New pharmacological targets in the treatment of heart failure: inhibition of free fatty oxidation by trimetazidine

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Abstract

Heart failure may promote alterations of cardiac metabolism, resulting in the depletion of myocardial ATP, phosphocreatine and creatine kinase with decreased efficiency of mechanical work. A direct approach to manipulate cardiac energy metabolism consists in modifying substrate utilization by the failing heart. To date, the most effective metabolic treatments include pharmacological agents that directly inhibit fatty acid oxidation. Trimetazidine (Vastarel® MR) appears to be the most investigated agent in this setting. The results of current research support the concept that shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism could be an effective adjunctive treatment in patients with heart failure. More specifically, very recent meta-analyses have confirmed that the additional use of trimetazidine in heart failure patients may yield a significant protective effect for all-cause mortality, cardiovascular events and hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously ameliorate left ventricular remodeling. Certainly, in order to clarify the exact therapeutic role of metabolic therapy in heart failure, a large multicenter randomized controlled trial should be performed.

Keywords: Carnitine palmitoyl transferase I; free fatty acid inhibitors; heart failure; left ventricular function; metabolic therapy; myocardial metabolism; trimetazidine

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Introduction

Recent studies in patients with heart failure have investigated the possibility of increasing cardiac performance without affecting oxygen consumption and hemodynamics by agents aimed at enhancing myocardial energy efficiency. Most investigators have focused their efforts on agents that shift energy substrate utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of ATP production per mole of oxygen utilized. Of the latter pharmacological class, trimetazidine (Vastarel® MR) is the most investigated drug in the context of heart failure. Trimetazidine has been shown to affect myocardial substrate utilization by inhibiting fatty acid oxidation and by shifting energy production from free fatty acids (FFA) to glucose oxidation [1] (Fig. 1). By increasing utilization of glucose and lactate,

