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# *Effects of Trimetazidine on Metabolic and Functional Recovery of Postischemic Rat Hearts*

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***Summary.*** **The objective of this study was to test the hypothesis that the beneficial effect of trimetazidine during reflow of ischemic hearts is mediated by energy sparing and ATP pool preservation during ischemia. Isolated rat hearts (controls and rats treated with $10^{-6}$ M trimetazidine, n = 17 per group) underwent the following protocol: baseline perfusion at normal coronary flow (20 minutes), low-flow ischemia at 10% flow (60 minutes), and reflow (20 minutes). We measured contractile function, $O_2$ uptake, lactate release, venous pH and $PCO_2$, and the tissue content of high-energy phosphates and their metabolites. During baseline, trimetazidine induced higher venous pH and lower $PCO_2$ without influencing performance and metabolism. During low-flow ischemia, trimetazidine reduced myocardial performance ($P = 0.04$) and ATP turnover ($P = 0.02$). During reflow, trimetazidine improved performance (91 ± 6% versus. 55 ± 6% of baseline), prevented the development of diastolic contracture and coronary resistance, and reduced myocardial depletion of adenine nucleotides and purines. ATP turnover during low-flow ischemia was inversely related to recovery of the rate-pressure product ($P = 0.002$), end-diastolic pressure ($P = 0.007$), and perfusion pressure ($P = 0.05$). We conclude that trimetazidine-induced protection of ischemic-reperfused hearts is also mediated by energy sparing during ischemia, which presumably preserves the ATP pool during reflow.**

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***Key Words.*** **trimetazidine, low-flow ischemia, bioenergetics, ATP metabolism, reperfusion**

In recent years, trimetazidine (TMZ, 1-[(2,3,4-trimethoxyphenyl) methyl] piperazine) has been proposed as an antianginal and antiischemic agent [1]. Unlike nitrates or $Ca^{2+}$ antagonists, this drug does not influence coronary blood flow nor myocardial $O_2$ consumption [2], thus presumably it protects energy metabolism. TMZ, indeed, limits high-energy phosphate depletion during ischemia [3], thereby reducing intracellular acidosis without $Ca^{2+}$ blocking activity [4]. Furthermore, TMZ has no effect on glycolytic flux [5] and free radical formation [6], although the latter finding is controversial [7], but, nevertheless, it protects sarcolemmal mechanical resistance in reoxygenated myocytes [8]. Taken together, these observations suggest that TMZ exerts its effect at the level of membrane ion exchange. However, studies aimed at assessing the effect of TMZ on $Na^+$,$K^+$-ATPase [9] and on mitochondrial $Ca^{2+}$ uptake [10] showed that this effect occurs only for TMZ levels much higher than those that protect the myocardium. Thus, despite extensive work, the mechanism of action of this drug deserves further investigation.

The crystalloid-perfused isolated heart is a valuable model to extend our knowledge of the mechanism of action of TMZ. In this model, the phenomena related to the presence of blood, nervous system, and humoral factors are ruled out. Furthermore, myocardial recovery from low-flow ischemia depends on residual coronary flow and on energy requirements during ischemia [11]. If the low ATP situation secondary to high energy demand with respect to supply is associated with substantial residual coronary flow, the membrane-diffusable metabolites of ATP are lost, thereby delaying ATP resynthesis during reflow. The subsequent impairment of recovery during reflow apparently overrides the protection afforded by free radical scavengers [12] and control of the reoxygenation rate [13].

In this study we tested the hypothesis that protection of ischemic-reperfused hearts by TMZ is associated with energy sparing during ischemia: The ATP pool is better preserved with reduced energy demand during ischemia, and this improves recovery during reflow. To this aim, isolated rat hearts were exposed to low-flow ischemia and reflow while monitoring performance and metabolism, either in the presence or absence of $10^{-6}$ M TMZ. We showed that TMZ improves the recovery of contractile function after low-flow ischemia and that cardioprotection is correlated with events related to energy sparing that occur during ischemia.

