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Original Article

Ginsenoside Rg1 and Rb1, in combination with salvianolic acid B, play different roles in myocardial infarction in rats

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Abstract

Background: The herb pair of *Salvia miltiorrhiza* and *Panax notoginseng* has widely been used for improving coronary and cerebral circulation in China. However, the exact contribution of the major active components of *S. miltiorrhiza* and *P. notoginseng* to cardioprotection is far from clear. In the present study, three representative ingredients, salvianolic acid B (SalB) from *S. miltiorrhiza* and ginsenoside Rg1 (Rg1) and ginsenoside Rb1 (Rb1) from *P. notoginseng*, were selected to elucidate the mechanism of the herb pair at the ingredient level.
Methods: The purity of SalB, Rg1, and Rb1 was >99%, as detected by high-performance liquid chromatography. Acute myocardial infarction was introduced by ligation of the left anterior descending coronary artery near the main pulmonary artery. Cardiac contractility was detected through a Mikro-tipped catheter, and cardiac infarct size was determined using triphenyltetrazolium chloride stain.
Results: The combination of SalB and Rg1, and not the combination of SalB and Rb1, improved heart contractility in rats with myocardial infarction. The different contributions of Rg1 and Rb1, in combination with SalB, to cardioprotection provides further direction to optimize and modernize the herbal medicines containing *S. miltiorrhiza* and *P. notoginseng*.
Conclusion: The combination of SalB and Rg1 may provide potential protection against myocardial infarction.

Keywords: acute myocardial infarction; ginsenoside Rb1; ginsenoside Rg1; *Panax notoginseng*; salvianolic acid B; *Salvia miltiorrhiza*

1. Introduction

The herb pair that is the focus of our investigation, derived from the roots of *Salvia miltiorrhiza* (Danshen in Chinese) and *Panax notoginseng* (Sanqi in Chinese), has been used widely for improving coronary or cerebral circulation in China as well as in Western countries.[1] Many kinds of commercially available preparations including this herb pair, known as Fufang Danshen formulae, have been marketed for a long time and are considered first-line drugs among all traditional Chinese medicines.[2] However, the detailed mechanism of the combination of *S. miltiorrhiza* and *P. notoginseng* has never been thoroughly elucidated. Active components in these two ingredients possess both the characteristic of complex formulae and the feature of simplicity to facilitate research. Therefore, study of the active components is the necessary foundation and a requisite cut-point for the full investigation of general herb pairs.[3]

Danqi tablet, a famous traditional recipe containing *S. miltiorrhiza* and *P. notoginseng*, has been officially recorded

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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in the Chinese Pharmacopeia since 1977 for improving coronary and cerebral circulation.[4] More than 100 compounds have been isolated and identified in *S. miltiorrhiza* and *P. notoginseng* to date,[5,6] but only a fraction of these compounds were confirmed to be responsible for their biological effects.[7,8] Salvianolic acid B (SalB) from *S. miltiorrhiza,* accompanied by ginsenoside Rg1 (Rg1) and ginsenoside Rb1 (Rb1) from *P. notoginseng*, have been used as phytochemical markers for the quality control of Danqi tablet.[9] SalB was reported to have antioxidant, anti-arteriosclerotic, and anti-inflammatory effects, and to prevent angina pectoris and myocardial ischemia.[10,11] Rb1 exhibits a sedative effect on the central nervous system, as well as anti-inflammation and vasodilation. Rg1 possesses antifatigue properties and also excites the central nervous system. SalB, Rg1, and Rb1 have been proved to be bioactive for the prevention and treatment of cardiovascular and cerebrovascular diseases.[12,13]

Recently, high performance liquid chromatography coupled with diode array and evaporative light scattering detectors (HPLC–DAD–ELSD) method was successfully applied to the simultaneous quantification of multicomponents in Danqi tablet.[14] Among the four major phenolic acids of *S. miltiorrhiza*, SalB accounts for 76.2%. Among the four major saponins of *P. notoginseng*, Rg1 accounts for 40.5% and Rb1 for 40.0%. It is unquestionable that the most abundant components among Danqi tablet are SalB (8.26 mg/g), Rg1 (15.15 mg/kg), and Rb1 (12.63 mg/kg).

