

Beneficial effects of trimetazidine (Vastarel®MR) in patients with chronic heart failure

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Abstract

The possibility of modifying cardiac metabolism by switching the fuel used by the myocardium could become increasingly important, especially in clinical conditions characterized by reduced energy availability, such as heart failure. Trimetazidine (Vastarel®MR), an inhibitor of free fatty acid (FFA) oxidation, holds the characteristics to play a fundamental role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from FFA metabolism and toward glucose metabolism has been shown to be an effective adjunctive treatment in terms of myocardial metabolism and left ventricular function improvement. These effects seem operative in heart failure syndromes regardless of their etiopathogenetic cause and are not confined to those of ischemic origin. In this paper, the recent literature on the beneficial therapeutic effects of trimetazidine on left ventricular dysfunction and heart failure is reviewed and discussed.

Keywords: systolic-dysfunction heart failure; left ventricular function; metabolic therapy; energy expenditure

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Introduction

Trimetazidine (TMZ) (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) (Vastarel®MR) has been reported to exert anti-ischemic properties without affecting myocardial oxygen consumption and blood supply [1]. The beneficial effect of this agent has been attributed to preservation of phosphocreatine and ATP intracellular levels [2] and reduction of cell acidosis [3–4], calcium overload [4] and free-radical-induced injury caused by ischemia [5]. More importantly, TMZ MR affects myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from free fatty acids (FFA) to glucose oxidation [6–7]. This effect appears to be predominantly caused by a selective block of long chain 3-ketoacyl CoA thiolase activity, the last enzyme involved in β -oxidation [8].

Effects of TMZ in patients with chronic heart failure

In chronic heart failure therapeutic strategies have traditionally focused on the modification of hemodynamic alterations that occur in the failing heart. However, in addition to hemodynamic

alterations, heart failure causes deep changes both in systemic and in cardiac metabolic milieu. In this context, recent studies performed in small groups of patients with post ischemic left ventricular dysfunction, have shown that TMZ may be beneficial in terms of left ventricular function preservation and control of symptoms [9–15]. On this basis, it has been shown that this pharmacological approach could also be useful in the treatment of patients with heart failure of various etiologies [16–19].

The beneficial effect of TMZ on left ventricular function has been attributed to preservation of intracellular phosphocreatine (PCr) and adenosinotriphosphate (ATP) [2]. Previous clinical studies using phosphorus-31 magnetic resonance spectroscopy to measure PCr/ATP ratios in human myocardium have shown that this ratio is reduced in failing human myocardium [20]. The PCr/ATP ratio is a measure of myocardial energetics, and its reduction may depend on imbalance of myocardial oxygen supply and demand [21] and reduction of the total creatine pool, a phenomenon known to occur in heart failure [22]. In a recent study performed in patients with heart failure of different etiologies who were receiving full standard medical therapy, TMZ-induced improvement of functional class and left ventricular function was associated with a 33% improvement of the PCr/ATP ratio, supporting the hypothesis that TMZ probably preserves myocardial high-energy phosphate intracellular levels [23]. These results appear particularly interesting in view of previous evidence indicating that the PCr/ATP ratio is a significant predictor of mortality [24].

Effects of TMZ on whole body energy metabolism of patients with heart failure

A higher resting metabolic rate has been observed in patients with heart failure [25–27], and this factor probably contributes to progressive worsening of the disease. 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 concentrations, epinephrine and norepinephrine [28]. Norepinephrine increases whole body oxygen consumption, circulating FFA concentrations, and FFA oxidation [29]. 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 [30]. 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 [30]. 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 [31]. In a very recent study, it has been shown that 3 months of treatment with TMZ 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 [32] (Fig. 1). The observation that the beneficial effect of TMZ on left ventricular function is also paralleled by a reduction of whole body rate of energy expenditure when compared to patients on conventional treatment underlies the possibility that the effect of TMZ 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, reduction of whole body energy demand could be one of the principal mechanisms by which TMZ could improve symptoms and left ventricular function in patients with heart failure.

