Anti-ischemic cardioprotection with trimetazidine

Pericle Di Napoli

Cardiovascular Section, SMDN-Centre for Cardiovascular Medicine and Cerebrovascular Disease Prevention, Sulmona (AQ), Italy; Villa Pini d'Abruzzo Clinic, Department of Cardiology, Heart Failure Unit, Chieti, Italy

Correspondence: Dr Pericle Di Napoli, Cardiovascular Section, SMDN-Centre for Cardiovascular Medicine and Cerebrovascular Disease Prevention, Via Trento, 41, 67039 Sulmona (AQ), Italy.
Tel/fax: +0039 0864 52716; e-mail: dinapoli@unich.it

Conflicts of interest: None.

Abstract

Alterations in cardiac metabolism are present in ischemic heart disease and heart failure, suggesting an increased utilization of non carbohydrate substrates for energy production, with a reduction in the efficiency of myocardial oxygen consumption and ischemia-reperfusion damage. A direct approach to the manipulation of cardiac energy metabolism consists in modifying substrate utilization. Trimetazidine is a pharmacological agent shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism. Recent studies suggest that trimetazidine has a positive influence on ischemia-reperfusion damage, endothelial function, and prognosis in patients with coronary artery disease.
■ *Heart Metab.* 2008;41:25–29.

Keywords: Endothelium, myocardial ischemia, nitric oxide, reperfusion damage, trimetazidine

The ischemia-reperfusion damage: from bench to bedside

It is commonly accepted that a rapid re-opening of an occluded vessel, by either mechanical means (coronary angioplasty or bypass surgery) or pharmacological means (thrombolytic or antiplatelet drugs), should be performed as soon as possible in patients with acute coronary syndromes. The opening of a coronary artery or the interruption of an ischemic period, such as in effort angina, exposes the entire heart to a complex cascade of events, so-called ''reperfusion injury'', that influences the final amount of cellular damage, the endothelial function, the degree of mechanical dysfunction, and the short- and long-term prognosis. Reperfusion injury may affect various aspects of myocardial and endothelial function, with different and complex pathophysiological consequences [1]. The term encompasses several events, including microvascular damage, reperfusion arrhythmias, reversible myocardial mechanical dysfunction (stunning), and cell death (apoptosis or necrosis). Oxidative stress, intracellular calcium overload, neutrophil activation, metabolic alterations, and excessive intracellular osmotic load have all been proposed to explain the pathogenesis and consequences of inflammatory injury in ischemic reperfused myocardium.

Inflammatory and endothelial damage

The inflammatory process characterizes early and late reperfusion and is involved in tissue damage. Neutrophils feature prominently in the inflammatory component of post-ischemic injury. Ischemia-reperfusion prompts a release of oxygen free radicals, cytokines, and other proinflammatory mediators that activate

Focus on Vastarel MR
Pericle Di Napoli

both the neutrophils and the coronary vascular endothelium [2]. Activation of these cells promotes the expression of adhesion molecules on both neutrophils and the endothelium; these recruit neutrophils on the endothelial surface and initiate a specific cascade of cell–cell interactions. This specific series of events is a prerequisite for the full expression of reperfusion injury, including endothelial dysfunction, microvascular collapse, impairment of blood flow (''no-reflow'' phenomenon), myocardial infarction and apoptosis [3]. Endothelium-derived factors, such as nitric oxide and adenosine, exhibit a wide range of effects against neutrophil-mediated events and modulate the inflammatory response after reperfusion [3]. Alterations in endothelial function are pivotal in the development of reperfusion damage and the no-reflow phenomenon; here, the enhanced release or increased bioavailability of nitric oxide appears to be central. Besides its well known vasodilatory effects, nitric oxide reduces microvascular dysfunction, platelet adhesion and aggregation, and leukocyte adherence or emigration [3,4].

Apoptotic cell death

Apoptosis is an energy-requiring physiological mechanism of cell death that regulates cell mass in many tissues; it is a genetically directed process that takes place in response to internal or external stimuli. Cardiomyocyte apoptosis has important pathophysiological consequences, contributing to functional abnormalities in the myocardium. It has been reported in a variety of cardiovascular diseases, including myocardial infarction or ischemia [5] and endstage heart failure [6]; a specific association with reperfusion injury has been suggested [7]. The cellular mechanisms underlying both ischemia-reperfusion injury and apoptosis may involve cellular calcium overload, left ventricle wall stresses, overproduction of oxygen-derived free radicals, cellular acidosis, inflammatory reaction, and microcirculatory dysfunction [7–9].