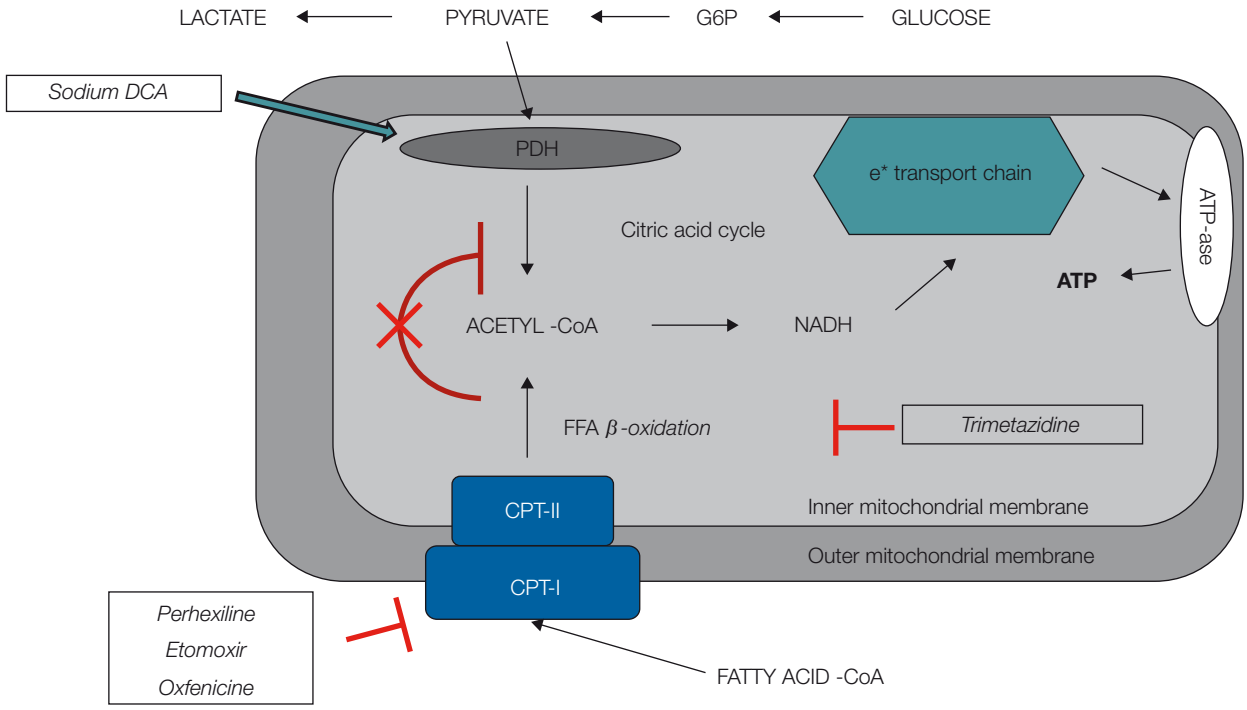

Fig. 1 *The effects of metabolic agents on myocardial metabolism. Carbohydrate metabolism may be directly increased by agents such as sodium dichloroacetate, which stimulates pyruvate dehydrogenase (PDH) activity by inhibiting pyruvate dehydrogenase kinase. Stimulation of PDH activity leads to enhanced glycolysis of glucose and utilization of lactate by the myocardium for aerobic respiration. Myocardial consumption of free fatty acids (FFA) is simultaneously inhibited, with the overall effect of a change of substrate utilization from predominantly FFA to glucose and lactate. Perhexilline, oxfenicine, and etomoxir prevent the uptake of FFA by inhibiting carnitine palmitoyltransferase I, which is a key mitochondrial enzyme involved in this process. Trimetazidine inhibits β-oxidation of FFA. These actions shift myocardial substrate use from FFA to glucose, which is more efficient in terms of energy production, leading to an oxigen-sparing effect. CoA = coenzyme A, CPT = carnitine palmitoyltransferase, DCA = dichloroacetate, FA = fatty acid, G6P = glucose-6-phosphate.*

which are more efficient fuels for aerobic respiration, the oxygen consumption efficiency of the myocardium can be improved by 16–26% [2].

The aim of this paper is to review the reported evidence on the protective effects of metabolic therapy, and its potential clinical application, in patients with heart failure.

Effects of metabolic modulation on left ventricular dysfunction

Based on the hypothesis that FFA inhibitors could act as metabolic modulators in the protection of ischemic myocardium, Brottier and colleagues [3] assessed the value of long-term treatment with trimetazidine in patients with severe ischemic cardiomyopathy. Twenty patients were randomly assigned to receive either placebo or trimetazidine. All patients on trimetazidine, at 6 months follow-up, reported a clinically considerable improvement in symptoms and showed a higher ejection fraction compared to patients on placebo. The authors concluded that their study recommended the use of trimetazidine as a complementary therapeutic tool in patients with severe ischemic cardiomyopathy.

On this basis, the effects of trimetazidine on dobutamine-induced left ventricular dysfunction in patients with coronary artery disease were assessed [4]. Patients were randomly assigned to a 15-day treatment period with either placebo or trimetazidine. They were then crossed over to the other regimen for another 15 days. At the end of each treatment period, a stress echo with dobutamine was performed. Both in resting condition and at peak dobutamine infusion, the wall motion score index was significantly lower on trimetazidine therapy than on placebo. Furthermore, trimetazidine induced an increase in dobutamine infusion time and dose before the development of ischemia. These results indicated that trimetazidine may not only protect from dobutamine-induced ischemic dysfunction, but could also improve resting regional left ventricular function, as shown by the significantly decreased peak and resting wall motion score index during the active

treatment period. A subsequent study confirmed these preliminary results [5].

Modulation of myocardial metabolism in post-ischemic heart failure

By keeping in mind the concept that 3-ketoacyl coenzyme A thiolase inhibitors should, therefore, be able to promote the utilization of glucose and non fatty substrates by the mitochondria, attention was focused on heart failure, in which the maintenance of metabolic efficiency is a crucial issue.

