

Effects of the seeds of *Allium fistulosum* extract on hemodynamics and myocardial oxygen consumption in dogs

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Abstract

Background: The purpose of this study was to evaluate the effects of the seeds of *Allium fistulosum* extract (SAFE) on hemodynamics and myocardial oxygen consumption in dogs.

Method: Dog models were divided into the control group (saline, 2 mL·kg⁻¹), SAFE low-, medium- and high-dose groups (15, 45, and 90 mg·kg⁻¹) and the positive control group (Xingling granule, 300 mg·kg⁻¹). Hemodynamic indices, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), left ventricular systolic blood pressure (LVSP), left ventricular end-diastolic blood pressure (LVEDP), maximum and minimum changes rate of left ventricular systolic blood pressure (+dp/dt max, -dp/dt max), myocardial oxygen consumption, myocardial oxygen uptake rate, coronary blood flow, coronary resistance, cardiac output, and vascular resistance, were observed in the experimental dog models.

Results: The results showed that LVEDP, +dp/dt max and -dp/dt max were slightly and temporarily reduced in the low- and medium-dose groups, and the other indices of HR, SBP, DBP, MAP, and LVSP were not significantly affected. The results also showed that SAFE significantly decreased myocardial oxygen consumption and the myocardial oxygen uptake rate, and there were no significant effects on coronary blood flow, coronary resistance, cardiac output, and vascular resistance.

Conclusions: SAFE had no significant effect on hemodynamic indices but had significant effects on the prevention of myocardial ischemia.

Introduction

Coronary heart disease (CHD) is one of the most serious diseases threatening human health worldwide [1]. Insufficient myocardial blood supply caused by epicardial coronary artery stenosis is considered the main cause of CHD. How to effectively prevent and treat angina pectoris in CHD has been an important topic in the medical field. Although modern medical treatment, intervention and surgical treatment are becoming increasingly mature, there are still some problems, such as no-reflow and restenosis after coronary intervention, drug tolerance and adverse reactions. Therefore, it is of great significance to find a new therapeutic regimen [2]. Traditional Chinese medicine has shown advantages in the treatment of CHD due to its multitarget and multilevel characteristics [3].

There are approximately 500 species of *Allium* in the Liliaceae family, and approximately 110 species, including varieties and introduced exotic species, are widely distributed in China and are used as vegetables and condiments. *Allium* mainly contains sulfur compounds, flavonoids, steroids, phenylpropanoids, alkaloids, vitamins, amino acids, polysaccharides, etc. They have been employed in traditional medical practice for their antimicrobial, antioxidant, antithrombotic, antitumor, and cancer prevention properties [4–10].

Allium fistulosum (Welsh onion) is an important household ingredient in eastern countries and is considered a good source of nutrients. According to the dictionary of Chinese drugs, the bulbs and roots of *A. fistulosum* are used for the treatment of febrile disease, headache, abdominal pain, diarrhea, snakebites, ocular disorders, and habitual abortion [11]. *A. fistulosum* has a variety of biological activities, including antifungal, antioxidant, α -glucosidase inhibitory, antiplatelet, antihypertensive, anticancer, antihypercholesterolemic, anti-inflammatory, and antiobesity activities [12–21]. The main chemical constituents of *A. fistulosum* seeds reported in the literature are fatty acids, steroidal sapogenins, steroidal saponins, phenolic acids, and proteins [22–24].

In recent years, the study of *Allium* has focused on its cardiovascular aspects [25–29]. Our previous study on the seeds of *A. fistulosum* extract (SAFE) demonstrated that SAFE can obviously reduce the degree of myocardial ischemia, the range of myocardial infarction and the injury of ischemic myocardial cells, and it can also obviously inhibit LDH (lactate dehydrogenase) and CK (creatine kinase) overflow and decrease the activity of LDH and CK in serum in rats and dogs [30]. To further investigate the pharmacodynamics of SAFE and utilize medicinal resources, in the present study, we reported the effects of SAFE on hemodynamics and myocardial oxygen consumption in dogs and expect to discover its medicinal function.