Metabolic changes

A metabolic protection of the ischemic myocardium appears to be a key factor in limiting reperfusion damage [9–11]. Major metabolic changes occurring during the early hours of myocardial infarction include increased secretion of catecholamines and production of circulating free fatty acids (FFAs). Under normal conditions, the myocardium depends on aerobic metabolism, with FFAs as the preferred energy source. During ischemia-reperfusion, FFA concentrations are greatly increased, and exert a toxic effect on the myocardium. This results in increased membrane damage, endothelial dysfunction, tissue inflammation, and decreased cardiac function. Decreasing plasma FFA concentrations and cardiac fatty acid oxidation, together with the stimulation of glucose and lactate uptake, might reduce these detrimental effects. This might be achieved by glucose–insulin–potassium (GIK) solutions at the time of reperfusion [12] and by inhibiting fatty acid oxidation with 3-ketoacyl coenzyme A thiolase inhibitors, such as trimetazidine [9].

Anti-ischemic cardioprotection with trimetazidine

The anti-ischemic cardioprotection achieved with trimetazidine may involve several aspects, summarized in *Table I* and *Figure 1*.

Trimetazidine limits accumulation of Na^+ and Ca^{2+} and depresses intracellular acidosis

Dysregulation of intracellular Ca^{2+} homeostasis plays an important part in mediating myocardial injury. A marked increase in cytosolic free Ca^{2+} has been reported in ischemic myocardial injury, and the occurrence of intracellular Ca^{2+} overload has been suggested to lead to arrhythmias, contractile failure, and cell death. It has been proposed that trimetazidine has a key role in limiting the intracellular accumulation of protons that is responsible for cell acidosis during ischemia (*Figure 1*). Under conditions of acid load such as no-flow ischemia, trimetazidine acts in a dose- and time-dependent way in limiting the accumulation of Na^+ and Ca^{2+} inside cardiac cells and depressing intracellular cell acidosis [13]. Trimetazidine also maintains intracellular adenosine triphosphate concentrations and increases plasma concentrations of adenosine, a nucleoside with protective

Table I. Anti-ischemic cardioprotection with trimetazidine: main effects.

Metabolic efficiency: shifting of ATP production to glucose oxidation, a more energetically efficient pathway
Protection of endothelial function (increase in endothelial nitric synthase activity and nitric oxide availability; reduction in endothelin-1)
Modulation of the myocardial inflammatory reaction (reduction of neutrophil infiltration and activation)
Limitation of accumulation of Na^+ and Ca^{2+} and intracellular acidosis
Reduction in necrotic and apoptotic cell death
Preservation of mitochondrial functions (reduction in mitochondrial permeabilization)
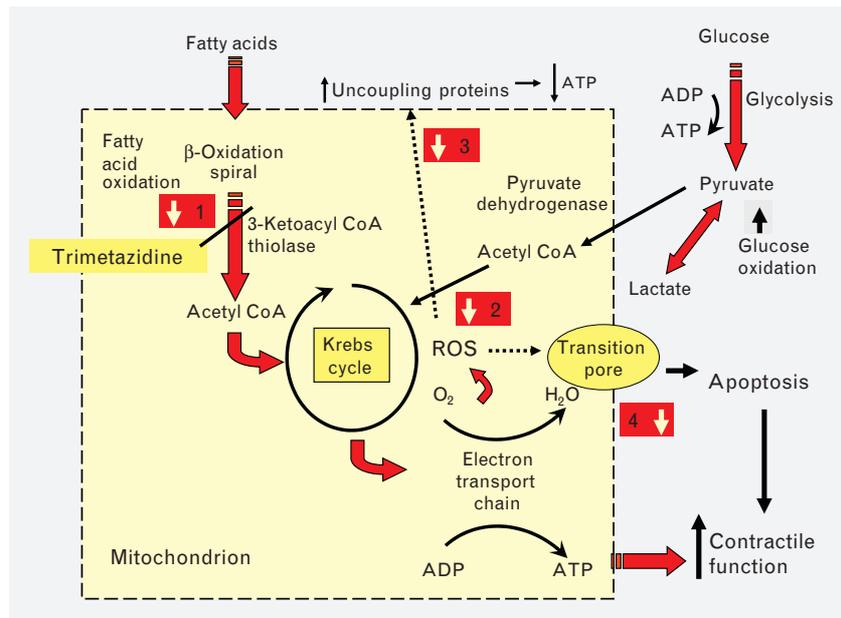Protection against toxicity induced by oxygen free radicals

