure of left ventricular afterload) at rest, and this tended to increase more during exercise in patients versus controls. As in HCM patients there was an acute dynamic lengthening of normalized TTPF in patients during exercise and a failure to increase left ventricular contractile function appropriately, attributable to the cardiac energetic impairment and to the increased left ventricular afterload [51]. The mechanisms responsible for this cardiac energetic impairment in HFnEF are uncertain. Many patients with the disorder have insulin resistance and elevated plasma FFA similar to that seen in systolic heart failure, and this almost certainly contributes [52]. Currently, there are no effective therapies for HFnEF, and the above pathophysiological observations provide a rationale for the evaluation of metabolic therapies in the disorder. We currently have a double blind placebo controlled trial of perhexiline in HFnEF underway (clinicaltrials.gov NCT00839228).

Conclusions

Cardiac energetic impairment plays an important pathophysiological role in systolic heart failure irrespective of etiology and in other diseases of heart muscle including HCM and HFnEF. Promising results have been obtained with metabolic modulators thought to increase cardiac energetic status by shifting cardiac substrate use away from fatty acids and towards carbohydrates, in systolic heart failure and in HCM. •

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