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Editorial

Trimetazidine: a novel protective role via maintenance of Na^+/K^+-ATPase activity?

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See article by El Banani et al. [31] (pages 688–696) in this issue.

Trimetazidine (1-[2,3,4-trimethoxybenzyl]-piperazine; TMZ) is a piperazine compound that has been demonstrated to protect against ischaemic injury in a variety of tissues [1–4]. As a cardiovascular therapeutic agent, TMZ is protective during coronary artery bypass graft surgery [5] and catheter angioplasty [6], has been effective in the treatment of angina [7,8] and reduces infarct size when given before thrombolysis in patients with anterior myocardial infarction [9]. There have been insights into some of the molecular mechanisms of action of TMZ, however, new mechanisms continue to be discovered [10–12]. The best known action of TMZ is inhibition of the β-oxidation pathway of fatty acid metabolism [13]. Inhibition of the β-oxidation pathway during ischaemia and reperfusion concomitantly increases glucose oxidation [13]. Protection from ischaemic injury by TMZ is hypothesized to be due to the increase in glucose oxidation leading to lower rates of glycolysis and less H^+ production [14–17]. Increased fatty acid oxidation and glycolysis do result in greater H^+ production [18,19] and ischaemic intracellular pH changes have been observed in TMZ-treated hearts [14]. The detrimental effect of glycolytic H^+ production in the ischaemic myocardium is thought to be due to increased Na^+/H^+ exchange activity [20–22]. H^+ activate the Na^+/H^+ exchanger [23], causing Na^+ influx. Na^+ efflux via the Na^+/K^+-ATPase is attenuated during ischaemia [24], therefore activation of the Na^+/H^+ exchanger leads to increased intracellular Na^+ [25–27]. The increased intracellular Na^+ stimulates Na^+/Ca^{2+} exchange [28], resulting in increased intracellular Ca^{2+} [25,29] and it is this high Ca^{2+} which exacerbates myocardial injury [21,25,29,30].

TMZ-mediated alterations in fatty acid and glucose metabolism should therefore lead to changes in ion homeostasis. Specifically, one would predict a decrease in ischaemic intracellular H^+, Na^+ and Ca^{2+} with TMZ. In a study published in this issue of *Cardiovascular Research*, El Banani et al. [31], examined the effects of TMZ on ionic changes during low-flow and zero-flow (total) ischaemia in isolated fatty-acid perfused rat hearts using ^{31}P and ^{23}Na nuclear magnetic resonance (NMR) spectroscopy. Like others, El Banani et al. [31] found perfusion with 1 μM TMZ to be cardioprotective, resulting in a 2-fold increase in post-ischaemic recovery of contractile function after low-flow ischaemia and a 5-fold increase after zero-flow ischaemia. However, they also found that the ionic effects of TMZ differed during low vs. zero-flow ischaemic protocols. In the low-flow ischaemic hearts, TMZ attenuated the ischaemic decrease in intracellular pH, consistent with the predicted attenuation of glycolysis subsequent to inhibition of β-oxidation by TMZ. However, the TMZ-treated low-flow ischaemic hearts did not exhibit an attenuation in ischaemic Na^+, implying that TMZ-mediated protection was not via decreased Na^+/H^+ exchange activity during ischaemia. Also, contrary to the findings in low-flow hearts, there was no effect of TMZ treatment on ischaemic intracellular pH in zero-flow hearts, however, ischaemic Na^+ was attenuated. The lack of a pH effect of TMZ in zero-flow hearts may be due to rapid glycolytic inhibition by a faster accumulation of metabolic products in zero vs. low-flow hearts, but in the absence of a pH effect, the role of glycolysis and Na^+/H^+ exchange activity in TMZ-mediated protection is questioned. During reperfusion, protective effects of TMZ were apparent in both low-flow and zero-flow hearts. In both groups, TMZ treatment resulted in greater increases in LVDP and faster decreases in both LVEDP and intracellular Na^+. These findings may imply that TMZ-mediated

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alterations in glucose metabolism occur primarily during reperfusion, however, the absence of a higher pH during reperfusion in TMZ-treated vs. untreated low or zero-flow hearts again argues against decreased glycolysis as the mechanism of TMZ-mediated protection. Interestingly, positive effects of TMZ have been demonstrated previously in the absence of changes in glycolysis during ischaemia or reperfusion [32]. So how is the protective effect of TMZ mediated if not via changes in glycolysis and H^+ production?

