Benefits of the metabolic approach in cardiac rehabilitation

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Abstract

Patients referred for cardiac rehabilitation may derive benefit from combining trimetazidine with exercise training, because both treatments produce similar effects in the cardiovascular system. Patients with viable myocardium should, in theory, obtain the greatest benefit, because trimetazidine improves the contractility of dysfunctional hibernating/stunned myocardium, whereas exercise has the documented ability to improve the endothelial vasomotor response of coronary arteries, to stimulate the coronary collateral circulation and small vessel growth, to improve left ventricular function, and to increase functional capacity. At present, however, there are no published reports on the efficacy of the combination of trimetazidine with exercise training.
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Keywords: Trimetazidine, exercise training, ischemic cardiomyopathy, endothelial function

Introduction

Trimetazidine has been reported to improve functional capacity and the contractile response to dobutamine in patients with ischemic cardiomyopathy. In a group of patients with ischemic cardiomyopathy and with clinical characteristics similar to those of the population described below, Belardinelli and Purcaro [1] demonstrated that the addition of trimetazidine 20 mg three times daily to standard medications for 2 months improved peak $\dot{V}O_2$ by 19% and left ventricular ejection fraction by 16% ($P < 0.001$ compared with placebo, for both). A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the amount of ATP produced per mole of oxygen is approximately 12% greater when glucose is the preferential substrate. As a consequence, the contractility of dysfunctional myocardium improves, and this effect translates into enhanced left ventricular function. The improvement in contractility induced by trimetazidine can have potential therapeutic and prognostic implications. An important effect may be an increase in stroke volume during daily submaximal physical activities, which would make possible a more active lifestyle and might contribute to improving both functional capacity and quality of life.

There are also many studies demonstrating that cardiac rehabilitation improves the functional capacity of patients with ischemic heart disease and chronic heart failure. A recent meta-analysis [2] revealed improvements in peak $\dot{V}O_2$ ranging from 12% to 31% that were associated with lower rates of re-admission to hospital and of mortality. Such improvements are the result of adaptations induced by training and involve skeletal muscle, oxygen transport capacity, endothelial function, pulmonary oxygen diffusion, and myocardial perfusion and contractility [3–7].

Patients referred for cardiac rehabilitation may derive benefits from combining trimetazidine with exercise training, because both treatments produce similar effects in the cardiovascular system. Trimetazidine is a metabolic modulator that inhibits a key

enzyme in fatty acid oxidation, and shifts cellular energy substrate preference from oxidation of fatty acids to that of glucose [8]. As a result of this action, both left ventricular systolic function and diastolic filling are improved in patients with ischemic and diabetic cardiomyopathy [1,9,11]. Patients with viable myocardium should, in theory, benefit the most from either trimetazidine or exercise training, because both improve contractility of dysfunctional hibernating/stunned myocardium, the former through a series of induced adaptations in myocardial cells and coronary vessels, the latter through metabolic modulation of myocardial cells.

Rationale for using trimetazidine in cardiac rehabilitation

Trimetazidine is a piperazine derivative with anti-ischemic properties that is used in clinical practice to treat patients with stable angina and ischemic cardiomyopathy [8]. It shifts energy substrate preference from fatty acids to glucose oxidation through inhibition of the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the production of ATP per mole of oxygen is higher when glucose is the preferential substrate.

There is evidence that trimetazidine, at doses of 20 mg three times daily orally, improves left ventricular function in patients with ischemic cardiomyopathy. In one study [1], 38 patients with postnecrotic left ventricular dysfunction and multivessel coronary artery disease were allocated randomly to two matched groups. One group received trimetazidine 20 mg three times daily for 8 weeks, and the second received placebo. Treated patients had significant improvements in systolic wall thickening score index at rest and at peak dobutamine infusion (13% and 21%, respectively, $P<0.001$), in left ventricular ejection fraction at rest and at peak dobutamine infusion (19.7% and 14.1%, $P<0.001$), and in peak $\dot{V}O_2$ (15%). These results are in agreement with the study by Brottier et al [9], who demonstrated an improvement in radionuclide ejection fraction after a 6-month treatment with trimetazidine at the same dose in 18 patients with ischemic cardiomyopathy in New York Heart Association Class III and IV. Similar improvements in left ventricular systolic performance and diastolic filling have been obtained more recently in patients with diabetic cardiomyopathy and in patients older than 75 years with coronary artery disease. No significant untoward events have been described, except for gastrointestinal symptoms [10].

