

Original Article

Protective effects of betaglucin on myocardial tissue during myocardial infarction in rats and dogs

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Aim: To test the protective effects of betaglucin, a novel beta-glucan, on models of myocardial infarction (MI) in rats and dogs.

Methods: The left anterior descending (LAD) coronary artery occlusion model was used to induce an MI in rats and dogs. Three doses of betaglucin (10, 30 and 100 mg/kg), propranolol (positive control, 1 mg/kg) and vehicle alone (5% glucose solution) were administered before LAD occlusion, and characteristics of the resulting MI were subsequently assessed. In anesthetized dogs, blood pressure, heart rate, ventricular function, coronary artery blood flow and myocardial oxygen consumption were determined before and after the drug administration.

Results: The MI mass in both rats and dogs was significantly reduced by betaglucin (30 and 100 mg/kg, $P < 0.01$) and propranolol ($P < 0.01$). In anesthetized dogs, coronary artery blood flow was increased significantly by betaglucin (30 and 100 mg/kg, $P < 0.01$), but blood pressure, heart rate and ventricular function were not changed ($P > 0.05$). High-dose betaglucin (100 mg/kg) increased myocardial oxygen consumption, but not to a statistically significant level ($P > 0.05$). The hemodynamic indexes were significantly changed by propranolol.

Conclusion: Betaglucin has protective effects on myocardial tissue during MI in rats and dogs and has no influence on hemodynamic parameters at a therapeutic dose. The increase in coronary artery blood flow induced by betaglucin might be beneficial in the treatment of patients with MI.

Keywords: betaglucin; glucan; myocardial infarction

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Introduction

Beta-glucans are glucose polymers consisting of a backbone of β -1,3-linked β -D-glucopyranosyl units with β -1,6-linked side chains of varying distribution and length. Recent studies have shown that β -glucan has favorable biological effects in mammals. It is a powerful immune stimulant that can be used to treat benign and malignant tumors^[1–3] and infectious diseases^[4–6]. Furthermore, it lowers cholesterol and triglyceride levels, normalizes blood sugar levels, heals and rejuvenates the skin and has various other beneficial effects on the immune system^[7]. More recently, it was reported that glucan phosphate reduced the area of myocardial infarction (MI) in rats^[8].

Some studies have suggested that β -glucans with different molecular weights might have different functions^[9, 10]. In general, β -glucans with a large molecular weight (such as lentinan

and schizophyllan) can modulate immune functions and have been used for the treatment of tumors^[9, 10]. Beta-glucans with intermediate or low molecular weights (such as glucan phosphate) can be used for the treatment of ischemic diseases^[8], and their effect on the immune system is reduced. Finally, β -glucans with very low molecular weights (< 5000 – $10\,000$, such as laminarin) are generally considered inactive^[11, 12].

To our knowledge, most β -glucans are polysaccharides with a large molecular weight. Recently, we identified a new β -glucan named betaglucin (β -1,6-oligoglucose branched β -1,3-glucan), which has a low molecular weight (5×10^4 g/mol) relative to other β -glucans (Figure 1). The present study was designed to investigate the effect of betaglucin on myocardial tissue during MI and on hemodynamic parameters in rats and dogs. Propranolol was used as a positive control drug.

Materials and methods

Drugs and animals

Betaglucin was prepared in our laboratory (purity $> 95\%$ by high-performance liquid chromatography) and dissolved in a 5% glucose solution (stored at 4 °C). Propranolol was pur-

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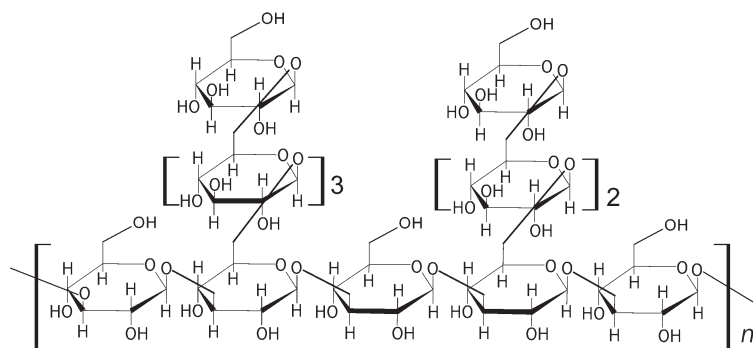


