

The improvement of trimetazidine on exercise performance in ischemic heart disease

Yundai Chen, Department of Cardiology, Chinese PLA General Hospital, Beijing 100853, China

Correspondence: Yundai Chen, Department of Cardiology, Chinese PLA General Hospital, Beijing 100853, China
e-mail: cyundai@medmail.com.cn

Abstract

Ischemic heart disease (IHD) patients with a decreased exercise capacity have increased angina attack rate and poor quality of life (QOL). Conventional hemodynamic drugs show limited improvement in exercise performance. Therefore we need new drugs that may further improve exercise capacity. Trimetazidine (TMZ) exerts its anti-ischemic effect by reducing fatty acid oxidation and stimulating glucose oxidation, which induces more ATP production. Recent studies have demonstrated TMZ improve ejection fraction of the IHD patients, all these lead to a better exercise capacity and QOL.

Keywords: trimetazidine (TMZ); ischemic heart disease (IHD); exercise capacity; exercise performance; quality of life (QOL); left ventricular ejection fraction (LVEF).

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Introduction

Ischemic heart disease (IHD) is the first contributor of death and disability in many countries [1]. Although IHD mortality rates have declined over the past four decades in some developed countries, IHD remains responsible for about one-third of all deaths in individuals over age 35, and most of the survivors suffer from severe symptoms, limited exercise capacity, poor quality of life (QOL) [2]. As the data showed, the annual rate of hospital admission is about 15% to 20% in IHD patients with heart failure treated with conventional hemodynamic drugs [3]. Hence, there remains a need to identify new drugs that may further improve outcome especially symptoms, exercise capacity, and left ventricular (LV) function, which are closely linked to QOL and the main reasons of hospital admission.

TMZ has been shown to be an effective drug for the treatment of stable angina both alone or in addition to hemodynamic drugs. Recent studies have demonstrated that TMZ not only relief angina symptoms, but also improve ejection fraction of the IHD patients with left ventricular dysfunction (LVD), all these lead to a better exercise capacity and QOL [4-6].

TMZ is a metabolic modulator that inhibits a key enzyme in fatty acid oxidation—the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase—and shifts cellular energy substrate reference from fatty acids to glucose oxidation. A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the number of moles of ATP produced per mole of oxygen consumed is approximately 12% higher for glucose than for fatty acids [7]. Therefore,

unlike the conventional anti-anginal agents, which act by producing hemodynamic changes to restore balance between myocardial oxygen supply and demand, TMZ increases cellular tolerance to ischemia by inhibiting fatty acid metabolism and, secondarily, stimulating glucose metabolism [8,9].

The aim of the article is to review the TMZ efficacy on exercise capacity, LV function, and QOL in IHD patients.

Effect of TMZ on exercise capacity

Exercise capacity is the maximum amount of physical exertion that a patient can sustain. IHD patients with a decreased exercise capacity have an increased angina attack rate and poor QOL.

TMZ has a metabolic mode of action and it has been shown to preserve energy balance and prevent disturbance of ion homeostasis during ischemia. Results from studies demonstrated that TMZ significantly improved exercise tolerance in patients with stable angina when used either as monotherapy or when combined with β -blockers or calcium antagonists.

A multicenter, randomized, double-blind, placebo-controlled, international study involving 223 patients with stable angina pectoris (class II or III of the Canadian Cardiovascular Society [CCS] classification) showed that TMZ significantly improve patients' functional capacity, after 8 weeks of treatment, at trough. Time to 1mm ST segment depression was significantly increased by 44 seconds comparing with the placebo group ($p = 0.005$). A significant difference was also evidenced for the time to onset of angina pectoris ($p = 0.049$) and for the reason for stopping the exercise ($p = 0.02$) [10]. In addition, TMZ was well tolerated.

A study by Sisakian et al involved a total of 82 patients with ischemic cardiomyopathy who previously suffered a myocardial infarction. Results demonstrated that a therapeutic intervention with TMZ in conjunction with the standard therapy, over a three-month period, is associated with improved tolerance to physical activity, the tolerance to physical activity improved by 30.0 ± 20.7 m in the TMZ group vs. 2.0 ± 18.85 m in the control group ($P < 0.001$) [11].

TMZ improves functional capacity not only in IHD patients, but also in heart failure patients. A study by Belardinelli involving 116 IHD patients with LVD showed that peak VO_2 was significantly increased by

25% in the TMZ + exercise training (ET) group ($P < 0.001$) [12]. This result is the first to demonstrate that TMZ potentiates the beneficial effects of ET on functional capacity. TMZ potentiates the effects of ET on cardiovascular performance through its action on cellular metabolism and on the oxidative balance. Metabolic modulation contributes to the improvement in cardiac performance and LV function, which are both enhanced by aerobic exercise through different mechanisms.

