EDITORIAL

“…drugs that act directly by increasing the energy supply in cardiac cells are of use, whatever the causal mechanism involved, and as such are essential for the optimal treatment of ischemia. To protect myocardial cells from ischemia, energy supply needs to match energy demand. β-Blockers have a positive impact, reducing energy demand, while metabolic agents, such as trimetazidine, increase energy supply. That is why the use of an agent like trimetazidine fully complements β-blocker therapy.”

Metabolic agents and angina treatment

by F. J. Pinto, *Portugal*

Fausto J. PINTO, MD, PhD, FESC, FACC
Department of Cardiology
University Hospital Santa Maria/CHLN, CCUL
University of Lisbon
Lisbon, PORTUGAL

Chronic ischemic heart disease (IHD) and stable angina are a major clinical problem worldwide. The prevalence of stable angina is estimated to be in the region of 20 000 to 50 000 per million in the general population.[1,2] According to the REACH (REduction of Atherothrombosis for Continued Health) registry of more than 38 000 patients, 3 in every 20 patients with established coronary artery disease (CAD) has had a major event or been hospitalized within the previous year.[3]

Despite great advances in the management of CAD patients in recent times, symptoms are still common in many patients, sometimes even after revascularization. In the Heart and Soul Study, over a third (38%) of outpatients with stable CAD had angina, ischemia, or both.[1] A substantial number of patients with typical angina do not have significant coronary atherosclerotic obstructions.[4] Furthermore, the prevalence of coronary atherosclerotic obstruction in patients with or without typical angina is similar and is age-related in both sexes.

The treatment of stable CAD includes several potential strategies, including revascularization procedures (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) and pharmacotherapy.[5] One of the potential strategies for the treatment of CAD consists in targeting cardiac cells directly and in particular the energetic origin of ischemia with the use of a metabolic agent, such as trimetazidine, on top of β-blockers and other vasoactive agents.[5]

Myocardial ischemia is multifactorial and, above all, a deficiency in energy

Recent data clearly show that above and beyond coronary atherosclerotic obstruction, IHD is due to a large number of mechanisms, including coronary vasomotor, microcirculatory, endothelial, and platelet dysfunction and inflammation, among others.[6] Because myocardial ischemia is multifactorial in nature, it should, above all, be defined as a deficiency in energy (in the form of ATP, adenosine triphosphate) at the cardiac cell level.[7] Under conditions of energy deficit, drugs that act directly by increasing the energy supply in cardiac cells are of use, whatever the causal mechanism involved, and as such are essential for the optimal treatment of ischemia.

To protect myocardial cells from ischemia, energy supply needs to match energy demand. β-Blockers have a positive impact, reducing energy demand, while metabolic agents, such as trimetazidine, increase energy supply. That is why the use of an agent like trimetazidine fully complements β-blocker therapy.

Address for correspondence:
Professor Fausto J. Pinto, Serviço de Cardiologia, Hospital de Santa Maria - Centro Hospitalar de Lisboa Norte, E.P.E., Av. Professor Egas Moniz, Piso 08, 1649-035 Lisboa, Portugal (email: faustopinto@medicina.ulisboa.pt/ fpinto@icvl.pt)

Medicographia. 2016;38:245-250

www.medicographia.com

Trimetazidine + β-blocker: an optimal combination for reducing angina

The TRIMPOL (TRIMetazidine in POLand) II study was one of the first studies to test the use of a metabolic agent on top of β-blockers in 426 patients with stable CAD.[8] It was a randomized, multicenter, double-blind, placebo-controlled parallel group study. Patients with documented CAD and stable, effort-induced angina uncontrolled by metoprolol received either placebo or trimetazidine 20 mg three times daily in addition to metoprolol 50 mg twice daily. In this study, 12 weeks' treatment with trimetazidine plus metoprolol significantly improved treadmill exercise test parameters and significantly reduced clinical symptoms compared with placebo plus metoprolol. This was achieved without any further hemodynamic changes in these patients. In addition to its antianginal efficacy, trimetazidine was well tolerated.