Figure 1. The chemical structure of betaglucon.

chased from Beijing Zizhu Pharmaceutical Co, Ltd (Beijing, China). All drugs were dissolved in the vehicle (5% glucose solution) before administration, and the administration volume was 5 mL/kg in both rats and dogs). Male Sprague-Dawley (SD) rats aged 12 weeks (300–400 g) were provided by the Sino-British SIPPR/BK Laboratory (Shanghai, China). Hybrid dogs of both sexes ($n=6$ in each group, body weight: 12–14 kg) were provided by the animal center of the Second Military Medical University. The rats and dogs were housed under controlled temperature (23–25 °C) and lighting (8:00–20:00 light, 20:00–8:00 dark) conditions with free access to food and drinking water. All animals used in the experiments received humane care. All surgical and experimental procedures were performed in accordance with the institutional animal care guidelines of the Second Military Medical University.

Determination of MI in rats

The surgical procedure to produce an MI was performed according to a well-accepted technique^[8, 13, 14]. Briefly, rats were anesthetized with pentobarbital sodium (45 mg/kg) and underwent a tracheal intubation for subsequent mechanical ventilation. The heart was exteriorized via a left thoracotomy and subjected to left anterior descending (LAD) coronary artery occlusion with a 6-0 polypropylene suture between the pulmonary outflow tract and the left atrium. The beating heart was then quickly returned to its original location, the thorax was immediately closed, and the air was removed. Rats were subsequently returned to their previously described cages. Four hours after the LAD coronary artery occlusion, the MI mass was measured according to previously reported methods^[15, 16]. Briefly, the rats were killed by an overdose of pentobarbital (200 mg/kg ip). The left ventricle (LV) was isolated and cut into four or five slices perpendicular to the cardiac long axis. The slices were stained for 30 min at 37 °C in a 0.1% solution of nitro blue tetrazolium (NBT) and a 0.2 mol/L phosphate buffer (sodium dihydrogen phosphate 87%+disodium hydrogenorthophosphate 13%). NBT stained the normal tissue deep blue and the necrotic tissue white. Stained and unstained tissues were isolated and weighed separately. MI mass was expressed as a fraction of the total LV weight^[17].

Determination of MI in dogs

Anesthesia was induced by intravenous injection of pentobar-

bitol sodium (30 mg/kg), and the dogs underwent a tracheal intubation for subsequent mechanical ventilation (SC-3 electrical ventilator, Shanghai Medical Equipment Factory, Shanghai, China). A left lateral thoracotomy was performed in the fourth intercostal space, the pericardium was incised, and the heart was suspended in a pericardial cradle. Before opening and fixing the pericardium, 2 mL of 2% lidocaine was injected intravenously. Infarction was induced by occlusion of the LAD coronary artery between the first and second diagonal branches. Surface electrocardiogram (ECG, V3 lead) and epicardial ECG tracings were recorded by the ALC-ECG16-32 point sync-epicardial electrogram system (Shanghai Alcott Biotech Co Ltd Shanghai, China) on anesthetized dogs at baseline before LAD occlusion, immediately after LAD occlusion, and again at 30 min, 60 min, 120 min, and 180 min after drug administration to assess for changes in the ST segment (the changes of surface ECG expressed as Δ ST; and the total changes of epicardial ECG expressed as Σ -ST). Three hours after LAD occlusion, the heart was stopped by injection of 2 mol/L KCl and removed from the chest. The infarction mass was determined using a method similar to the one used for rats.