Materials and methods

Materials

The seeds of *A. fistulosum* were collected in Zigong, Sichuan Province, China, and authenticated by Prof. Han-Ming Zhang of the Department of Pharmacognosy, School of Pharmacy, Naval Medical University, Shanghai, China; a voucher specimen (No. 20040947) was deposited in the Department of Pharmacognosy, School of Pharmacy, Naval Medical University. SAFE was prepared by the following method: the air-dried seeds of *A. fistulosum* were refluxed three times with water at 100°C (2 h, each), the extract was passed through an AB-8 resin column, the column was washed with 5 volumes of water, eluted with 5 volumes of 50% ethanol, and the eluent was recovered

after drying at 60°C. Afterward, the extract was freshly prepared, when needed, by dissolving it in normal saline. Xingling granule (XLKL, Shanghai Xingling Technology Pharmaceutical Co., Ltd., Shanghai, China; batch No. 20030201) was employed as a positive control.

Animal groupings

Healthy hybrid dogs were randomly divided into five groups: the model group (normal saline, 2 mL·kg⁻¹), SAFE low dose group (SAFE-L, 15 mg·kg⁻¹), SAFE medium dose group (SAFE-M, 45 mg·kg⁻¹), SAFE high dose group (SAFE-H, 90 mg·kg⁻¹), and XLKL group (300 mg·kg⁻¹) in the experimental model of hemodynamics and myocardial oxygen consumption. All methods are reported in accordance with ARRIVE guidelines.

Dog hemodynamics model

The dogs were anesthetized intravenously with 3% sodium pentobarbital (30 mg·kg⁻¹) and fixed to the operating table in the supine position. Then, the trachea was separated and intubated. The right femoral artery was separated, and a cardiac catheter was inserted retrogradely. The arterial blood pressure was recorded by inserting an arterial catheter, and the right common carotid artery was isolated. Two catheters were connected to the pressure sensor. The pressure signal was amplified by a carrier wave and connected to the Powerlab System 8S Physiological Recorder (ML785/8S, AD Instruments, Sydney, NSW, Australia). Needle electrodes were inserted subcutaneously into the limbs and connected to an AC Amplifier (AB -621 G) for monitoring a standard two-lead ECG. The data were monitored and stored in real time by computer chart 4.12 software (ML785/8S, AD Instruments, Sydney, NSW, Australia). The dogs were stable for 30 minutes after the operation for recording base values before administration. The negative control group was given normal saline (2 mL·kg⁻¹), the positive control group was given XLKL (300 mg·kg⁻¹), and the treatment group was given SAFE. HR, SBP, DBP, MAP, LVSP, LVEDP, +dp/dt max and -dp/dt max were observed. The observation time was before and 15, 30, 60, 90, 120, and 180 min after administration. After the test, the related indices were analyzed by chart 4.12 software [31, 32].

Dog myocardial oxygen consumption model

The dogs were anesthetized with 30 mg·kg⁻¹ iv sodium pentobarbital. Their bodies were kept at a constant temperature using a thermostatic operating table, and tracheal intubation was performed. An SC-M5 anesthesia ventilator was connected after exposing the chest to provide mechanical ventilation with a breathing rate of 16–18 times·min⁻¹ and ventilation with room air (tidal volume, 350–550 mL·kg⁻¹·min⁻¹). The left femoral artery was separated, and a catheter was inserted centripetally to monitor and record the peripheral blood pressure. The right femoral artery was separated for arterial blood gas analysis. The chest was opened along the left fourth intercostal space to expose the heart, and the cardiac package was cut to make a heart hammock. The root of the ascending aorta and the upper part of the left anterior descending coronary artery were freed, and the aortic flow (cardiac output) and coronary flow were measured by a magnetic flow meter with a proper internal diameter. The right jugular vein was separated, a cardiac catheter was inserted, and the opening of the coronary sinus was detected with the finger along the junction of the right atrium and right ventricle inferior vena cava. A cardiac catheter was inserted into the coronary sinus, and the cardiac catheter was fixed. Blood samples of the coronary sinus and femoral artery (0.5% heparin anticoagulation) were collected at the same time. PO₂, pH, and arterial and venous oxygen content were measured by a blood gas analyzer. The arterial and venous blood gases were analyzed before and 15, 30, 60, 90, 120, and 180 min after administration of saline, SAFE and XLKL, and mean blood pressure, cardiac output and coronary flow were recorded at 15, 30, 60, 90, 120, and 180 min at the same time. At the end of the experiment, the heart was weighed and counter current perfused with 10–15 ml 10% Shanghai advanced carbon ink into the area below the measurement site of the electromagnetic flowmeter. Black areas were excised and weighed to calculate myocardial oxygen consumption. Myocardial oxygen consumption was calculated before and 15, 30, 60, 90, 120, and 180 min after administration. The formula is:

(1). Myocardial oxygen consumption (ml/min/100 g) = coronary blood flow (ml/min/100 g) × (arterial oxygen content - coronary sinus oxygen content).

