Metabolic remodeling as a target preventing myocardial dysfunction: focus on trimetazidine

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Abstract

During the past decade significant declines in cardiovascular mortality have been observed due to the wider use of reperfusion and the optimization of medical therapy. Although rates of procedural success are high in patients with acute and chronic ischemic heart disease, improvement in heart function is not always achieved due to reperfusion injury, microvascular obstruction and the no-reflow syndrome. Insufficient oxygen supply and lack of metabolic adaptation lead to the activation of a complex cascade of reactions including increased reactive oxygen species production, activation of oxidative stress, cellular damage, triggering of apoptosis, progressive cell loss and deposition of extracellular collagen matrix. These mechanisms lead to heart remodeling and progression of heart failure, and have similar features to those of nonischemic cardiopathy. Malicious metabolic remodeling may be prevented by protective mechanisms such as ischemic preconditioning, heart metabolism switch to more efficient energy substrate utilization and transfer. Therefore, adjunctive metabolic medical therapy is being recognized as a reasonable therapeutic option. Of the available therapies, trimetazidine is one of the most effective drugs with confirmed clinical benefits. The mechanisms of heart protection targeted by trimetazidine are quite complex and are reviewed in this article. ■ Heart Metab; 2014;62:22–26

Keywords: Cardiomyopathy; ischemia; metabolic remodeling; reperfusion; trimetazidine.

Introduction

Despite advances in the management of patients with ischemic heart disease, the greater accessibility of timely invasive and surgical care and a decline in mortality outcomes are still not always satisfactory. The importance of adjunctive therapies targeting different mechanisms of alteration in heart metabolism is being increasingly recognized.

Reperfusion is usually associated with a rapid reintroduction of coronary blood flow into the ischemic region, and may cause the activation of a complex enzymatic cascade of reactions leading to additional cellular damage and myocardial cell loss, finally resulting in heart remodeling, the development of ischemic cardiomyopathy and heart failure. Heart remodeling is a complex process involving "genome expression, molecular, cellular and interstitial changes that are manifested clinically in changes in size, shape and function of the heart after cardiac injury" [1]. Mechanisms decreasing cellular wall permeability and preventing cellular damage by optimization of heart metabolism, switching energy substrate from fatty acid utilization towards glucose oxidation and reducing oxidative stress are currently being studied. Therefore

Abbreviations

CRP: C-reactive protein; **FFA:** free fatty acid; **MI:** myocardial infarction; **mPTP:** mitochondrial permeability transition pore; **ROS:** reactive oxygen species; **TNFα:** tumor necrosis factor alpha

an understanding of metabolic cascades triggered by ischemic insult help to develop means of acute and long-term therapeutic cardiac protection.

Among the available drugs with cardioprotective properties, trimetazidine (1-[2,3,4-trimethoxy-benzyl] piperazine dihydrochloride) is one with clinical efficacy. Recent large acute myocardial infarction (MI) registry data (KAMIR) suggest survival benefits and a reduction in the incidence of new MI in patients treated with trimetazidine [2]. The drug has antianginal effects and shows clinical benefit in patients with recurrent angina, although its direct impact on heart contractility and vascular resistance is disputable [3, 4]. Trimetazidine has complex potential targets among which are oxidative stress, inflammatory pathways and endothelial

function, and it improves heart rate variability in patients with ischemic cardiopathy suggesting a broader spectrum of indications [5].

Heart metabolism and trimetazidine

Trimetazidine is a selective 3-ketoacyl-coenzyme A thiolase inhibitor reducing free fatty acid (FFA) oxydation. Inhibition of FFA oxidation shifts metabolism towards glucose oxidation. Glucose is more efficient than FFA and requires less oxygen for equivalent ATP production. Glucose uptake is regulated inversely by FFA. This effect may be achieved by targeting β-oxidation inhibition using trimetazidine (*Figure 1*).