Michaelides et al performed a randomized, double-blind, controlled trial in angina patients who were symptomatic despite treatment with propranolol.[9] The trial demonstrated that adding trimetazidine to treatment significantly decreased the mean number of angina attacks (-63%) twice as much as adding isosorbide dinitrate (-31%). This finding might be explained by the mode of action of trimetazidine, which provides a synergistic and complementary approach to hemodynamic agents, such as β-blockers. In a recent meta-analysis of almost 20 000 angina patients, trimetazidine was shown to be as effective as calcium channel blockers or nitrates at reducing ischemia and angina symptoms.[10]

Nesukay demonstrated that directly adding trimetazidine to β-blockers in over 1400 patients with stable angina allowed for a quick reduction in angina symptoms, regardless of whether or not these patients who were on β-blockers were also on nitrates or calcium channel blockers.[11]

Adding trimetazidine to β-blockers: evidence of improved prognosis in ischemic patients

In a recent heart failure registry, approximately 40% of chronic heart failure patients were found to have heart failure of ischemic origin.[12] In a contemporary meta-analysis in nearly 1000 patients with heart failure, of mainly ischemic origin (93%), Gao et al showed that adding trimetazidine significantly reduced all-cause mortality as well as cardiovascular events and hospitalization for heart failure (P<0.01 versus placebo).[13] In post–myocardial infarction patients with stable angina and heart failure, the use of modified-release trimetazidine was related to a significant reduction in major adverse cardiac events (cardiac death, nonfatal myocardial infarction, acute stroke, need for coronary revascularization, and hospitalization for unstable angina or heart failure) after 6 years of follow-up.[14]

Selected abbreviations and acronyms

CABG	coronary artery bypass graft
CAD	coronary artery disease
DES	drug-eluting stent
IHD	ischemic heart disease
MACCE	major adverse cerebrovascular or cardiovascular event
PCI	percutaneous coronary intervention
REACH	REduction of Atherothrombosis for Continued Health
TRIMPOL	TRIMetazidine in POLand

Adding trimetazidine to decrease ischemic reperfusion injury during revascularization and angina recurrence afterwards

Labrou et al have investigated whether the administration of trimetazidine before and after PCI minimizes procedure-induced myocardial damage and improves left ventricular function 1 and 3 months after PCI.[15] Twenty-four hours after PCI, troponin I levels were >1 ng/mL in 26% of patients treated with trimetazidine versus 44% of patients in the control group. Forty-eight hours after revascularization, troponin levels remained elevated in 15% vs 32% of patients. About a fifth (22%) of patients in the trimetazidine group had creatine kinase MB (CK-MB) levels >5 ng/mL, 24 hours after PCI, compared with 40% in the control group.

The number of patients with an ejection fraction <50% was significantly reduced in the trimetazidine-treated group compared with the control group at 1 and 3 months after PCI: 11% versus 16% (P=0.046) after 1 month and 4% versus 16% (P=0.017) after 3 months. A significant improvement in regional wall motion versus placebo was noted after treatment with trimetazidine. The use of trimetazidine appeared to minimize myocardial reperfusion injury during PCI and improved global and regional wall motion 1 and 3 months after PCI, according to the authors.

The incidence of stent restenosis has risen, as increasing numbers of patients are treated with drug-eluting stents (DES). Chen et al[16] evaluated whether long-term treatment with trimetazidine reduced the incidence of stent restenosis in 768 patients who underwent PCI with DES. The group on long-term trimetazidine treatment 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 patients exhibited a higher left ventricular ejection fraction than control patients (65.4±10.7% vs 63.1±10.4%; P=0.006). The incidence of major adverse cerebrovascular or cardiovascular events (MACCEs) was also lower in the trimetazidine group at 1-year follow-up (6.1% vs 10.8%; P=0.032). Treatment with trimetazidine was found to predict a reduction in stent restenosis (odds ratio [OR], 0.376; 95% CI, 0.196 to 0.721; P=0.003). The authors concluded that trimetazidine treatment effectively reduced the incidence of stent restenosis and MACCEs 1 year after DES implantation.