An intriguing potential mechanism is implicated by the intracellular Na^+ measurements of El Banani et al. [31]. In both low-flow and zero-flow hearts, intracellular Na^+ levels during reperfusion were lower in TMZ-treated than in untreated hearts. In fact, in untreated zero-flow hearts, intracellular Na^+ increased for the first 7 min of reperfusion, whilst in the TMZ-treated hearts, intracellular Na^+ decreased immediately upon reflow (within the first 30-s measurement). Van Emous et al. [33] demonstrated a similar increase in intracellular Na^+ during the first few minutes of reperfusion when the Na^+/K^+-ATPase was inhibited by ouabain. The possibility exists, therefore, that the Na^+/K^+-ATPase is inhibited in fatty acid-perfused hearts and this inhibition is relieved by TMZ. Interestingly, the Na^+/K^+-ATPase is reversibly inhibited by palmitoyl carnitine [34] and TMZ, at the same concentration used this study [31], attenuates the ischaemia-induced increase in levels of long chain acyl carnitines, such as palmitoyl carnitine [16]. In addition, unpublished observations from the same laboratory indicate a similar rapid decrease of intracellular Na^+ upon reperfusion of fatty-acid perfused hearts treated with etomoxir, a carnitine palmitoyltransferase-1 inhibitor which also decreases long chain acyl carnitines [35]. As inhibition of Na^+/K^+-ATPase activity leads to increased intracellular Na^+ and Ca^{2+} and exacerbation of injury [24,36,37], maintenance of post-ischaemic Na^+/K^+-ATPase activity by reduction of acyl carnitine levels by TMZ may explain the beneficial effect of TMZ in the experiments of El Banani et al. [31] and others [32], in the absence of evidence of decreased glycolysis. This hypothesis is consistent with the observation in the El Banani study [31] that LVEDP was lower during reperfusion in TMZ-treated vs. untreated hearts; LVEDP being proportional to intracellular Ca^{2+} [38]. Maintenance of Na^+/K^+-ATPase activity during ischaemia in the TMZ-treated zero-flow hearts may also explain the observation of lower ischaemic intracellular Na^+ levels in the absence of alterations in pH.

Although the documented increase in glucose oxidation, as well as other reported mechanisms such as decreased myocardial oxygen consumption with lower fatty acid catabolism [39] and TMZ-mediated antioxidant and mitochondrial effects [9–11], may explain some of the protection afforded by TMZ, the findings of El Banani et al. [31] indicate a novel and intriguing potential protective mechanism. Future studies measuring Na^+/K^+-ATPase activity during ischaemia and reperfusion in TMZ-treated and untreated hearts, concurrent with measurements of glycolysis and glucose oxidation, will determine whether maintenance of Na^+/K^+-ATPase activity indeed contributes to the protective effects of the powerful therapeutic agent, trimetazidine.