In general, heart function depends largely on oxygen supply/demand and energy metabolism. Energy metabolism could be briefly described as three major cascades of reactions: substrate utilization, high energy phosphate production by oxidative phosphorylation and energy transfer and utilization [6]. Substrate utilization mainly involves FFA uptake and oxidation and to a lesser extent glycolysis. Energy transfer starts in the mitochondria where ATP is transformed
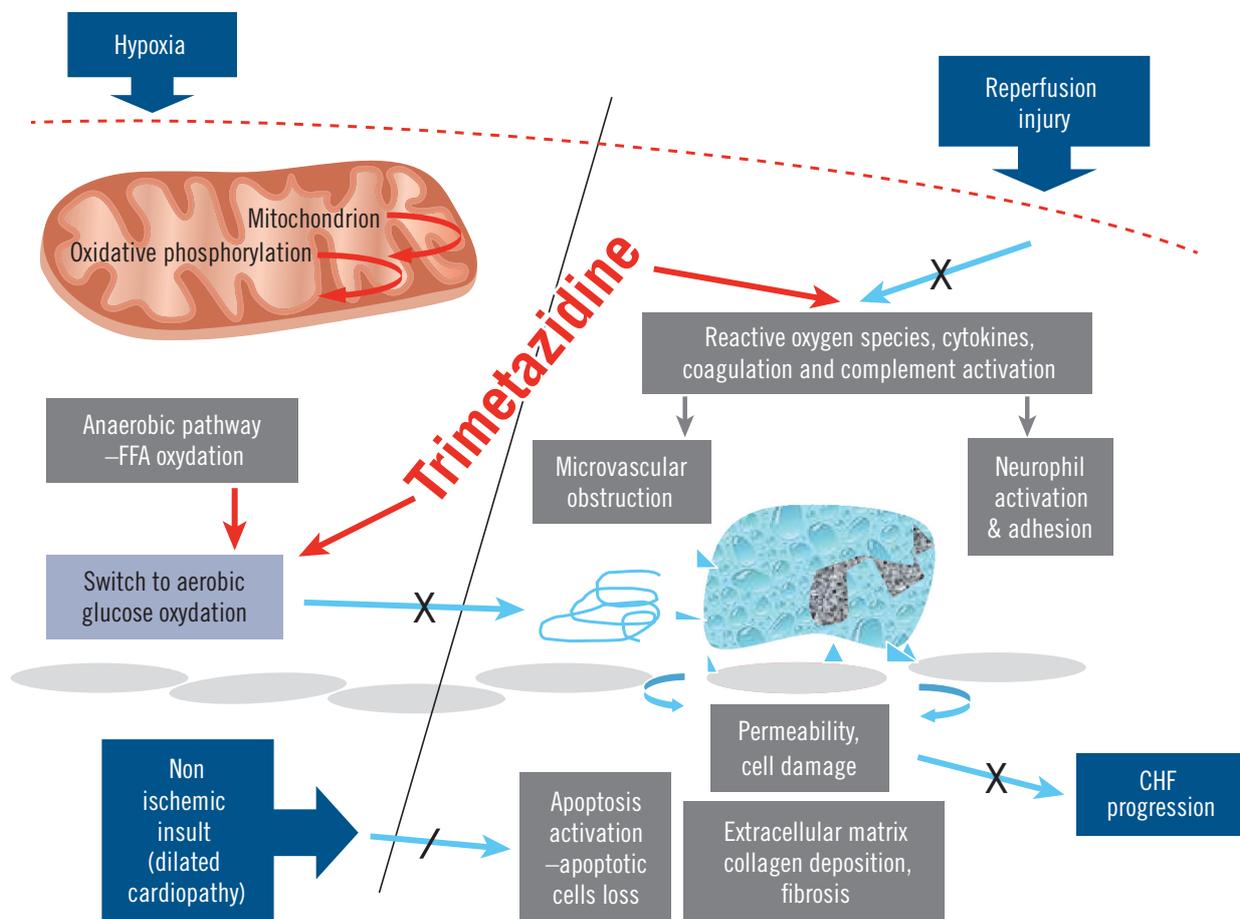