To elucidate the mechanism involved in the combination of *S. miltiorrhiza* and *P. notoginseng* at the active components level, we evaluate the cardioprotection of SalB in combination with Rg1 and in combination with Rb1 separately.

2. Methods

2.1. Purity detection of SalB, Rg1, and Rb1

SalB, Rg1, and Rb1 were purchased from Shanghai Yousi Bio-Tech Co., Ltd. (Shanghai, China). The purity of these compounds was analyzed by HPLC. Briefly, SalB, Rg1, or Rb1 solution was filtered through a 0.45 μm membrane and injected into the Agilent 1100 HPLC system (Agilent Technologies, Palo Alto, CA, USA). The column configuration consisted of a Zorbax Extend SB-C_{18} column (5 μm, 250 mm × 4.6 mm). The sample injection volume was 10 μL. The detection wavelength was set at 280 nm for SalB and Rg1, and at 203 nm for Rb1. The mobile phase for SalB or Rg1 consisted of acetonitrile (A) and 0.05% aqueous trifluoroacetic acid (V/V) (B), using a gradient elution of 2–10% A at 0–7 minutes, 10–30% A at 7–20 minutes, 23–27% A at 20–35 minutes, and 27–60% A at 35–50 minutes. The mobile phase for Rb1 consisted of acetonitrile (A) and 0.03% aqueous phosphoric acid (V/V) (B), using an isocratic elution of 30% A.

2.2. Preparation of rats with acute myocardial infarction and their treatment with compounds

Wistar male rats (230–250 g) were purchased from the Shanghai Center of Experimental Animals (Shanghai, China), part of the Chinese Academy of Sciences. Recommendations from the "Guide for the Care and Use of Laboratory Animals" published by the US National Institutes of Health were followed throughout. All procedures involving animals were approved by the Institutional Animal Care and Use Committee at Shanghai Institute of Materia Medica (Shanghai, China; IACUC number: SIMM-AE-GDA-2010-06). Acute myocardial infarction (AMI) was introduced by ligation of the left anterior descending coronary artery near the main pulmonary artery. The sham operation was performed using an identical procedure, except that the suture was passed under the coronary artery without ligation.

Two sets of experiments were conducted to detect the cardioprotective capacity of the combinations of SalB and Rg1, and SalB and Rb1. The ratio of SalB to Rg1 (2:5) or that of SalB to Rg1 (2:5) was set because the content of SalB was 8.26 mg/g, Rg1 was 15.15 mg/kg, and Rb1 was 12.63 mg/kg in a Danqi tablet.[14] The detailed protocol is shown in Fig. 1. A compound or a combination of compounds (60 mg/kg) was given twice through intragastric administration during the entire experiment. The first compound was administered at 1 hour after surgery, and the second treatment was initiated 1 hour before sampling.

To detect the cardioprotective capacity of the combination of SalB and Rg1, animals were randomly assigned into five groups: sham-operated rats were given saline (Sham), AMI rats were given saline (AMI), AMI rats were given 60 mg/kg SalB (SalB), AMI rats were given 60 mg/kg Rg1 (Rg1), and AMI rats were given 60 mg/kg SalB plus Rg1 (SalB–Rg1, and the ratio of SalB to Rg1 was 2:5).

To detect the cardioprotection of the combination of SalB and Rb1, animals were also randomly assigned into five groups: sham-operated rats were given saline (Sham), AMI rats were given saline (AMI), AMI rats were given 60 mg/kg SalB (SalB), AMI rats were given 60 mg/kg Rb1 (Rb1), and AMI rats were given 60 mg/kg SalB plus Rb1 (SalB–Rb1, the ratio of SalB to Rb1 was 2:5).