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## Materials and Methods

### Heart perfusion

Male Sprague-Dawley rats (weighing 250–280 g) were heparinized and anesthetized with sodium thiopental (100 mg/kg). Hearts (average weight, 0.90 ± 0.05 g) were excised, immersed in isotonic saline (20°C), and mounted on the perfusion system [11]. The time required for these operations never exceeded 45 seconds and was typically in the 15–30 second range. Langendorff perfusion started immediately with Krebs-Henseleit medium containing 2.0 mM free $Ca^{2+}$ and 11 mM glucose (pH 7.41 ± 0.01, means ± SE, 37°C). When required, $10^{-6}$ M TMZ (Servier Laboratories, France) was added to the medium, which was equilibrated at $PO_2$ = 670 ± 6 mmHg and $PCO_2$ = 36 ± 1 mmHg in membrane oxygenators [14]. A peristaltic pump (Gilson, France) delivered the medium at desired flows to the filter (8 μm pore size, 47 mm diameter, Nucleopore Corp., Pleasanton, CA), preheater, and aortic cannula. All perfusion system components, including the heart chamber, oxygenator, flow distribution valve box, and preheater, were connected to a 1760 W external water bath (Endocal, Neslab Instruments, Newington, NH) kept at 37.5°C. A latex balloon introduced into the left ventricle was connected to a pressure transducer (Harvard Apparatus model 52-9966, Natick, MA) to monitor performance. An additional transducer connected to the aortic cannula provided the coronary perfusion pressure. A cannula was inserted into the pulmonary artery to collect the venous return and to monitor venous $PO_2$ by an $O_2$-sensing electrode (Yellow Springs, Inc., model 5300 Oxygen Monitor, Yellow Springs, OH). The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH publication no. 85-23, revised 1985).

### Experimental protocol

All hearts were divided into two groups: control (Krebs-Henseleit medium only) and those thoroughly perfused in the presence of $10^{-6}$ M TMZ. Hearts were stabilized for 20 minutes at flow = 15 mL/min for baseline measurements. During this period the volume of the intraventricular balloon was adjusted to an end-diastolic pressure of 10 mmHg and was kept constant thereafter. Then, hearts underwent low-flow ischemia for 60 minutes by reducing the flow to 1.5 mL/min, followed by 30 minutes reperfusion under the same conditions as baseline (n = 7 per group). Additional hearts served to derive morphological data and to assess structural and ultrastructural derangement (n = 2 per group at the end of reperfusion, plus one heart at the end of baseline). In other experiments hearts were freeze-clamped either at the end of baseline (n = 4 per group) or at the end of ischemia (n = 6 per group), to measure tissue high-energy phosphates and their metabolites.

### Measurements

Myocardial performance was continuously monitored by a LabView system (National Instruments, Austin, TX) running on a Macintosh Quadra 700 (Apple, Cupertino, CA). The measured parameters include end-diastolic (EDP) and peak systolic (PSP) pressures, maximal rate of pressure development ($LVdP/dt_{max}$), coronary perfusion pressure (CPP), and venous $PO_2$. From these parameters we derived the heart rate (HR), left-ventricle developed pressure (LVDP = PSP – EDP), and myocardial contractile work (LVDP•HR). Venous [lactate] (Sigma Diagnostics, St. Louis, MO) pH and $PCO_2$ (Ciba Corning M238 Blood Gas Analyzer, Milan, Italy) were measured at the end of baseline, low-flow ischemia, and reflow. In addition, the creatine kinase release during the first 5 minutes of reflow was measured in two hearts per group using an enzymatic test (Sigma Diagnostics, St. Louis, MO) optimized for maximal sensitivity.

To measure the myocardial level of high-energy phosphates and their metabolites, after obtaining hemodynamic data hearts were quickly ($t < 1$ s) frozen with large aluminum clamps that were precooled at liquid nitrogen temperature. Freeze-clamp was performed simultaneously with the removal of the intraventricular balloon because in separate experiments (not shown) the levels of ATP and phosphocreatine were the same as those observed in hearts freeze-clamped with the balloon in the left ventricle. Frozen tissue was extracted with 0.5 M perchloric acid, neutralized, and assayed for ATP, phosphocreatine, ADP, AMP, inosine-5′-phosphate, adenosine, inosine, xanthine, hypoxanthine, urate, and creatine by HPLC methods [15].

