

Effect of shenfu injection on gastrointestinal microcirculation in rabbits after myocardial ischemia-reperfusion injury

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Abstract

AIM: To investigate the effect of shenfu injection on gastrointestinal microcirculation after myocardial ischemic-reperfusion (IR) injury in rabbits and probe into the mechanism.

METHODS: Forty healthy flap-eared white rabbits were randomly divided into 4 groups: IR injury control group (group I), shenfu injection 5 mL/kg per h group (group II), shenfu injection 10 mL/kg per h group (group III) and shenfu injection 20 mL/kg per h group (group IV). The four groups were treated with Lactated Ringer's solution, shenfu injection 5, 10, and 20 mL/kg per h were infused intravenously 30 min before experiment respectively. The values of hemodynamics [mean arterial pressure (MAP), heart rate (HR), gastric intramucosal partial pressure of carbon dioxide (PCO₂), blood gas analysis and pH] were measured and compared with those before myocardial ischemia, 60 min after myocardial ischemia and 60, 90, and 180 min after reperfusion.

RESULTS: The MAP, HR and gastric intramucosal pH were (70.50 ± 4.50) kPa, (165 ± 14) beats per min, 7.032 ± 0.024 in group I 60 min after myocardial ischemia, which were significantly decreased compared with those before myocardial ischemia (88.50 ± 9.75 kPa, 217 ± 18 beats per min, 7.112 ± 0.035, *P* < 0.05). The MAP, HR and gastric intramucosal pH were significantly decreased in group I 60, 90, and 180 min after reperfusion (61.50 ± 5.25 kPa, 133 ± 31 beats per min, 6.997 ± 0.025) compared with those before reperfusion respectively (*P* < 0.05), whereas the values were insignificantly different in groups II, III or IV after reperfusion, compared with those before reperfusion, and there were no significant differences between groups II, III, and IV after reperfusion.

CONCLUSION: Pre-infusion of shenfu injection has a

protective effect on gastrointestinal microcirculation after myocardial IR injury in rabbits, in a dose independent manner.

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Key words: Shenfu injection; Myocardial ischemic-reperfusion injury; Gastrointestinal microcirculation

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INTRODUCTION

Ischemia-reperfusion injury is a significant etiological factor of organ dysfunction, and it is important to investigate protective measures for anti-ischemia reperfusion injury. Myocardial ischemia reperfusion injury can induce myocardial metabolic disturbance, organ and functional damage, hemodynamic change, cardiac output decrease, reduction of gastrointestinal tract blood flow and oxygen dysmetabolism^[1]. The gastrointestinal mucosa has rich blood supply, being fairly sensitive to ischemia and oxygen deficiency, and is usually involved first after hypoxia. It is one of internal organs that have decrease of blood flow early and obviously but recover lastly. In this study, we investigated the effect of shenfu injection on gastrointestinal microcirculation after myocardial ischemic-reperfusion injury and probed into the mechanism of protective effect of shenfu injection through animal experiments in rabbits. Shenfu injection is a traditional Chinese medicine. The main pharmaceutical compounds are shenfu and fuji.

MATERIALS AND METHODS

Materials

This was a random controlled animal experimental study carried out in the Institute of Cardiology and Anesthesiology of Qingdao Medical University. Forty healthy flap-eared white rabbits were provided by Animal Centre of Affiliated Hospital of Qingdao Medical University [certificate number: FYXK (LU20030035)], including males and females, weighing 2.3-3.1 kg, with a

mean 2.46 ± 0.29 kg. They were fed with entire nutrition forage. Every rabbit ate about 150 g of foodstuffs, twice a day with free access to water. Rabbits were housed in an airy, quiet and light room with room temperature at 20°C - 22°C , one in each cage. Forty rabbits were randomly divided into 4 groups with 10 rabbits in a group, including ischemia-reperfusion control group (group I); shenfu injection 5 mL/kg per h group (group II); shenfu injection 10 mL/kg per h group (group III); shenfu injection 20 mL/kg per h group (group IV). Rabbits were fasted for 12 h before experiment. There was no significant difference in weight between four groups.