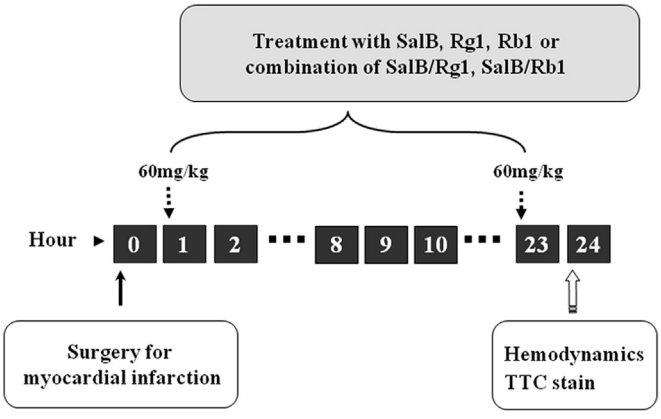

Fig. 1. Experimental design. Compounds or combination of compounds was given twice through intragastric administration during the whole experiment. Rb1 = ginsenoside Rb1; Rg1 = ginsenoside Rg1; SalB = salvianolic acid B; TTC = triphenyltetrazolium chloride.

2.3. Measurements of hemodynamic parameters

One hour after the second treatment of compounds through intragastric administration, the rats were anesthetized with choral hydrate (335 mg/kg). A Mikro-tipped SPR-320 catheter (Millar Instruments Inc., Houston, TX, USA) was inserted through the right carotid artery and into the left ventricle. The heart rate, mean arterial pressure, and left ventricular systolic pressure (LVSP) of rats were recorded by a PowerLab 8/30 instrument (ADInstruments, Bella Vista, NSW, Australia), where the maximum rate of pressure development ($+dP/dt_{max}$) and the maximum rate of relaxation ($-dP/dt_{min}$) were all derived or calculated from the continuously obtained pressure signal. All the parameters were analyzed using Chart 5 Pro software (ADInstruments).

2.4. Infarct size determination on the left ventricle

After measurement of hemodynamic parameters, the rats were sacrificed and their hearts were quickly excised. The left ventricle was sliced into six 1.2−1.5-mm-thick sections perpendicular to the long axis of the heart. The sections were then incubated in phosphate buffered saline containing 0.1% triphenyltetrazolium chloride (TTC) at 37°C for 15 minutes. Thereafter, the weights of the TTC-stained area, and the TTC-negative stained area were measured. Myocardial infarct size was expressed as a percentage of the infarct part (TTC-negative stain) to the whole heart (TTC-stain plus TTC-negative stain).

2.5. Statistical analysis

All quantitative values were expressed as mean ± standard error and analyzed by SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). The mean values of the data from different groups were compared using a one-way analysis of variance. After confirming the equal variances, the least-significant difference was used to compare the differences between the two groups. A p value of <0.05 was considered to be statistically significant.

3. Results

3.1. Purity of SalB, Rg1, and Rb1

Four types of phenolic acids from *S. miltiorrhizae* were identified based on the number of benzene rings in their structure. SalB is a tetramer, and its chemical structure is shown in Fig. 2A. Rg1 is a 20 (S)-protopanaxatriol saponin, while Rb1 is a 20 (S)-protopanaxadiol saponin. The chemical structures of Rg1 and Rb1 are shown in Fig. 2B and C, respectively. The purity of SalB, Rg1, and Rb1 was evaluated by HPLC, and the purity of SalB was 99.8% (Fig. 2D), Rg1 was 99.8% (Fig. 2E), and Rb1 was 99.6% (Fig. 2F).

