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Research Article

Effects of Trimetazidine on Rat Heart Muscle during Hypoxia and Reperfusion

Mustafa Emre[1]* and Toygar Emre[2]

[1]Faculty of Medicine, Department of Biophysics, Çukurova University, Turkey

[2]Faculty of Engineering, Department of Industry, Boğaziçi University, Turkey

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***Corresponding author:** Mustafa Emre, PhD, Faculty of Medicine, Department of Biophysics, Çukurova University, Turkey, E-mail: memre@cu.edu.tr

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Abstract

Objective: Trimetazidine (TMZ) is a cardioprotective drug with anti-ischemic and anti-hypoxic metabolic actions. This study aims to investigate the impact of TMZ on the contractile and recovery properties of isolated papillary heart muscle under normoxic and hypoxic conditions.

Methods: Left ventricular papillary muscles were harvested from 40 Wistar rats. After a 10-minute equilibration period in a normoxic bath, contractile and relaxation responses were recorded in normoxic and hypoxic baths with varying concentrations of TMZ (0 M, 5 x 10^{-6} M, and 5 x 10^{-5} M). The specimens were then re-perfused with oxygenated Krebs-Henseleit solution (95% O_2 and 5% CO_2) and equilibrated for 10 minutes in a normoxic bath. Recovery contractile and relaxation responses were measured.

Results: Both doses of TMZ had a negative inotropic effect on muscle ($p < 0.001$), resulting in a limited decline in biomechanical performance in the hypoxic bath ($p < 0.001$). However, both doses of TMZ also increased the recovery biomechanical performance compared to the control group ($p < 0.001$).

Conclusions: Under normoxic conditions, TMZ pretreatment alone did not show any cardioprotective effect. However, adding TMZ at a concentration of 5 x 10^{-6} M, a therapeutic level in humans, reduced ischemic contracture and improved postischemic recovery of contraction forces in both pretreated and control groups. Despite trimetazidine's negative inotropic effect under normoxic conditions, near-therapeutic doses of the drug have significant protective effects on isolated papillary heart muscle contractility, leading to improved contractile function under hypoxic conditions.

Introduction

In recent years, a new therapeutic concept has emerged as a strategy in the treatment of ischemic states, aiming to prevent or offset the effects of intracellular alterations caused by hypoxia. According to this concept, drugs should compensate, at least in part, for the effects of hypoxia and prolong the period of reversibility from hypoxic damage without harmful consequences to cells and the whole organ. TMZ (1-(2,3,4-trimethoxy-benzyl) piperazine dihydrochloride) is a cardioprotective drug with anti-ischemic and antihypoxic metabolic action. Trimetazidine, used as an anti-anginal medication, exhibits cardioprotective effects by shifting energy production from fatty acid oxidation to glucose oxidation [1,2]. In addition to its cardiac protective abilities, recent evidence suggests that trimetazidine may also enhance skeletal muscle performance in both humans and rats [3-7]. These desired effects have been experimentally assessed in various models [3-7]. While there are several experimental studies in the literature on the effect of TMZ on ischemic contracture [5,8-10] and the contractile function of the whole heart [11], its effect on the contractile function of isolated papillary heart muscle remains unclear. Trimetazidine has been reported to have clinical applications in heart failure and its protective effect on the myocardium [12]. Conducting such a study can help examine the contraction and relaxation properties of isolated papillary heart muscle independent of hemodynamic and neurohormonal influences [13].

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This study aims to determine whether TMZ has a beneficial effect on the contractile and recovery properties of isolated papillary heart muscle under normoxic and hypoxic conditions.

Materials and methods

This study investigated the effects of TMZ on isolated papillary rat left heart muscle under normoxic and hypoxic conditions. Drug concentrations of 5 x 10^{-6} M and 5 x 10^{-5} M were used, similar to therapeutic levels for cardiovascular disorders. Animals were not pre-treated with TMZ.

This study tested the effect of TMZ on isolated papillary rat left heart muscle under normoxic and hypoxic conditions. We used the left ventricular papillary muscle to compare our results with other studies. We used drug concentrations of 5 x 10^{-6} M and 5 x 10^{-5} M, which are within the therapeutic range for cardiovascular disorders [14]. Animals were not pre-treated with TMZ.