To assess the structural and ultrastructural derangement at the end of reflow, additional hearts were arrested by perfusing them with 2.5% (v/v) ice-cold glutaraldehyde. Arrested hearts were quickly immersed in the same glutaraldehyde solution, then the left ventricle was cut into 1–2 mm thick slices, mapped, and processed for light microscopy (tetrazolium blue, hematoxylin and eosin staining). Transmission electron microscopy was performed on specimens from four different left ventricle sites per each heart. Sections were stained with uranyl acetate and lead citrate, as described previously [12], and finally were observed with a CEM 902 (Zeiss Ikon, Germany) electron microscope. To evaluate damage we used the semiquantitative grading system, which is based on the established criteria of myocardial ischemic injury [16]. Briefly, this system considers the following parameters: nuclear margination and clumping of chromatin, mitochondrial enlargement, changes in myocardial fibers, interstitial edema, and hemorrhage. We assigned scores from 1 (no or mild changes) to 4 (marked or severe changes) to each of these parameters, and then we averaged the scores. Reference score 4 damage was obtained by exposing an additional heart to 1 hour of anoxia followed by reoxygenation as reported earlier [12].

### *Calculations*

Calculations included: (1) $O_2$ uptake ($VO_2$; from the difference between arterial and venous $PO_2$, $O_2$ solubility coefficient [17], and actual coronary flow); (2) lactate release from [lactate] and flow; (3) ATP turnover rate as the sum of the two components yielding energy in the form of ATP under the selected experimental conditions, which are anerobic glycolysis, by assuming an ATP-to-lactate ratio of 1.0, and oxidative metabolism, by assuming a P/O ratio of 3 [14]; (4) total content of adenine nucleotides and purines as the sum of ATP, ADP, AMP, inosine-5′-phosphate, adenosine, inosine, xanthine, hypoxanthine, and urate; (5) energy charge, as ([ATP] + 0.5 [ADP])/([ATP] + [ADP] + [AMP]); and (6) base excess from pH and $PCO_2$ [18]. This parameter allows the assessment of whether an apparently abnormal pH value is due to changes in volatile ($CO_2$) or fixed ($H^+$) acidity.

### *Statistics*

Data are expressed as the mean ± SE. To detect interactions between TMZ treatment and three consecutive perfusion conditions (baseline, low-flow ischemia, and reflow), we used two analysis of variance (ANOVA) procedures (StatView, Abacus Concepts, Berkeley, CA), depending on the variable being tested: two-way, repeated measures ANOVA for variables available for each heart under the three conditions; and factorial, six groups ANOVA for variables such as the myocardial metabolite content. In both cases, if the ANOVA test was significant ($P < 0.05$), the TMZ and control hearts were compared using the Bonferroni/Dunnett multiple comparison procedure, that is, by correcting the significance of the test for the number of comparisons. The latter correction was not applied for variables available or meaningful during low-flow ischemia only.

## *Results*

### *Mechanical performance*

Figure 1 shows myocardial work (LVDP•HR) and EDP during baseline, low-flow ischemia, and reflow. TMZ did not significantly affect myocardial function during baseline (see also Table 1), but during low-flow ischamia TMZ depressed $LVdP/dt_{max}$, LVDP, and LVDP•HR. During reflow these variables were higher in TMZ than control hearts. In addition, EDP and CPP were lower in TMZ-treated hearts.

### *Metabolism*

Table 1 shows that TMZ did not significantly affect $VO_2$, neither during baseline nor during low-flow ischemia, but $VO_2$ was higher in TMZ hearts during reflow. The high coronary flow during baseline and reflow led to excessive dilution of venous [lactate], which was not detectable under right flow conditions. Therefore, the ATP turnover rate during baseline and reflow was calculated only from $VO_2$, assuming that the contribution of anerobic glycolysis was negligible. In contrast, venous [lactate] was measurable in both groups during low-flow ischemia: It was less in TMZ than in control hearts (1.10 ± 0.07 vs. 1.35 ± 0.05, n = 13 per group, $P = 0.008$).

Because flow was the same in the two groups, different venous [lactate] values implied different rates of lactate release (1.62 ± 0.10 vs. 1.98 ± 0.08 μmoles / min, $P = 0.008$). Hence, the ATP turnover rate during low-flow ischemia was calculated from both lactate release and $VO_2$, as explained in Material and Methods. It was higher in control than TMZ hearts ($P = 0.018$). Furthermore, TMZ transiently reduced acidosis and hypercapnia during baseline. Phosphocreatine tissue content was unchanged by TMZ, but the content of ATP, total adenine nucleotides, and purines during reflow was higher in TMZ than in control hearts.