Measurement of blood pressure, heart rate and ventricular function in anesthetized dogs

Dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv) and placed on a ventilator. A catheter connected to a pressure transducer was introduced into the femoral artery to record the blood pressure and heart rate. After making an incision in the neck, a catheter connected to a pressure transducer was introduced into the LV through the right carotid artery. LV systolic pressure (LVSP), end-diastolic pressure (LVEDP), and the maximal rates of pressure rise ($+dp/dt$) and fall ($-dp/dt$) were measured or calculated for each group. The stable ventricular pressure was recorded for 10 min. The means of LVSP, LVEDP, and $\pm dp/dt$ during the last 5 min were analyzed.

Measurement of coronary artery blood flow and myocardial oxygen consumption in dogs

Anesthesia was induced by intravenous injection of pentobarbital sodium (30 mg/kg), and dogs underwent a tracheal intubation for subsequent mechanical ventilation. A left lateral

thoracotomy was performed in the fourth intercostal space, the pericardium was incised, and the heart was suspended in a pericardial cradle. A probe was connected to the left circumflex coronary artery, and the blood flow was recorded by an electromagnetic blood flow meter system (Nihon Konden, Japan). The value was expressed as mL/min per 100 g of myocardium supplied by a coronary artery. A catheter connected to a pressure transducer was introduced into the femoral artery. Blood was collected from the femoral artery and the coronary sinus for blood gas analysis (DH-1300 blood gas analyzer, Nanjing Analytical Instrument Factory Co, Ltd, Nanjing, China). The value of the myocardial oxygen consumption was expressed as the amount of blood flow in the coronary artery \times (arterial oxygen saturation - coronary sinus oxygen saturation).

Protocol

Experiment 1: Effect of betagluclon on MIs in rats

The experiment was performed in 12-week-old male SD rats. Fifty animals were randomly divided into five groups: a vehicle control group (5% glucose solution), three betagluclon groups (10, 30, and 100 mg/kg) and a propranolol group (1 mg/kg), with $n=10$ in each group. The drugs were injected into the abdominal cavity 30 min before LAD occlusion using the above-mentioned methods. The heart rate was recorded by the electrocardiograph. Four hours later, the rats were killed, and the heart was harvested to measure the infarct mass.

Experiment 2: Effect of betagluclon on MIs in dogs

The experiment was performed in anesthetized dogs weighing from 12 to 14 kg. Thirty animals were randomly divided into five groups: a vehicle control group, three betagluclon groups (10, 30, and 100 mg/kg) and a propranolol group (1 mg/kg), with $n=6$ in each group. Drugs were injected via the femoral vein 30 min before LAD occlusion. Surface and epicardial ECGs were recorded using the above-mentioned methods before and after drug administration. Three hours after LAD occlusion, the dogs were killed, and the heart was harvested to measure the infarct mass.

Experiment 3: The effect of betagluclon on blood pressure, heart rate and ventricular function in anesthetized dogs

The experiment was performed in anesthetized dogs. Thirty animals were randomly divided into five groups: a vehicle control group, three betagluclon groups (10, 30, and 100 mg/kg) and a propranolol group (1 mg/kg), with $n=6$ in each group. Drugs were injected via the femoral vein after stabilization of vital signs for 30 min. Blood pressure, heart rate and ventricular function were recorded using the above-mentioned methods before and after drug administration.

Experiment 4: The effect of betagluclon on coronary artery blood flow and myocardial oxygen consumption in anesthetized dogs

The experiment was performed in anesthetized dogs. Thirty animals were randomly divided into five groups: a vehicle

control group, three betagluclon groups (10, 30, and 100 mg/kg) and a propranolol group (1 mg/kg), with $n=6$ in each group. Drugs were injected via the femoral vein after stabilization for 30 min. Coronary artery blood flow and myocardial oxygen consumption were measured using the above-mentioned methods before and after administration.

Statistical analysis

Data are expressed as the means \pm standard errors. Comparisons among the five groups or between different time points within a group were made using one-way analysis of variance (ANOVA). $P<0.05$ was considered statistically significant.

