

Modulation of metabolic changes in patients with heart failure by selective inhibition of 3-ketoacyl coenzyme A thiolase

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Abstract

A direct approach to manipulating cardiac energy metabolism consists of modifying substrate utilization by the heart. Pharmacological agents that directly inhibit fatty acid oxidation include inhibitors of 3-ketoacyl coenzyme A thiolase, the last enzyme involved in β -oxidation. The most extensively investigated agent of this group of drugs is trimetazidine. Clinical studies have shown that trimetazidine can substantially increase the ischemic threshold in patients with effort angina. However, the results of current research also support the concept that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by the use of trimetazidine could be an effective adjunctive treatment in patients with heart failure, in terms of improvement in left ventricular and endothelial function and glucose metabolism. The recent literature on the protective effects of this new class of drugs on left ventricular dysfunction is reviewed and discussed.

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Introduction

Wasting of subcutaneous fat and skeletal muscle are relatively common in heart failure and suggest an increased utilization of non carbohydrate substrates for energy production [1]. In fact, fasting blood ketone bodies [2], and fat oxidation during exercise [3], have been shown to be increased in patients with heart failure. Insulin resistance has been found to be associated with heart failure [4] and the consequent impaired suppression of lipolysis could determine the development of ketosis. Experimental studies have shown that sodium dichloroacetate stimulates pyruvate dehydrogenase activity by inhibiting pyruvate dehydrogenase kinase [5]. Stimulation of pyruvate dehydrogenase activity leads to enhanced glycolysis

of glucose and utilization of lactate by the myocardium for aerobic respiration. Myocardial consumption of free fatty acids is simultaneously inhibited, with the overall effect of a change of substrate utilization from predominantly non esterified free fatty acids to glucose and lactate [6], finally resulting in improved left ventricular mechanical efficiency [7].

A number of different approaches have been used to manipulate energy metabolism in the heart. These involve both indirect measures and the use of agents that act directly on the heart to 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. One approach consists of directly modifying

substrate utilization by the heart. Trimetazidine 1 (2,3,4, trimethoxybenzyl-piperazine dihydrochloride) has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from free fatty acid to glucose oxidation [8]. Despite experimental evidence indicating that this effect is predominantly caused by a selective block of long-chain 3-ketoacyl coenzyme A thiolase [9], the last enzyme involved in β -oxidation, this issue remains controversial [10,11]. Recent studies have outlined the potential benefits of this agent on regional and global myocardial dysfunction. These beneficial effects can be explained by the fact that, by increasing the utilization of glucose and lactate, which are more efficient fuels for aerobic respiration, the efficiency of oxygen consumption of the myocardium can be improved by 16–26% [12].

In this paper we will review and summarize the reported evidence on the protective effects of trimetazidine on left ventricular dysfunction and its potential clinical application in patients with heart failure.

Effects of metabolic modulation with trimetazidine in left ventricular dysfunction

On the basis of the hypothesis that trimetazidine could act as a metabolic modulator in the protection of ischemic myocardium, Brottier and colleagues [13] assessed the value of long-term treatment with trimetazidine in patients with severe ischemic cardiomyopathy who were already receiving conventional therapy. Twenty patients were allocated randomly to groups receive to either placebo or trimetazidine. At 6-month follow-up, all the patients receiving trimetazidine reported a clinically considerable improvement in symptoms and showed a greater ejection fraction than those receiving placebo. The investigators concluded their study, recommending the use of trimetazidine as a complementary therapeutic tool in patients with severe ischemic cardiomyopathy.

On the basis of these findings, the effects of trimetazidine on dobutamine-induced left ventricular dysfunction in patients with angiographically proven coronary artery disease were assessed [14]. Patients were blindly and randomly assigned to a 15-day period of treatment with either placebo or trimetazidine; they were then crossed over to the other regimen for another 15 days. At the end of each period of treatment, a stress echo test with dobutamine was performed. Both in the resting condition and at peak infusion of dobutamine, the wall motion score index was significantly lower with trimetazidine therapy than with placebo. Furthermore, trimetazidine induced an increase in both the dose of dobutamine administered and the duration of dobutamine

infusion 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 [15].