### *Myocardial damage*

Light and electron microscopic analyses revealed minor alterations (average score ~1), without signs of irreversible myocardial damage in both control and TMZ hearts. Creatine kinase release during reflow was <0.1 U/L/min in both groups, that is, <1% of that observed during reoxygenation after 1 hour of anoxia.

### *Energy demand versus recovery*

To test the hypothesis that cardioprotection elicited by TMZ is partially mediated by energy sparing during low-flow ischemia, Figure 2 shows the correlation between the ATP turnover rate during low-flow ischemia, an index of energy demand, and LVDP ;sL HR during reflow, an index of mechanical recovery. The data fit a line with a negative slope (−12.9 ± 3.3, $P = 0.002$, 95% confidence limits −20.0 to −5.7). Similar relations also occur when substituting LVDP • HR with EDP ($P = 0.007$), CPP ($P = 0.05$), and $LVdP/dt_{max}$ ($P = 0.01$), but not with $VO_2$.

## *Discussion*

### *Critique of the model*

The aims of this study were (1) to determine the acute effects of TMZ on myocardial function and metabolism during low-flow ischemia and reflow, and (2) to assess the correlations between bioenergetics during low-flow ischemia and recovery during reflow. The experimental conditions employed induced reproducible myocardial dysfunction in control hearts without leading to arrest. Lack of blood in the perfusion medium excluded possible effects of TMZ on neutrophil accumulation [19] and on thrombin-induced platelet aggregation [20]. Strict temperature control (± 0.5 °C), using the same volume of the intraventricular balloon, the same coronary flow, and the same $O_2$ supply in the two groups ruled out differences in loading conditions. Because animals were not pretreated, these observations relate to acute metabolic effects of TMZ

