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The administration of oxytocin during early reperfusion, dose-dependently protects the isolated male rat heart against ischemia/reperfusion injury

Masood Aali Anvari [a], Alireza Imani [a], Mahdieh Faghihi [a], Seyed Morteza Karimian [a,*], Maryam Moghimian [b], Maryam Khansari [a]

[a] Department of physiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of physiology, School of Medicine, Gonabad University of Medical Sciences, Khorasan Razavi, Iran

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ABSTRACT

In our previous study, the administration of oxytocin (OT) could precondition the heart against ischemia/reperfusion injury. In this study, to investigate the cardiac postconditioning effect of oxytocin, isolated rat hearts were mounted on a Langendorff perfusion apparatus. In all groups, the hearts underwent 30 min of regional ischemia followed by 120 min of reperfusion. In the ischemia/reperfusion (IR) group, ischemia and reperfusion was induced. In the ischemic postconditioning (Ipost) group, hearts underwent 6 cycles of 10 s reperfusion and 10 s ischemia at the beginning of reperfusion. In the other groups (III-IX), OT was perfused 5 min before the onset of reperfusion and continued for 25 min with following doses (Molar): 10^{-12}, 5×10^{-12}, 8×10^{-12}, 10^{-11}, 2×10^{-11}, 5×10^{-11}, and 10^{-10}. The infarct size and coronary effluent levels of creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH) and malondialdehyde (MDA) were calculated at the end of reperfusion. The infarct size decreased considerably in Ipost group compared to IR group ($P<0.05$). Also, the infusion of oxytocin by doses of 8×10^{-12} M, 10^{-11} M and 2×10^{-11} M dose-dependently reduced infarct size ($P<0.05$) significantly compared to the IR group. LDH level in coronary effluent was markedly decreased in Ipost group and treatment with oxytocin by doses of 8×10^{-12} M, 10^{-11} M, 2×10^{-11} M and 5×10^{-11} M ($P<0.05$) compared to IR group. Ipost, OT $2\times10^{-11}$and 10^{-11} M significantly decreased CK-MB level ($P<0.05$). Ipost, OT 8×10^{-12}, 10^{-11} and 2×10^{-11} M significantly decreased MDA level as compared to IR group. Our study shows that oxytocin dose-dependently exerts cardiac postconditioning.

1. Introduction

Ischemic heart disease is one of the main causes of mortality worldwide, which demands effective measures against it. Inducing a rapid reperfusion in ischemic heart is very important and essential for maintaining its normal function, but reperfusion creates ischemia/reperfusion phenomenon which causes an extensive myocardial injuries (Balakumar et al., 2009).

In this regard, it has been demonstrated that ischemic postconditioning (Ipost) as a valuable procedure can reduce ischemia/reperfusion-induced injury in the heart. In this method, inducing several sequences of short reperfusion/ischemia episodes instantly at the beginning of reperfusion following an index ischemia reduces the extent of injury in the heart (Sun et al., 2005; Zhao et al., 2003). Postconditioning can also be induced by administration of pharmacological agents at the end of ischemia and early reperfusion (Schipke et al., 2006).

It has been reported that postconditioning can reduce the myocardial infarct size in different species of animals such as dogs (Zhao et al., 2003), rats (Kin et al., 2004; Pinheiro et al., 2009) and rabbits (Yang et al., 2004).

The generation of free radicals during ischemia/reperfusion participates in tissue damages and it seems that attenuation of oxidative stress is one of the mechanisms of postconditioning (Schipke et al., 2006).

Oxytocin (OT) as a neurohypophysial hormone is principally produced in magnocellular neurons of the hypothalamus (Landgraf and Neumann, 2004; Pournajafi-Nazarloo et al., 2007).

Generally, OT is known as a neurohormone with its original action on uterus and mammary glands; but existence of equal amount of OT in both sexes indicates that OT has another function in other tissues (Gimpl and Fahrenholz, 2001).

Nowadays OT is also considered to be a cardiovascular hormone. Also, it was reported that systemic administration of OT has considerable effect on cardiovascular function (Gutkowska et al., 2000; Jankowski et al., 1998, 2000; Petty et al., 1985).