At that point it became a priority to gain an understanding both of the mechanisms beyond the observed improvement in resting left ventricular function induced by trimetazidine and of whether this effect could also be operative in patients for whom left ventricular dysfunction represented the main clinical problem.

Modulation of myocardial metabolism by trimetazidine in postischemic heart failure

Keeping in mind the concept that trimetazidine 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 maintenance of metabolic efficiency is a crucial issue.

In diabetic patients with ischemic dilated cardiomyopathy, the effects of the addition of trimetazidine to standard treatment were assessed, as judged by symptoms, exercise tolerance, and left ventricular function [16]. Thirteen such patients who were receiving conventional therapy were randomly allocated in a double-blind fashion, first to receive either placebo or trimetazidine, each arm lasting 15 days, and then again to receive placebo or trimetazidine for two additional periods of 6 months. In both the short and the long term, trimetazidine showed a significant beneficial effect on left ventricular function and control of symptoms, compared with placebo (*Figure 1*). The observed short-term benefit of trimetazidine was maintained in the long term and contrasted with the natural history of the disease, as shown by the mild but consistent decrease in ejection fraction while patients were receiving placebo. These results paved the way to additional studies, which have invariably confirmed the positive effects of trimetazidine in patients with postischemic left ventricular dysfunction [17–19].

Modulation of myocardial metabolism by trimetazidine in heart failure of different etiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to preservation of intracellular concentrations of phosphocreatine and ATP [20]. Previous clinical studies using

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Trimetazidine and left ventricular dysfunction

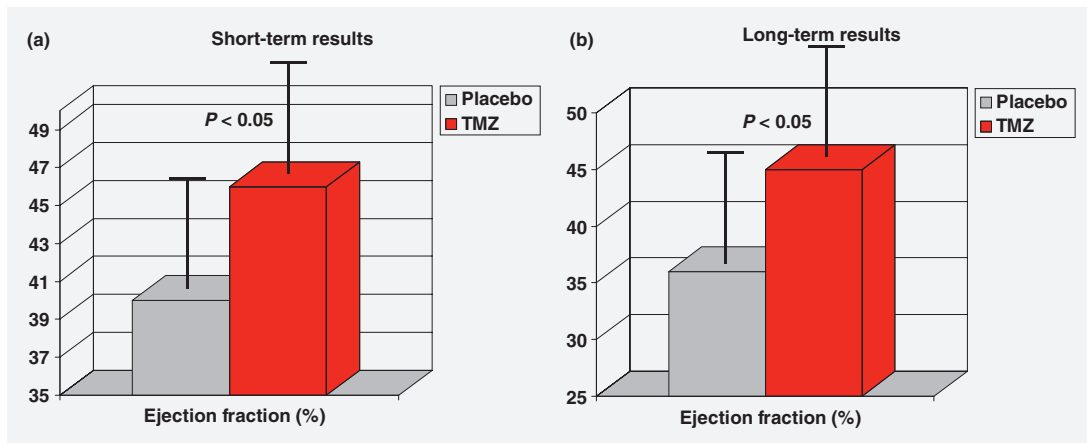


Figure 1. (a) Short-term and (b) long-term effects of trimetazidine (■) and placebo (□) on ejection fraction in diabetic patients with postischemic cardiomyopathy. The histograms demonstrate the significant beneficial effects (mean \pm 1 SD) of trimetazidine compared with placebo. (Modified from Fragasso et al. [16], with permission.).

phosphorus-31 magnetic resonance spectroscopy to measure phosphocreatine:ATP (PCr:ATP) ratios in human myocardium have shown that this ratio is reduced in failing human myocardium [21]. The PCr:ATP ratio is a measure of myocardial energetics and its reduction may be related to an imbalance between myocardial oxygen supply and demand [22], and a reduction in the total creatine pool, a phenomenon known to occur in heart failure [23]. In a recent study performed in patients with heart failure of different etiologies who were receiving full standard medical treatment, we observed that the trimetazidine-induced improvements in functional class and left ventricular function were associated with an improvement in the PCr:ATP ratio, supporting the hypothesis that trimetazidine probably preserves the intracellular concentrations of myocardial high-energy phosphate [24]. These results appear to be

of particular interest, especially in view of previous evidence indicating the PCr:ATP ratio is a significant predictor of mortality [25].