Results

Experiment 1: Effect of betagluclon on MIs in rats

Data are shown in Figure 2. None of the three doses of betagluclon had a significant impact on the heart rate ($P>0.05$), whereas 1 mg/kg of propranolol markedly reduced the heart rate ($P<0.05$ at all time points from 5 to 180 min after administration; Figure 2A). Compared with the vehicle control group, betagluclon (30 and 100 mg/kg) significantly reduced the infarct mass (absolute infarct mass: 78 ± 5.69 , 99 ± 5.37 (respectively) *vs* 182 ± 22.4 mg; ratio of infarct mass to LV: $10.6\%\pm 0.96\%$, $11.4\%\pm 0.76\%$ (respectively) *vs* $21.3\%\pm 2.24\%$, $P<0.05$). Moreover, propranolol also significantly reduced the infarct mass in rats with MIs (absolute infarct mass: 72 ± 5.69 *vs* 182 ± 22.4 mg; ratio of infarct mass to LV: $8.81\%\pm 0.62\%$ *vs* $21.3\%\pm 2.24\%$, $P<0.05$).

Experiment 2: Effect of betagluclon on MIs in dogs

Data are shown in Figure 3. After LAD occlusion, the values of the Δ ST and Σ -ST were elevated. Compared with the vehicle control group, the values of Δ ST and Σ -ST were not significantly different in the group receiving low-dose betagluclon (10 mg/kg), whereas they were markedly decreased in the groups that had larger doses of betagluclon (30 and 100 mg/kg) as well as in the propranolol group. The higher-dose betagluclon groups (30 and 100 mg/kg), compared with the vehicle control group, had a significantly decreased absolute infarct mass [3.17 ± 0.21 , 2.31 ± 0.22 (respectively) *vs* 4.58 ± 0.26 g] and ratio of infarct mass to LV ($6.61\%\pm 0.41\%$, $4.03\%\pm 0.19\%$ (respectively) *vs* $9.96\%\pm 0.53\%$, $P<0.05$). Propranolol also significantly reduced the infarct mass in rats with MIs (absolute infarct mass: 3.67 ± 0.31 *vs* 4.58 ± 0.26 g; ratio of infarct mass to LV: 6.94 ± 0.53 *vs* $9.96\pm 0.53\%$, $P<0.05$).

Experiment 3: The effects of betagluclon on blood pressure, heart rate and ventricular function in dogs

Betagluclon did not change blood pressure or heart rate, but propranolol significantly decreased blood pressure and heart rate in anesthetized dogs ($P<0.05$; Figure 4A). The indexes of ventricular function, including LVSP, $+dp/dt$ and LVEDP, were not significantly changed in the betagluclon groups except for the group receiving the largest dose (100 mg/kg). In that group, the parameter of LVEDP at the 60-min point after drug administration was markedly decreased ($P<0.05$). Propranolol