Figure 1. Mechanisms of mitochondrial anti-ischemic effects of trimetazidine: from metabolism to myocardial protection. During myocardial ischemia-reperfusion or heart failure, increased catecholamine concentrations activate β-adrenergic pathways in adipocytes, thereby increasing systemic free fatty acid concentrations. Fatty acids are activated inside the cardiomyocyte to form long-chain fatty acyl coenzymes A, which may induce gene expression of cardiac-enriched uncoupling proteins and enter the mitochondrial fatty acid β-oxidation spiral. Reducing equivalents generated subsequently enter the mitochondrial respiratory chain complexes, resulting in the generation of a proton gradient across the inner mitochondrial membrane. Protons located within the intermitochondrial membrane space re-enter the mitochondrial matrix through ATP synthase, resulting in mitochondrial ATP synthesis. Mitochondrial ATP is exported to the cytosol by adenine nucleotide translocator, proposed to form part of the mitochondrial permeability transition pore. With increased β-adrenergic stimulation and mitochondrial fatty acid β-oxidation, concentrations of mitochondrial reactive oxygen species (ROS) may increase and activate uncoupling proteins or promote transition pore opening, or both. This in turn will result in proton leakage and dissipation of the membrane potential, thereby diminishing mitochondrial ATP production. Transition pore opening will also trigger programmed cell death (apoptosis). Acute or chronic administration of trimetazidine induces the partial inhibition of fatty acid β-oxidation (1) and determines the increase in glucose oxidation, energetically useful in ischemic heart. These metabolic changes could induce a reduction in ROS-induced cell damage (2), and in uncoupling proteins (3), with an inhibition of apoptosis (4). The final effect is a reduction in cellular damage and an improvement in cardiac function.

effects in myocardial ischemia [14]. In a recent randomized, double-blind, cross-over study comparing placebo and trimetazidine, Fragasso et al [15] assessed the effects of trimetazidine on the left ventricular phosphocreatine and adenosine triphosphate (PCr : ATP) ratio in patients with heart failure by means of in-vivo phosphorus-31 magnetic resonance spectroscopy. The mean cardiac PCr : ATP ratio was increased by 33% with trimetazidine, suggesting that the effects of trimetazidine are associated with the preservation of myocardial high-energy phosphate concentrations.

Trimetazidine reduces cell damage: necrosis and apoptosis

Various studies demonstrated that, in experimental conditions, trimetazidine reduces the myocardial damage caused by ischemia-reperfusion [9]. In patients with acute myocardial infarction, pretreatment with trimetazidine (40 mg orally about 15 min

before thrombolysis, and then 20 mg every 8 h) can decrease the time to creatine kinase normalization, suggesting that trimetazidine reduces reperfusion damage and infarct size in patients with acute myocardial infarction who undergo thrombolysis, and affects remodeling after myocardial infarction [16]. Ruixing et al [17] reported that, in a rabbit model of ischemia-reperfusion, trimetazidine also reduced cardiomyocyte apoptosis and ischemia-reperfusion injury via antioxidant properties.

Trimetazidine preserves mitochondrial functions

Mitochondria are key factors in energy production in cells. Lipid oxidation is responsible for the production of much ATP resynthesis in the heart, but this process is less oxygen-efficient than glucose oxidation. During ischemia, lipid oxidation is suddenly blocked, but it is markedly increased during reperfusion, causing accumulation of potentially toxic metabolites (acyl

carnitines, acyl coenzyme A, lysophospholipids). Trimetazidine inhibits the production of deleterious lipid metabolites and it can also reduce mitochondrial damage, inhibiting mitochondrial permeability transition-pore opening, and protects the heart from prolonged ischemia-reperfusion injury [18].

