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Trimetazidine in the era of PCI

Olímpio R. França Neto

Quanta Diagnóstico e Terapia, Instituto Paranaense de Cardiologia, Curitiba, Brazil

Correspondence: Olímpio Ribeiro França Neto, MD, FESC, Instituto Paranaense de Cardiologia, Rua Silveira Peixoto, 1040, Curitiba- PR - 80240-120 Brazil
E-mail: olimpiofranca@yahoo.com.br

Abstract: Guideline-directed medical therapy and coronary revascularization by percutaneous coronary intervention (PCI) are important approaches to treating patients with ischemic heart disease. However, even after PCI and with guideline-directed medical therapy, a significant percentage of patients still present with angina. In addition, PCI can also induce myocardial ischemia, myocardial injury, and reperfusion injury. Trimetazidine, an anti-ischemic agent widely used for the treatment of coronary artery disease, has cytoprotective actions that could protect against ischemia and reperfusion injury in patients undergoing PCI. Several trials have shown that trimetazidine improves left ventricular ejection fraction and reduces elevated cardiac troponin levels, angina attacks, and ischemic ST-T changes on the electrocardiogram in patients undergoing PCI. Moreover, the use of trimetazidine in patients submitted to revascularization results in an improvement in exercise stress test parameters, such as time to ischemic ST-segment depression, time to onset of angina, and exercise test duration, as well as a reduction in the weekly number of angina attacks and nitrate consumption. This article will review the effects of trimetazidine on patients submitted to percutaneous coronary interventions. ■ *Heart Metab*. 2019;78:20-23

Keywords: ischemic heart disease; metabolic protection; percutaneous coronary intervention; trimetazidine

Introduction

Ischemic heart disease is the major cause of death and disability worldwide, except in the lowest-income countries.[1] Angina pectoris, the most frequent clinical presentation of ischemic heart disease, increases progressively in its prevalence among adults aged 40 years and older, ranging from 4% to more than 11%.[2,3] Angina not only affects quality of life, but it is also associated with an increased risk of cardiovascular events.[4]

Percutaneous coronary intervention (PCI) is a vital strategy for managing obstructive coronary artery disease. Lifestyle management, control of risk factors, guideline-directed medical therapy, and myocardial revascularization are the recommended therapies for patients with ischemic heart disease.[5,6] However, despite contemporary treatments, angina remains a debilitating problem. Large clinical trials consistently indicate that many patients present persistent symptoms or signs of myocardial ischemia, even with guideline-directed medical therapy and revascularization; in some studies, this proportion varies from 25% to 35%.[3,7-10] Restenosis, coronary atherosclerosis progression, and incomplete revascularization provide reasons for the recurrence of symptoms in a percentage of patients even after successful PCI. At the same time, functional causes, such as vasomotor abnormalities of epicardial coronary arteries and/or coronary microvascular dysfunction, could provide a justification for symptoms in the other patients.[11]

In addition, PCI may also induce coronary spasm or endothelial cell injury and the debris from atherosclerotic plaques or thrombi may cause coronary artery distal embolization, thereby leading to myocardial ischemia or myocardial injury. Peri- and postprocedural myocardial injury or necrosis play an essential prognostic role after PCI.[12]

Lastly, reperfusion injury is a pathophysiological phenomenon that occurs because of damage to the myocardium after restoring blood flow after a certain period of coronary occlusion. The production of oxygen free radicals caused by reperfusion of an ischemic heart can lead to damaged cardiac cells. PCI can cause a transient ischemia of the myocardium, leading to metabolic changes, including disturbances in the electrical activity and contractility of myocardial cells associated with hemodynamic disturbances.[13]

The effects of trimetazidine

Trimetazidine is an anti-ischemic agent commonly employed as part of the treatment for coronary artery disease. It works by inhibiting the long-chain mitochondrial 3-ketoacyl coenzyme A thiolase, and gives a stimulus to pyruvate dehydrogenase, which leads to a change in cardiac energy metabolism from fatty acid oxidation to glucose oxidation. As a result, trimetazidine has cytoprotective properties, providing a reduction in myocardial cell acidosis and calcium overload, preservation of intracellular ATP levels, an increase in the antioxidant capacity, and protection against oxygen free radical–induced toxicity.[5,14,15]