The effects of the addition of trimetazidine to standard treatment of patients with diabetes, with ischemic dilated cardiomyopathy on symptoms, exercise tolerance and left ventricular function, were assessed [6]. Thirteen such patients on conventional therapy were randomly allocated to either placebo or trimetazidine, each arm lasting 15 days, and then again with placebo or trimetazidine for two additional 6-month periods. Both in the short and long terms, trimetazidine showed a significant beneficial effect on left ventricular function and control of symptoms, compared to placebo. The observed short-term trimetazidine benefit was maintained in the long term and contrasts with the natural history of the disease, as shown by the mild but consistent decrease in the ejection fraction when on placebo. These results paved the way to additional studies, which have invariably confirmed the positive effects of trimetazidine in patients with post-ischemic left ventricular dysfunction [7–11].

Modulation of myocardial metabolism in heart failure of different etiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to the preservation of phosphocreatine (PCr) and ATP intracellular levels [12]. The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on an imbalance of myocardial oxygen supply and demand [13], and a reduction of the total creatine pool, a phenomenon known to occur in heart failure [14]. In a recent study performed in patients with heart failure of different etiologies on full standard medical therapy, trimetazidine improved functional class and left ventricular function in association with an improvement of the PCr/ATP ratio, supporting the hypothesis that trimetazidine probably preserves myocardial high energy phosphate intracellular levels [15]. These results appear particularly relevant, especially in view of previous evidence indicating that the PCr/ATP ratio is a significant predictor of mortality [16].

Based on the results of this pilot study, it has also been tested whether trimetazidine could also be beneficial in a more consistent group of patients with systolic dysfunction heart failure of different etiologies [17]. Compared to patients on conventional therapy alone, those on trimetazidine improved functional class, exercise tolerance, quality of life, left ventricular function and plasma B-type natriuretic peptide levels. These beneficial effects on left ventricular function could explain the subsequent observation of a potential anti-arrhythmic effect of trimetazidine in patients with post-ischemic heart failure [18].

Effects of metabolic therapy on whole-body energy metabolism of patients with heart failure

A higher resting metabolic rate has been observed in patients with heart failure [19–21], and this factor probably contributes to progressive worsening of the disease. The rate of energy expenditure is related to increased serum FFA oxidation, and both energy expenditure and serum FFA oxidation are inversely correlated with left ventricular ejection fraction and positively correlated with growth hormone (epinephrine and norepinephrine) concentrations [22]. Norepinephrine increases whole-body oxygen consumption, circulating FFA concentrations, and FFA oxidation [23]. These changes have been attributed to stimulation of hormone-sensitive lipase in adipose tissue, and to stimulation of oxygen consumption independent of lipolysis by norepinephrine [24]. These data, together with close correlations between plasma norepinephrine concentrations, energy expenditure at rest and FFA oxidation, make increased sympathetic activity the most likely explanation for alterations in fuel homeostasis in patients with heart failure [24]. Therefore, intervention strategies aimed at optimizing global and cardiac metabolism could be useful for interrupting the vicious circle of reduced function at greater metabolic expenses in different cardiac conditions [25]. In a very recent study, it has been shown that 3 months' treatment with trimetazidine added to usual treatment consistently reduces whole-body resting energy expenditure along with improved functional class, quality of life and left ventricular function in patients with systolic heart failure, regardless of its etiology and diabetic

status [26] (Fig. 2). The observation that the beneficial effect of trimetazidine on left ventricular function is also paralleled by a reduction in the whole-body rate of energy expenditure when compared to patients on conventional treatment underlies the possibility that the effect of trimetazidine may be mediated through a reduction of metabolic demand at the level of the peripheral tissues and, in turn, in some sort of central (cardiac) relief. Therefore, a reduction of whole-body energy demand could be one of the mechanisms by which trimetazidine could improve symptoms and left ventricular function in patients with heart failure.

Systematic literature search on the beneficial effect of trimetazidine in heart failure

A systematic literature search was recently conducted by Gao and colleagues [27] to identify randomised controlled trials of trimetazidine for heart failure. The results of the search identified 17 trials with data for 955 patients. Trimetazidine therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic and non-ischemic heart failure. With trimetazidine therapy, the New York Heart Association classification was also improved, as was exercise duration. More importantly, trimetazidine had a significant protective effect for all-cause mortality (RR 0.29, 95% CI 0.17 to 0.49; $P < 0.00001$) and cardiovascular events and hospitalization (RR 0.42, 95% CI 0.30 to 0.58; $P < 0.00001$).

