

Effects on global metabolism by regulation of substrate utilization in heart failure

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Abstract

In patients with chronic heart failure, exertional intolerance is a major clinical problem. Muscle factors that limit exercise capacity are unrelated to central hemodynamics. While cardiac cachexia represents the most extreme form of loss of muscle mass in chronic heart failure, a more subtle form of lean body mass changes clearly exists, as is evident by the loss of skeletal muscle observed in patients with non-cachectic congestive heart failure. Previous studies have shown that pharmacological manipulation of cardiac substrate utilization with agents that directly inhibit fatty acid oxidation could improve cardiac function and, accordingly, global metabolism efficiency. The most extensively investigated agent of this group of drugs is trimetazidine, a 3-ketoacyl-coenzyme A thiolase (3-KAT) inhibitor. Clinical studies have shown that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by 3-KAT inhibitors could be an effective adjunctive treatment in patients with heart failure in terms of left ventricular function and global metabolism improvement. In this article, the recent literature on the beneficial effects of this new potential use of 3-KAT inhibitors on left ventricular dysfunction and global metabolism is reviewed and discussed. ■ *Heart Metab.* 2014;64:23–27

Keywords: diabetes; global metabolism; heart failure; left ventricular function; trimetazidine

Wasting of subcutaneous fat and skeletal muscle is relatively common in heart failure (HF) and suggests an increased utilization of noncarbohydrate substrates for energy production.¹ In fact, fasting blood ketone bodies² as well as fat oxidation during exercise³ have been shown to be increased in patients with HF. Insulin resistance has been found to be associated with HF⁴ and the consequent impaired suppression of lipolysis could determine the development of ketosis, thereby, determining reduced metabolic efficiency. Heart and arm skeletal muscle glucose uptake is inversely related

to serum free fatty acid (FFA) levels,⁵ and increased FFA flux from adipose to non-adipose tissue amplifies metabolic derangements that are characteristic of the insulin resistance syndrome.⁶ New findings suggest that raised FFA levels not only impair glucose uptake in heart and skeletal muscle, but also cause alterations in the metabolism of vascular endothelium leading to premature cardiovascular disease.⁷

Conversely, by increasing utilization of glucose and lactate, which are efficient fuels for aerobic respiration, the oxygen consumption efficiency of the myocardium and skeletal muscle can be improved

Abbreviations

3-KAT inhibitor: 3-ketoacyl-coenzyme A thiolase inhibitor; **ATP:** adenosine triphosphate; **ET-1:** endothelin-1; **FFA:** free fatty acid; **HF:** heart failure; **PCr:** phosphocreatine

by 16% to 26%.⁸ Trimetazidine has been shown to directly inhibit fatty acid oxidation by blocking 3-ketoacyl-coenzyme A thiolase (3-KAT), the last enzyme involved in β -oxidation. Trimetazidine has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from FFA to glucose oxidation.⁹ Several studies have outlined the potential benefits of this agent on regional and global myocardial dysfunction. Therefore, 3-KAT inhibitors could also play a beneficial role in terms of glucose metabolism homeostasis, at both the cardiac and skeletal muscle level.

Modulation of myocardial metabolism by 3-KAT inhibitors in postischemic heart failure

By keeping in mind the concept that trimetazidine should be able to promote the utilization of glucose and nonfatty substrates by the mitochondria, attention has been focused on heart failure, where maintenance of metabolic efficiency is a crucial issue.

The effects of adding trimetazidine to the standard treatment for diabetic patients with ischemic dilated cardiomyopathy were assessed¹⁰ on symptoms, exercise tolerance, and left ventricular function over short-term and long-term periods. In both cases, trimetazidine induced a significant beneficial effect on left ventricular function and control of symptoms compared with placebo. These results paved the way for additional studies, which have invariably confirmed the positive effects of trimetazidine in patients with postischemic left ventricular dysfunction.^{11–13}