References

[1] Baumert H, Goujon JM, Richer JP et al. Renoprotective effects of trimetazidine against ischaemia–reperfusion injury and cold storage preservation. Transplantation 1999;68:300–303.
[2] Settaf A, Morin D, Lamchouri F et al. Trimetazidine ameliorates the hepatic injury associated with ischaemia–reperfusion in rats. Pharmacol Res 1999;39:211–216.
[3] Tetik C, Ozden A, Calli N et al. Cytoprotective effect of trimetazidine on 60 minutes of intestinal ischaemia–reperfusion injury in rats. Transplant Int 1999;12:108–112.
[4] Gil Loyazaga P, Hernandez E, Carricondo F, Simon F, Poch-Broto J. Trimetazidine prevents cochlear lesions induced by intraperitoneal and perilymphatic administration of kainic acid. Brain Res 1999;826:95–103.
[5] Fabiani JN, Ponzio O, Emerit I. Cardioprotective effect of trimetazidine during coronary artery graft surgery. J Cardiovasc Surg 1992;3:486–490.
[6] Birand A, Kudaiberdieva GZ, Batyraliev TA, Akgul F, Usal A. Effects of trimetazidine on heart rate variability and left ventricular systolic performance in patients with coronary artery disease after percutaneous transluminal angioplasty. Angioplasty 1997;48:413–422.
[7] Dalla-Volta S, Maraglino G, Della-Valentina P, Viena P, Desideri A. Comparison of trimetazidine with nifedipine in effort angina. A double-blind, crossover study. Cardiovasc Drug Ther 1990;4:853–860.
[8] Detry JM, Sellier P, Pennaforte S et al. Trimetazidine: a new concept in the treatment of angina. Comparison with propanolol in patients with stable angina. Br J Clin Pharmacol 1994;37:279–288.
[9] 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 Drug Ther 1999;13:423–428.
[10] Ancerewicz J, Migliavacca E, Carrupt PA et al. Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. Free Radic Biol Med 1988;25:113–120.
[11] Morin D, Elimadi A, Sapena R et al. Evidence for the existence of 3[H]trimetazidine binding sites involved in the regulation of the mitochondrial permeability transition pore. Br J Pharmacol 1998;123:1385–1394.
[12] Guarnieri C, Finelli C, Zini M, Muscari C. Effects of trimetazidine on the calcium transport and oxidative phosphorylation of isolated rat heart mitochondria. Basic Res Cardiol 1997;92:90–95.
[13] Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The anti-anginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl CoA thiolase. Circ Res 2000;86:580–588.
[14] Lavanchy N, Martin J, Rossi A. Anti-ischemic effects of trimetazidine: ^{31}P NMR spectroscopy in the isolated rat heart. Arch Int Pharmacodyn Ther 1987;286:97–110.
[15] Stanley WC, Lopaschuk GD, Hall JL, McCormack JD. Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions. Potential for pharmacological interventions. Cardiovasc Res 1997;33:243–257.
[16] El Banani H, Bernard M, Cozzone P, James F, Feuvray D. Ionic and

