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The cardioprotective effects of trimetazidine

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Abstract

This review summarizes the available evidence on the cardioprotective effects of trimetazidine, focusing on clinical studies in a large spectrum of patients, including those with stable angina pectoris, acute myocardial infarction, ischemic cardiomyopathy, heart failure, and those undergoing percutaneous coronary intervention. The cardioprotective effects of trimetazidine have been proven both in experimental and in clinical studies. However, the evidence for a more robust clinical benefit (hard end points) is still awaited. ■ *Heart Metab*. 2016;70:24-27

Keywords: angina; cardioprotection; trimetazidine

Introduction – trimetazidine's mechanism of action

Trimetazidine was described almost 50 years ago as the first cytoprotective anti-ischemic metabolic agent; it improves myocardial glucose utilization through inhibition of fatty acid metabolism. Trimetazidine inhibits β-oxidation of fatty acids by blocking long-chain 3-ketoacyl-coenzyme A thiolase (LC 3-KAT), which enhances glucose oxidation. In an ischemic cell, energy obtained during glucose oxidation requires less oxygen consumption than would the β-oxidation process. Potentiation of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischemia. By preserving energy metabolism in cells exposed to hypoxia or ischemia, trimetazidine prevents a decrease in intracellular adenosine triphosphate (ATP) levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow while maintaining cellular homeostasis.

One study evaluated the direct cardioprotective effect of trimetazidine on isolated rat cardiomyocytes. Pretreatment of ventricular myocytes with trimetazidine increased cell resistance to hypoxic stress. The authors concluded that this cytoprotective effect was not mediated through an antioxidant activity, but rather can be related to a modification in lipid metabolism.[1] Another experimental study investigated whether trimetazidine reduces the ionic imbalance induced by ischemia and reperfusion. During low-flow ischemia, the major effect of trimetazidine was a significant reduction in intracellular acidosis, whereas during total ischemia, the main effect of trimetazidine was a significant reduction in sodium gain. Trimetazidine-induced attenuation of ionic imbalance was associated with a significantly improved recovery of ventricular function on reperfusion, as assessed by a lower increase in diastolic pressure and an increased recovery of developed pressure. These data provided evidence that specific myocardial metabolic modula-

Abbreviations

ATP: adenosine triphosphate; **ATPCI:** The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention; **EMIP-FR:** European Myocardial Infarction Project – Free Radicals; **LC 3-KAT:** long-chain 3-ketoacyl-coenzyme A thiolase; **PCI:** percutaneous coronary intervention; **PCr:** phosphocreatine

tion plays a significant role in reducing ionic imbalance during ischemia and reperfusion.[2] Kantor et al analyzed the effects of trimetazidine on fatty acid and glucose metabolism in isolated working rat hearts and on the activities of various enzymes involved in fatty acid oxidation. This study confirmed that the antianginal effects of trimetazidine occur due to an inhibition of LC 3-KAT activity, resulting in a reduction in fatty acid oxidation and a stimulation of glucose oxidation.[3] MacInnes et al found that trimetazidine and ranolazine improved ischemic cardiac function.[4] Another study demonstrated that trimetazidine inhibition of LC 3-KAT decreases fatty acid oxidation and stimulates glucose oxidation, resulting in an improvement in cardiac function and efficiency after ischemia.[5] Recently, trimetazidine pretreatment was found to inhibit microembolization-induced myocardial apoptosis and improve cardiac function. The cardioprotective effect appeared to be mediated by the blockade of the mitochondrial apoptotic pathway.[6]

Clinical studies with trimetazidine

The first report on the use of trimetazidine for the treatment of angina pectoris was published in 1967.[7] Trimetazidine has been shown to have an antianginal effect, increasing exercise capability without producing any significant change in heart rate or systolic blood pressure.

Two studies compared the effects of trimetazidine with two established antianginal drugs. Dalla-Volta et al compared trimetazidine efficiency with that of nifedipine in 39 male patients with effort angina. The number of weekly angina attacks and the results of exercise testing did not differ between trimetazidine and nifedipine groups.[8] Detry et al compared the effects of trimetazidine with propranolol in a double-blind, parallel-group, multicenter study in patients with stable angina and positive exercise test (typical anginal pain with ST-segment depression of ≥1 mm and horizontal or downward-sloping extension of the ST segment for ≥80 ms after the J point; or ST-segment depression ≥ 3 mm and no anginal pain). After 3 months, similar antianginal efficacy and similar exercise duration were observed between the trimetazidine and propranolol groups. With both drugs, there was a trend toward decreased ischemic episodes in patients who experienced ambulatory ischemia as assessed by Holter monitoring. The results suggested that trimetazidine and propranolol have similar efficacy in patients with stable angina pectoris.[9] Patients with stable angina had a clinically important improvement after combination treatment with diltiazem and trimetazidine, without adverse hemodynamic events or increased side effects.[10]

The largest of similar studies, a randomized, multicenter, double-blind trial assessed the anti-ischemic efficacy and tolerability of trimetazidine in combination with metoprolol among 426 patients with stable, effort-induced angina and documented coronary artery disease. After 12 weeks, there were significantly greater improvements in the metoprolol-plus-trimetazidine group than in the metoprolol-plus-placebo group in the following: time to 1-mm ST-segment depression, total workload, time to onset of angina, maximum ST-segment depression, mean weekly number of angina attacks, mean weekly nitrate consumption, and grade of anginal pain. The tolerability of trimetazidine was excellent.[11]

A small randomized, double-blind study analyzed the effects of trimetazidine on the severity of myocardial ischemia during balloon angioplasty of the left anterior descending coronary artery. Trimetazidine decreased the maximum ST-segment shift and delayed its onset. Placebo had no effect on these parameters. These results support the hypothesis that trimetazidine has a direct anti-ischemic effect on human myocardial cells.[12]

The largest trial with trimetazidine was EMIP-FR (European Myocardial Infarction Project - Free Radicals[13]). This prospective, double-blind trial randomized 19 725 patients with acute myocardial infarction to intravenous trimetazidine or placebo. No difference was found between trimetazidine and placebo for the main end point, 35-day (short-term) mortality. Patients undergoing thrombolytic therapy showed a tendency toward a higher short-term death rate with trimetazi-

dine than with placebo (trimetazidine, 11.3%; placebo, 10.5%; *P*=0.15); those not receiving thrombolytic therapy demonstrated the opposite trend (trimetazidine, 14.0%; placebo, 15.1%; *P*=0.14).