Fig. 1 *Mechanisms of myocardial protection and applications of trimetazidine. CHF, congestive heart failure; FFA, free fatty acid.*

to phosphocreatine and ADP. Phosphocreatine leaves the mitochondria and enters the cytosol where reformation of ATP is catalyzed and free creatine re-enters the mitochondria [6]. Phosphorylation is important for energy-dependent Ca^{2+} sensitivity and cycling, and Ca^{2+}-dependent Ca release is one of the cornerstones of contraction. It activates myofilaments by binding to troponin C, which influences the interaction between actin and myosin. Then Ca^{2+} is removed back to the sarcoplasmatic reticulum by Ca^{2+} ATPase and outside the cell by the Na/Na exchanger in the presence of K^+/Na^+-ATPase. In settings of myocardial ischemia inhibition of Na^- may occur due to energy deficit and results in intracellular Na^+ and Ca^{2+} overload and enhanced production of reactive oxygen species (ROS) and intracellular acidosis.

Importantly, in low-flow states and in heart failure patients trimetazidine influences all three cascades of reactions: energy source utilization by FFA oxidation antagonism; energy transfer and utilization maintaining phosphocreatine concentrations; intracellular ATP, reducing intracellular Na^+ and Ca^{2+} load and diminishing intracellular acidosis [7].

Adaptation and maladaptation

Heart metabolism is flexible and exhibits a great extent of adaptation. Under physiological conditions an increase in glycogen oxidation and prolonged glucose and lactate oxidation is observed and FFA metabolism is not greatly affected. In pathological conditions, such as ischemia, diabetes switch to fatty acid metabolism is present. Depletion of adaptation capabilities in settings of increased oxygen demand or decreased coronary blood flow leads to metabolic remodeling when the heart loses the flexibility of metabolism switch from one to another energy source. During ischemia long-chain saturated fatty acid oxidation is associated with diminished myocyte function and may induce apoptosis. Alternatively, enhanced glucose uptake and glucose transporter overexpression reduces ischemia-induced apoptosis [8].

Diminished coronary perfusion leads to decreased oxygen consumption and activation of maladaptive pathways. Reversible changes occur in hibernating myocardium with preserved viability and reduced oxygen demand. Short-term hibernation is associated with reduced Ca responsiveness while prolonged hibernation may result in fetal gene expression and metabolic switch from fat to glucose metabolism,

glycogen accumulation and changes in cells signaling, an increase in the number of dysfunctional mytochondria, collagen deposition, macrophage infiltration, fibrosis, depletion of sarcomeres and activation of cell loss mechanisms. More profound changes occur in stunned myocardium and result from inhibition of Na-K-ATPase, an increase in intracellular Na^+ and Ca^{2+} overload and stimulation of ROS production and depression of contractile function in near normal coronary flow. ROS production may be opposed to some extent by trimetazidine. Electronic paramagnetic resonance spectroscopy revealed that cardiac oxygen radical production at reflow was reduced by trimetazidine independently of direct scavenger effects [9].

Necrotic and apoptotic cell loss, inflammation, endothelial function and myocardial protection with trimetazidine

Ischemia, hibernation, stunning and cell damage may coexist. In response to prolonged ischemia a complex cascade of changes in cell metabolism and signaling may lead to myocardial injury and trigger further structural remodeling. Ischemia-associated heart remodeling involves different mechanisms, such as necrotic or apoptotic cell loss due to atherothrombosis and secondary to coronary microembolization and microvascular dysfunction in the presence of patent epicardial flow. Microvascular obstruction after reperfusion and activation of the expression of abnormal genes are leading to apoptotic cell loss, electrophysiological remodeling and inflammation with leukocyte infiltration. In viable cardiomyocytes adjacent to microinfarct zones the overexpression of tumor necrosis factor alpha (TNFα) triggering apoptosis is observed [10]. Microvascular dysfunction may occur after reperfusion and it is characterized by diminished microvascular tissue perfusion, injury, microthrombosis and extravascular compression of capillaries [11].