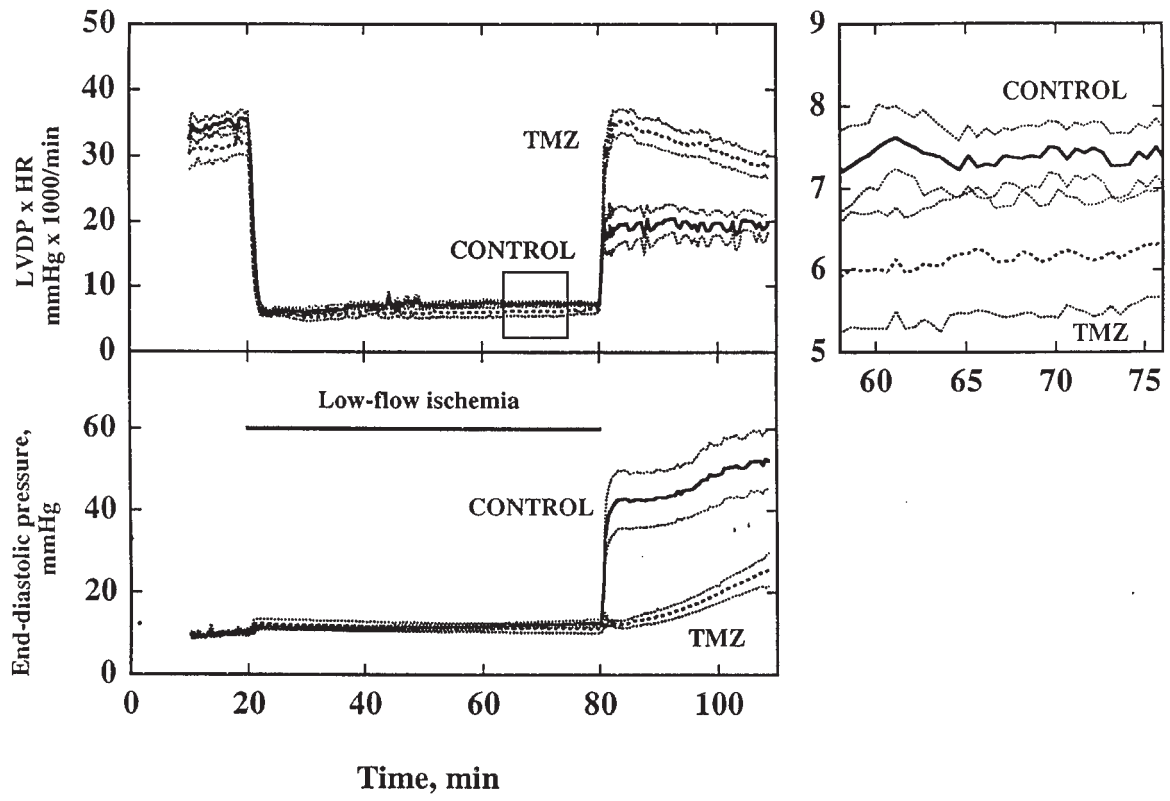


*Fig. 1. Time course of developed pressure (LVDP) • heart rate (HR) (upper panel) and of end-diastolic pressure (lower panel) during the experimental protocol in control (solid line) and TMZ-treated (dotted line) hearts (n = 7 per group). The inset shows enlargement relative to LVDP • HR at the end of low-flow ischemia.*

on cardiac muscle. The TMZ-induced reduction of acidosis and lower base excess during baseline perfusion indicate that TMZ influences fixed acids rather than $CO_2$ metabolism, in agreement with previous $^{23}$Na-NMR studies that indicate TMZ affects the $Na^+/H^+$ antiport. [4]

We explored the properties of isolated hearts at the TMZ concentration ($10^{-6}$ M) that was previously efficient with regard to ischemia protection [5]. Of interest, in that study rats were pretreated with TMZ (3 mg/kg body weight, twice daily for 5 days), but we showed that $10^{-6}$ M TMZ is protective regardless of animal pretreatment. This concentration is within the range of therapeutic blood levels in treated patients with cardiovascular disorders [21]. A higher concentration ($5 \bullet 10^{-4}$ M) of TMZ was used in studies aimed at investigating electrophysiological properties in cardiac myocytes [22]. Besides being unrealistic in clinical settings, that concentration has already been shown to exacerbate ischemic injury in isolated rat hearts [5].

### *Protective effects of TMZ*

In this model TMZ protects postischemic hearts, especially early during reflow. The protection may decrease for prolonged (>30-minute) reflow times, consistent with the observation in isolated ventricular myocytes that $3 \bullet 10^{-4}$ M TMZ slows the recovery of intracellular pH [23]. Nevertheless, TMZ acutely protects myocardial contractility ($LVdP/dt_{max}$, LVDP, and LVDP • HR). In addition because the ventricular balloon volume remained constant throughout the experiment, the lower increase EDP indicates decreased diastolic contracture. Moreover, coronary flow was the same in the two groups; therefore, the lower CPP indicates less coronary resistance in TMZ hearts. All these mechanical improvements are accompanied by increased levels of ATP, total adenine nucleotides and purines, but not phosphocreatine. The latter feature is a consequence of the lack of irreversible injury, as shown by electron microscopy, and the observation that the sum of phosphocreatine + creatine decreases only for overt membrane damage [24].

The present study indicates that a portion of the beneficial effect of TMZ is exerted through energy-sparing during low-flow ischemia. Decreased LVDP•HR during low-flow ischemia is accompanied by lower lactate release, that is, a lower rate of anaerobic metabolism. Because aerobic metabolism is the same in the two groups, the ATP turnover rate decreases to a greater extent in TMZ-perfused hearts.

***Table 1.*** *Myocardial performance and metabolism at the end of baseline, low-flow ischemia, and reflow for control and TMZ hearts*