Trimetazidine protects against toxicity induced by oxygen free radicals

In mitochondria and endothelial or myocardial cells, trimetazidine reduces membrane damage induced by oxygen free radicals. This effect has also been reported in red cells after oral administration [19]. The drug acts as a potent antioxidant, and this mechanism of action could explain its cardioprotective role during ischemia and reperfusion, in which oxygen free radicals are generated and implicated in cardiac cell injury. Trimetazidine, at concentrations greater than $100\ \mu mol/L$, competed with cytochrome *c* in scavenging oxy radicals formed by the reaction catalyzed by the action of the xanthine oxidase enzyme upon xanthine. This scavenger effect was also observed when oxy radicals were generated by active human neutrophils [20].

Trimetazidine protects endothelial function and modulates the myocardial inflammatory reaction

Various studies have demonstrated that trimetazidine reduces inflammation and improves endothelial function in both acute conditions (ischemia-reperfusion damage, coronary angioplasty, thrombolysis) and chronic conditions (ischemic cardiomyopathy, stable angina). Trimetazidine maintains the integrity of cell membranes and of mitochondrial structure, and ensures the protection of myocardial cells that are at risk (*Figure 1*). Trimetazidine also protects postischemic hearts from neutrophil-mediated injury [21]. Tritto et al [22] reported that trimetazidine inhibited neutrophil activation in vitro and reduced cardiac oxygen radical production at reflow, independently of direct scavenger effects. Trimetazidine is also a useful drug in preventing inflammation after percutaneous transluminal coronary angioplasty (PTCA) [23,24]. Pre-procedural treatment with oral trimetazidine for 3 days significantly suppressed the increase in inflammatory markers before and shortly after PTCA [24]. Recent studies have analyzed the impact of trimetazidine on markers of inflammation in chronic ischemic heart disease. In patients with ischemic cardiomyopathy, we found [25] that plasma concentrations of C-reactive protein remained unchanged in the group of patients receiving trimetazidine, whereas a progressive increase in concentration was seen throughout the follow-up period (18 months) in the control group; this anti-inflammatory effect could be involved in the significant reduction in mortality and admissions to hospital observed in the same patients after 48 months of treatment [26]. In addition, a decrease in the serum concentrations of endothelin-1 has been reported in patients with diabetes receiving treatment with trimetazidine, both after short-term (2 weeks) and after long-term (6 months) treatment [27]. The mechanisms responsible for these favorable effects of trimetazidine on the inflammatory profile and endothelial function are poorly known. We have reported [28] that, in isolated rat heart subjected to ischemia and reperfusion, trimetazidine reduced ischemia-reperfusion damage and increased endothelial nitric oxide synthase mRNA and protein concentrations. In this way, trimetazidine exerts a significant, nitric-oxide-dependent, cardioprotection against ischemia-reperfusion injury and preserves the coronary endothelium. Preservation of the production of endothelial nitric oxide synthase and its bioavailability appears also to be a critical factor in the decrease in release of endothelin-1 and the preservation of endothelial function. Recently, Belardinelli et al [29] reported that trimetazidine improved endothelium-dependent relaxation in patients with ischemic cardiomyopathy. This effect was associated with antioxidant properties as measured by a reduction in plasma malondialdehyde and lipid hydroperoxide concentrations.

Conclusions

In the ischemic myocardium, metabolic antianginal treatment with trimetazidine induces a shift from utilization of FFAs towards utilization predominantly of glucose, increasing ATP generation per unit of oxygen consumption. This represents an innovative approach to the treatment of ischemic heart disease and to the reduction of ischemia-reperfusion damage. Trimetazidine offers unique positive effects and it is useful in improving ischemic cell metabolism and in reducing cell injury and endothelial dysfunction. All these effects could be clinically relevant, improving prognosis and quality of life in patients with coronary artery disease. ■

REFERENCES

1. Ambrosio G, Tritto I. Reperfusion injury: experimental evidence and clinical implications. *Am Heart J*. 1999;138:S69–S75.
2. Becker IC, Ambrosio G. Myocardial consequences of reperfusion. *Prog Cardiovasc Dis*. 1987;30:23–41.
3. Jordan JE, Zhao ZQ, Vinten-Johansen J. The role of neutrophils in myocardial ischemia-reperfusion injury. *Cardiovasc Res*. 1999;43:860–878.
4. Di Napoli P, Taccardi AA, De Caterina R, Barsotti A. Pathophysiology of ischemia-reperfusion injury: experimental data. *Ital Heart J*. 2002;3 (suppl 4):24S–28S.