Necrotic cell loss results from a no-flow state or reperfusion injury and is remarkable for an increase in mitochondrial membrane permeability, cell swelling, lysis and the fragmentation of cell structures and activation of inflammatory pathways. Apoptotic cell death occurs in low-flow states and may be triggered by severe energy depletion and ATP deficit and also by reperfusion injury. Apoptosis follows either intrinsic mitochondria-mediated or extrinsic membrane-mediated pathways. Oxidative stress and the accumulation of ROS and Ca^{2+} overload contribute to caspase activation. The intrinsic

pathway involves these mechanisms impacting voltage-anion channel-gated functioning of the mitochondrial permeability transition pore (mPTP). mPTP opening is caused mainly by reperfusion and facilitates a release in cytosol apoptosis-inducing factors [12]. The extrinsic pathway is receptor-mediated and may be activated by oxidative stress late after reperfusion.

These metabolic changes may be attenuated by protective mechanisms. It has been proved that repetitive short episodes of ischemia may induce more effective adaptation to subsequent ischemia by receptor-mediated ischemic preconditioning. Ischemic preconditioning is being executed by mitochondrial mKATP channel opening and the prevention of mPTP opening [13, 14].

Trimetazidine influences mitochondrial membrane permeability and apoptotic cell loss diminishing oxidative stress and inhibiting mPTP opening, and also reduces caspase 3 activity [15]. The prevention of necrotic cell loss and limitation of inflammatory cascades may also be achieved using trimetazidine before reperfusion [16]. In several studies it has been demonstrated that pretreatment with trimetazidine limits the effects of myocardial ischemia during percutaneous angioplasty [17]. The efficacy of trimetazidine in terms of the prevention of ischemia–reperfusion injury may be attributable to the lowered generation of ROS and activation of "defensive" signaling pathways [18]. The drug administered before reperfusion ameliorates myocardial injury by activation of the pro-survival Akt enzyme and p38 mitogen-activated protein kinase [19].

Attenuating extensive tissue injury the drug also reduces the systemic inflammation associated with reperfusion. Kuralay et al reported that in patients with coronary artery disease undergoing percutaneous intervention, 3 days' pretreatment with trimetazidine (60 mg/day) was associated with lower levels of C-reactive protein (CRP), TNFα and nitrites, suggesting an anti-inflammatory effect [16]. In experimental studies, trimetazidine inhibited neutrophil accumulation after myocardial ischemia and reperfusion and reduced neutrophil-mediated injury [9, 20].

In excessive cytokine (TNFα, IL-1, IL-6), chemokine and platelet activation, complement-mediated cascades may enhance myocardial injury and dysfunction. TNFα may act by "immediate" and "late" nitric oxide (NO)-dependent pathways [21]. Alterations in NO synthesis regulation and sensitivity, downregulation of eNOS and progressive endothelial dysfunction increase in vasoconstrictive endothelin 1 release, resulting from reperfusion damage and no-reflow phenomenon are important contributors to myocardial dysfunction. Di Napoli et al demonstrated in an experimental study beneficial effects of trimetazidine on eNOS exporession partially preventing the progression of these mechanisms [22].

Changes in cell shape and functional properties, cell loss, collagen deposition in the extracellular matrix and fibrosis are attributable to ischemic and non-ischemic heart remodeling; therefore, the heart protection mechanism to some extent shares similar features in ischemic and dilated cardiomyopathy. Major factors contributing to cell injury and the extent and reversibility of dysfunction are the severity of the ischemic episode, the presence of preconditioning, time to reperfusion along with other influences such as environmental factors and comorbidities (eg, diabetes or glucose intolerance). It has been reported that in patients with chronic ischemic heart disease trimetazidine exhibits anti-inflammatory properties. In a study of patients with ischemic dilated cardiomyopathy CRP-levels remained unchanged in the trimetazidine arm during the 18-month period of follow-up, whereas in controls a progressive increase in CRP was registered [23]. Similarly, in diabetes patients with idiopathic dilated cardiomyopathy steady levels of CRP were registered at 6 months after study initiation in the trimetazidine group as opposed to a significant CRP increase in controls. It should be noted that in that study therapy with trimetazidine was associated with a decline in N-terminal pro brain natriuretic peptide levels, improvement in left ventricular contractility and prolonged 6-minute walk test [24]. The better performance of trimetazidine in diabetes patients with idiopathic dilated cardiomyopathy may be partly explained also by the extracardiac effects of the drug, which beyond cardiac FFA oxidation impacts whole body insulin sensitivity countering the myocardial damage of insulin resistance, as was hypothesized by the authors [25]. In addition, the beneficial effects of trimetazidine on heart remodeling in the prevention of nonischemic cardiopathy may be potentially associated with the inhibition of pressure overload-induced cardiac fibrosis through the NADPH oxidase–ROS–connective tissue growth factor signaling pathway [26].

