The Protective Effects of Trimetazidine on Normothermic Ischemic Myocardium in Rats

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ABSTRACT: The protective effects of trimetazidine on postischemic cardiac function were studied using isolated working rat heart preparations in which global ischemia had been induced with normothermic cardioplegia. After 30 minutes of reperfusion, following a 25 minutes period of ischemia, the addition of $10^{-6} \text{ M}$ or $10^{-5} \text{ M}$ trimetazidine to the cardioplegic solution significantly increased the per cent recovery of the cardiac output: from $54.8 \pm 4.1$ per cent in the control group to $81.0 \pm 3.2$ per cent ($p<0.01$) and $79.6 \pm 4.0$ per cent ($p<0.01$), respectively, although lower ($10^{-7} \text{ M}$) or higher ($10^{-4} \text{ M}$) doses of the drug failed to result in any change. $10^{-5} \text{ M}$ trimetazidine also produced a significantly greater recovery of both the postischemic aortic flow: from $47.8 \pm 4.9$ per cent to $72.2 \pm 3.8$ per cent ($p<0.01$) and the coronary flow: from $80.6 \pm 2.9$ per cent to $105.2 \pm 6.3$ per cent ($p<0.002$). However, trimetazidine did not influence the recovery of either aortic pressure or heart rate. These results suggest that trimetazidine does give some protection to the heart during ischemia and reperfusion.

KEY WORDS: trimetazidine, myocardial protection, ischemia, reperfusion, cardioplegia

INTRODUCTION

Trimetazidine, 1-(2,3,4-trimethoxybenzyl) piperazine dihydrochloride, (TMZ) has been used as an antianginal drug for patients with ischemic heart disease.\textsuperscript{1,2} The pharmacological properties of TMZ include; 1) a coronary vasodilating action,\textsuperscript{2} 2) a calcium antagonist-like action,\textsuperscript{3} 3) the inhibition of intracellular potassium loss during ischemia,\textsuperscript{1,3,4} 4) an anti-platelet effect\textsuperscript{5} and 5) an oxygen free radical scavenging action.\textsuperscript{6-10} All these actions are known to provide myocardial protection against ischemic insult. In the present study, we assessed the effectiveness of trimetazidine on postischemic cardiac function, using isolated working rat heart preparations under conditions of normothermic ischemia employing a crystalloid cardioplegic solution.

MATERIALS AND METHODS

This study was performed using W.K.A. rats weighing between 340 and 400 g. The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg per kg). Heparin (2 mg) was administered into the femoral vein to prevent clotting. After one minute, the heart was excised rapidly and immersed in an icecold Krebs-
Henseleit bicarbonate buffer (KHB) solution and cannulated in the perfusion apparatus. The KHB solution contained 138.9 mM glucose and was gassed with 95 per cent oxygen and 5 per cent carbon dioxide (pH 7.4 at 35°C).

The experimental protocol is shown in Fig. 1. After 10 minutes of Langendorff perfusion under a pressure of 80 cm H₂O, the heart was converted to a working mode for another 10 minutes via the left atrium at a filling pressure of 18 cm H₂O. The preischemic values of aortic flow, coronary flow, cardiac output, heart rate and aortic pressure were then obtained. By clamping the aortic and left atrial cannula and flushing in the cardioplegic solution (35°C) via the aortic cannula, the heart was subjected to normothermic (35°C) global ischemia for 25 minutes. At the end of the ischemic period, the heart was reperfused in the Langendorff mode for 5 minutes and then in the working mode for 25 minutes. Measurements of functional recovery were taken after 10, 15 and 30 minutes of reperfusion.

The cardioplegic solution used was composed of Na⁺ 90 mM/L, K⁺ 20 mM/L, Ca²⁺ 0.1 mM/L, Cl⁻ 100 mM/L, HCO₃⁻ 10 mM/L and glucose 25 g/L. The osmolarity was maintained at 340 mOsm/L and the pH at 7.8. To investigate the effects of TMZ on the myocardium, different concentrations (10⁻⁷, 10⁻⁶, 10⁻⁵, 10⁻⁴ M) of the drug were added to the cardioplegic solution.

Five to ten rats were studied in each group and the results were statistically analyzed using the paired or unpaired Student's t-test. All values obtained were expressed as the mean ± SEM.

**RESULTS**

**Recovery of cardiac output**

The recovery of postischemic cardiac output was expressed as a percentage of the preischemic value. As shown in Fig. 2, following a 30 minute period of reperfusion with 10⁻⁶ and 10⁻⁵ M TMZ, the per cent recovery of cardiac output had significantly increased; to 81.0 ± 3.2 per cent (p<0.01) with 10⁻⁵ M and 79.6 ± 4.0 per cent (p<0.01) with 10⁻⁴ M, as compared to 54.8 ± 4.1 per cent in the control group. On the other hand, higher (10⁻⁴ M) or lower (10⁻⁷ M) doses proved ineffective. Thus, as can be seen in Fig. 2, there was bell-shaped relationship between the dose of TMZ in the cardioplegic solution and the recovery of cardiac output following the ischemic episode. Moreover, it should be noted that a higher dose of TMZ decreased the functional recovery to 37.7 ± 5.4 per cent.

![Fig. 1. The protocol of the experimental model. The white arrow indicates the time of cardioplegia injection and the black arrows indicate the time of measurement of the left ventricular function; at completion of the control perfusion and three times during the reperfusion. L=Langendorff perfusion, W=working mode perfusion, LV function=left ventricular function](image)

![Fig. 2. The effect of TMZ on the recovery of cardiac output. All data are expressed as a percentage of the preischemic value. Vertical bars represent the standard error of the mean.](image)