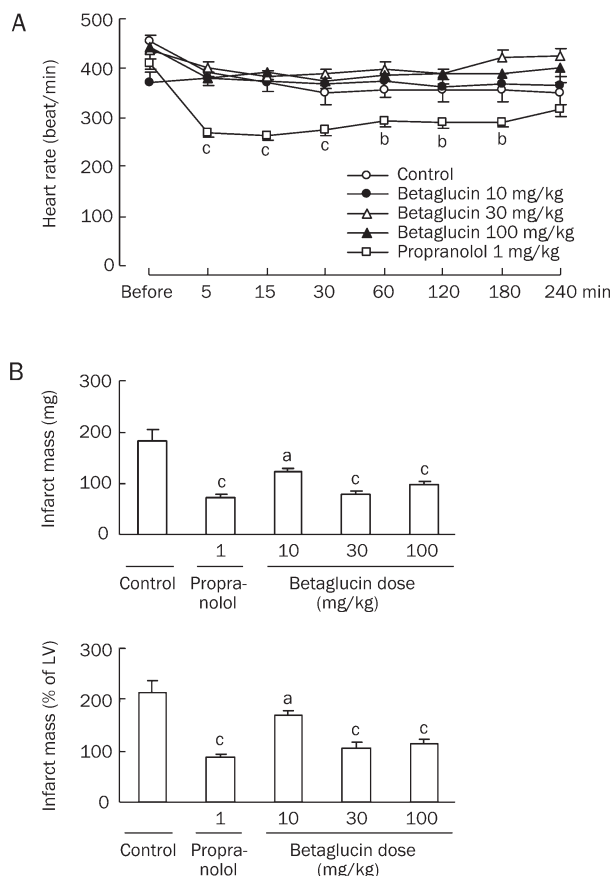


Figure 2. Betaglucin reduced myocardial infarction (MI) in SD rats subjected to LAD occlusion. (A) The effect of betaglucin on the heart rate of rats subjected to LAD occlusion. (B) Betaglucin reduced the MI mass after 4 h of occlusion. The heart was removed and the infarct mass was determined by NBT staining. LAD coronary artery, left anterior descending coronary artery; Infarct mass ratio was expressed as a fraction of the total left ventricle (LV). (○), control, $n=10$; (●), betaglucin 10 mg/kg, $n=10$; (△), betaglucin 30 mg/kg, $n=10$; (▲), betaglucin 100 mg/kg, $n=10$; (□), propranolol 1 mg/kg, $n=10$. Values are expressed as means±standard errors. ^a $P>0.05$, ^b $P<0.05$, ^c $P<0.01$ compared to before administration.

significantly decreased LVSP and $+dp/dt$ in anesthetized dogs ($P<0.01$; Figure 4B).

Experiment 4: The effect of betaglucin on coronary artery blood flow and myocardial oxygen consumption in dogs

Data are summarized in Figure 5. Betaglucin (30 and 100 mg/kg) significantly increased coronary artery blood flow by 11.5 and 14.7 mL/min, respectively ($P<0.05$). Betaglucin (100 mg/kg) increased the index of oxygen consumption by about 9 mL/min, but this was not found to be statistically significant ($P>0.05$). However, in the propranolol-treated group, both the indexes of blood flow and oxygen consumption were significantly decreased ($P<0.05$).

Discussion

In this study, our results show that betaglucin has protective effects on myocardial tissue during MI in rats and dogs and