Modulation of myocardial metabolism by 3-KAT inhibitors in heart failure of different etiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to the preservation of intracellular levels of phosphocreatine (PCr) and adenosine triphosphate (ATP).¹⁴ Previous clinical studies using ³¹P magnetic resonance

spectroscopy (³¹P-MRS) to measure PCr/ATP ratios in the myocardium have shown that this ratio is reduced in the failing human myocardium.¹⁵ The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on an imbalance in myocardial oxygen supply and demand. A reduction in the total creatine pool, a phenomenon known to occur in HF, may also lead to a reduction in the PCr/ATP ratio. In patients with HF of different etiologies on full standard medical therapy, it has been observed that the trimetazidine-induced improvement in functional class and left ventricular function is associated with an improvement in the PCr/ATP ratio, which supports the hypothesis that trimetazidine preserves intracellular levels of myocardial high-energy phosphate.¹⁶ These results appear particularly interesting, especially in view of previous evidence indicating that the PCr/ATP ratio is a significant predictor of mortality.¹⁷

Based on the results of this pilot study, it has also been tested whether trimetazidine, added to the usual treatment, could be beneficial in a more consistent group of patients with systolic-dysfunction heart failure of different etiologies.¹⁸ Compared with patients on conventional therapy alone, those on trimetazidine showed improvement in functional class, exercise tolerance, quality of life, and left ventricular function (Figure 1). Plasma B-type natriuretic peptide (BNP)

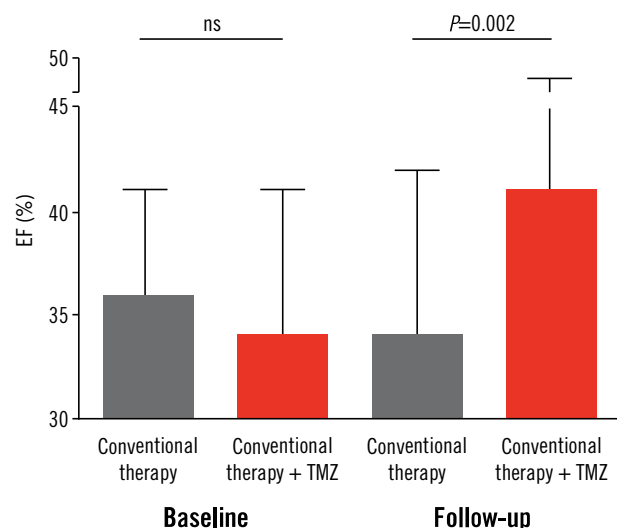


Fig. 1 Long-term effects of trimetazidine on ejection fraction in patients with heart failure of different etiologies. Histograms (mean \pm 1 SD) show the significant beneficial long-term effects of trimetazidine compared with conventional therapy alone.

Abbreviations: EF, ejection fraction; ns, not significant; SD, standard deviation; TMZ, trimetazidine.

Based on reference 18: Fragasso G et al. J Am Coll Cardiol. 2006;48:992–998.

levels were also significantly reduced in patients on trimetazidine compared with conventional therapy alone. Two recent meta-analyses and an international multicenter retrospective study have invariably confirmed these findings.^{19–21}

Modulation of glucose metabolism by 3-KAT inhibitors

Patients with HF are insulin resistant. Recent studies have identified a direct relationship between endothelial dysfunction and insulin resistance.²² When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles.²³ In this context, a therapeutic option could be to induce muscles directly to reduce FFA utilization in favor of glucose oxidation. The use of a partial fatty acid inhibitor could play a very specific role. In fact, 3-KAT inhibitors should be able to promote the utilization of glucose and nonfatty substrates by the mitochondria. Apart from improving left ventricular function in cardiac patients, it has been shown recently that trimetazidine could also improve overall glucose metabolism in the same patients, indicating an attractive ancillary pharmacological property of this class of drugs.

The well-known insulin resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction, where the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are grossly reduced. Since a major factor in the development and progression of HF is a reduced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including glycolysis and glucose oxidation. Therefore, the effects of trimetazidine on glucose metabolism could be dependent on both improved cardiac efficiency and improved peripheral glucose extraction and utilization. Finally, considering the known relation between endothelin-1 (ET-1) concentration and glucose metabolism abnormalities,²² the observed beneficial effects of trimetazidine on glucose metabolism could also partly be ascribed to the positive effect of the drug on reducing ET-1 levels.

On this ground, forearm glucose and lipid metabolism as well as forearm release of endothelial

vasodilator and vasoconstrictor factors have been evaluated during a prolonged inhibition of β -oxidation by trimetazidine in patients with postischemic left ventricular dysfunction. Trimetazidine increased both insulin-induced forearm glucose oxidation and forearm cyclic guanosine monophosphate release, while forearm ET-1 release was decreased.²⁴ These effects of trimetazidine at the skeletal muscle level add a new therapeutic window in the treatment of patients with heart failure and insulin resistance.