More recently, interest has begun to focus on the antioxidant properties of trimetazidine and on its potential beneficial effect on endothelial function. As demonstrated by Fragasso et al [11], trimetazidine decreases the plasma concentrations of endothelin-1 in patients with ischemic cardiomyopathy and diabetes.

An antioxidant effect of trimetazidine is suggested by a reduction in systemic markers of oxidant stress, such as malondialdehyde and hydroperoxides. There is evidence from both experimental and clinical studies that free radicals are increased in chronic heart failure [12,13]. Prasad et al [14] found that leukocyte-mediated production of oxygen-derived free radicals was increased 4-fold in patients with heart failure as compared with controls. Recently, Belardinelli et al [15] demonstrated that trimetazidine improved endothelium-dependent vasodilation in a group of 51 patients (ages 51.4 ± 6 years) with ischemic cardiomyopathy and chronic heart failure, and that this effect was correlated both with decreased plasma concentrations of malondialdehyde and hydroperoxides and with enhanced functional capacity. No change in the endothelium-independent vasorelaxation was detected.

Clinical study of trimetazidine combined with exercise

Despite the potentially favorable premises suggested by the effects of trimetazidine or exercise training used separately, there are no published reports on the effects of trimetazidine in patients referred for cardiac rehabilitation. We studied 86 patients (72 men and 14 women, mean age 59 ± 9 years) with ischemic heart disease and left ventricular dysfunction who were referred for cardiac rehabilitation. Coronary risk factors were present in 72 of them (diabetes in 36). Patients were allocated randomly to three matched groups. One group (TMZ + training, $n=30$) received trimetazidine in a dose of 20 mg three times daily orally for 8 weeks in addition to standard medications, and underwent a supervised program of exercise training at 60% of peak $\dot{V}O_2$, three times a week for 8 weeks. A second group ($n=30$) underwent supervised exercise training alone, and the third group ($n=26$) acted as controls.

Peak $\dot{V}O_2$ was significantly increased in both the TMZ + training group (from $16.4 \pm 3.2\ ml \cdot kg \cdot min^{-1}$ to $20.5 \pm 3.4\ ml \cdot kg \cdot min^{-1}$) (*Figure 1*) and the exercise group (from $16.3 \pm 3.3\ ml \cdot kg \cdot min^{-1}$ to $18.8 \pm 3.1\ ml \cdot kg \cdot min^{-1}$), whereas it was unchanged in controls ($P<0.001$ for the TMZ + training group compared with the exercise group, and compared with controls). Left ventricular ejection fraction improved in the TMZ + training group (from $38 \pm 7\%$ to $43 \pm 8\%$) and in the exercise group (from $35 \pm 6\%$ to $39.5 \pm 5\%$), as a result of a reduction in end-systolic volume, but no changes were observed in controls ($P<0.05$ for the TMZ + training group

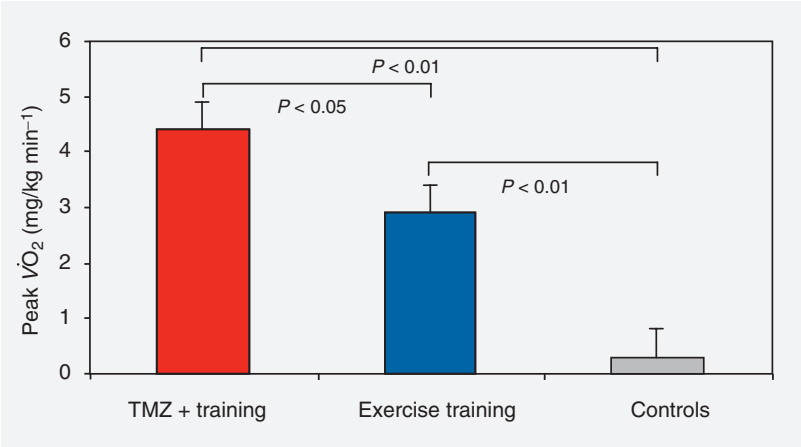

Figure 1. Changes in peak oxygen uptake ($\dot{V}O_2$) between study entry and 8 weeks in the three groups: trimetazidine (TMZ) plus exercise training, exercise training, and untrained controls. P values obtained by Mann–Whitney test.

compared with the exercise group, and compared with controls). We speculate that trimetazidine potentiates the effects of exercise training on dysfunctional myocardium and on endothelial cells, as represented schematically in *Figure 2*.