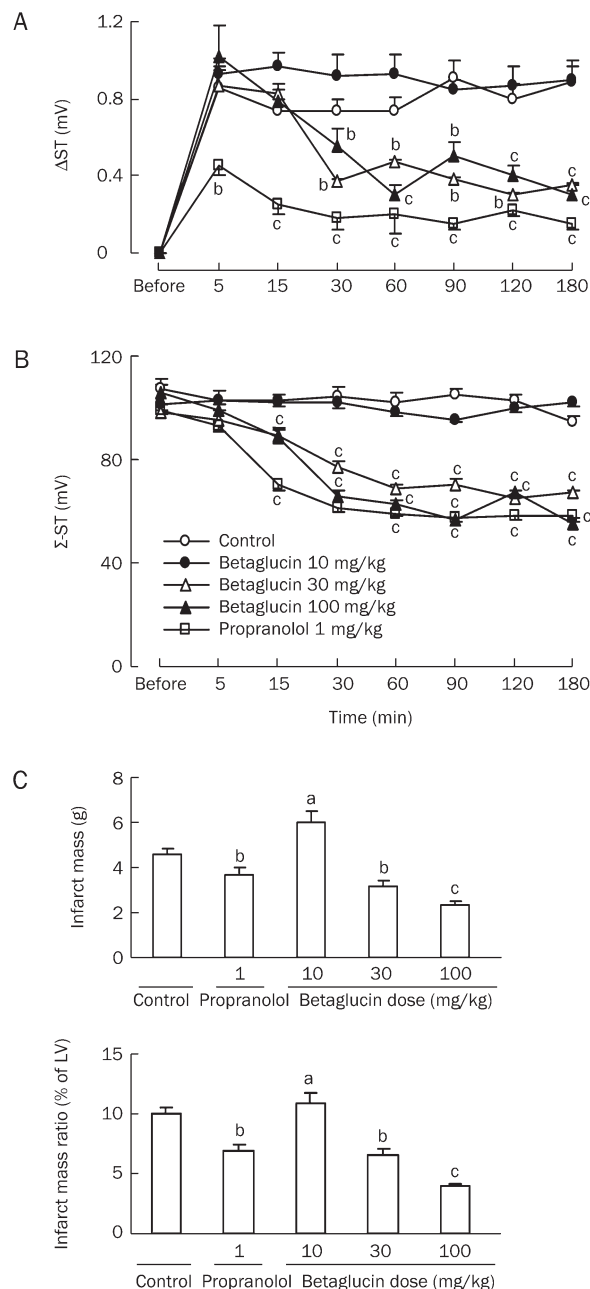


Figure 3. Betaglucin reduced MI in dogs subjected to LAD occlusion. (A) The values of the ST segment of surface electrocardiogram (ECG) (Δ ST), (B) epicardial ECG (Σ -ST) were significantly elevated by LAD occlusion. The elevation can be inhibited by higher doses of betaglucin (30 and 100 mg/kg) and propranolol (1 mg/kg) (A, B, C). (C) Compared to control group, higher doses (30 and 100 mg/kg) of betaglucin significantly reduced the infarct mass of dogs. Infarct mass ratio was expressed as a fraction of the total left ventricle (LV). Propranolol also got the similar results. (○), control, $n=6$; (●), betaglucin 10 mg/kg, $n=6$; (△), betaglucin 30 mg/kg, $n=6$; (▲), betaglucin 100 mg/kg, $n=6$; (□), propranolol 1 mg/kg, $n=6$. Values are expressed as means±standard errors. ^a $P>0.05$, ^b $P<0.05$, ^c $P<0.01$ compared to vehicle control group.

has no side effects on hemodynamic parameters at therapeutic doses.