We have previously depicted preconditioning effects of OT on the ischemic-reperfused heart injury but to our knowledge, there are no studies about postconditioning effect of OT. It is probable that postconditioning is more likely to be feasible as a clinical application to patients than preconditioning.

* Corresponding author. Tel./fax: +98 21 66419484.
E-mail address: karimian@tums.ac.ir (S.M. Karimian).

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Hence, the cardiac postconditioning effect of OT was evaluated in this study.

2. Materials and methods

2.1. Preparation of isolated hearts

Male Wistar rats (200–250 g) were housed in an air-conditioned colony room on a12 h light/dark cycle at 21–23 °C with free access to food and water. The animals were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and given heparin sodium (500 IU). Hearts were rapidly excised and placed in an ice-cold buffer, and mounted on a constant pressure (80 mm Hg) Langendorff-perfusion apparatus. All experiments were conducted in accordance with the institutional guidelines of Tehran University of Medical Sciences (Tehran, Iran) and the National Institutes of Health guidelines for the care and use of laboratory animals.

Hearts were perfused retrogradely with modified Krebs–Henseleit bicarbonate buffer containing (in mmol/l): NaHCO3 25; KCl 4.7; NaCl 118.5;MgSO4 1.2;KH2PO4 1.2; glucose 11; CaCl2 2.5 gassed with 95% O2 5% CO2 (pH 7.35–7.45 at 37 °C). A latex, fluid-filled, isovolumic balloon was inserted into the left ventricle through the left atrial appendage and was inflated in order to give an end diastolic pressure of 8 to 10 mm Hg and connected to a pressure transducer (Harvard). Two thin stainless steel electrodes fixated at the ventricular apex and right atrium, were employed to record electrocardiogram for heart rate monitoring.

A surgical needle was passed under the origin of the left anterior descending coronary artery, and the ends of the suture were passed through a pipette tip to form a snare. Regional ischemia was induced by tightening the snare and reperfusion was performed by releasing the ends of the suture. The perfusion apparatus was water-jacketed to maintain constant perfusion temperatures of 37 °C. Hearts were allowed to beat spontaneously throughout the experiments. The left ventricular developed pressure (the difference between the left ventricular systolic and diastolic pressure) and the heart rate (as hemodynamic parameters) were monitored with a domestic program (Ossilo Graph Monitor, Biomed). Coronary flow was measured for 1 min at the end of baseline, ischemia, 60 min and 120 min of reperfusion. Coronary effluent was collected for creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH) and malondialdehyde (MDA) measurement at the end of reperfusion.

2.2. Experimental protocol

After heart isolation and prior to baseline period, all hearts were perfused and allowed to stabilize for 20 min. In all groups, hearts underwent 30 min of regional ischemia followed by 120 min of reperfusion. The experimental design is illustrated in Fig. 1. All animals were randomly divided into experimental groups as follows (n = 8):

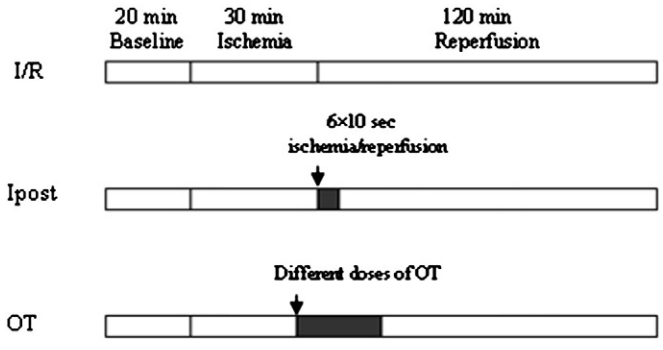

Fig. 1. Schematic illustration of experimental groups (n = 8). Ipost, ischemic postconditioning; I/R, ischemia/ reperfusion; OT, oxytocin.

(I) ischemia/ reperfusion (IR) group: hearts underwent 30 min of regional ischemia followed by 120 min of reperfusion; (II) Ipost group: after 30 min of ischemia, hearts underwent 6 cycles of 10 s reperfusion and 10 s regional ischemia at early phase of reperfusion. In the other groups (III-IX), OT was perfused 5 min before the onset of reperfusion and continued for 25 min with following doses (Molar): 10^{-12}, 5×10^{-12}, 8×10^{-12}, 10^{-11}, 2×10^{-11}, 5×10^{-11}, and 10^{-10}. Administration of OT was performed via the infusion pump which was connected to the main perfusion cannula. The experimental conditions were constant throughout the experiment.