In fact, in the presence of dysfunctional viable myocardium, trimetazidine, as a metabolic modulator, improves left ventricular function and cardiovascular efficiency, which may shift the balance between endothelial vasodilating and vasoconstricting substances in favor of the former. A reduction in oxidative stress may enhance endothelial function by decreasing the rate of inactivation of nitric oxide caused by the products of lipid peroxidation and reactive oxygen species [16]. Conversely, trimetazidine may exert a direct effect on endothelial cells,

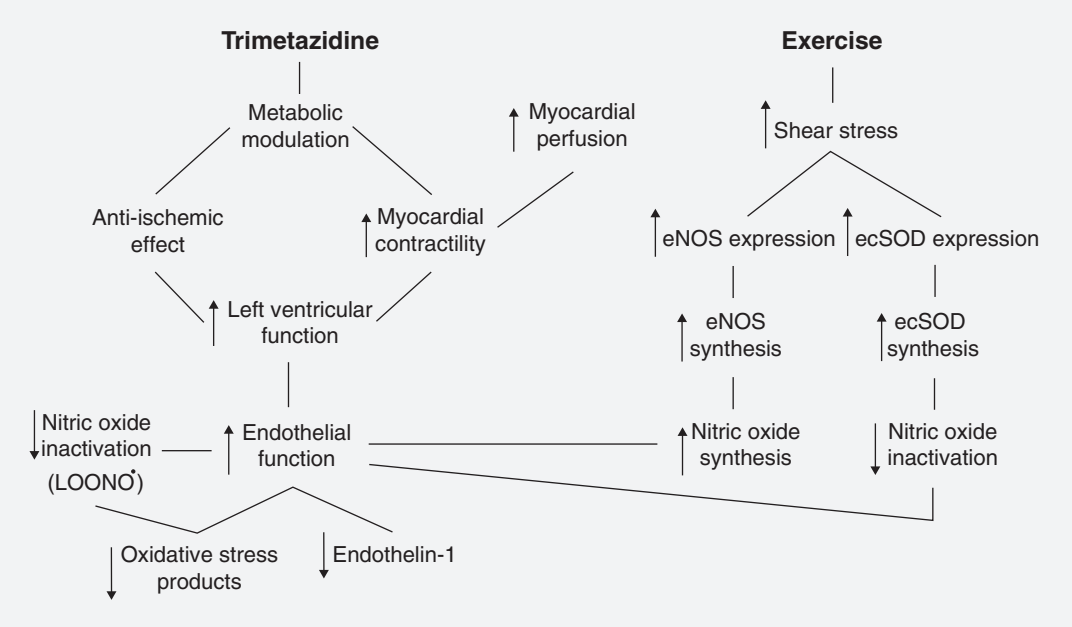

Figure 2. Both trimetazidine and exercise improve left ventricular function, the former through metabolic modulation, the latter through intermittent bouts of increased shear stress. In ischemic cardiomyopathy, exercise improves myocardial perfusion through at least four mechanisms: improvement in endothelium-dependent relaxation of coronary vessels, arterial remodeling (Glagov effect), coronary collateral circulation (arteriogenesis), and small vessel growth (angiogenesis). The improvement in left ventricular function is associated with enhanced endothelial function. Trimetazidine directly reduces nitric oxide inactivation through a decrease in lipid peroxidation (less LOONO•). This effect is associated with decreased plasma levels of systemic markers of oxidative stress, such as malondialdehyde and hydroperoxides, and endothelin-1. The indirect effect of trimetazidine on endothelial function depends on its anti-ischemic properties and on the contractility of dysfunctional myocardium, which both contribute to improving left ventricular function. The improvement in endothelium-dependent vasorelaxation contributes to enhancing functional capacity. eNOS, endothelial nitric oxide synthase; ecSOD, extracellular superoxide dismutase*.*

acting as a chelator of the transition metals that are able to cross the lipid barrier, and thus protecting the endothelium from free radicals [17].

Summary

The findings of the investigation described above indicate that the combination of trimetazidine with exercise training potentiates the effect of exercise training and produces more marked improvements in functional capacity, left ventricular systolic function, and endothelium-dependent relaxation of the brachial artery than are achieved through exercise training alone, in patients with ischemic cardiomyopathy who are referred for cardiac rehabilitation. Patients with several coronary risk factors are those who may benefit most from a combination of trimetazidine with exercise training. Trimetazidine potentiates the effects of exercise training on the endothelium and functional capacity, possibly through its metabolic and antioxidant actions. As both endothelium-dependent relaxation and functional capacity are measures of outcome both in patients with coronary artery disease and in healthy individuals, improvements in one or both should reflect a better outcome or longer life expectancy, or both.

*See glossary for definition of these terms. ■

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