Complex effects of trimetazidine also include electro-physiological effects, such as a reduction of Q–T interval dispersion, beneficial effects on heart rate variability in

patients with ischemic cardiopathy, which may result from an improvement of ATP-dependent signaling and from a reduction in cardiac fibrosis [27, 28].

In summary, in patients with acute and chronic ischemic heart disease, nonischemic dilated cardiopathy associated with low-flow states or deep metabolic heart remodeling, in addition to traditional therapy adjunctive metabolic treatment is a reasonable option [29]. Trimetazidine is a drug with established clinical benefits and a complex mechanism of action, switching heart metabolism from FFA to more effective glucose metabolism, preventing reperfusion injury, activation of inflammatory cascades, endothelial dysfunction, apoptosis, diminishing heart fibrosis and also structural and electrophysiological remodeling. ■

REFERENCES

1. Cohn JN, Ferrari R, Sharpe N (2000) Cardiac remodeling – concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. On behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 35(3):569–582

2. Kim JS, Kim CH, Chun KJ, Kim JH, Park YH, Kim J et al (2013) Effects of trimetazidine in patients with acute myocardial infarction: data from the Korean Acute Myocardial Infarction Registry. Clin Res Cardiol Epub ahead of print

3. Szwed H (2004) Clinical benefits of trimetazidine in patients with recurrent angina. Coron Artery Dis 15(Suppl. 1):S17–21

4. Hu B, Li W, Xu T, Chen T, Guo J (2011) Evaluation of trimetazidine in angina pectoris by echocardiography and radionuclide angiography: a meta-analysis of randomized, controlled trials. Clin Cardiol 34(6):395–400

5. Gunes Y, Guntekin U, Tuncer M, Sahin M (2009) Improved left and right ventricular functions with trimetazidine in patients with heart failure: a tissue Doppler study. Heart Vessels 24(4):277–282

6. Neubauer S (2007) The failing heart – an engine out of fuel. N Engl J Med 356(11):1140–1151

7. Fragasso G, Rosano G, Baek SH, Sisakian H, Di Napoli P, Alberti L et al (2013) Effect of partial fatty acid oxidation inhibition with trimetazidine on mortality and morbidity in heart failure: Results from an international multicentre retrospective cohort study. Int J Cardiol 163(3):320–325

8. Malhotra R, Brosius FC III (1999) Glucose uptake and glycolysis reduce hypoxia-induced apoptosis in cultured neonatal rat cardiac myocytes. J Biol Chem 274(18):12567–12575

9. Tritto I, Wang P, Kuppusamy P, Giraldez R, Zweier JL, Ambrosio G (2005) The anti-anginal drug trimetazidine reduces neutrophil-mediated cardiac reperfusion injury. J Cardiovasc Pharmacol 46(1):89–98

10. Li L, Zhao X, Lu Y, Huang W, Wen W (2010) Altered expression of pro- and anti-inflammatory cytokines is associated with reduced cardiac function in rats following coronary microembolization. Mol Cell Biochem 342(1–2):183–190

11. Reffelmann T, Kloner RA (2002) The "no-reflow" phenomenon: basic science and clinical correlates. Heart ;87(2):162–168