3.2. Neither the combination of SalB and Rg1, nor the combination of SalB and Rb1 decreased infarct size in rats

To determine the protective effect of SalB−Rg1 or SalB−Rb1 on myocardial injury in our system, we dissected rat hearts and stained them with TTC to evaluate the infarct size. The representative TTC stain for SalB−Rg1 is shown in Fig. 3A, and the quantitative data of infarct size are given in Fig. 3B. Ligation of the left anterior descending coronary artery induced a significant increase in infarct size in the AMI group (17.73 ± 3.22%) compared with the Sham group ($p < 0.001$), whereas 60 mg/kg SalB (14.43 ± 4.61%), 60 mg/kg Rg1 (18.11 ± 7.10%), and 60 mg/kg SalB−Rg1 (17.14 ± 6.08%) did not attenuate the infarct size compared with the AMI group.

The representative TTC stain for SalB−Rb1 is shown in Fig. 3C, and the quantitative data of infarct size are presented in Fig. 3D. Ligation of the left anterior descending coronary artery induced a significant increase in infarct size in the AMI group (22.31 ± 5.65%) compared with the Sham group

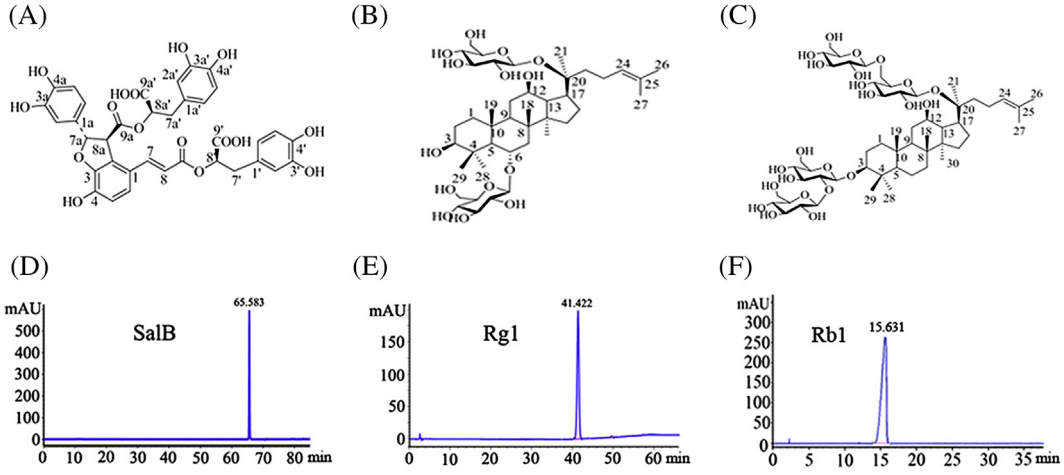

Fig. 2. Structure and purity of SalB, Rg1, and Rb1. Chemical structures of (A) SalB, (B) Rg1, and (C) Rb1. Representative HPLC chromatograms of (D) SalB, (E) Rg1, and (F) Rb1. The purity of every compound was >99%. HPLC = high-performance liquid chromatography; Rb1 = ginsenoside Rb1; Rg1 = ginsenoside Rg1; SalB = salvianolic acid B.