metabolic imbalance as potential factors of ischemia–reperfusion injury. Am J Cardiol 1998;82:25K–29K.
[17] Fantini E, Demaison L, Sentex E, Grynberg A, Athias P. Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. J Mol Cell Cardiol 1994;26:949–958.
[18] Neely JR, Feuvray D. Metabolic products and myocardial ischemia. Am J Pathol 1981;102:282–291.
[19] Dennis SC, Gevers W, Opie LH. Protons in ischaemia: where do they come from; where do they go to? J Mol Cell Cardiol 1991;23:1077–1086.
[20] Cross HR, Opie LH, Radda GK, Clarke K. Is high glycogen beneficial or detrimental to the ischaemic rat heart? A controversy resolved. Circ Res 1996;78:482–491.
[21] Tani M, Neely JR. Role of intracellular Na^+ in Ca^{2+} overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. Possible involvement of H^+–Na^+ and Na^+–Ca^{2+} exchange. Circ Res 1989;65:1045–1056.
[22] Dizon J, Burkhoff D, Tauskela J et al. Metabolic inhibition in the perfused rat heart: evidence for glycolytic requirement for normal sodium homeostasis. Am J Physiol 1998;274:H1082–9.
[23] Lazdunski M, Frelin C, Vigne P. The sodium/hydrogen exchange system in cardiac cells: its biochemical and pharmacological properties and its role in regulating internal concentrations of sodium and internal pH. J Mol Cell Cardiol 1985;17:1029–1042.
[24] Cross HR, Radda GK, Clarke K. The role of Na^+/K^+ ATPase activity during low flow ischemia in preventing myocardial injury: A ^{31}P, $^{23}Na^+$ and ^{87}Rb NMR spectroscopic study. Magn Res Med 1995;34:673–685.
[25] Murphy E, Perlman M, London RE, Steenbergen C. Amiloride delays the ischemic-induced rise in cytosolic free calcium. Circ Res 1991;68:1250–1258.
[26] Pike MM, Kitakaze M, Marban E. ^{23}Na NMR measurements of intracellular sodium in intact perfused ferret hearts during ischemia and reperfusion. Am J Physiol 1990;259:H1767–1773.
[27] Weiss RG, Lakatta EG, Gerstenblith G. Effects of amiloride on metabolism and contractility during reoxygenation in perfused rat hearts. Circ Res 1990;66:1012–1022.
[28] Cross HR, Lu L, Steenbergen C, Philipson KD, Murphy E. Overexpression of the cardiac Na^+/Ca^{2+} exchanger increases susceptibility to ischemia/reperfusion injury in male, but not female, transgenic mice. Circ Res 1998;83:1215–1223.
[29] Marban E, Kitakaze M, Koretsune Y et al. Quantification of $[Ca^{2+}]_i$ in perfused hearts. Critical evaluation of the 5F-BAPTA and nuclear magnetic resonance method as applied to the study of ischemia and reperfusion. Circ Res 1990;66:1255–1267.
[30] Gao WD, Atar D, Liu Y et al. Role of troponin I proteolysis in the pathogenesis of stunned myocardium. Circ Res 1997;80:393–399.
31 El Banani H, Bernard M, Baetz D, Cabanes E, Cozzone PJ, Lucien A, Feuvray D. Changes in intracellular sodium and pH during ischaemia–reperfusion are attenuated by trimetazide. Comparison between low- and zero-flow ischaemia. Cardiovasc Res 2000;47:688–696.
[32] Boucher FR, Hearse DJ, Opie LH. Effects of trimetazidine on ischemic contracture in isolated perfused rat hearts. J Cardiovasc Pharmacol 1994;24:45–49.
[33] Van Emous JG, Schreur JHM, Ruigrok TJC, Van Echteld CJA. Both Na^+/K^+-ATPase and Na^+/H^+ exchange are immediately active upon post-ischemic reperfusion in isolated rat hearts. J Mol Cell Cardiol 1998;30:337–348.
[34] Tanaka M, Gilbert J, Pappano AJ. Inhibition of sodium pump by L-palmitoylcarnitine in single guinea-pig ventricular myocytes. J Mol Cell Cardiol 1992;24:711–720.
[35] Kantor PF, Dyck JS, Lopaschuk GD. Fatty acid oxidation in the reperfused ischemic heart. Am J Med Sci 1999;318:3–14.
[36] Kim M, Akera T. O_2 free radicals: cause of ischemia–reperfusion injury to cardiac Na^+/K^+-ATPase. Am J Physiol 1987;252:H252–H257.
[37] Murphy E, Aiton JF, Horres CR, Lieberman M. Calcium elevation in cultured heart cells: its role in cell injury. Am J Physiol 1983;245:C316–C321.
[38] Narita H, Nagao T, Sato M, Nakajima H, Kiyomoto A. Ischemia–reperfusion induced elevation of diastolic tension in the isolated guinea-pig heart and the effects of calcium antagonists. Jpn Heart J 1983;24:277–288.
[39] Liu B, El Alaoui-Talibi Z, Clanachan AS, Schulz R, Lopaschuk GD. Uncoupling of contractile function from mitochondrial TCA cycle activity and O_2 consumption during reperfusion of ischemic rat hearts. Am J Physiol 1996;270:H72–H80.