| Parameter | ANOVA *P* | Baseline | | Low flow ischemia | | Reflow | |
|---|---|---|---|---|---|---|---|
| | | Control | TMZ | Control | TMZ | Control | TMZ |
| n | | 17 | 17 | 13 | 13 | 7 | 7 |
| Heart rate ($min^{-1}$) | .05 | 245 ± 8 | 249 ± 13 | 145 ± 7 | 161 ± 7 | 201 ± 5 | 231 ± 9 |
| End-diastolic pressure (mmHg) | .0007 | 10.4 ± 0.4 | 9.6 ± 0.2 | 12.5 ± 0.7 | 11.8 ± 0.6 | 52.7 ± 8.2 | 24.6 ± 3.3[a] |
| $LVdP/dt_{max}$ (mmHg/s) | .002 | 3465 ± 195 | 3288 ± 111 | 1188 ± 59 | 1016 ± 43[b] | 2418 ± 209 | 3203 ± 194[a] |
| Coronary pressure (mmHg) | .01 | 72 ± 2 | 66 ± 1 | 20 ± 1 | 15 ± 1[b] | 112 ± 7 | 92 ± 5[a] |
| Venous $pO_2$ (mmHg) | .03 | 158 ± 20 | 150 ± 25 | 13 ± 3 | 13 ± 4 | 220 ± 65 | 62 ± 30[a] |
| Developed pressure (mmHg) | .006 | 139 ± 6 | 130 ± 6 | 51 ± 2 | 39 ± 2[b] | 97 ± 9 | 124 ± 7[a] |
| Developed pressure • heart rate (mmHg • $10^3$ / min) | <.0001 | 33.7 ± 1.4 | 31.6 ± 1.1 | 7.2 ± 0.3 | 6.3 ± 0.3[b] | 19.5 ± 1.9 | 28.5 ± 1.7[a] |
| $O_2$ uptake (μmoles/min) | .03 | 10.7 ± 0.4 | 10.9 ± 0.5 | 1.4 ± 0.1 | 1.4 ± 0.1 | 9.5 ± 1.4 | 12.7 ± 0.6[a] |
| ATP turnover rate (μmoles/min) | .03 | 64.5 ± 2.5 | 65.5 ± 3.2 | 10.26 ± 0.08 | 9.90 ± 0.12[b] | 57.0 ± 7.3 | 76.3 ± 3.7[a] |
| Venous pH | <.0001 | 7.29 ± 0.01 | 7.34 ± 0.01[a] | 7.04 ± 0.02 | 7.09 ± 0.02 | 7.32 ± 0.02 | 7.33 ± 0.03 |
| Venous $pCO_2$ (mmHg) | <.0001 | 47 ± 1 | 41 ± 1[a] | 86 ± 3 | 77 ± 3[b] | 44 ± 2 | 43 ± 3 |
| Base excess, (mM) | NS | −1.9 ± 0.2 | −2.4 ± 0.1 | −1.8 ± 0.2 | −1.8 ± 0.2 | −2.3 ± 0.2 | −2.2 ± 0.1 |
| n | | 4 | 4 | 6 | 6 | 7 | 7 |
| ATP (μmoles/g dw) | .003 | 17.4 ± 0.8 | 21.9 ± 1.3 | 12.3 ± 1.9 | 13.4 ± 1.2 | 12.5 ± 1.8 | 18.2 ± 1.9[c] |
| Phosphocreatine (μmoles/g dw) | NS | 43.2 ± 9.4 | 49.5 ± 14.4 | 28.9 ± 6.1 | 35.1 ± 6.6 | 52.1 ± 13.1 | 69.2 ± 12.3 |
| Total adenine nucleotides and purines (μmoles/g dw) | .01 | 27.3 ± 1.4 | 34.4 ± 2.0 | 23.0 ± 2.6 | 26.2 ± 1.6 | 21.4 ± 2.5 | 29.8 ± 2.9[c] |
| Energy charge | .04 | .830 ± .004 | .826 ± .015 | .778 ± .016 | .758 ± .025 | .818 ± .018 | .811 ± .007 |
| Phosphocreatine + creatine (μmoles/g dw) | NS | 77.6 ± 6.1 | 87.7 ± 13.7 | 68.3 ± 7.2 | 81.8 ± 5.2 | 78.4 ± 13.1 | 95.8 ± 13.1 |

Mean ± SE is reported for all available data.

[a]Significantly different from control (two-way, repeated measure ANOVA followed by the Bonferroni/Dunnett multiple comparison test).

[b]Significantly different from control (two-way, repeated measure ANOVA uncorrected for the number of comparisons, only for low-flow ischemia data).

[c]Significantly different from control (one-way, six-group factorial ANOVA followed by the Bonferroni/Dunnett multiple comparison test).

NS = not significant; dw = dry weight.