(2). Myocardial oxygen uptake rate (%) = (arterial oxygen content - coronary sinus oxygen content) / arterial oxygen × 100%.

(3). Vascular resistance (TPR, dyn·s·cm⁻⁵) = mean arterial pressure [MAP (KPa)] × 80 / cardiac output [CO (L/min)].

(4). Coronary resistance (KPa/mL/min) = mean blood pressure [MAP(KPa)] / coronary blood flow [CBF(mL/min/100 g)] [33–36].

Statistical Analysis

All experimental data were expressed as ± S. Statistical analysis was performed with one-way ANOVA, using SPSS 10.0 statistical software (SPSS Inc., Chicago, Illinois, USA), p < 0.05 was considered significant.

Results

Effect of SAFE on hemodynamicsindices in anesthetized dogs.

The results showed that the LVEDP of the low-dose group at 60 min, the + dp/dt max of the medium-dose group at 90 min, and the -dp/dt max of the medium-dose group at 90 min were decreased compared with those of the normal saline group ($P < 0.05$). The -dp/dt max of the medium-dose group at 60 and 90 min was also decreased compared with that before administration ($P < 0.05$). Apart from the above differences, parameters such as HR, SBP, DBP, MAP, LVSP, +dp/dt max and -dp/dt max at other than the above time points were not significantly different in the experimental groups compared with those in the normal saline group at the same time point or compared to those before administration. The results are shown in Fig. 1.

Effect of SAFE on myocardial oxygen consumption

The myocardial oxygen consumption of the high-dose group of SAFE was decreased compared with that of the normal saline group at 60 and 90 min, and there was no significant difference in other doses at the same time point. There was a significant difference in the medium-dose group at 60 and 90 min ($P < 0.05$) and in the high-dose group at 15–180 min ($P < 0.05$) compared with before administration. The experimental results are listed in Table 1.

Table 1

Effect of SAFE on myocardial oxygen consumption (mL·min⁻¹·100g⁻¹) in anesthetized dogs (± s, n = 5)

Group	Dose (mg·kg ⁻¹)	Before administration	After administration					
			15 min	30 min	60 min	90 min	120 min	180 min
Control	2 mL	203.2 ± 12.3	207.1 ± 13.3	210.3 ± 11.6	213.7 ± 12.3	219.6 ± 18.7	221.9 ± 17.6	212.4 ± 14.1
XLKL	300	221.9 ± 27.0	216.4 ± 27.4	202.5 ± 31.2	209.1 ± 29.4	211.5 ± 14.4	222.6 ± 18.1	223.8 ± 14.1
SAFE-L	15	214.2 ± 19.5	208.5 ± 16.6	201.0 ± 18.8	201.4 ± 19.3	209.0 ± 20.8	211.0 ± 23.5	219.2 ± 19.4
SAFE-M	45	226.9 ± 18.4	211.1 ± 16.0	205.6 ± 18.2	194.7 ± 16.3 [△]	203.9 ± 10.5 [△]	215.2 ± 14.5	225.0 ± 24.5
SAFE-H	90	232.5 ± 5.2	210.3 ± 10.0 ^{△△}	195.9 ± 20.4 ^{△△}	188.2 ± 18.9 ^{*△△}	194.3 ± 11.6 ^{*△△}	200.0 ± 13.3 ^{△△}	208.0 ± 16.3 [△]

* $P < 0.05$, compared with the saline group at the same time point; [△] $P < 0.05$, ^{△△} $P < 0.01$ compared with before administration.

Effect of SAFE on myocardial oxygen uptake rate

SAFE significantly and dose-dependently decreased the rate of myocardial oxygen uptake. Compared with the normal saline group at the same time point, the 3 doses of SAFE groups and XLKL group all showed significant differences at 15–180 min ($P < 0.05$), while compared to before administration, the XLKL group experienced a decrease only at 60 min, the low dose group experienced a decrease only at 30 min, the medium dose group experienced a decrease from 30 to 120 min, and the high dose group experienced a decrease at all time points after administration ($P < 0.05$). The experimental results are listed in Table 2.