2.3. Infarct size measurement

At the end of reperfusion, left anterior descending coronary artery was reoccluded, and Evans blue dye was infused via aorta to differentiate the ischemic zone from the nonischemic zone. Hearts were frozen for 24 h and then sliced into 2-mm transverse sections from apex to base. Slices were then incubated with 1% triphenyltetrazolium chloride (TTC in 0.1 M phosphate buffer, pH 7.4) for a period of 20 min at 37 °C. TTC reacts with the viable tissue, producing a red formazan derivative, which is distinct from the white necrotic tissue once fixated in 10% formalin for 24 h. The area at risk, left ventricle and infarcted size were measured by using Photoshop program (Ver. 7.0, Adobe System, San Jose, CA, USA).

Area at risk was expressed as a percentage of left ventricle and infarct size was expressed as a percentage of area at risk (IS/AAR).

2.4. Measurement of CK-MB, LDH and MDA levels in coronary effluent

The levels of CK-MB, LDH and MDA were calculated in coronary effluent samples at the end of reperfusion period. CK-MB and LDH levels were determined with specific CK-MB and LDH Kits (Pars Azmoon, Teheart ratean, Iran), using an autoanalyzer (Roche Hitachi Modular DP Systems; Mannheim, Germany). The MDA level, as a marker for assessment of oxidative stress, was calculated by a tiobarbitoric acid (TBA) method. In brief, 1.5 ml of perfusate was added to 0.5 ml of a solution containing 30% trichloroacetic acid, 0.75% TBA, and 0.5 N HCl, and then inserted in a water bath 100 °C for 20 min. After cooling, the samples were centrifuged and lipid peroxidation was determined spectrophotometrically at 532 nm (Ambrosio et al., 1991).

2.5. Chemicals substances

Oxytocin and TTC were obtained from Sigma-Aldrich (Deisenhofen, Germany) and general laboratory chemicals were acquired from Merck (Darmstadt, Germany). Stock solution of oxytocin was dissolved in distilled water and added to the Krebs-Henseleit bicarbonate buffer and equilibrated with O2 (95%)–CO2 (5%) (pH 7.4 at 37 °C).

2.6. Statistical analyses

Data are expressed as means ± S.E.M. Statistical comparison of means between groups was made by one-way ANOVA and a subsequent Tukey test for infarcted size ratio and biochemical parameters and Two-way ANOVA was done for hemodynamic parameters. Significant differences were determined as $P<0.05$.

3. Results

3.1. Hemodynamic function

Table 1 shows heart rate and left ventricular developed pressure changes during the experiments. Heart rate was decreased in all groups at the end of reperfusion compared to their baseline and it indicated that Ipost and different doses of OT had no effect on heart rate. Left ventricular developed pressure in IR, OT 10^{-10} M, OT 2×10^{-11} M

Table 1
Hemodynamics parameters.

	Baseline	End of reperfusion	
	HR (bpm)	HR (bpm)	LVDP (% of baseline)
IR	202.3 ± 3.7	114.7 ± 16.93[a]	54.82 ± 2.6[a]
Ipost	216.5 ± 3.78	132.16 ± 11.8[a]	58.74 ± 2.4
OT 10^{-12} M	233.6 ± 21.76	124.4 ± 14.94[a]	38.12 ± 4.7[a]
OT 5×10^{-12} M	236 ± 22.48	134 ± 9.38[a]	67.66 ± 2.4
OT 8×10^{-12} M	265 ± 22.4	169.75 ± 10[a]	82.52 ± 3.6
OT 10^{-11} M	218.7 ± 7.6	147.1 ± 8.4[a]	58.99 ± 0.8
OT 2×10^{-11} M	215 ± 21.67	160.75 ± 11.1[a]	77.78 ± 1.9
OT 5×10^{-11} M	250 ± 12.9	135 ± 27.1[a]	41.89 ± 1.8[a]
OT 10^{-10} M	221.6 ± 7.46	113.2 ± 12.4[a]	53.91 ± 2.2[a]