Tissue preparation

This study followed ethical guidelines and was approved by the ethics committee of Çukurova University Health Sciences Experimental Application and Research Center (SABIDAM) under protocol number TTU-2022-14632. Approval was also obtained from the Animal Experiments Local Ethics Committee of Çukurova University Faculty of Medicine on 20.01.2022.

After cervical dislocation, the hearts were quickly removed, and left ventricular papillary muscles were excised. The preparations were placed in a Plexiglas chamber for continuous perfusion (6 - 8 mL/min) with oxygenated Krebs solution containing 95% O_2 and 5% CO_2 with the following concentrations in mmol/L: 113 NaCl, 4.7 KCl, 1.2 $MgSO_4 \cdot 7H_2O$, 1.9 $CaCl_2 \cdot 2H_2O$, 1.2 KH_2PO_4, 25 $NaHCO_3$, 11.5 glucose, pH 7.4.

Forty male Wistar rats were anesthetized and their hearts were perfused using the Langendorff technique. Left ventricular papillary muscles were isolated and perfused with oxygenated Krebs-Henseleit Solution [15]. The muscles were then placed in a tissue bath and suspended between platinum electrodes for further experimentation.

After a 15-20 minute adaptation period to stabilize the tissue under in vitro conditions, left ventricular papillary muscles, including chordae tendinae, were quickly isolated from the myocardium. The mean length of the isolated muscles was 5.5 ± 0.5 mm, width 1.3 ± 0.2 mm, and weight 31 ± 3 mg. They were positioned between platinum electrodes and suspended in an organ bath containing 20 mL of oxygenated KH solution. The preparations were consistently aerated with a mixture of 95% O_2 and 5% CO_2, and the temperature was maintained at 36 ± 0.3 °C, with a pH range between 7.35 and 7.45.

All animal procedures were performed according to the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health and approval of the ethics committee of our institution were obtained before the commencement of the study.

Experimental protocols

After a 10-minute equilibration period, a supra-maximal stimulating voltage (15% higher than the maximal pulse for all muscle fibers) was used to measure peak developed tension at a specific length. Supra-maximal impulses were delivered at 0.1 Hz with a Harvard double-channel. Isometric contraction forces were measured using a Grass FT-0.3 force-displacement transducer, Grass polygraph, and Hitachi digital storage oscilloscope.

The perfusion liquid was a Krebs-Henseleit crystalloid buffer equilibrated with 95% O_2 / 5% CO_2 for normoxic conditions and 20% O_2 / 5% CO_2 / 75% N_2 for hypoxic conditions [10]. It had a pH of 7.4 and contained NaCl, KCl, $MgSO_4$, CaCl, KH_2PO_4, $NaHCO_3$, and glucose.

TMZ was added to the perfusate at concentrations of 10^{-5} M and 10^{-6} M (MW = 339.27). In the initial experiments, contractile functions of isolated papillary heart muscle were recorded at baseline for 45 minutes after a 20-minute equilibration period in normoxic and hypoxic bath conditions (Figure 1). TMZ was then added to each bath to achieve final concentrations of 10^{-6} M and 10^{-5} M, and contractile function was recorded for another 45 minutes in both normoxic and hypoxic conditions. The specimens were washed out, aerated with Krebs solution containing 95% O_2 and 5% CO_2, and re-immersed in the original bath conditions.

Relaxation functions were recorded for 50 minutes, with specimens stimulated at 5-minute intervals and washed and aerated with fresh Krebs solution at 10-minute intervals. In the following experiments, specimens were washed and aerated with Krebs solution containing 95% O_2 and 5% CO_2. After equilibrating for 10 minutes in the appropriate bath conditions, the recovery of contractile and relaxation functions was assessed in normoxic and hypoxic conditions at baseline or final concentrations of 10^{-6} M and 10^{-5} M TMZ (Figure 2).