Xu et al[17] also appraised the effects of trimetazidine after DES implantation on recurrent angina pectoris and left ventricular structure in elderly patients with multivessel CAD and with diabetes mellitus and a left ventricular ejection fraction >50%. After 2 years, patients in the trimetazidine group were shown to have significant reductions in the incidence and severity of angina pectoris, compared with the control group, as well as a reduction in silent myocardial ischemia and increase in angina pectoris–free survival. Left ventricular function and structure in trimetazidine-treated patients were relatively stable after 2 years, but in control patients these parameters deteriorated. Adjunctive therapy with trimetazidine after DES implantation appears to have a beneficial effect in preventing recurrent angina pectoris as well as in improving left ventricular function and structure in elderly multivessel CAD patients with diabetes.

Conclusion

Chronic IHD is still a significant clinical burden in daily practice, and in stable angina β-blockers and revascularization procedures are extensively used treatments. Although the current pharmacological treatment of angina with vasoactive agents is effective, the addition to therapy of metabolic antianginal agents that act directly at the cardiac cell level could provide further treatment benefits, by targeting alternative mechanisms of ischemia. Moreover, use of these metabolic agents during and after revascularization procedures may also offer additional benefits, by decreasing ischemic reperfusion injury and decreasing angina recurrence. Targeting the cardiac cell directly and addressing the energetic origin of ischemia with metabolic agents—such as trimetazidine—on top of treatment with vasoactive agents—such as β-blockers—seems a clinically pertinent strategy for managing IHD as effectively as possible. ■

References

1. 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: the Heart and Soul Study. *Arch Intern Med.* 2008;168:1423-1428.
2. Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J.* 2006; 27:1610-1619.
3. Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA.* 2007; 297:1197-1206.
4. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). *Circulation.* 2011;124:2423-2432.
5. Montalescot G, Sechtem U, Achenbach S, et al; Task Force Members. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* 2013;34:2949-3003.
6. Crea F, Camici PG, De Caterina R, Lanza GA. Chronic ischaemic heart disease. In: Camm AJ, Lüscher TF, Serruys PW, eds. *The ESC Textbook of Cardiovascular Medicine.* 2nd ed. New York, NY: Oxford University Press Inc.; 2009.
7. Marzilli M, Merz CN, Boden WE, et al. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *J Am Coll Cardiol.* 2012;60:951-956.
8. Szwed H, Sadowski Z, Elikowski W, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). TRIMetazidine in POLand. *Eur Heart J.* 2001;22:2267-2274.
9. Michaelides AP, Spiropoulos K, Dimopoulos K, Athanasiades D, Toutouzas P. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina. *Clin Drug Invest.* 1997;13:8-14.
10. Danchin N, Marzilli M, Parkhomenko A, Ribeiro JP. Efficacy comparison of trimetazidine with therapeutic alternatives in stable angina pectoris: a network meta-analysis. *Cardiology.* 2011;120:59-72.
11. Nesukay E. Assessment of the most effective combination of antianginal medications in the treatment of patients with stable angina pectoris. *Circulation.* 2012;125:e773. doi:10.1161/CIR.0b013e31824fcdb3. Poster P144.
12. Maggioni AP, Dahlström U, Filippatos G, et al; Heart Failure Association (HFA) of the European Society of Cardiology. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2013;15:808-817.
13. Gao D, Ning N, Niu X, Hao G, Meng Z. Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. *Heart.* 2011;97:278-286.
14. Lopatin YM, Ilyukhin OV, Ilyukhina MV, Kalganova EL, Tarasov DL, Ivanenko VV. Long-term trimetazidine modified release therapy improves prognosis in post-myocardial infarction patients with angina pectoris and heart failure. *Eur Heart J.* 2012;33(suppl abstract):346-347. Abstract 2052.
15. Labrou A, Giannoglou G, Zioutas D, Fragakis N, Katsaris G, Louridas G. Trimetazidine administration minimizes myocardial damage and improves left ventricular function after percutaneous coronary intervention. *Am J Cardiovasc Drugs.* 2007;7:143-150.
16. 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; 174:634-639.
17. 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;34:251-258.

Keywords: *β-blocker; cardiac metabolism; myocardial ischemia; revascularization; stable angina; trimetazidine*