58.99 ± 0.8 bpm, beat per minute; HR, heart rate; Ipost, ischemic postconditioning; I/R, ischemia/reperfusion; LVDP, left ventricular developed pressure; M, molar; OT, oxytocin. Data are presented as mean ± S.E.M.
[a] P<0.05 compared to their baselines.

and OT 10^{-12} M groups decreased significantly at the end of reperfusion compared to their baseline, but left ventricular developed pressure didn't change in other groups (Ipost, OT 2×10^{-11} M, OT 10^{-11} M, OT 5×10^{-12} M and OT 8×10^{-12} M).

3.2. Coronary flow

Table 2 shows the coronary flow (ml/min) in different groups. Statistical analysis showed that coronary flow was significantly reduced at the end of ischemia, 60 min and 120 min of reperfusion periods as compared to its baseline in each group and administration of different doses of OT could not improve the coronary flow.

3.3. Infarct size and area at risk

There were no significant differences in the ratio of area at risk to total left ventricular area between the hearts in all experimental groups. The ratio of infarct size to area at risk (%) decreased considerably from 36.35 ± 0.48 in ischemia/reperfusion group to 16.42 ± 1.73 (P<0.05) in ischemic postconditioning group. Postconditioning with different doses of oxytocin 8×10^{-12} M, 10^{-11} M and 2×10^{-11} M groups significantly and dose-dependently reduced infarct size to 27.7 ± 1, 11.6 ± 0.8 and 28 ± 2.3 (P<0.05) respectively vs. the IR group (Fig. 2).

3.4. Biochemical analysis

The levels of LDH, CK-MB and MDA in coronary effluent were used to monitor the damage of myocardium. LDH levels in coronary effluent markedly decreased in ischemic postconditioning group compared to the IR group. Treatment with oxytocin by doses of 8×10^{-12} M, 10^{-11} M, 2×10^{-11} M and 5×10^{-11} M (P<0.05) prevented elevation of LDH level in coronary effluent after ischemia/reperfusion (Fig. 3A).

Ischemic postconditioning, OT 2×10^{-11} and 10^{-11} M significantly decreased CK-MB level (P<0.05) as compared to the IR group (Fig. 3B).

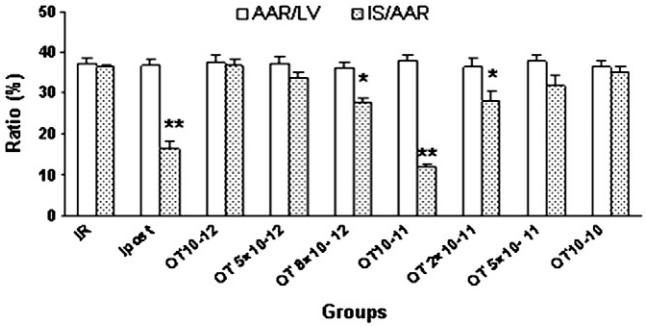

Fig. 2. Myocardial infarct size in different groups (n = 8). AAR, area at risk; IS, infarct size; Ipost, ischemic postconditioning; IR, ischemia/reperfusion; LV, left ventricle; OT, oxytocin. Data are presented as mean ± S.E.M. ** P<0.01 and * P<0.05 compared to IR group.

Ipost, OT 8×10^{-12}, 10^{-11} and 2×10^{-11} M significantly decreased MDA level as compared to the IR group (Fig. 3C).

3.5. Dose–response studies

Postconditioning with oxytocin decreased post-ischemic infarct size, LDH, CK-MB and MDA in a U-shaped dose-dependent manner. Maximum cardioprotective effect of oxytocin was achieved by 10^{-11} M.

4. Discussion

This study showed that treatment with OT during the end of ischemia and early reperfusion period can protect the isolated rat heart against ischemia/reperfusion injury. This study also showed that OT can imitate ischemic postconditioning effect in a dose dependent manner. Treatment with OT after local ischemia can protect myocardium from ischemic injury and dose dependently reduces infracts size.

OT did not change heart rate in comparison with the IR group which shows that OT's protecting effect on infracted heart is not related to this hemodynamic parameter effect and it can be due to cytoprotective effect of OT. Also, it seems that reduction of infarct size by some doses of OT has resulted in better the left ventricular function with improved left ventricular developed pressure.