In the initial experiments, isolated papillary cardiac muscle underwent 20 minutes of ischemia followed by a 20-minute stabilization period in normoxic and hypoxic bath

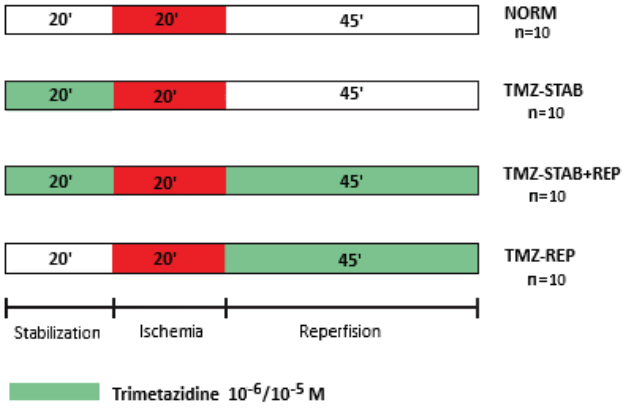

Figure 1: Experimental protocols.

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conditions. TMZ was then introduced at concentrations of 10^{-6} M and 10^{-5} M, and contraction function was monitored for 45 minutes under both normoxic and hypoxic conditions (Figure 1). The samples were subsequently rinsed with Krebs solution and returned to their original bath conditions for relaxation function recording.

In the second set of experiments, specimens were ventilated with Krebs solution and allowed to stabilize for 20 minutes under various bath conditions. The recovery of contraction and relaxation functions was then assessed under normoxic and hypoxic conditions with 10^{-6} M and 10^{-5} M TMZ concentrations (Figure 2).

Statistical analysis

The experimental parameter values were expressed as mean ± SD. Statistical analysis was performed using the statistical package SPSS version 10.0. Paired t-tests were used to analyze the differences between the control values and the corresponding values for both doses of TMZ under normoxic and hypoxic conditions. Values of $p < 0.001$ were considered statistically significant.

Results

Contractile function assessments measure contraction force (Cf, g), contraction time (Ct, ms), relaxation half-time (½Rt, ms), contraction rate (+dP/dt, g/s), and (-dP/dt, g/s). Recovery assessments include recovery contraction force (Rcf, g), recovery time (Rt, minutes), recovery contraction rate (+dPr/dt, g/s), and recovery relaxation rate (-dPr/dt, g/s).

Contractile function of isolated papillary heart muscle

In the normoxic bath, adding 10^{-6} M and 10^{-5} M TMZ to the bathing solution significantly decreased Cf, Ct, and ½Rt values ($p < 0.001$, Figure 2, Table 1).

While +dP/dt values did not change significantly in the 10^{-6}M TMZ solution, a significant change was observed in the 10^{-5} M TMZ solution ($p < 0.001$).

Baseline -dP/dt values remained unchanged for both TMZ doses. In the hypoxic bath, there was a significant increase in Cf values for both TMZ doses, while Ct values showed no significant change compared to baseline ($p < 0.001$). ½Rt values decreased significantly only in the 10^{-6} M TMZ solution ($p < 0.001$), but ±dP/dt increased significantly for both TMZ doses compared to baseline values ($p < 0.001$, Table 1).

Recovery contractile function of isolated papillary heart muscle

In the normoxic bath, Rcf values in 10^{-5} M and 10^{-6} M TMZ solutions reached control levels in 8.3 and 8.8 minutes, respectively, after washing and aeration of the muscle specimens.

In the 10^{-5} M TMZ solution, +dPr/dt values decreased significantly ($p < 0.001$), while in the 10^{-6} M TMZ solution, there was no significant change compared to baseline values. The -dPr/dt values increased significantly in the 10^{-6} M TMZ