### *TMZ and energy sparing*

The mechanism underlying energy sparing during ischemia remains to be elucidated, but less acidosis is not implied because it should increase, not decrease, contractile function [25]. Furthermore, changes in pyruvate dehydrogenase are not likely because these changes occur at TMZ concentrations much higher than those that prevent ischemic contracture [26]. Finally, changes in glycolytic flux regulation were ruled out [5]. It is possible that the observed energy sparing during ischemia shares some common mechanisms with the recently reported TMZ-induced inhibition of free fatty acid oxidation [27].

Irrespective of the mechanisms underlying energy sparing, our results are consistent with the $^{31}$P-NMR finding that $6 \bullet 10^{-7}$ M TMZ improves phosphocreatine and ATP levels during low-flow ischemia [3]. Lack of data on performance and the ATP metabolite level during ischemia, not measurable with $^{31}$P-NMR techniques, makes it difficult to understand why in that study TMZ failed to improve postischemic performance. Indeed, ATP reconstitution during reflow is limited by precursor availability rather than by cellular phosphorylation capacity [28]. Furthermore, the intracellular level of these precursors critically depends on energy demand and coronary flow during ischemia [11].

The relationship between energy sparing during ischemia and recovery has a metabolic background. At constant coronary flow, low energy demand prevents intracellular buildup of ATP catabolites, that is, adenine nucleotides and purines [11]. Because some of these are permeable through the cell membrane [29], residual flow selectively removes them, thereby decreasing their tissue levels during reflow. Greater availability of adenine nucleotides and purines early during reflow helps the heart to quickly resynthesize ATP, thereby improving recovery [30]. This result is obtained even from relatively small declines in the ATP turnover rate: Using the data reported here, if the 3.5% decline in the ATP turnover rate is protracted for 60 minutes, the final gain in ATP content can be calculated as (10.26 μmoles/minutes) × (60 minutes) × (3.5%) = 21.5 μmoles/heart, which corresponds to >10

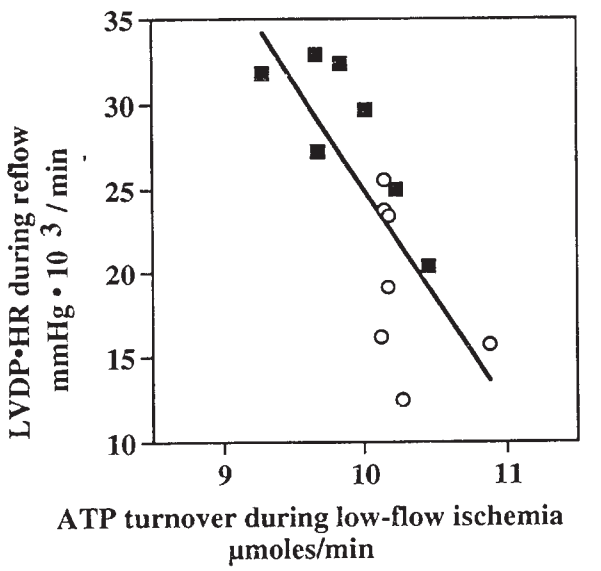


***Fig. 2.*** *Relation between the ATP turnover rate at the end of low-flow ischemia and the recovery of LVDP • HR at the end of reflow in control (empty symbols) and TMZ-treated (filled symbols) hearts (n = 7 per group). When all data are taken together, they fit a straight line: y = +12.9 x + 154, multiple r = 0.75, significance of the F-test P = 0.002.*

times the actual tissue ATP content [11]. This consideration also explains why comparable levels of TMZ apparently do not have measurable effects for short ischemia times [31].

Although any extrapolation to clinical settings should be made with caution, the pharmacological protection elicited by TMZ on postischemic hearts seems to involve several cell paths. These include improved ATP synthesis secondary to increased mitochondrial $Ca^{2+}$ uptake [10], limited acidosis through modulation of the $Na^+/H^+$ antiport [4], and energy sparing during ischemia (this study). In principle the last two effects may be distinguished by withdrawing TMZ at the time of reflow. However, TMZ activity might last longer than its presence, if, for example, it is mediated by inhibition of some enzymes.

## *Conclusions*

One-micromolar TMZ significantly protects ischemic-reperfused hearts in this model. Although a major component of this protection is linked to membrane ion exchange, a significant component is mediated by energy sparing during low-flow ischemia, which protects the ATP pool during reflow.

## *Acknowledgments*

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