Methods

After being anaesthetized by an intravenous injection of thiopental sodium (20 g/L) with a dosage of 25 mg/kg, rabbits were incised at trachea, and an endotracheal catheter was inserted and connected to an animal breathing apparatus with 100% inhaling oxygen, 10-13 mL/kg tidal volume, 20-30 breath frequency per min and 1.2 inspiration/expiration ratio. Pressure of carbon dioxide at the end of expiration was kept at 4.7-5.3 kPa. A tube was inserted into right internal carotid vein for infusion of fluid and shenfu injection; an arterial puncture needle was inserted into the femoral artery and connected to a pressure-energy transducer to monitor blood pressure, heart rate and sample blood while mean artery pressure was kept between 69.75-90.00 kPa. Meanwhile, a 14F TRIP Tonometry catheter was inserted into stomach. During the experiment fentanyl (25 $\mu\text{g}/\text{kg}$) and vecuronium bromide (0.1 mg/kg) were administrated to maintain anaesthesia. We did not record baseline values until blood pressure, heart rate and breath were stable for 10 min while calculating pH according to Henderson-Hasselbalch formula^[2]. Groups I, II, III, and IV were infused with natrium lacticum Ringer's solution 8 mL/kg per h, shenfu injection 5 mL/kg per h, shenfu injection 10 mL/kg per h and shenfu injection 20 mL/kg per h through the vein respectively 30 min before the model of myocardial ischemia reperfusion was established. The pericardium was unfolded after chest was opened and the heart was exposed thoroughly. The left coronary artery anterior descending branch (LAD) was identified and main branch ligated at mid or upper 1/3 with double clinch. The ligature was unclamped for reperfusion after ischemia for 60 min.

Main observation index

Baseline levels of mean artery pressure, heart rate and pH value, at myocardial ischemia for 60 min and after reperfusion for 60, 90, and 180 min were recorded respectively.

Statistical analysis

All data were analyzed with SPSS 10.0 statistical package. Data were expressed as mean \pm SD, analyzed with Student's *t*-test between intra-group and with ANOVA between groups. A value of $P < 0.05$ was considered to have statistical significance.

Table 1 Physiologic indexes after myocardial ischemia-reperfusion injury (mean \pm SD, $n = 10$)

Group	Mean artery pressure (kPa)	Heart rate (beats/min)	pH value
Baseline level			
Group I	95.25 \pm 6.00	206 \pm 13	7.129 \pm 0.038
Group II	88.50 \pm 9.75	217 \pm 18	7.112 \pm 0.035
Group III	86.25 \pm 8.25	198 \pm 15	7.131 \pm 0.045
Group IV	90.75 \pm 6.75	221 \pm 22	7.122 \pm 0.037
Ischemia 60 min			
Group I	70.50 \pm 4.50 ^a	165 \pm 14 ^a	7.032 \pm 0.024 ^a
Group II	87.00 \pm 10.50	201 \pm 17	7.108 \pm 0.023
Group III	84.75 \pm 4.50	195 \pm 20	7.125 \pm 0.031
Group IV	87.75 \pm 5.25	213 \pm 16	7.119 \pm 0.026
Reperfusion 60 min			
Group I	61.50 \pm 5.25 ^{a,c}	133 \pm 31 ^{a,c}	6.997 \pm 0.025 ^{a,c}
Group II	85.50 \pm 9.00	197 \pm 12	7.121 \pm 0.022
Group III	96.75 \pm 6.00	199 \pm 16	7.114 \pm 0.032
Group IV	94.50 \pm 12.00	208 \pm 13	7.126 \pm 0.019
Reperfusion 90 min			
Group I	57.75 \pm 6.00 ^{a,c}	119 \pm 25 ^{a,c}	6.953 \pm 0.019 ^{a,c}
Group II	81.75 \pm 10.50	210 \pm 22	7.118 \pm 0.033
Group III	84.00 \pm 6.75	205 \pm 17	7.128 \pm 0.027
Group IV	81.00 \pm 11.25	214 \pm 21	7.125 \pm 0.026
Reperfusion 180 min			
Group I	48.75 \pm 3.00 ^{a,c}	94 \pm 16 ^{a,c}	6.911 \pm 0.017 ^{a,c}
Group II	86.25 \pm 5.25	204 \pm 25	7.127 \pm 0.024
Group III	90.75 \pm 9.00	216 \pm 21	7.132 \pm 0.034
Group IV	85.50 \pm 4.50	200 \pm 18	7.120 \pm 0.029