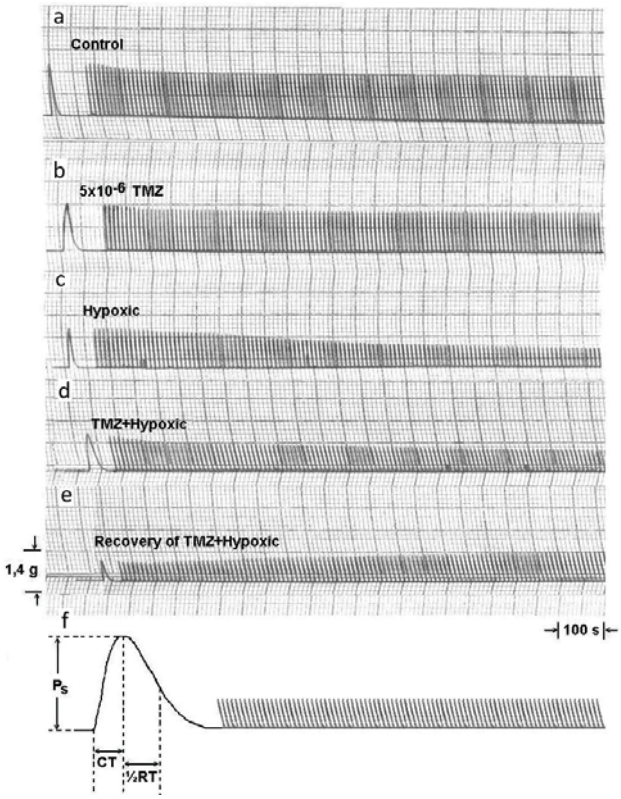

Figure 2: Effects of TMZ on contractile function (traces a-d) and recovery of contractile function (trace e) of isolated papillary heart muscle under control (normoxic) and hypoxic conditions. Trace f shows the definition of the contractility parameters.

Table 1: The effect of TMZ on the mechanical parameters of the isolated papillary rat heart muscles in normoxic and hypoxic bath conditions (mean ± SD, n: 20).

Parameters	p	Normoxic			p	Hypoxic		
		Control	10^{-6} TMZ	10^{-5} TMZ		Control	10^{-6} TMZ	10^{-5} TMZ
Cf (g)	0.001 0.001	1.52 ± 0.01	1.35 ± 0.02	1.23 ± 0.01	0.001 0.001	0.83 ± 0.01	1.12 ± 0.01	0.95 ± 0.01
Ct (ms)	0.001 0.001	137.8 ± 1.7	130.4 ± 2.4	134.3 ± 1.3	NS NS	125.8 ± 1.5	125.8 ± 2.3	126.2 ± 1.6
½RT	0.001 0.001	80.1 ± 1.7	76.1 ± 2.2	75.9 ± 1.5	0.001 NS	84.4 ± 1.7	81.4 ± 1.9	83.6 ± 1.7
+dP/dt (g/s)	NS 0.001	28.0 ± 0.9	28.8 ± 0.7	25.1 ± 0.9	0.001 0.001	15.2 ± 0.5	21.6 ± 0.9	18.3 ± 1.0
-dP/dt (g/s)	NS NS	21.2 ± 0.8	22.1 ± 0.4	21.2 ± 0.4	0.001 0.001	13.0 ± 0.1	16.3 ± 0.6	13.4 ± 0.7

Cf: Contraction force; Ct: Contraction time; ½RT: Relaxation half-time; +dP/dt: Contraction rate; -dP/dt: Relaxation rate; NS: Non Significant

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solution ($p < 0.001$), but not in the 10^{-5} M TMZ solution (Table 2).

In the hypoxic bath, TMZ significantly increased Rcf values for isolated papillary heart muscle compared to baseline ($p < 0.001$, Figure 3). The Rt was shorter with TMZ compared to control times ($p < 0.001$). ±dPr/dt values also increased significantly with TMZ compared to baseline ($p < 0.001$, Table 2,).

Discussion

Studies show that TMZ can help reduce ischemic contracture, improve contractile function [11,16,17], and counteract the post-ischemic rise in diastolic pressure [8,10,18,19] in the heart under hypoxic conditions.

Emre, et al. found that TMZ prevented the fatigue-induced reduction in contraction force [7]. Guarneieri, et al. [3] found that high doses of TMZ during ischemia raise mitochondrial Ca^{2+} levels and boost ATP production by enhancing oxoglutarate dehydrogenase activity. TMZ does not directly block Ca^{2+} entry but may help reduce intracellular acidosis by limiting ATP depletion during ischemia [5]. Allibardi, et al. found that TMZ protected myocardial contractility during ischemia by reducing lactate release and lowering anaerobic metabolism [17].