5. Ruixing Y, Dezhai Y, Jiaquan L. Effects of cardiotrophin-1 on hemodynamics and cardiomyocyte apoptosis in rats with acute myocardial infarction. *J Med Invest*. 2004;51:29–37.

6. Sharov VG, Sabbah HN, Shimoyama H, Goussev AV, Lesch M, Goldstein S. Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. *Am J Pathol*. 1996;148:141–149.

7. Fliss H, Gattinger D. Apoptosis in ischemic and reperfused rat myocardium. *Circ Res*. 1996;79:949–956.

8. Di Napoli P, Taccardi AA, Grilli A, et al. Left ventricular wall stress as a direct correlate of cardiomyocyte apoptosis in patients with severe dilated cardiomyopathy. *Am Heart J*. 2003;146:1105–1111.

9. Barsotti A, Di Napoli P. Trimetazidine and cardioprotection during ischemia-reperfusion. *Ital Heart J*. 2004;5:29S–36S.

10. Lopaschuk GD, Saddik M. The relative contribution of glucose and fatty acids to ATP production in hearts reperfused following ischemia. *Mol Cell Biochem*. 1992;116:111–116.

11. Oliver MF, Opie LH. Effects of glucose and fatty acids on myocardial ischemia and arrhythmias. *Lancet*. 1994;343:155–158.

12. Díaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. *Circulation*. 1998;98:2227–2234.

13. El Banani H, Bernard M, Baetz D, et al. Changes in intracellular sodium and pH during ischaemia-reperfusion are attenuated by trimetazidine. Comparison between low- and zero-flow ischaemia. *Cardiovasc Res*. 2000;47:688–696.

14. Blardi P, de Lalla A, Volpi L, Auteri A, Di Perri T. Increase of adenosine plasma levels after oral trimetazidine: a pharmacological preconditioning? *Pharmacol Res*. 2002;45:69–72.

15. Fragasso G, Perseghin G, De Cobelli F, et al. Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. *Eur Heart J*. 2006;27:942–428.

16. Di Pasquale P, Lo Verso P, Bucca V, et al. Effects of trimetazidine administration before thrombolysis in patients with anterior myocardial infarction: short-term and long-term results. *Cardiovasc Drugs Ther*. 1999;13:423–428.

17. Ruixing Y, Wenwu L, Al-Ghazali R. Trimetazidine inhibits cardiomyocyte apoptosis in a rabbit model of ischemia reperfusion. *Transl Res*. 2007;149:152–160.

18. 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;39:893–899.

19. Maridonneau-Parini I, Harpey C. Effects of trimetazidine on membrane damage reduced by oxygen free radicals in human red cells. *Br J Clin Pharmacol*. 1985;20:148–151.

20. Guarnieri C, Muscari C. Anti oxy-radical properties of trimetazidine. *Res Commun Chem Pathol Pharmacol*. 1989;64:215–225.

21. Williams FM, Tanda K, Kus M, Williams TJ. Trimetazidine inhibits neutrophil accumulation after myocardial ischaemia and reperfusion in rabbits. *J Cardiovasc Pharmacol*. 1993;22:828–833.

22. 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;46:89–98.

23. Kuralay F, Altekin E, Yazlar AS, Onvural B, Goldeli O. Suppression of angioplasty-related inflammation by preprocedural treatment with trimetazidine. *Tohoku J Exp Med*. 2006;208:203–212.

24. 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.

25. Di Napoli P, Taccardi AA, Barsotti A. Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. *Heart*. 2005;91:161–165.

26. Di Napoli P, Di Giovanni P, Gaeta MA, Taccardi AA, Barsotti A. Trimetazidine and reduction in mortality and hospitalization in patients with ischemic dilated cardiomyopathy: a post hoc analysis of the Villa Pini d'Abruzzo Trimetazidine Trial. *J Cardiovasc Pharmacol*. 2007;50:585–589.

27. Fragasso G, Piatti PM, Monti L, et al. Short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am Heart J*. 2003;146:E18–E25.

28. Di Napoli P, Chierchia S, Taccardi AA, et al. Trimetazidine improves post-ischemic recovery by preserving endothelial nitric oxide synthase expression in isolated working rat hearts. *Nitric Oxide*. 2007;16:228–236.

29. Belardinelli R, Solenghi M, Volpe L, Purcaro A. Trimetazidine improves endothelial dysfunction in chronic heart failure: an antioxidant effect. *Eur Heart J*. 2007;28:1102–1108.