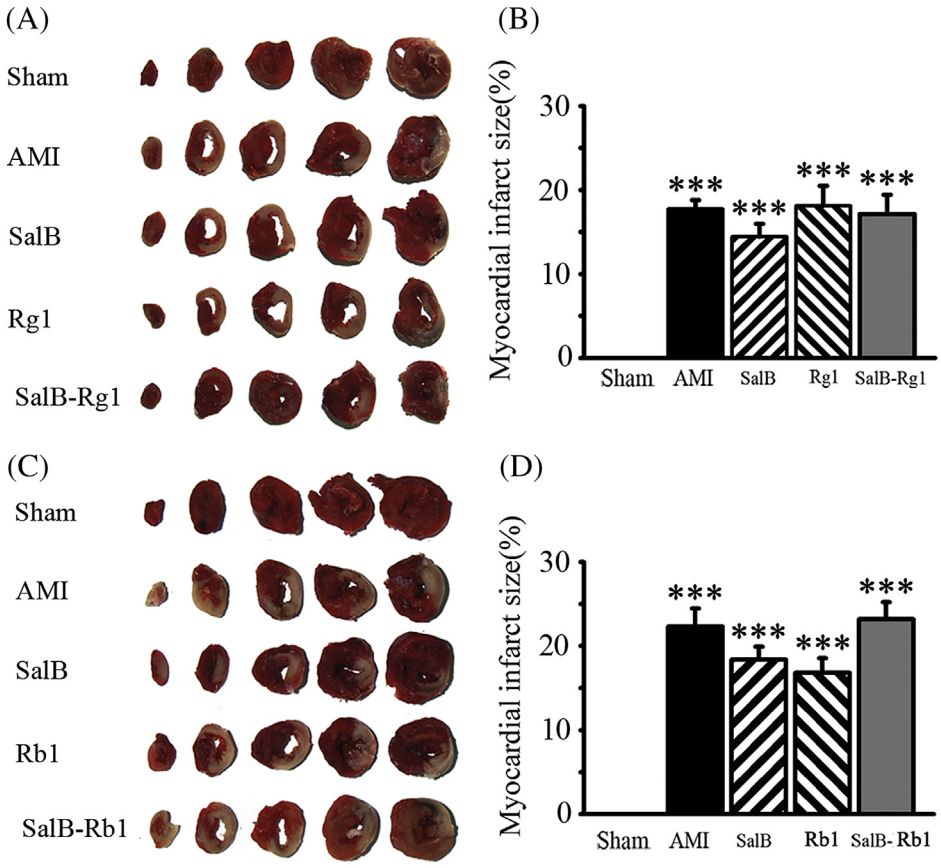

Fig. 3. Neither the combination of SalB and Rg1, nor the combination of SalB and Rb1 decreased infarct size in rats. Representative photographs of TTC stain for combination of (A) SalB and Rg1, and (C) SalB and Rb1. (B) Quantitative results for TTC stain for combination of SalB and Rg1, and (D) SalB and Rb1. All the values are expressed as mean ± SE; $n = 10$ for each group. ***$p < 0.001$ versus Sham rats. AMI = acute myocardial infarction; Rb1 = ginsenoside Rb1; Rg1 = ginsenoside Rg1; SalB = salvianolic acid B; SE = standard error; TTC = triphenyltetrazolium chloride.

($p < 0.001$); whereas 60 mg/kg SalB (18.39 ± 4.57%), 60 mg/kg Rb1 (16.83 ± 4.9%), and 60 mg/kg SalB−Rb1 (23.17 ± 6.74%) did not attenuate the infarct size compared with the AMI group.

3.3. Combination of SalB and Rg1 improved left ventricle contractility

The major hemodynamic parameters were measured to evaluate the left ventricle contractility after treatment with SalB−Rg1 (Fig. 4). No influence of SalB, Rg1, and SalB−Rg1 was found on the mean pressure and heart rate. The left ventricle dysfunction was confirmed in the AMI rats, compared with the Sham group, with a significant decrease of $+dP/dt_{max}$ (6371.1 ± 1174.2 mmHg/s vs. 8831.2 ± 1697.4 mmHg/s, $p < 0.01$), $-dP/dt_{min}$ (−5247.9 ± 1266.5 mmHg/s vs. −8489.8 ± 2866.3 mmHg/s, $p < 0.01$), and LVSP (91.0 ± 8.7 mmHg vs. 103.4 ± 8.9 mmHg, $p < 0.05$), and an increase of end-diastolic pressure (EDP; 9.0 ± 5.7 mmHg vs. 0.6 ± 3.2 mmHg, $p < 0.01$). SalB−Rg1 treatment partially reversed the impairment of left ventricle function by improving $+ dP/dt_{max}$ (8149.86 ± 1066.11 mmHg/s vs. 6371.06 ± 1174.17 mmHg/s, $p < 0.01$) compared with the AMI group. No significant improvement was found in cardiac contractility by SalB−Rg1 treatment, based on the LVSP, $+dP/dt_{max}$, $-dP/dt_{min}$, and EDP values.