Trimetazidine favorably alters the level of oxidative stress markers. In the study by Iskesen et al,[14] it increased the level of superoxide dismutase and glutathione peroxidase (major antioxidant enzyme systems that limit intracellular accumulation of oxygen free radicals during normal aerobic metabolism) and decreased the level of malondialdehyde (end product of lipid peroxidation). Trimetazidine also reduces membrane damage induced by reactive oxygen species and protects tissue from free radicals with its antioxidant effects.[16,17] These effects are particularly useful in the reperfusion period. Some experimental studies have shown that trimetazidine can prevent a sharp increase in the permeability of mitochondrial membranes, decreasing the rate of cardiomyocyte apoptosis.[18,19]

Several clinical trials have shown that trimetazidine significantly improves left ventricular ejection fraction, reduces elevated cardiac troponin levels, angina attacks, and ischemic ST-T changes on the electrocardiogram in patients undergoing PCI.[20-24] Polonski et al performed an open, randomized clinical trial (RCT) that assessed the effect of pretreatment with trimetazidine on the degree of ischemia during PCI. The intervention group (n=22) received oral trimetazidine as a pretreatment. The mean ST-segment elevation during all balloon inflations was significantly lower in the trimetazidine group than in the control group (-1.66±1.50 mm vs 3.29±1.59 mm, $P=0.001$). Similarly, the maximal amplitude of the T-wave alterations was 4.50±2.90 mm with trimetazidine vs 9.25±4.97 mm in control patients ($P=0.0005$). Angina and rhythm disturbances were more frequent in the control group.[20]

The effect of preprocedural acute oral administration of trimetazidine on PCI-induced myocardial injury was evaluated by Bonello et al in 266 patients with stable angina pectoris and single-vessel disease undergoing PCI. Before the intervention, patients were randomly distributed to one of two groups. One group received a loading dose of 60 mg of trimetazidine, while the other group did not receive this loading dose. Postprocedural cTnI levels were significantly reduced in the trimetazidine group at all time points (from 6 hours to 24 hours).[21]

In the study by Chen et al in 101 patients with stable or unstable angina pectoris who were randomized to either the trimetazidine (n=54) or the control (n=47) group before PCI. Prior to coronary angiography, one group was given oral trimetazidine, 20 mg three times a day for 5±2 days in addition to a loading dose of 60 mg 30 minutes before PCI. The dosage each day was maintained for 4 weeks postprocedure. No patient in the trimetazidine group presented with angina during the procedure; however, 12 patients (25.5%) in the control group presented with angina ($P<0.001$). The trimetazidine group showed fewer changes in the ST-segment and T wave during balloon dilatation in the PCI procedure (60.8% vs 78.3%; $P<0.05$). Four weeks after the PCI, the trimetazidine group presented with a higher ejection fraction (66.6±7.1% vs 63.0±7.7%; $P=0.03$). See ref 22 for further details.

Xu et al examined the effect of trimetazidine on recurrent angina pectoris and left ventricular structure in elderly patients with multivessel coronary heart disease and diabetes mellitus after drug-eluting stent implantation. Seven hundred patients with coronary heart disease undergoing coronary angiography were randomized to receive trimetazidine or placebo after being treated with a drug-eluting stent. During the 2-year follow-up, the incidence ($P=0.024$) and sever-

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ity of angina was significantly improved in the trimetazidine group (n=255), in addition to silent myocardial ischemia (*P*=0.009) and angina pectoris–free survival (*P*=0.011).[24]

Zhang et al performed a meta-analysis of randomized controlled trials to evaluate the effect of trimetazidine on patients undergoing PCI. Nine studies involving 778 patients were included. Additional use of trimetazidine significantly improved left ventricular ejection fraction and reduced elevated cardiac troponin Ic level, angina attacks during PCI, and ischemic ST-T changes on the electrocardiogram during PCI. Additional use of trimetazidine for patients undergoing PCI may reduce myocardial injury during the procedure and improve cardiac function *(Figure 1)*.[22]

Furthermore, according to different trials, recurrent angina affects one-third to one-fifth of patients submitted to a successful PCI within a 1-year follow-up.[8-11] The subgroup analysis of the Trimpol II study showed that the addition of trimetazidine to metoprolol in symptomatic patients with a history of revascularization for coronary artery disease (PCI or coronary artery bypass grafting) resulted in a significant improvement in time to 1-mm ST-segment depression (385.1±144.6 seconds vs 465.0±143.8 seconds; *P*<0.01), exercise test duration (466.9±144.8 second vs 524.4±131.5 second; *P*=0.048), total workload, and time to onset of angina. The weekly number of angina attacks and nitrate consumption were also significantly reduced in the trimetazidine group when compared with placebo.[25]