On the basis of the results of that pilot study, we tested whether trimetazidine, added to usual treatment, could also be beneficial in a more consistent group of patients with systolic-dysfunction heart failure of different etiologies [26]. Compared with patients receiving conventional treatment alone, those receiving trimetazidine exhibited improvement in functional class, exercise tolerance, quality of life, and left ventricular function (ejection fraction; Figure 2), and used reduced amounts of diuretic drugs and of digoxin. The plasma concentration of B-type natriuretic peptide was also significantly reduced in the patients receiving trimetazidine, compared with those given conventional therapy alone.

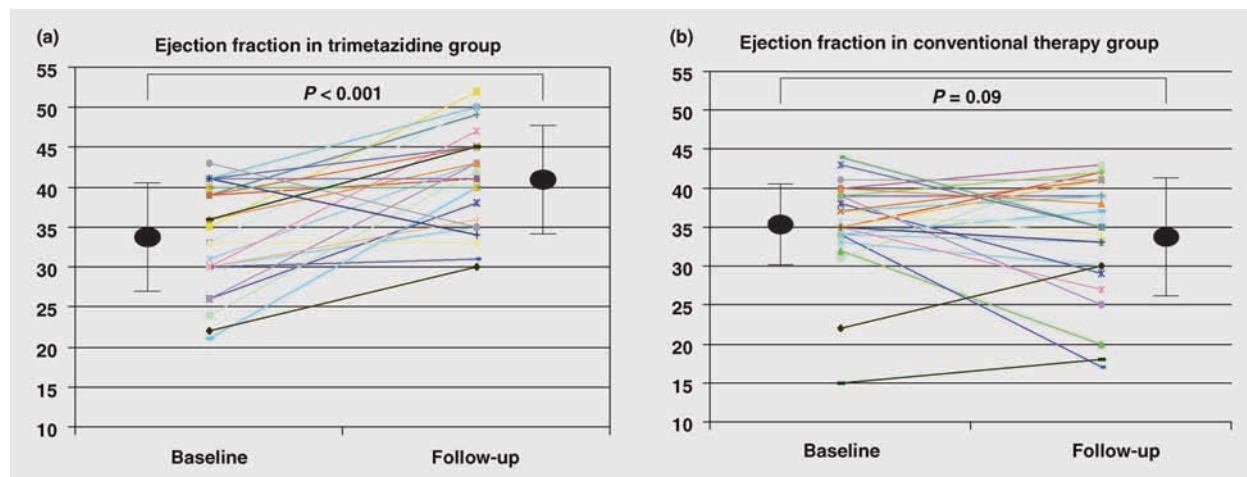


Figure 2. Long-term effects of (a) trimetazidine and (b) placebo on ejection fraction in patients with heart failure of different etiologies. The figure shows a clear beneficial effect on ejection fraction (individual values and mean \pm 1 SD) of trimetazidine compared with placebo. (Modified from Fragasso et al [26], with permission.).

These data confirm that selective inhibition of 3-ketoacyl coenzyme A thiolase by trimetazidine represents a new therapeutic window in the treatment of patients with systolic-dysfunction heart failure of different etiologies, not only that secondary to ischemic heart disease.

Conclusions

Metabolic modulators such as trimetazidine could have an important role in the therapeutic strategy for patients with heart failure. Shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by the use of trimetazidine could also be an effective adjunctive treatment in patients with heart failure, in terms of improving their left ventricular metabolism and function. These effects seem to operate in heart failure syndromes regardless of their etiopathogenetic cause, and are not confined to those of ischemic origin. Although it seems highly likely that these benefits would translate into improved survival, a multicenter trial is required to ascertain whether this is indeed the case. The time has come to test this huge potential therapeutic advancement in heart failure syndromes, which still suffer very high rates of morbidity and mortality. ■