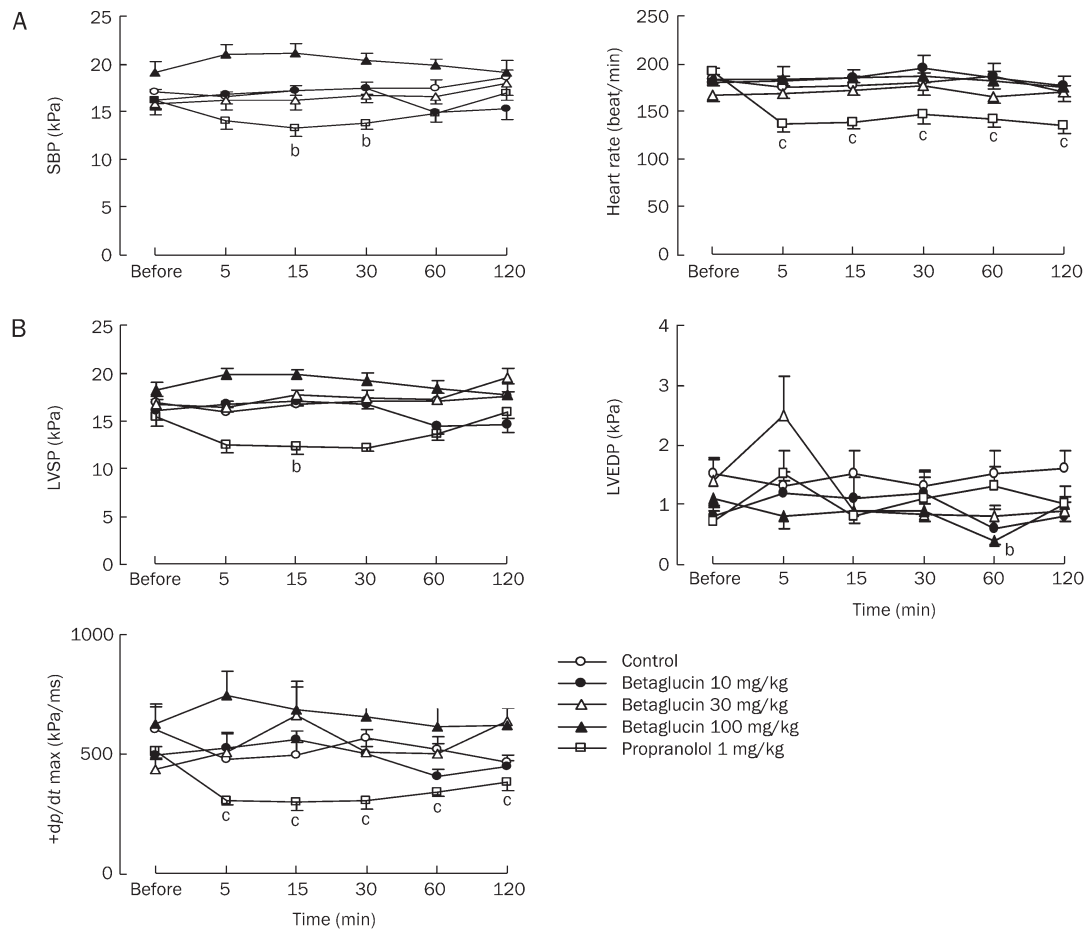


Figure 4. The effect of betagluclon on blood pressure, heart rate and ventricular function in anesthetized dogs. (A) The blood pressure and heart rate had no change in betagluclon groups. (B) All 3 doses of betagluclon had no influence on the ventricular function, including: the left ventricular systolic function (LVSP); the end-diastolic pressure (LVEDP) and the maximal rates of pressure rise (+dp/dt) and of pressure fall (-dp/dt). Meanwhile, betagluclon (100 mg/kg) significantly decreased the parameters of LVEDP after administration for 60 min. (○), control, $n=6$; (●), betagluclon 10 mg/kg, $n=6$; (△), betagluclon 30 mg/kg, $n=6$; (▲), betagluclon 100 mg/kg, $n=10$; (□), propranolol 1 mg/kg, $n=6$. Values are expressed as means±standard errors. ^b $P<0.05$, ^c $P<0.01$ compared to before administration.