The long-term (2-year) effect of trimetazidine on myocardial perfusion (assessed by gated single-photon emission computerized tomography [SPECT]) was investigated in 200 patients with ischemic left ventricular dysfunction and multivessel coronary artery disease. The frequency of anginal episodes per week was lower in the trimetazidine group than in the placebo group (3.9 vs 5.7; *P*<0.01). With trimetazidine treatment, the duration of peak exercise increased significantly over baseline values.[14]

Fragasso et al analyzed the effects of trimetazidine on cardiac phosphocreatine (PCr) and ATP ratio in 12 patients with heart failure by means of ^{31}P-magnetic resonance spectroscopy. Patients were randomized in a double-blind, crossover study to placebo or trimetazidine for two periods of 90 days. At the end of each period, all patients underwent exercise testing, echocardiography, and magnetic resonance spectroscopy. On trimetazidine, New York Heart Association (NYHA) class decreased, whereas ejection fraction and metabolic equivalents (METS) increased. The mean cardiac PCr/ATP ratio was increased by 33% with trimetazidine. Trimetazidine improved functional class and left ventricular function in patients with heart failure. These effects were associated with the observed trimetazidine-induced increase in the PCr/ATP ratio, indicating preservation of the myocardial high-energy phosphate levels.[15]

A single-center, prospective, randomized study evaluated the effect of preprocedural oral trimetazidine on percutaneous coronary intervention (PCI)-induced myocardial injury in 266 patients with stable angina pectoris and single-vessel disease who were randomly assigned to two groups. Cardiac troponin I (cTnI) levels were measured before and 6, 12, 18, and 24 hours after PCI. Postprocedural cTnI levels were significantly reduced at all time points and the total amount of cTnI released after PCI (calculated as the area under the curve) was significantly reduced in the trimetazidine group.[16]

Di Napoli et al investigated the effects of trimetazidine on exercise tolerance and on plasma levels of B-type natriuretic peptide (BNP) and cardiac troponin T (cTnT) in 50 patients with ischemic cardiomyopathy who were randomized to receive trimetazidine or placebo. After 6 months, left ventricular ejection fraction and NYHA class did not change in patients of either group. However, in the trimetazidine group, a significant increase in exercise tolerance was detected (6-minute walking test). BNP and cTnT were significantly reduced during trimetazidine treatment.[17]

Finally, a recent retrospective cohort study evaluated the long-term effect of trimetazidine on morbidity and mortality in 669 patients with chronic heart failure (CHF): 362 patients were on trimetazidine due to symptom persistence despite uptitration of optimal CHF therapy, whereas the remaining patients continued conventional CHF therapy alone. Trimetazidine improved global survival and reduced the hospitalization rate for cardiovascular causes.[18]

Study	Indication	Effect of TMZ
Dalla-Volta et al,[8] 1990	Stable angina	TMZ not different from nifedipine.
Detry et al,[9] 1994	Stable angina	TMZ not different from propranolol.
Manchanda et al,[10] 1997	Stable angina	TMZ + diltiazem more effective than dilthiazem alone.
Szwed et al,[11] 2001	Stable angina	TMZ + metoprolol superior to placebo + metoprolol.
Kober et al,[12] 1992	Balloon angioplasty	TMZ delayed ischemia.
EMIP-FR Group,[13] 2000	Acute myocardial infarction	No effect of TMZ on 35-day mortality.
El-Kady et al,[14] 2005	Ischemic LV dysfunction	TMZ improved exercise tolerance and myocardial perfusion.
Fragasso et al,[15] 2006	Heart failure	TMZ improved NYHA class, LVEF, and exercise tolerance.
Bonello et al,[16] 2007	Percutaneous coronary intervention	TMZ decreased cardiac troponin I levels after percutaneous coronary intervention.
Di Napoli et al,[17] 2007	Ischemic cardiomyopathy	TMZ improved exercise tolerance and reduced BNP and troponin T levels. No effect on LVEF and on NYHA class.
Fragasso et al,[18] 2013	Heart failure	TMZ improved survival and reduced hospital admissions.

Table I *Summary of clinical studies with trimetazidine.*
Abbreviations: *BNP, B-type natriuretic peptide; EMIP-FR, European Myocardial Infarction Project – Free Radicals; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TMZ, trimetazidine.*

Conclusion

To summarize, small- and medium-sized studies in angina patients have shown that trimetazidine delays the onset of ischemia associated with exercise, significantly decreases the frequency of angina attacks, and leads to a significant decrease in the use of nitrates *(Table I)*. Trimetazidine improves left ventricular function in patients with coronary heart disease. It has also been shown to be effective in patients with ischemic heart failure. With regard to mortality, only one retrospective study[18] demonstrated a potential benefit, whereas other studies did not find differences in hard clinical end points. The ongoing large, international, randomized ATPCI trial (The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention) may elucidate the clinical benefits of metabolic cardioprotection. ■

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