TMZ inhibits fatty acid oxidation in ischemic rat hearts by blocking the enzyme long-chain 3-ketoacyl CoA thiolase, leading to increased glucose oxidation [1,2]. By altering the coupling of glycolysis to glucose oxidation, TMZ reduces proton production, leading to decreased tissue acidosis. This may help limit sodium and calcium overload in myocytes by inhibiting certain ion exchange processes. TMZ has also been proposed to modulate intracellular acidosis by affecting the H^+/Na^+ antiport [20].

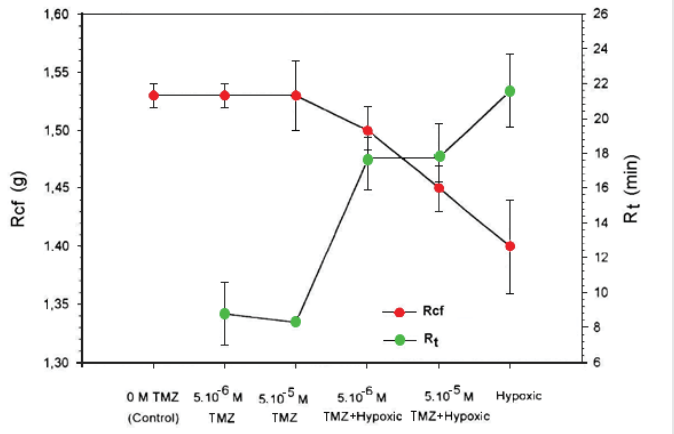

Figure 3: Effect of TMZ on the recovery time (Rt) and recovery contraction force (Rcf) of the isolated papillary rat heart muscle under normoxic and hypoxic bath conditions.

While studies have shed light on how TMZ works during cellular ischemia, it remains unclear how these processes impact the mechanical function of the heart muscle. Data on the mechanical function of TMZ-treated myocardial muscle during ischemia and reperfusion are limited. This study compares the mechanical performance of TMZ-treated heart muscle to control muscle during these conditions. The study found a significant decrease in contractile function in 10^{-6} M and 10^{-5} M TMZ solutions under normoxic and near-normothermic conditions. Contractile function in 10^{-6} M and 10^{-5} M TMZ solutions decreased under hypoxic conditions. Additionally, there was an increase in recovery of contractile function in 10^{-6} M and 10^{-5} M TMZ solutions under hypoxic conditions.

Our tests showed that both doses of TMZ caused a significant decrease in the contractile function of the isolated papillary heart muscle in normoxia (Table 1). These results support previous findings that high concentrations of TMZ solution can decrease left ventricular contractile function before ischemia [5]. The cause of the negative inotropic effect is unclear and requires further investigation. One possible explanation is the switch from fatty acid to glucose oxidation, which may limit energy availability to the myocytes and reduce contractility under normoxic conditions.

In our experiments, we found that adding a dose of 10^{-6} M TMZ to the hypoxic bath preserved the ischemic contractile properties of the papillary rat heart muscle better than 10^{-5} M TMZ (Table 1). This concentration of TMZ has been shown to restore ATP synthesis in isolated mitochondria [20], while higher concentrations do not have a significant protective effect [10].

Lower concentrations of TMZ may improve energy regulation in ischemic cells by enhancing Ca^{+2} uptake by mitochondria and ATP synthesis. This effect may involve a shift from fatty acid oxidation to glucose oxidation for energy production. The reason for the loss of this effect at higher concentrations is unknown.

Table 2: Effects of TMZ on the recovery time and recovery contraction forces and recovery velocity of shortening and velocity of relaxation on the isolated papillary rat heart muscle in normoxic and hypoxic bath conditions (mean ± SD, n: 20).