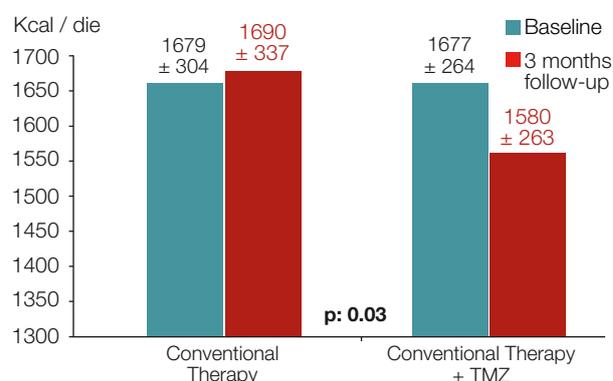


Fig. 1 Rate of energy expenditure (Kcal/die) measured by indirect calorimetry at baseline and 3 months follow-up in patients with heart failure receiving conventional therapy alone (left histograms) or conventional therapy plus trimetazidine (right histograms) (adapted with permission from reference [32]).

Additional potential beneficial pharmacological effects of TMZ in heart failure

It has been observed that TMZ could reduce endothelin release in cardiac patients [12, 33–34]. Growth factors, vasoactive substances and mechanical stress are involved in the endothelin-1 (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 [35].

TMZ-induced reduction of intracellular acidosis in ischemic myocardium could not only influence myocardial but also endothelial membranes [5]. By decreasing endothelial damage, TMZ could inhibit ET-1 release that, in turn, will finally decrease myocardial damage. A second hypothesis is that, by just decreasing the effects of chronic myocardial ischemia, TMZ could inhibit ET-1 release. Therefore, the observed decrease in ET-1 release with TMZ, could likely be linked to TMZ-induced reduction of myocardial ischemia. Finally, keeping in mind the close relation between endothelium and insulin sensitivity, the observed effects of TMZ on endothelial function could also explain the beneficial action of TMZ on glucose metabolism. In fact, apart from improving left ventricular function in cardiac patients, it has been recently shown that TMZ could also improve overall glucose metabolism in the same patients, indicating an attractive ancillary pharmacological property of this class of drugs [12, 33]. In fact, the 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. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscles to metabolize glucose are grossly reduced. Indeed, since a major factor in the development and progression of heart failure is already a reduced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, TMZ stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of TMZ on glucose metabolism could therefore be dependent by a) improved cardiac efficiency; b) improved peripheral glucose extraction and utiliza-

tion. Both mechanisms could definitely be beneficial in heart failure patients.

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

A systematic search of the literature was recently conducted by Gao et al. to identify randomized controlled trials of TMZ for heart failure [36]. They considered reports of trials comparing TMZ with placebo control for chronic heart failure in adults, with outcomes including all-cause mortality, hospitalization, cardiovascular events, changes in cardiac function parameters and exercise capacity. The results of the search identified 17 trials with data for 955 patients. TMZ therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic (7.37%; 95% CI 6.05 to 8.70; $p < 0.01$) and non-ischemic heart failure (8.72%; 95% CI 5.51 to 11.92; $p < 0.01$). With TMZ therapy, New York Heart Association classification was also improved ($p < 0.01$), as was exercise duration ($p < 0.01$). More importantly, TMZ 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; $p < 0.00001$). These data confirm that TMZ might be an effective strategy for treating heart failure and that a large multicenter randomized controlled trial should be performed, in order to clarify its therapeutic role in this setting.

Conclusion

TMZ could have an important role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism appears as an effective adjunctive treatment in patients with heart failure, in terms of left ventricular metabolism and function improvement. These effects are operative in heart failure syndromes regardless of their etiopathogenetic cause and are not confined to those of ischemic origin.

However, despite a very recent meta-analysis has evidenced that these benefits also translate into improved survival, a randomized placebo controlled multicenter trial is definitely warranted in order to objectively investigate the role of TMZ in the therapeutic armamentarium of heart failure. •

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