Effects of 3-KAT inhibitors on endothelial function

Trimetazidine can reduce endothelin release in cardiac patients.^{13,24,25} Growth factors, vasoactive substances, and mechanical stresses are involved in the ET-1 increase in heart failure patients. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac ET-1 expression in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction.²⁶ A causal role for ET-1 has been indicated in the vascular adaptation to skeletal muscle deconditioning, which is similar to other conditions.²⁷

Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium could influence not only myocardial membranes, but also endothelial membranes.²⁸ By decreasing endothelial damage, trimetazidine could inhibit ET-1 release and, in turn, decrease myocardial damage. A second hypothesis is that by just decreasing the effects of chronic myocardial ischemia, trimetazidine could inhibit ET-1 release. Additionally, considering the close relationship between the endothelium and insulin sensitivity, the observed effects of trimetazidine on endothelial function could also explain the beneficial action of trimetazidine on global glucose metabolism.²⁴

Effects of trimetazidine on whole-body energy metabolism in patients with heart failure

A higher resting metabolic rate has been observed in patients with HF,^{29–31} which probably contributes to progressive worsening of the disease. The rate of energy expenditure is related to increased serum FFA oxidation. Both energy expenditure and serum FFA oxidation are inversely correlated with left ventricular ejection fraction and positively correlated with

concentrations of the growth hormones epinephrine and norepinephrine.³² Norepinephrine increases whole-body oxygen consumption, circulating FFA concentrations, and FFA oxidation.³³ These changes have been attributed to stimulation of hormone-sensitive lipase in adipose tissue and stimulation of oxygen consumption independent of lipolysis by norepinephrine.³⁴ This 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 HF. 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.³⁵

In a recent study, it has been shown that 3 months of treatment with trimetazidine added to the 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 HF, regardless of the etiology or the patient's diabetic status (Figure 2).³⁶ The observa-

underlies the possibility that the effect of trimetazidine may be mediated through a reduction in metabolic demand at the level of the peripheral tissues and, in turn, in some sort of central (cardiac) relief. Therefore, reduction in whole-body energy demand could be one of the principal mechanisms by which trimetazidine could improve symptoms, exercise tolerance, and left ventricular function in patients with heart failure.

Conclusions

Trimetazidine, a partial inhibitor of fatty acid oxidation, could have an important role in the therapeutic strategy of patients with heart failure and exertional intolerance. More specifically, shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by using trimetazidine may be an effective adjunctive treatment in patients with heart failure, especially in terms of left ventricular and skeletal muscle metabolism and function improvement. These effects seem operative in heart failure syndromes regardless of the etiopathogenetic cause and not confined to those of ischemic origin. ■

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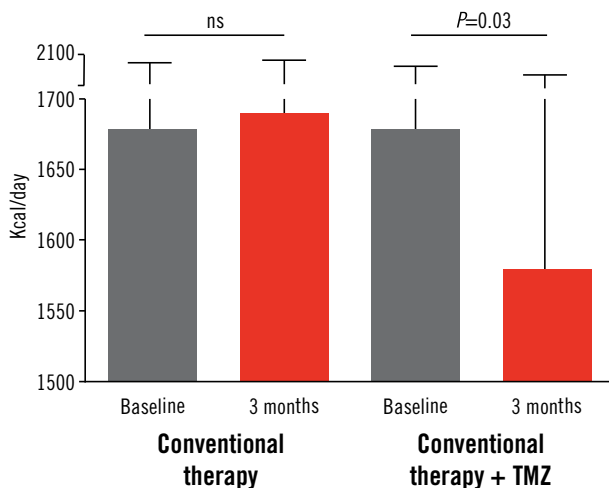


Fig. 2 Rate of energy expenditure in heart failure patients. Rate of energy expenditure (kcal/d) measured by indirect calorimetry at baseline and a 3-month follow-up in patients with heart failure receiving conventional therapy alone (left histograms) or conventional therapy plus trimetazidine (right histograms).

Abbreviations: ns, not significant; TMZ, trimetazidine.

Modified after reference 36: Fragasso G et al. *Heart.* 2011;97:1495-1500. Copyright © 2011, BMJ Publishing Group Ltd and the British Cardiovascular Society.

tion 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 with patients on conventional treatment,

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