Table 2
Effect of SAFE on myocardial oxygen uptake rate (%) in anesthetized dogs ($\pm$ s, n = 5)

Group	Dose (mg·kg ⁻¹)	Before administration	After administration					
			15 min	30 min	60 min	90 min	120 min	180 min
Control	2 mL	84.4 $\pm$ 4.5	87.0 $\pm$ 6.8	89.5 $\pm$ 8.2	90.0 $\pm$ 7.4	88.8 $\pm$ 4.5	91.2 $\pm$ 7.6	97.8 $\pm$ 8.7 Δ
XLKL	300	76.1 $\pm$ 8.2	73.4 $\pm$ 8.4*	64.4 $\pm$ 8.2**	67.0 $\pm$ 7.6** $\Delta\Delta$	68.4 $\pm$ 5.7**	75.3 $\pm$ 6.5**	80.2 $\pm$ 6.5**
SAFE-L	15	77.0 $\pm$ 7.8	74.9 $\pm$ 7.5*	70.8 $\pm$ 5.6** Δ	70.4 $\pm$ 5.3**	74.2 $\pm$ 4.6**	76.6 $\pm$ 6.1*	80.7 $\pm$ 5.2**
SAFE-M	45	81.8 $\pm$ 5.1	74.0 $\pm$ 5.6*	68.9 $\pm$ 5.5** $\Delta\Delta$	65.3 $\pm$ 3.0** $\Delta\Delta$	67.9 $\pm$ 1.8** $\Delta\Delta$	73.1 $\pm$ 4.0** Δ	81.0 $\pm$ 6.2**
SAFE-H	90	81.9 $\pm$ 5.3	71.4 $\pm$ 3.2** $\Delta\Delta$	61.9 $\pm$ 3.8** $\Delta\Delta$	58.7 $\pm$ 6.4** $\Delta\Delta$	61.3 $\pm$ 4.1** $\Delta\Delta$	64.5 $\pm$ 5.0** $\Delta\Delta$	70.2 $\pm$ 4.1** $\Delta\Delta$
*P < 0.05, **P < 0.01, compared with the saline group at the same time point; Δ P < 0.05, $\Delta\Delta$ P < 0.01, compared with before administration.								

Effects of SAFE on coronary flow, coronary resistance, cardiac output and vascular resistance

Regarding the effects of SAFE on coronary flow, coronary resistance, cardiac output and vascular resistance, the results showed that there were no significant differences in the low-, medium-, and high-dose groups and the XLKL group compared with the normal saline group and before administration. The results are shown in Table 3-Table 6.

Table 3
Effect of SAFE on coronary flow (mL·min⁻¹) in anesthetized dogs ($\pm$ s, n = 5)

Group	Dose (mg·kg ⁻¹)	Before administration	After administration					
			15 min	30 min	60 min	90 min	120 min	180 min
Control	2 mL	43.0 $\pm$ 7.2	42.8 $\pm$ 7.3	42.2 $\pm$ 7.3	42.8 $\pm$ 7.4	42.0 $\pm$ 7.6	42.8 $\pm$ 7.3	42.0 $\pm$ 1.7
XLKL	300	42.6 $\pm$ 9.9	43.2 $\pm$ 10.2	46.4 $\pm$ 12.1	45.8 $\pm$ 11.2	45.6 $\pm$ 11.5	44.2 $\pm$ 11.3	41.8 $\pm$ 10.1
SAFE-L	15	43.2 $\pm$ 5.3	43.2 $\pm$ 5.1	43.8 $\pm$ 5.3	44.4 $\pm$ 6.2	44.0 $\pm$ 6.0	43.6 $\pm$ 6.4	42.6 $\pm$ 6.1
SAFE-M	45	42.2 $\pm$ 9.1	43.4 $\pm$ 9.3	45.4 $\pm$ 9.9	45.2 $\pm$ 10.1	44.4 $\pm$ 9.5	44.0 $\pm$ 8.9	42.6 $\pm$ 9.8
SAFE-H	90	42.6 $\pm$ 7.2	43.4 $\pm$ 6.9	46.2 $\pm$ 7.3	47.0 $\pm$ 7.6	46.2 $\pm$ 6.8	45.6 $\pm$ 7.4	45.2 $\pm$ 6.8

Table 4
Effect of SAFE on coronary resistance (kPa·mL⁻¹·min⁻¹) in anesthetized dogs (± s, n = 5)