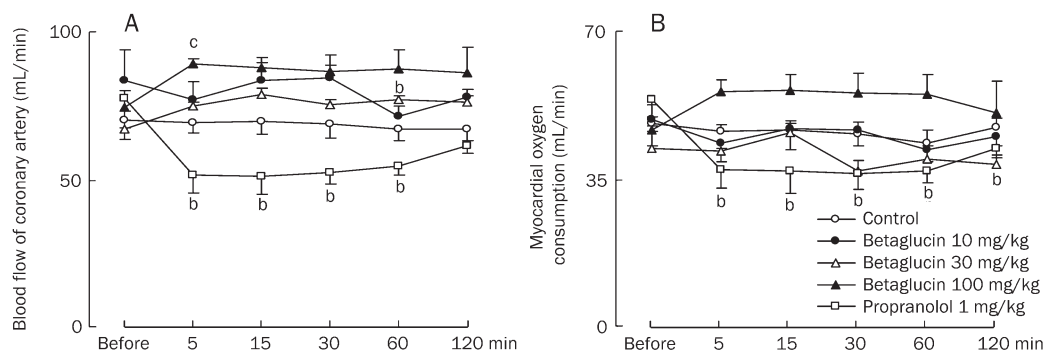


Figure 5. The effect of betagluclon on the blood flow of coronary artery and myocardial oxygen consumption in dogs (A) Higher doses of betagluclon (30 and 100 mg/kg) increased the blood flow of coronary artery significantly. (B) Betagluclon (10 and 30 mg/kg) did not increase the myocardial oxygen consumption, while 100 mg/kg increased the consumption but not significantly. The value of blood flow of coronary artery is expressed as mL/min per 100 g myocardium donated by coronary artery. The value of myocardial oxygen consumption is expressed as: the value of blood flow of coronary artery×(arterial oxygen saturation-coronary sinus oxygen saturation). (○), control, $n=10$; (●), betagluclon 10 mg/kg, $n=6$; (△), betagluclon 30 mg/kg, $n=6$; (▲), betagluclon 100 mg/kg, $n=6$; (□), propranolol 1 mg/kg, $n=6$. Values are expressed as means±standard errors. ^b $P<0.05$, ^c $P<0.01$ compared to before administration.

In the past decade, the large molecular weight and non-dissolubility of β -glucan has limited its wide use. Recently, some β -glucans with relatively low molecular weight have been prepared. Beta-glucans with similar weights have similar functions^[9-12]. One study has shown that glucan phosphate, a relatively low-molecular-weight β -glucan (molecular weight: 150000), exerts cardioprotective effects by modulating Toll-like-receptor-mediated signaling^[8]. Betaglucan, (C₆H₁₀O₅)_n with $n \approx 309$, is a β -1,6-oligoglucose-branched β -1,3-glucan with a molecular weight of 5×10^4 g/mol. Because it has a molecular weight similar to that of glucan phosphate, we hypothesized that betaglucan might also have a beneficial effect on ischemic diseases. Therefore, in this study, we used two animal models to investigate its effects on MI and hemodynamic parameters. In rats with MIs, the middle and high doses of betaglucan significantly reduced the infarct mass and had no influence on the heart rate. In hybrid dogs, both 30 and 100 mg/kg of betaglucan markedly inhibited the elevation of the ST segment induced by the occlusion of the LAD coronary artery and significantly reduced the MI mass.

According to the Guideline of New Drug Development issued by the State Food and Drug Administration of China, we selected propranolol as the positive control drug because of its proven protective effects on myocardial tissue affected by MI^[18]. In this study, the results showed that propranolol significantly decreased the infarct mass in rats and dogs. However, some important indexes, including blood pressure, coronary artery blood flow and ventricular function, were also significantly changed by propranolol. These effects may limit its wide use in the treatment of acute MI. Conversely, betaglucan did not affect the heart rate in dogs with intact and MI-affected myocardium. It also had no influence on the ventricular function, except for diastolic function at the largest dose of betaglucan. Most importantly, it increased coronary artery blood flow and had no influence on myocardial oxygen consumption at the proper dose. All these factors indicate that it may be potentially useful in the treatment of MI.

The mechanisms of betaglucan's action in the treatment of MI remain unclear. According to some results presented in the present work and some findings based on glucan phosphate^[8], the possible mechanisms may be summarized as follows: (1) increasing coronary blood flow, which is a main finding in the present work; (2) inhibition of the inflammatory reaction, which is an important pathological process in acute MI; inhibition of inflammation is beneficial in MI subjects, and we hypothesize that betaglucan, similar to glucan phosphate, possesses an anti-inflammatory effect; and (3) improving energy metabolism. These mechanisms should be investigated and confirmed with further studies.

Obviously, a number of limitations of the present work also need to be considered. The possible mechanism of betaglucan in the treatment of MI should be clearly elucidated. Additionally, experiments considering its long-term toxicity have not yet been performed to clarify its safety profile. Further investigation is warranted to appropriately understand its properties.

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Author contribution

Jian-guo LIU and Ding-feng SU designed research; Jiao QIAN, Jian-guo LIU, Ai-jun LIU, and Zhi-peng WEN performed research; Jing-hang WANG and Wei ZHANG contributed new analytical tools and reagents; Jiao QIAN and Li-li LIN analyzed data; Ai-jun LIU and Ding-feng SU wrote the paper.

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