Benefits of TMZ on exercise tolerance were further confirmed by meta-analysis of Agustín Ciapponi et al, which involved 1378 patients with stable angina from 23 studies. Results showed that TMZ significantly increased the time to 1mm ST segment depression [0.32 (0.15, 0.48)] [13]. These meta-analysis also demonstrated that TMZ could significantly improve exercise capacity both as monotherapy and when used in conjunction with selected hemodynamically active anti-anginal drugs.

Effect of TMZ on left ventricular ejection fraction

For patients with LVD, the improvement in left ventricular ejection fraction (LVEF) is likely the main factor determining the observed improvement of quality of life and exercise tolerance. As mention above, the conventional therapy efficacy is still far from satisfaction. Recently, more and more evidences showed that TMZ is the promising additional therapy for LVD.

In the study of Fragasso et al, 55 patients with heart failure (NYHA II-IV) were randomly allocated to either conventional therapy plus TMZ or conventional therapy alone. After 13 months treatment, TMZ significantly improved NYHA functional class compared with the conventional therapy ($p < 0.0001$), and significantly increased LVEF from 36% to 43% ($p = 0.002$), whereas LVEF was significantly decreased from 38% to 34% in conventional therapy group [14]. These results indicate that long-term TMZ therapy could improve left ventricular function, leading to a better exercise performance.

Although the mechanism of TMZ improving LV function has not been clear so far, there are some hypothesis focuses on "energy starvation" [15]. As well-established anti-ischemic effects in patients with coronary heart disease, TMZ stimulates glucose use and ATP production, and then ameliorates the "energy starvation" state by inhibiting free fatty acid oxidation,

which may finally translate into mechanical efficiency. Furthermore, several studies and meta-analysis [16] have also demonstrated that TMZ was equally effective in patients with HF of ischemic and non-ischemic origin. These data confirm the metabolic mode of action of TMZ. Indeed, heart failure is known to be the consequences of metabolic abnormalities. Therefore, efficacy of TMZ in these patients with heart failure and non-ischemic origin is a proof of the metabolic mode of action of TMZ. Besides the energy metabolic modulating effect, Tuunanen et al [17] found some extra cardiac metabolic effects of TMZ when treating patients with idiopathic dilated cardiomyopathy. Nineteen non-diabetic patients with idiopathic dilated cardiomyopathy were included and randomized into TMZ or placebo group on the top of standard medication. After 3 months follow-up, LVEF in TMZ group was significantly increased, and glucose homeostasis were improved as well as insulin sensitivity. These extra cardiac metabolic changes may indirectly improve myocardial glucose metabolism and glycolysis, amplifying the effects mediated by the decrease in FFA oxidation observed in the cardiac tissue.

A recent meta-analysis conducted by Junbo Ge demonstrated TMZ could reverse cardiac remodeling. The meta analysis involved 884 CHF patients in 16 ran-

domized controlled trials (RCTs) [18], and found that TMZ therapy was not only improve the left ventricular end-systolic diameter (WMD: -6.67 mm, $p < 0.0001$) and left ventricular end-diastolic diameter (WMD: -6.05 mm, $p < 0.0001$), but also increase of total exercise time (WMD: 63.75 seconds, $p < 0.0001$) (Fig. 1).

Our team carried out a trial to investigate the myocardial protection efficacy of TMZ in percutaneous coronary intervention (PCI) patients [19]. TMZ was given 30 minutes before procedure and continued for 4 weeks. Result showed LVEF in the TMZ group was significantly improved compared with placebo (66.6% vs. 63.0%, $p = 0.03$). The data also underlines the cardio protection effect of TMZ in LVD treatment, including protecting membrane from oxidative damage, blocking calcium overload, inhibiting inflammation and apoptosis, and improving endothelial function. Our data further confirm the adjunct of TMZ opens a new therapeutic window for PCI patients to improve LV function.

Effect of TMZ on quality of life

QOL predicts not only short-term but also long-term mortality in patients with IHD. Therefore the treatments of IHD should focus not only on improving life expectancy, symptoms, functional status, but also QOL.