Parameters	p	Normoxic			p	Hypoxic		
		Control	10^{-6} TMZ	10^{-5} TMZ		Control	10^{-6} TMZ	10^{-5} TMZ
R_{cf} (g)	NS NS	1.53 ± 0.02	1.53 ± 0.01	1.53 ± 0.03	0.001 0.001	0.40 ± 0.04	1.50 ± 0.02	1.45 ± 0.02
R_t (min)	- -	-	8.8 ± 1.2	8.3 ± 0.9	0.001 0.001	21.6 ± 2.1	17.2 ± 1.6	17.8 ± 1.9
+dPr/dt (g/s)	NS 0.001	28.0 ± 0.9	27.8 ± 0.8	26.8 ± 1.3	0.001 0.001	21.2 ± 1.2	28.0 ± 1.1	23.0 ± 0.9
-dPr/dt (g/s)	0.001 NS	21.2 ± 0.8	22.0 ± 0.9	21.2 ± 0.4	0.001 0.001	21.0 ± 1.3	21.9 ± 0.9	19.7 ± 0.8

R_{cf}: Recovery contraction force; R_t: Recovery time; +dPr/dt: Recovery contraction rate; -dPr/dt: Recovery relaxation rate; NS: Non Significant

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Our study showed that immersing isolated rat heart muscle in a hypoxic bath with TMZ, followed by oxygenated reperfusion, improved contractile function compared to baseline values (Table 2). The use of 10^{-6} M TMZ resulted in better preservation of function. Several studies have shown that 10^{-6} M TMZ has a positive effect on post-ischemic recovery of contractile function after normothermic cardioplegia [10,17,21].

ATP and creatine phosphate levels were higher in TMZ-pretreated heart muscle during reperfusion [4]. TMZ may help save energy in the heart during ischemia, leading to increased ATP and creatine phosphate levels that can benefit the myocytes during reperfusion [18]. TMZ may improve contractile function recovery by enhancing ATP synthesis during reperfusion.

In this study, adding TMZ did not affect contraction time under hypoxic conditions, but significantly shortened relaxation time. This may be due to increased sarcoplasmic Ca^{+2} levels or early repolarization, possibly caused by increased oxoglutarate dehydrogenase activity and ATP synthesis, or enhanced K^+ influx from increased Na^+/K^+/ATPase activity.

To investigate the impact of TMZ on muscle performance, the relationship between shortening extent and relaxation rate was studied. TMZ was found to significantly affect shortening and relaxation velocity in isolated papillary heart muscle, limiting performance decline under hypoxic conditions. Maximal shortening depends on cross-bridge formation rate and Ca^{+2} releases. Relengthening velocity is determined by ATP processes and muscle forces. Relaxation enhancement is influenced by Na^+/K^+/ATPase activity.

Hisatome, et al. studied the effect of TMZ on Na^+/K^+/ATPase activity, or the Na^+/K^+ pump, in guinea-pig ventricular muscles [22]. The effect of TMZ on the enzyme in myocardial tissue was compared to that in the liver, jejunum, and kidney. TMZ weakly inhibited cardiac Na^+/K^+/ATPase activity, but only at non-physiological drug concentrations; therefore, it has no clinically significant effect on this cell membrane process. Consequently, it is quite likely that a TMZ-mediated increase in relaxation rate in ischemic heart muscle is due to an associated increase in the extent of shortening rather than an enhancement of the relaxation process itself. Hisatome, et al. studied the effect of TMZ on Na^+/K^+/ATPase activity in guinea-pig ventricular muscles [22]. They found that TMZ weakly inhibited cardiac Na^+/K^+/ATPase activity at non-physiological drug concentrations, but this is not clinically significant. Therefore, the increase in relaxation rate in ischemic heart muscle with TMZ is likely due to increased shortening rather than enhanced relaxation.

In summary, adding therapeutic doses of TMZ to the hypoxic bath solution has a significant impact on the mechanical performance of the papillary heart muscle. TMZ helps maintain contractility during ischemia and reperfusion, possibly by affecting myocardial energy metabolism and ion permeability in mitochondria [23-25]. TMZ may be a helpful addition in ischemic hearts during open cardiac operations with long cross-clamp times due to its negative inotropic effect. More research is needed to understand how TMZ's dose-dependent anti-ischemic action works in heart muscle.

In conclusion, this study suggests that therapeutic doses of TMZ have anti-ischemic effects. Further research is needed to understand the underlying mechanisms in heart muscle.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could create a conflict of interest.

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