Group I: Ischemia-reperfusion control group; group II: Shenfu injection 5 mL/kg per h; group III: Shenfu injection 10 mL/kg per h; group IV: Shenfu injection 20 mL/kg per h. ^a $P < 0.05$ vs baseline level; ^c $P < 0.05$ vs ischemia 60 min.

RESULTS

None of the 40 rabbits died during experiment. Hemodynamics index and pH value changes of stomach mucosa are shown in Table 1.

DISCUSSION

Studies show^[3] that myocardial IR injury often induces gastric intramucosal ischemia and oxygen deficiency. The gastrointestinal microcirculation is very sensitive to ischemia and oxygen deficiency and the gastrointestinal mucous membrane is a perfect region for supervision, while the pH value of gastric intramucosa (Phi) has become a regional index for tissue perfusion. In recent years, the pH value of gastric intramucosa has been a sensitive index to reflect gastric intramucosal ischemia and oxygen deficiency^[4]. The main effective ingredients of shenfu injection are panaxoside and myoctionine^[5]. According to the literature, panaxoside not only has an important role in antistress, antioxygenation and myocardial ischemia, but also has definite protective and therapeutic activity against myocardial ischemia injury, renal ischemia reperfusion injury, and spinal cord ischemia injury^[6,7]. However, reports about its effect on gastrointestinal micro-circulation are rare. The current study showed that the mean arterial blood pressure and heart rate in group I decreased progressively, both

were lower than that in baseline condition ($P < 0.05$) in myocardial reperfusion model when myocardial ischemia lasted for 60 min, or after reperfusion for 60, 90, 180 min. However, those indexes of three shenfu groups were not significantly changed ($P > 0.05$) when myocardial ischemia lasted for 60 min, or after reperfusion for 60, 90, 180 min, and there were no significant differences between three shenfu groups. Therefore we suppose that hemodynamics were unstable after myocardial ischemia reperfusion, which induced the decrease of blood pressure and heart rate. On the other hand, shenfu injection could improve the hemodynamics during myocardial ischemia reperfusion, and the protective effect was not significantly dose dependent. Moreover, pH value of group I decreased significantly compared with that of baseline level ($P < 0.05$). The pH value of shenfu injection therapeutic groups II, III, IV did not change ($P > 0.05$), which proved that shenfu injection could improve and prevent the hypoperfusion and disturbance of oxygenation in gastrointestinal microcirculation after myocardial ischemia and reperfusion, and has an important protective role in gastrointestinal microcirculation. We designed 3 dose groups: 5, 10, and 20 mL/kg per h and discovered that the pH value in different groups was not changed significantly ($P > 0.05$). This showed that pre-infusion of shenfu injection had an effective protective function on gastrointestinal microcirculation after myocardial IR injury in rabbits, in a dose independent manner. After myocardial ischemia reperfusion, because of hemodynamic instability, gastrointestinal tract hypoperfusion, oxygenation disorder, generation of free radicals and the role of cytokines, activation and releasing of mediators of inflammation, gastrointestinal microcirculation was disturbed^[8,9], leading to gastric intramucosal ischemia, hypoxia, and pH decrease. The protection of shenfu injection on gastrointestinal microcirculation is associated with many factors^[10,11], such as myocardial preservation, stabilization of hemodynamics, antioxygenation, reduced production of free radicals, degradation of cytokines and inhibition of the activation and release of mediators of inflammation.

In summary, myocardial ischemia reperfusion injury can induce gastrointestinal microcirculation dysfunction.

Shenfu injection has protective effect on gastrointestinal microcirculation after myocardial IR injury in rabbits, with no obvious dose-effect relationship. Shenfu injection may improve gastrointestinal microcirculation mainly through myocardial preservation, and stabilization of hemodynamics. Our study provides strong evidence for the protective effect of shenfu injection against IR injury.

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