3.4. Combination of SalB and Rb1 did not improve left ventricle contractility

The major hemodynamic parameters were measured to evaluate the left ventricle contractility after treatment with SalB−Rb1 (Fig. 5). No influence of SalB and SalB−Rb1 was found on the mean pressure and heart rate. The left ventricle dysfunction in the AMI rats was confirmed, compared with the Sham group, with a significant decrease of LVSP (101.9 ± 11.7 mmHg vs. 119.9 ± 17.3 mmHg, $p < 0.05$), $+dP/dt_{max}$ (6354.9 ± 1414.9 mmHg/s vs. 9653.7 ± 2505.9 mmHg/s, $p < 0.01$), and $-dP/dt_{min}$ (−5063.4 ± 1914.9 mmHg/s vs. −8432.2 ± 1339.9 mmHg/s, $p < 0.01$), and an increase of EDP (9.7 ± 3.9 mmHg vs. 5.2 ± 3.4 mmHg, $p < 0.05$). No significant improvement was found on cardiac contractility by SalB, Rb1, or SalB−Rb1 treatment, comparing with the AMI group.

4. Discussion

The present study unraveled the different effects of Rg1 and Rb1, in combination with SalB, on cardiac protection *in vivo*.

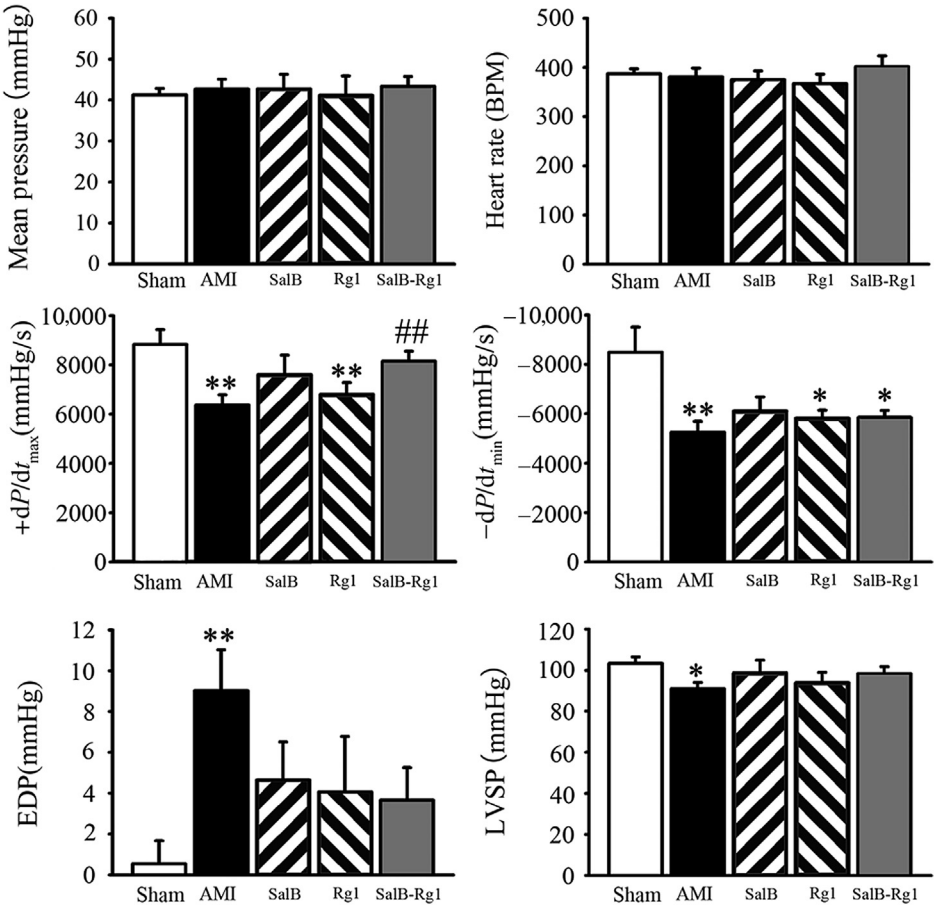

Fig. 4. Combination of SalB and Rg1 improved cardiac function of AMI rats. All the values are expressed as mean ± SE; $n = 10$ for each group. *$p < 0.05$ versus Sham. **$p < 0.01$ versus Sham. ##$p < 0.01$ versus AMI. AMI = acute myocardial infarction; $+dP/dt_{max}$ = maximum rate of pressure development for contraction; $-dP/dt_{min}$ = maximum rate of pressure development for relaxation; EDP = end-diastolic pressure; LVSP = left ventricular systolic pressure; Rb1 = ginsenoside Rb1; Rg1 = ginsenoside Rg1; SalB = salvianolic acid B; SE = standard error.

The combination of SalB and Rg1 showed significant improvement in cardiac contractility in rats with myocardial infarction, but not the combination of SalB and Rb1. This emphasizes the need to understand the individual and collective actions of herbal ingredients and further elucidate the therapeutic mechanism of the herbal pairs.