REFERENCES

- Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. *Progr Cardiovasc Dis.* 1972;15:289–329.
- Lommi J, Kupari M, Koskinen P, et al. Blood ketone bodies in congestive heart failure. *J Am Coll Cardiol.* 1996;28:665–672.
- Riley M, Bell N, Elborn JS, et al. Metabolic response to graded exercise in chronic heart failure. *Eur Heart J.* 1993;14:1484–1488.
- Paolisso G, De Riu S, Marrazzo G, et al. Insulin resistance and hyperinsulinemia in patients with chronic heart failure. *Metabolism.* 1991;40:972–977.
- Mc Veigh JJ, Lopaschuck GD. Dichloroacetate stimulation of glucose oxidation improves recovery of ischemic rat hearts. *Am J Physiol Heart Circ Physiol.* 1990;259:H1070–H1085.
- Nicholl TA, Lopaschuck GD, McNeill GH. Effects of free fatty acids and dichloroacetate on isolated working diabetic rat hearts. *Am J Physiol Heart Circ Physiol.* 1991;261:H1053–H1059.
- Bersin RM, Wolfe C, Kwasman M, et al. Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. *J Am Coll Cardiol.* 1994;23:1617–1624.
- Fantini E, Demaison L, Sentex E, et al. Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. *J Mol Cell Cardiol.* 1994;26:949–958.
- Kantor PF, Lucien A, Kozak R, et al. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res.* 2000;86:580–588.
- Lopaschuck GD, Barr R, Thomas PD, et al. Beneficial effects of trimetazidine in ex vivo working ischemic hearts are due to a stimulation of glucose oxidation secondary to inhibition of long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res.* 2003;93:e26–e32.
- MacInness A, Fairman DA, Binding P, et al. The antianginal trimetazidine does not exert its functional benefit via inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res.* 2003;93:e33–e37.
- Lopaschuck GD, Stanley WC. Glucose metabolism in the ischemic heart. *Circulation.* 1997;95:313–315.
- Brottier L, Barat JL, Combe C, et al. Therapeutic value of a cardioprotective agent in patients with severe ischemic cardiomyopathy. *Eur Heart J.* 1990;11:207–212.
- Lu C, Dabrowski P, Fragasso G, et al. Effects of trimetazidine on ischemic left ventricular dysfunction in patients with coronary artery disease. *Am J Cardiol.* 1998;82:898–901.
- Belardinelli R, Purcaro A. Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischaemic cardiomyopathy. *Eur Heart J.* 2001;22:2164–2170.
- Fragasso G, Piatti PM, Monti L, et al. Short and long term beneficial effects of partial free fatty acid inhibition in diabetic patients with ischemic dilated cardiomyopathy. *Am Heart J.* 2003;146:E1–E8.
- Rosano GMC, Vitale C, Sposato B, et al. Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: a double-blind placebo-controlled study. *Cardiovasc Diabetol.* 2003;2:16/1–16/9.
- Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J.* 2004;25:1814–1821.
- Di Napoli P, Taccardi AA, Barsotti A. Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. *Heart.* 2005;91:161–165.
- Lavanchy N, Martin J, Rossi A. Anti-ischemia effects of trimetazidine: ³¹P-NMR spectroscopy in the isolated rat heart. *Arch Int Pharmacodyn Ther.* 1987;286:97–110.
- Conway MA, Allis J, Ouwerkerk R, et al. Detection of low PCr to ATP ratio in failing hypertrophied myocardium by ³¹P magnetic resonance spectroscopy. *Lancet.* 1991;338:973–976.
- Yabe T, Mitsunami K, Inubushi T, et al. Quantitative measurements of cardiac phosphorus metabolites in coronary artery disease by ³¹P magnetic resonance spectroscopy. *Circulation.* 1995;92:15–23.
- Nascimben L, Ingwall JS, Pauletto P, et al. The creatine kinase system in failing and nonfailing human myocardium. *Circulation.* 1996;94:1894–1901.
- Fragasso G, De Cobelli F, Perseghin G, et al. Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. *Eur Heart J.* 2006;27:942–948.
- Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation.* 1997;96:2190–2196.
- Fragasso G, Pallosi A, Puccetti P, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with systolic dysfunction heart failure. *J Am Coll Cardiol.* 2006. In press.