These data are in accordance with our previous studies in preconditioning effect of oxytocin in the anesthetized rat heart in which, exogenous administration of OT protected the heart against ischemia/reperfusion injuries (Houshmand et al., 2009).

We have also demonstrated that endogenous release of OT contributes to the formation of ischemic preconditioning and blockage of OT receptors with atosiban prevented cardioprotective effect of ischemic preconditioning (Alizadeh et al., 2011).

In this study, oxytocin also reduced biochemical parameters such as CK-MB, LDH (biochemical injury markers) and MDA (oxidative stress marker) in comparison with ischemia/reperfusion group.

Table 2
Coronary flow (ml/min).

	End of baseline	End of ischemia	End of 60 min reperfusion	End of 120 min reperfusion
IR	7.2 ± 0.4	5.48 ± 0.4[a]	5.02 ± 0.34[a]	4.17 ± 0.38[a]
Ipost	7.6 ± 1.25	4.11 ± 0.49[a]	4.11 ± 0.86[a]	2.5 ± 0.46[a]
OT 10^{-12} M	5.88 ± 0.22	2.78 ± 0.21[a]	2.36 ± 0.45[a]	1.98 ± 0.34[a]
OT 5×10^{-12} M	5.63 ± 0.92	2.46 ± 0.24[a]	2.43 ± 0.38[a]	1.63 ± 0.43[a]
OT 8×10^{-12} M	10.45 ± 1.68	3.85 ± 0.78[a]	5.15 ± 0.4[a]	3.35 ± 0.72[a]
OT 10^{-11} M	6.74 ± 0.69	3.85 ± 0.67[a]	3.18 ± 0.63[a]	2.55 ± 0.55[a]
OT 2×10^{-11} M	8.22 ± 0.56	5.1 ± 0.61[a]	3.1 ± 0.54[a]	2.55 ± 0.45[a]
OT 5×10^{-11} M	6.42 ± 1.01	3.27 ± 0.53[a]	2.82 ± 0.65[a]	2.3 ± 0.81[a]
OT 10^{-10} M	7.52 ± 1.44	4.54 ± 2.11[a]	2.9 ± 1.06[a]	2.16 ± 0.69[a]

Ipost, ischemic postconditioning; I/R, ischemia/reperfusion; M, molar; OT, oxytocin. Data are presented as Mean ± S.E.M.
[a] P<0.05 compared to their baselines.