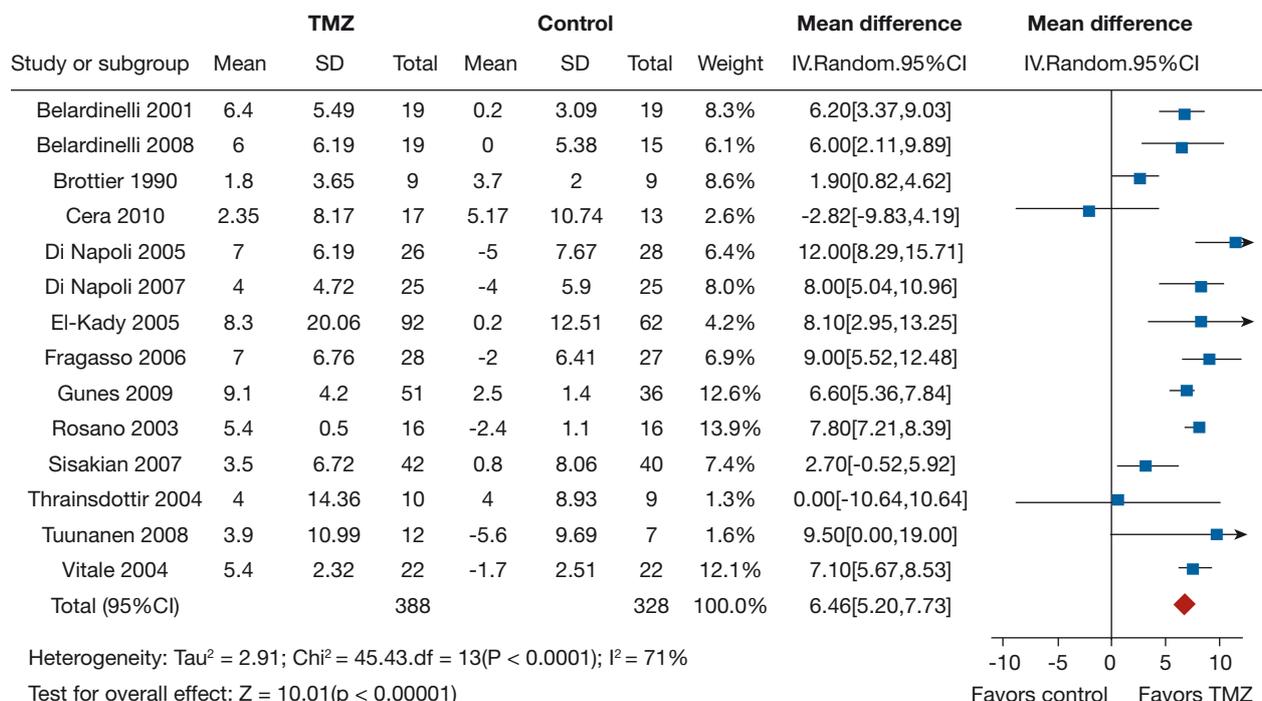


Fig. 1 Forest plots for left ventricular ejection fraction.

Available data showed that TMZ has a positive impact on QOL in patients with IHD. A RCT by Vitale et al aimed to assess the effects of TMZ in addition to standard cardiovascular therapy on QOL parameters in 62 elderly patients with IHD [20]. The overall assessment of QOL by a visual analog scale showed an improvement in patients allocated to TMZ at 6 months (from 4.1 ± 0.6 to 6.4 ± 0.8 , $P < 0.01$) and no changes in patients allocated to placebo (from 4.3 ± 0.7 to 4.2 ± 0.9 , $P > 0.05$). Physical QOL, evaluated by a MacNew Quality of Life After Myocardial Infarction questionnaire (MacNewQLMI), significantly improved in TMZ arm ($32\% \pm 5\%$ vs. $-1\% \pm 3\%$, $P < 0.01$). Social QOL evaluated by MacNewQLMI with TMZ compared with placebo also obtained similar results ($39\% \pm 4\%$ vs. $-2\% \pm 5\%$, $P < 0.01$). This study confirmed that in elderly patients with IHD TMZ improves clinical condition and QOL. Another study by Marazzi et al also evaluated the effects of TMZ on QOL in patients with ischemic dilated cardiomyopathy and got the similar results.

The effect of TMZ on reverse remodeling may explain its effect on QOL. The improvement in ventricular performance may cause a reduction in symptoms and an improvement in functional capacity and QOL. Another mechanism is the increase in muscle strength related to the improved hemodynamic conditions and in part could be related to a direct effect of TMZ on skeletal muscle.

TMZ improves clinical condition and QOL not only in IHD patients, but also in heart failure patients. A study by Fragasso et al [21] enrolled 55 patients with heart failure secondary to IHD, who were randomly allocated to conventional therapy plus TMZ or conventional therapy alone. QOL was assessed with two tests: visual analogue scale and LVD questionnaire (LVD-36) in order to measure the impact of LVD on daily life. The study demonstrated a significant decrease in LVD-36 score (from 18 to 15, $p=0.038$) in favor of TMZ. The improvement in LV function is likely the main factor determining the observed improvement of QOL including increased exercise tolerance and decreased NYHA functional class.

Conclusions

Exercise capacity and QOL becomes more and more important in IHD management. Available data strongly suggest that TMZ improves exercise performance, LV

function, and QOL in IHD patients and these benefits are possibly due to its metabolic mechanism. Therefore, the adjunct of a metabolic drug to conventional hemodynamic drugs should be used widely in these patients. •

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