Although the efficacy-driven approach is now widely applied in studies of this herb pair, the ultimate purpose of investigation is to provide reasonable, secure, and effective indications for pharmacy medication and prescription in actual clinical practice.[15] Studies on active ingredients and their mechanisms are crucial for further development of herb pairs. The most abundant and active component of *S. miltiorrhiza* is SalB,[16] while the most abundant and active components of *P. notoginseng* are Rg1 and Rb1.[17] Detecting the effects of combinations of representative ingredients from *S. miltiorrhiza* and *P. notoginseng* on cardioprotection, which is the usual clinical indication, would provide further direction for modernization of the traditional medicines containing this herb pair.

Besides the chemical structure, differences between Rg1 and Rb1 in terms of bioactivity were also reported recently.[18] Angiogenesis in the human body is regulated by two sets of counteracting factors, angiogenic stimulators and inhibitors.[19] Rg1 promotes functional neovascularization into a polymer scaffold *in vivo* and proliferation, chemoinvasion, and tubulogenesis of endothelial cells *in vitro*.[20] By contrast, Rb1 exerts an opposing effect and inhibits the earliest step in angiogenesis—the chemoinvasion of endothelial cells.[21] In our present study, the different effects of Rg1 and Rb1 in combination with SalB were observed on cardioprotection *in vivo*, providing a new difference between the effects of Rg1 and Rb1. Additionally, further research is very important to clarify whether the difference between Rg1 and Rb1, in combination with SalB, is related to the different effects of the two compounds on angiogenesis or not.

Many ingredients of herbs are inactive individually but become active in combinations, called coalist combinations, which are common in herb pairs.[22] In the present study, our finding suggests that coalist actions exist between SalB and Rg1. Rg1 is well known as a cosolvent, which can decrease the surface tension of menstruum.[23] Therefore, Rg1 may promote the dissolution of SalB. Pharmacological research has indicated that SalB focuses on expanding blood vessels, whereas