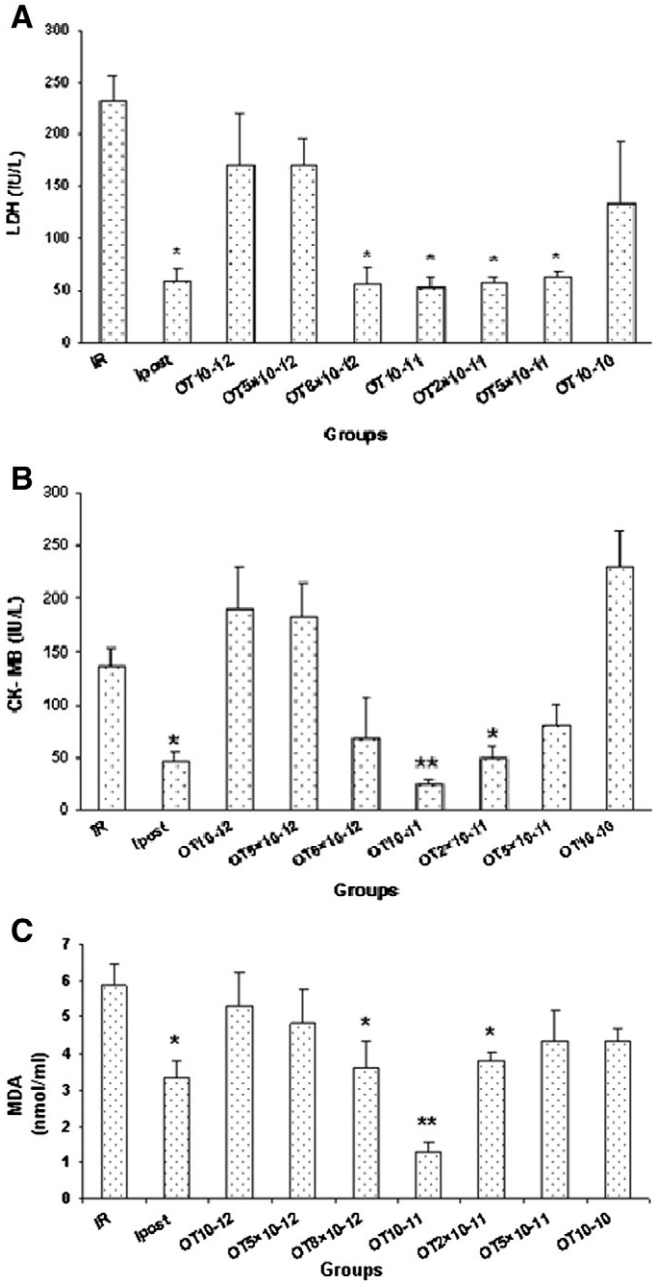

Fig. 3. Levels of LDH (A), CK-MB (B) and MDA (C) in coronary effluent at the end of reperfusion period in different groups (n = 8). Ipost, ischemic postconditioning; IR, ischemia–reperfusion; OT, oxytocin. Data are presented as mean ± S.E.M. * $P<0.05$ and ** $P<0.01$ compared to IR group.

Myocardial injuries lead to the release of CK-MB and LDH, as tissue enzymes, in coronary effluent, and raised levels of these enzymes is evidence for myocytes injury. In this regard, one of the ways to assess the degree of cardioprotective effect of agents is the measurement of the coronary effluent levels of CK-MB and LDH (Ajmani et al., 2011; Taliyan et al., 2010). Thus, reduced plasma levels of CK-MB and LDH due to oxytocin infusion confirms the cardioprotective effect of this agent against myocardial injuries.

The evaluation of MDA level is a method for the assessment of lipid peroxidation due to oxidative stress.

It is commonly accepted that the generation of the free radicals contributes to the pathogenesis of ischemia/reperfusion phenomenon. The event of oxidative stress due to enhanced free radical generation leads to changes in membrane permeability and membrane lipid bilayer disturbance and plays an essential role in ischemia/reperfusion injuries. It was exhibited that postconditioning leads to reduction of free radical formation, and consequently cardioprotective effect of postconditioning is related to reduction of oxidative stress (Penna et al., 2009).

Previously it has been reported that OT can protect the kidney tissue against ischemia/reperfusion injury with reduction of lipid peroxidation and is mediated by nitric oxide (NO) production (Tugtepe et al., 2007). Also, the role of NO as a postconditioning trigger in ischemic/reperfused heart has been shown (Luna-Ortiz et al., 2011).

It has been revealed that OT may release atrial natriuretic peptide (ANP) (Gutkowska et al., 1997) which has antioxidative properties (De Vito et al., 2010). In addition, ANP administration at reperfusion period exerts the cardioprotective effect in acute myocardial infarction (Kitakaze et al., 2007). Therefore, it seems that OT-induced cardiac postconditioning may be mediated via NO production or the release of ANP.

In addition, oxytocin lessens oxidative renal damage in pyelonephritic rats through its antioxidant effect by inhibition of the free radical waterfall cascade and secretion of cytokines (Biyikli et al., 2006). Iseri et al. (2005) showed that MDA is increased in acetic acid induced colitis which OT reduces MDA and lipid peroxidation and also, administration of oxytocin prevented the decrease in tissue glutathione level, as an intracellular antioxidant, in colonic inflammation. In agreement with these studies, it seems that OT via the maintenance of antioxidant capacity against oxidative stress reduces cardiac ischemia/reperfusion injury.

Conclusion: In summary, dose dependent administration of OT at the end of regional myocardial ischemia and beginning of reperfusion reduces the extent of cardiac injury and mimics the ischemic postconditioning. Also, it seems that cardioprotective effect of OT is related to reduction of oxidative stress. Our results suggest that OT protects the heart and may represent a novel approach for the protection of the heart after ischemia.

Acknowledgments

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