12. Nagata S (1997) Apoptosis by death factor. Cell 88:355–365

13. Argaud L, Gateau-Roesch O, Chalabreysse L et al (2004) Preconditioning delays Ca2+-induced mitochondrial permeability transition. Cardiovasc Res 61(1):115–122

14. Baines CP, Liu GS, Birincioglu M, Critz SD, Cohen MV, Downey JM (1999) Ischemic preconditioning depends on interaction between mitochondrial KATP channels and actin cytoskeleton. Am J Physiol ;276(4 Pt 2):H1361–1268

15. Argaud L, Gomez L, Gateau-Roesch O, Couture-Lepetit E, Loufouat J, Robert D et al (2005) Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. J Mol Cell Cardiol 39(6):893–899

16. Kuralay F, Altekin E, Yazlar AS, Onvural B, Goldeli O (2006) Suppression of angioplasty-related inflammation by pre-procedural treatment with trimetazidine. Tohoku J Exp Med 208(3):203–212

17. Poloński L, Dec I, Wojnar R, Wilczek K (2002) Trimetazidine limits the effects of myocardial ischaemia during percutaneous coronary angioplasty. Curr Med Res Opin 18(7):389–396

18. Kutala VK, Khan M, Mandal R, Ganesan LP, Tridandapani S, Kalai T et al (2006) Attenuation of myocardial ischemia—reperfusion injury by trimetazidine derivatives functionalized with antioxidant properties. J Pharmacol Exp Ther 317(3):921–928

19. Khan M, Meduru S, Mostafa M, Khan S, Hideg K, Kuppusamy P (2010) Trimetazidine, administered at the onset of reperfusion, ameliorates myocardial dysfunction and injury by activation of p38 mitogen-activated protein kinase and Akt signaling. J Pharmacol Exp Ther 333(2):421–429

20. Williams FM, Tanda K, Kus M, Williams TJ (1993) Trimetazidine inhibits neutrophil accumulation after myocardial ischaemia and reperfusion in rabbits. J Cardiovasc Pharmacol 22(6):828–833

21. Cokkinos DV, Pantos C, Heusch G, Taegtmeyer H (2005) Myocardial ischemia: from mechanisms to therapeutic potentials. Springer, Science and Business Media, New York, USA, p. 204

22. Di Napoli P, Chierchia S, Taccardi AA, Grilli A, Felaco M, De Caterina R et al (2007) Trimetazidine improves post-ischemic recovery by preserving endothelial nitric oxide synthase expression in isolated working rat hearts. Nitric Oxide 16(2):228–236

23. Di Napoli P, Taccardi AA, Barsotti A (2005) Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. Heart 91(2):161–165

24. Zhao P, Zhang J, Yin XG, Majaraj P, Narraindoo S, Cui LQ et al (2013) The effect of trimetazidine on cardiac function in diabetic patients with idiopathic dilated cardiomyopathy. Life Sci 92(11):633–638

25. Tuunanen H, Engblom E, Naum A, Någren K, Scheinin M, Hesse B et al (2008) Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. Circulation118(12):1250–1258

26. Liu X, Gai Y, Liu F, Gao W, Zhang Y, Xu M et al (2010) Trimetazidine inhibits pressure overload-induced cardiac fibrosis through NADPH oxidase–ROS–CTGF pathway. Cardiovasc Res 88(1):150–158

27. Cera M, Salerno A, Fragasso G, Montanaro C, Gardini C, Marinosci G et al (2010) Beneficial electrophysiological effects of trimetazidine in patients with postischemic chronic heart failure. J Cardiovasc Pharmacol Ther 15(1):24–30

28. Gunes Y, Guntekin U, Tuncer M, Sahin M (2009) The effects of trimetazidine on heart rate variability in patients with heart failure. Arq Bras Cardiol 93(2):154–158

29. Zhang L, Lu Y, Jiang H, Zhang L, Sun A, Zou Y et al (2012) Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. J Am Coll Cardiol 59(10):913–922