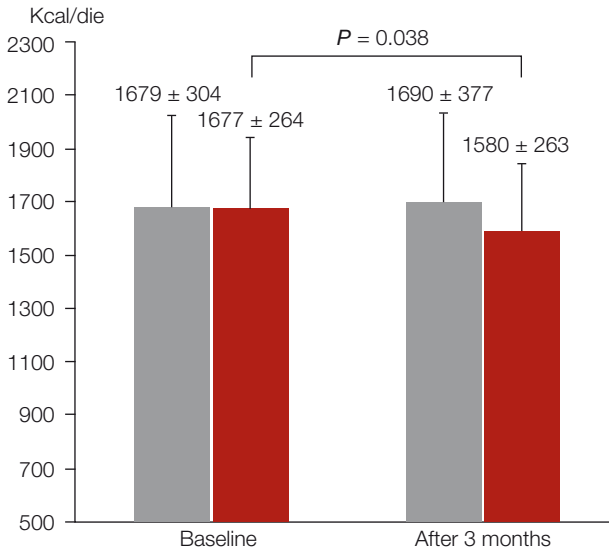

Fig. 2 *The rate of energy expenditure in patients with heart failure at baseline and 3 months after receiving either conventional therapy alone (grey histograms) or conventional therapy and trimetazidine (red histograms). Adding trimetazidine to conventional heart failure therapy reduced the rate of energy expenditure of the whole organism (P = 0.038). Adapted with permission from Fragasso et al [26]. HF = heart failure, TMZ = trimetazidine.*

Finally, a very recent meta-analysis has confirmed that additional use of trimetazidine in heart failure patients may decrease hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously ameliorate left ventricular remodeling [28].

Effects of metabolic modulation on left ventricular diastolic dysfunction

Both animal models of left ventricular pressure overload and clinical studies in humans with hypertension implicate abnormal myocardial metabolism in the development of left ventricular diastolic dysfunction. Myocardial fatty acid metabolism is also a key modulator of diastolic dysfunction [29–31]. It has recently been shown that in symptomatic hypertrophic cardiomyopathy, perhexiline, a modulator of substrate metabolism, ameliorates cardiac energetic impairment, corrects diastolic dysfunction, and increases exercise capacity [32]. Animal studies have shown that trimetazidine could also improve the function of pressure overload hypertrophied left [33] and right [34] hearts. These studies support the hypothesis that energy deficiency contributes to the pathophysiology and provides a rationale for further consideration of metabolic therapies in hypertrophic cardiomyopathy.

Another cardiac condition characterized by early diastolic involvement is the so-called diabetic cardiomyopathy. This is a condition characterized functionally by myocyte hypertrophy, prominent interstitial fibrosis and initially preserved systolic function in the presence of diastolic dysfunction. After a long latent phase, systolic dysfunction, left ventricular dilation and symptomatic heart failure usually ensue. Therefore, an optimal control of diabetes and frequently occurring copathologies, such as hypertension, is advocated. On these grounds, it has recently been hypothesized that the early administration of a metabolic modulator such as trimetazidine may prevent or ameliorate diabetic cardiomyopathy [35]. This hypothesis is substantiated by the previous observation that trimetazidine may increase both insulin-induced forearm glucose oxidation and forearm cyclic-guanosine monophosphate release, with a decrease in forearm endothelin-1 release [36]. These ancillary effects of

trimetazidine could be particularly effective in preventing or ameliorating the cardiovascular complications of diabetes. Certainly, further studies aimed at evaluating the role of cardiac metabolic modulation in patients with diabetes are necessary.

Conclusions

Metabolic therapy could play an important role in the therapeutic strategy of patients with heart failure. At present trimetazidine, a partial FFA oxidation inhibitor, appears to be the most promising agent for the metabolic approach to heart failure. Although highly suggestive, whether the observed benefits would translate into improved survival should be ascertained by multicenter trials. The time has come to test this potentially huge therapeutic advance in heart failure syndromes, which still have very high morbility and mortality rates. •

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