

Metabolic modulation in dilated cardiomyopathy

Helena Tuunanen and Juhani Knuuti

Turku PET Centre, University of Turku, Finland, Department of Medicine, Turku University Hospital, Turku, Finland

Correspondence to Correspondence: Helena Tuunanen, Department of Medicine, Turku University Hospital, PO Box 51, 20521 Turku, Finland.

Tel: 358 2 313 0000; e-mail: heltuu@utu.fi

Management of patients with dilated cardiomyopathy (DCM) and chronic heart failure (HF) remains challenging. There is a need for novel medical therapies independent of the neurohormonal axis that improve cardiac performance. Experimental and preliminary clinical studies have demonstrated that metabolic modulators enhancing myocardial glucose metabolism directly or indirectly by limiting free fatty acid (FFA) metabolism, may improve left ventricular (LV) function in HF. This paper reviews the literature on the effects of metabolic modulators on human HF (both ischemic and idiopathic). The effects of acute metabolic modulation (mainly by manipulating circulating substrate levels) and long-term metabolic modulation (trimetazidine, perhexiline, etomoxir) are discussed.

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Introduction

Metabolic modulation is linked to glucose being a more energy-efficient fuel than free fatty acids (FFAs). Cardiac FFA and glucose metabolism are tightly coupled, which means that inhibition of one results in an increment in another. Several different agents can achieve a myocardial metabolic switch from oxidation of FFAs towards that of glucose. In this paper we focus on metabolic shift achieved by 1) manipulating circulating substrate levels (nicotinic acid and its derivatives, glucose-insulin-potassium infusion), 2) FFA betaoxidation inhibitors (trimetazidine, ranolazine), 3) carnitine palmitoyltransferase (CPT)-1 blockers (perhexiline, etomoxir), and 4) dichloroacetate (direct carbohydrate oxidation activator).

Acute metabolic modulation

In small groups of patients with heart failure (HF), intravenous infusion of dichloroacetate [1] or glucose-insulin-potassium [2] and intracoronary infusion of

pyruvate [3,4] has been associated with improved cardiac function. Compared with double-blind placebo, three-day treatment with trimetazidine improved ejection fraction (EF) and enhanced myocardial perfusion in patients with prior myocardial infarction and ischemic HF [5]. However, the positive effects of trimetazidine were lost in patients with severe left ventricular (LV) dysfunction, possibly due to large, metabolically inactive scar tissue in these patients. In contrast, Wiggers et al. [6] demonstrated that acute substrate availability modulation does not influence cardiac function in hibernating myocardium either at rest or after exercise. The study included substrate modulation either with insulin-glucose (high insulin, low FFA) and somatostatin-heparin (high FFA, low insulin). Furthermore, a previous study demonstrated that acute FFA deprivation in patients with idiopathic dilated cardiomyopathy (DCM), in contrast to healthy controls, uncouples cardiac contractile function from oxidative metabolism so that myocardial efficiency deteriorates further [7]. Thus, these preliminary studies suggest that acute manipulation of substrate levels may not be a promising form of therapy in HF.

Long-term metabolic modulation

A first study in the early 1990s showed that compared with double-blind placebo, six-month treatment with trimetazidine improves EF in patients with ischemic HF medicated with digoxin and diuretics only [8]. Thereafter, trimetazidine has been shown to improve not only EF in both ischemic [9–15] and non-ischemic HF [11,16], but also regional myocardial wall motion both at rest and during dobutamine-induced stress [9,13] as well as to enhance LV diastolic function [15] and to reverse LV remodeling [10,11,15,17] in patients with ischemic HF. The clinical effects of trimetazidine include improvement in exercise tolerance, New York Heart Association (NYHA) class and quality of life [10,12,15,17,18] in patients with ischemic HF. Interestingly, the largest study [18], involving 200 patients with multivessel coronary artery disease and mildly impaired LV function (EF <50%), demonstrated surprisingly pronounced improvement in survival rates after two years of treatment with trimetazidine (92% with trimetazidine versus 62% with placebo, $p < 0.0001$).

The metabolic effects of trimetazidine include improvement in whole-body insulin sensitivity in patients with ischemic HF and type II diabetes treated with diet only [17]. Furthermore, Monti et al. [19] showed that improvement in whole-body insulin sensitivity by trimetazidine is accompanied by a metabolic shift from FFA to glucose oxidation in skeletal muscle during euglycemic hyperinsulinemia in diabetic HF patients. Trimetazidine also improved metabolism at the myocardial level, as evidenced by increased myocardial phosphocreatine (PCr)-adenosine-5'-triphosphate (ATP) ratio in non-diabetic patients with ischemic HF [12]. Additionally, there is some evidence that trimetazidine limits inflammatory response [10] and improves endothelial function [20] in HF patients.

Our recent positron emission tomography (PET) study including non-diabetic patients with idiopathic DCM demonstrated improvement in EF after three months of treatment with trimetazidine as compared with placebo (*Fig. 1*) [16]. Trimetazidine had no effect on myocardial FFA uptake and only minor inhibitory effects on myocardial FFA oxidation (*Fig. 2*), suggesting another major mechanism contributing to the benefit in the study. Rather, our data showed increased whole-body insulin sensitivity in idiopathic DCM, as also found by Fragasso et al. in diabetic ischemic HF patients [17], thus hypothetically countering the myocardial damage of insulin resistance. Furthermore, the positive effects of trimetazidine on LV function were especially evident in patients with a high degree of beta-blockade, strongly suggesting an additive effect of these two modalities of therapy.