The incidence of stent restenosis has risen as more patients are being treated with drug-eluting stents. Chen et al evaluated, in 768 patients who underwent PCI with drug-eluting stents, whether treatment with long-term trimetazidine reduced the incidence of stent restenosis. The trimetazidine group had a lower incidence of stent restenosis compared with the control group (4.2% vs 11.1%; *P*=0.001). At the 30-day follow-up, the trimetazidine-treated patients also presented with a higher left ventricular ejection fraction than control patients (65.4±10.7% vs 63.1±10.4%; *P*=0.006).[26]

Finally, we look forward to seeing the ATPCI trial results, a new international, phase 3 study evaluating the clinical impact of adding a metabolic agent to post–PCI angina treatment. ATPCI is a multicenter, randomized, double-blind, placebo-controlled study in patients treated with trimetazidine for 2 to 4 years. ATPCI, which stands for "EfficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Interventions," will encompass 6007 patients from 27 countries up to 30 days after PCI. The primary efficacy end point of ATPCI is the time to the first occurrence of: (i) cardiac death; (ii) hospitalization for a cardiac event; (iii) recurrent or persistent angina that results in the addition, switching, or the increase of the dose of one of the evidence-based antianginal drugs; and (iv) recurrent or persistent angina, leading to a coronary angiography. The primary safety end point is the incidence of serious emergency adverse events with trimetazidine.[27]

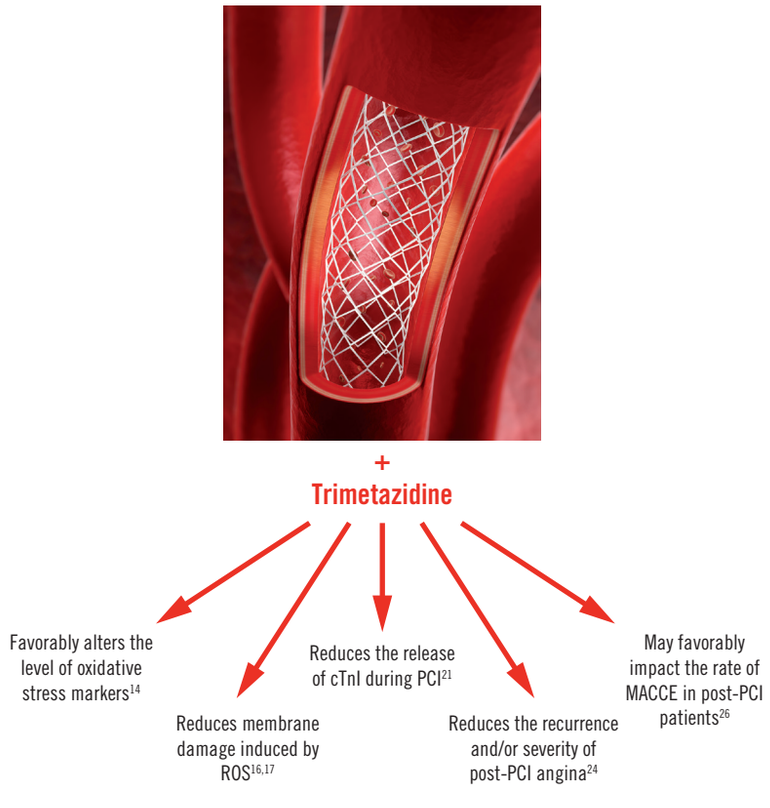

Figure 1 *Effects of trimetazidine on patients undergoing PCI.*

Conclusion

In summary, trimetazidine is a metabolic agent that protects the heart from ischemic damage and oxidative stress. In patients with stable angina undergoing revascularization, trimetazidine may prevent reperfusion injury and damage to cardiac cells, improve left ventricular function, and reduce angina and electrocardiographic ischemic changes during PCI. It can also improve exercise stress test parameters and reduce angina episodes after revascularization. The ATPCI trial should contribute to a better understanding of the benefits of trimetazidine in patients with angina pectoris treated by percutaneous coronary interventions. ■