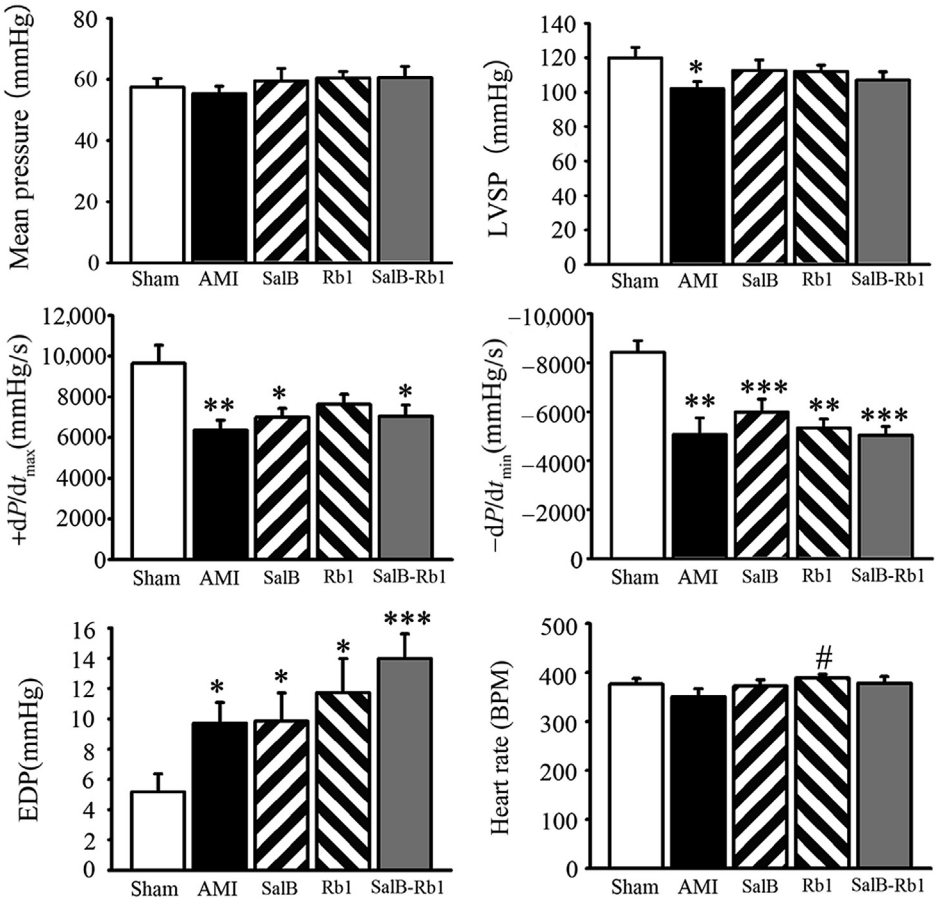

Fig. 5. Combination of SalB and Rb1 did not improve cardiac function of AMI rats. All the values are expressed as mean ± SE; $n = 10$ for each group. *$p < 0.05$ versus Sham. **$p < 0.01$ versus Sham. ***$p < 0.001$ versus Sham. $^{\#}p < 0.05$ versus AMI. AMI = acute myocardial infarction; $+dP/dt_{max}$ = maximum rate of pressure development for contraction; $-dP/dt_{min}$ = maximum rate of pressure development for relaxation; EDP = end-diastolic pressure; LVSP = left ventricular systolic pressure; Rb1 = ginsenoside Rb1; Rg1 = ginsenoside Rg1; SalB = salvianolic acid B; SE = standard error.

Rg1 mainly participates in protecting cardiac myocytes.[24,25] In the present study, the improvement in cardiac contractility by the combination of the two ingredients may be attributed to the different protective mechanisms of SalB and Rg1.

In conclusion, a combination of SalB from *S. miltiorrhiza* and Rg1 from *P. notoginseng* exhibited significant improvement on cardiac contractility in rats with myocardial infarction. However, no improvement attributable to the combination of SalB and Rb1 was observed in the same investigation, suggesting different contributions of Rg1 and Rb1, in combination with SalB, to cardioprotection. Elucidation of the exact roles of the major components of *S. miltiorrhiza* and *P. notoginseng* would promote the optimization and modernization of traditional medicines containing this herb pair.

Acknowledgments

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