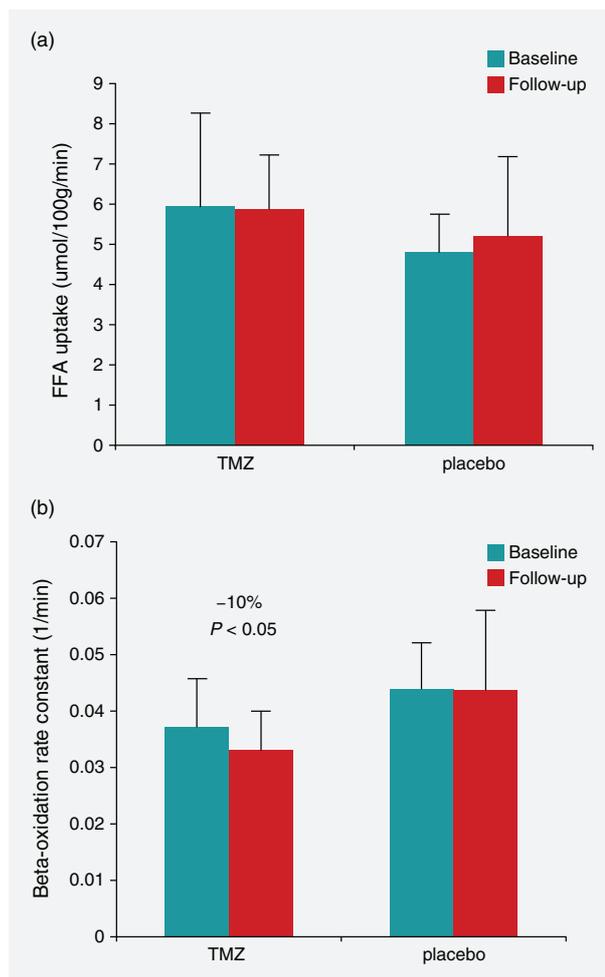


Figure 1. Myocardial A) free fatty acid (FFA) uptake and B) beta-oxidation rate constant at baseline (blue bars) and after three months of treatment with trimetazidine (TMZ) or placebo (red bars) in patients with idiopathic dilated cardiomyopathy and heart failure. Reprinted with permission from Tuunanen et al. [16].

The other agents reported in long-term metabolic interventions are the carnitine palmitoyltransferase (CPT)-1 blockers etomoxir and perhexiline. A small open-label study without a control group demonstrated that three months of treatment with etomoxir might improve EF both at rest and after maximal exercise in patients with chronic HF [21]. However, due to the liver toxicity of etomoxir revealed in the Etomoxir for the Recovery of Glucose Oxidation (ERGO) study [22], it was judged not to be a candidate for further development for treatment of patients with HF. A double-blind placebo-controlled study demonstrated that eight weeks of administration of perhexiline improves EF, resting and peak dobutamine stress regional myocardial function, peak exercise oxygen consumption, and quality of life, as well as normalizes skeletal muscle phosphocreatine recovery after exercise in both ischemic and non-ischemic HF patients

New therapeutic approaches

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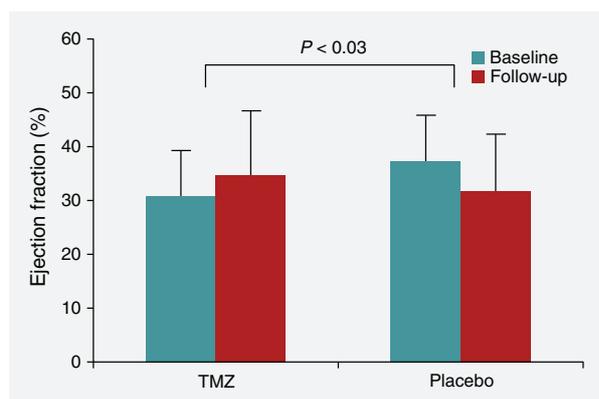


Figure 2. Ejection fraction at baseline (blue bars) and after three months treatment (red bars) with trimetazidine (TMZ) or placebo in patients with idiopathic dilated cardiomyopathy and heart failure. Reprinted with permission from Tuunanen et al. [16].

[23]. Furthermore, a retrospective multi-center database analysis in the United Kingdom revealed that perhexiline therapy is well tolerated and provides symptomatic relief in approximately 59% of patients with chronic HF and/ or refractory angina [24]. In contrast, a recent study [25] including 36 patients with post-infarction HF showed that one-year administration of perhexiline has no impact on exercise capacity and does not improve the deformation of abnormal myocardial segments in these patients.

Summary

The concept that metabolic agents may optimize myocardial energy metabolism and allow more efficient production of energy from glucose than from FFAs is appealing. However, studies on the effects of metabolic modulation on patients with HF have yielded conflicting results. At present trimetazidine, a partial FFA beta-oxidation inhibitor, appears to be the most promising agent for the metabolic approach. Larger clinical randomized multi-center studies are warranted to confirm the effects of these agents on patients with HF. ■

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