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REFERENCES

1. Global Burden of Disease 2016 Causes of Death Collaborators. Global, regional, and national age-specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1151-1210.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38-e360.
3. Huqi A, Marzilli M. Refractory angina or inappropriate antianginal therapy? *Heart Metab*. 2017;72:4-8.
4. Gehi AK, Ali S, Na B, Schiller NB, Whooley MA. Inducible ischemia and the risk of recurrent cardiovascular events in outpatients with stable coronary heart disease: the heart and soul study. *Arch Intern Med*. 2008;168(13):1423-1428.
5. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;34(38):2949-3003.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165.
7. Hueb W, Soares PR, Gersh BJ, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol*. 2004;43:1743-1751.
8. BARI Investigators. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. *JAMA*. 1997;277:715-721.
9. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
10. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) Study. *J Am Coll Cardiol*. 2010;56(3):177-184.
11. Niccoli G, Montone RA, Lanza GA, Crea F. Angina after percutaneous coronary intervention: the need for precision medicine. *Int J Cardiol*. 2017;248:14-19.
12. Demirelli S, Karakelleoğlu S, Gündoğdu F, et al. The impact of trimetazidine treatment on left ventricular functions and plasma brain natriuretic peptide levels in patients with non-ST segment elevation myocardial infarction undergoing percutaneous coronary intervention. *Korean Circ J*. 2013;43(7):462-467.
13. Martins GF, Siqueira Filho AG, Santos JB, et al. Trimetazidine on ischemic injury and reperfusion in coronary artery bypass grafting. *Arq Bras Cardiol*. 2011;97(3):209-216.
14. Iskesen I, Saribulbul O, Cerrahoglu M, et al. Trimetazidine reduces oxidative stress in cardiac surgery. *Circ J*. 2006;70(9):1169-1173.
15. Marzilli M. Cardioprotective effects of trimetazidine: a review. *Curr Med Res Opin*. 2003;19(7):661-72.
16. Kuralay F, Altekin E, Yazlar AS, Onvural B, Goldeli O. Suppression of angioplasty-related inflammation by pre-procedural treatment with trimetazidine. *Tohoku J Exp Med*. 2006;208(3):203-212.
17. Dézsi C. Trimetazidine in practice: review of the clinical and experimental evidence. *Am J Ther*. 2016;23(3):e871-e879.
18. Tritto I, Wang P, Kuppusamy P, Giraldez R, Zweier JL, Ambrosio G. The anti-anginal drug trimetazidine reduces neutrophil-mediated cardiac reperfusion injury. *J Cardiovasc Pharmacol*. 2005;46(1):89-98.
19. Argaud L, Gomez L, Gateau-Roesch O, et al. Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. *J Mol Cell Cardiol*. 2005;39(6):893-899.
20. Poloński L, Dec I, Wojnar R, Wilczek K. Trimetazidine limits the effects of myocardial ischaemia during percutaneous coronary angioplasty. *Curr Med Res Opin*. 2002;18(7):389-396.
21. Bonello L, Sbragia P, Amabile N, et al. Protective effect of an acute oral loading dose of trimetazidine on myocardial injury following percutaneous coronary intervention. *Heart*. 2007;93(6):703-707.
22. Zhang Y, Ma XJ, Shi DZ. Effect of trimetazidine in patients undergoing percutaneous coronary intervention: a meta-analysis. *PLoS One*. 2015;10(9):e0137775.
23. Kazmi DH, Kapoor A, Sinha A, et al. Role of metabolic manipulator trimetazidine in limiting percutaneous coronary intervention-induced myocardial injury. *Indian Heart J*. 2018;70(suppl 3):S365-S371.
24. Xu X, Zhang W, Zhou Y, et al. Effect of trimetazidine on recurrent angina pectoris and left ventricular structure in elderly multivessel coronary heart disease patients with diabetes mellitus after drug-eluting stent implantation: a single-centre, prospective, randomized, double-blind study at 2-year follow-up. *Clin Drug Investig*. 2014;34(4):251-258.
25. Ruzyllo W, Szwed H, Sadowski Z, et al. Efficacy of trimetazidine in patients with recurrent angina: a subgroup analysis of the TRIMPOL II study. *Curr Med Res Opin*. 2004;20(9):1447-1454.
26. Chen J, Zhou S, Jin J, et al. Chronic treatment with trimetazidine after discharge reduces the incidence of restenosis in patients who received coronary stent implantation: a 1-year prospective follow-up study. *Int J Cardiol*. 2014;174(3):634-639.
27. Ferrari R, Ford I, Fox K, et al. A randomized, double-blind, placebo-controlled trial to assess the efficAcy and safety of Trimetazidine in patients with angina pectoris having been treated by percutaneous coronary intervention (ATPCI study): Rationale, design, and baseline characteristics. *Am Heart J*. 2019;210:98-107.