Group	Dose (mg·kg ⁻¹)	Before administration	After administration					
			15 min	30 min	60 min	90 min	120 min	180 min
Control	2 mL	0.31 ± 0.04	0.31 ± 0.04	0.31 ± 0.05	0.31 ± 0.04	0.31 ± 0.04	0.31 ± 0.04	0.31 ± 0.04
XLKL	300	0.32 ± 0.07	0.30 ± 0.08	0.28 ± 0.07	0.29 ± 0.07	0.29 ± 0.07	0.31 ± 0.08	0.31 ± 0.07
SAFE-L	15	0.29 ± 0.04	0.29 ± 0.04	0.28 ± 0.04	0.28 ± 0.05	0.28 ± 0.04	0.28 ± 0.05	0.29 ± 0.06
SAFE-M	45	0.31 ± 0.09	0.30 ± 0.09	0.28 ± 0.08	0.28 ± 0.09	0.29 ± 0.07	0.29 ± 0.07	0.29 ± 0.08
SAFE-H	90	0.31 ± 0.04	0.29 ± 0.02	0.27 ± 0.03	0.26 ± 0.03	0.27 ± 0.02	0.27 ± 0.02	0.28 ± 0.02

Table 5
Effect of SAFE on cardiac output (L·min⁻¹) in anesthetized dogs (± s, n = 5)

Group	Dose (mg·kg ⁻¹)	Before administration	After administration					
			15 min	30 min	60 min	90 min	120 min	180 min
Control	2 mL	1.08 ± 0.22	1.09 ± 0.20	1.08 ± 0.20	1.09 ± 0.21	1.08 ± 0.19	1.08 ± 0.17	1.04 ± 0.16
XLKL	300	1.06 ± 0.26	1.07 ± 0.27	1.08 ± 0.25	1.07 ± 0.25	1.05 ± 0.27	1.06 ± 0.25	1.05 ± 0.24
SAFE-L	15	1.04 ± 0.14	1.03 ± 0.16	1.04 ± 0.15	1.02 ± 0.17	1.04 ± 0.16	1.04 ± 0.14	1.03 ± 0.15
SAFE-M	45	1.05 ± 0.24	1.05 ± 0.24	1.05 ± 0.27	1.04 ± 0.24	1.03 ± 0.27	1.03 ± 0.26	1.02 ± 0.24
SAFE-H	90	1.13 ± 0.20	1.13 ± 0.17	1.14 ± 0.18	1.14 ± 0.20	1.13 ± 0.18	1.11 ± 0.17	1.11 ± 0.15

Table 6
Effect of SAFE on vascular resistance (TPR, dyn·s·cm⁻⁵) in anesthetized dogs (± s, n = 5)

Group	Dose (mg·kg ⁻¹)	Before administration	After administration					
			15 min	30 min	60 min	90 min	120 min	180 min
Control	2 mL	993.0±191.3	973.3±208.3	986.6±223.1	965.6±200.3	975.1±200.4	975.1±203.5	993.0±137.4
XLKL	300	1021.8±238.5	994.6±260.9	963.4±224.6	994.0±230.2	1010.6±223.2	1011.7±245.8	989.6±202.2
SAFE-L	15	970.6±158.8	968.4±155.1	958.3±161.1	989.5±181.0	951.2±150.2	953.6±160.6	947.0±186.7
SAFE-M	45	996.3±287.3	977.9±306.3	979.2±309.4	977.5±270.9	1011.5±300.3	1014.5±291.0	981.3±290.1
SAFE-H	90	930.3±184.0	902.1±148.6	866.2±152.2	877.5±159.3	887.9±161.5	910.6±189.0	913.3±187.8

Discussion

CHD is myocardial damage caused by an imbalance between coronary blood flow and myocardial needs due to altered coronary circulation. By ligating the coronary artery of anesthetized dogs, a myocardial ischemic disease model can be well replicated. The change in ST-segment voltage in epicardial electrocardiography is a reliable index to reflect the degree of myocardial ischemia, and the reduction in the degree of myocardial ischemia is an important index to evaluate the therapeutic effect of anti-myocardial ischemia drugs. CK exists widely in the plasma membrane, especially in myocardial cells. When myocardial cells are injured, CK overflows, and its activity in blood increases; the higher the serum CK activity is, the more serious the myocardial injury is. LDH is released from tissue and cells into body fluids during myocardial infarction, and LDH activity in coronary sinus blood can also reflect the degree of myocardial injury. In our previous study, a model of acute myocardial ischemia in dogs was used, and the extent and degree of myocardial ischemia were measured by

epicardial electrocardiogram and quantitative histology (N-BT staining method), and CK and LDH contents were detected by biochemical assays. The results have showed that SAFE can significantly reduce the degree of myocardial ischemia, infarcted area, and elevation of serum CK and LDH levels in dogs after coronary ligation [30].

Myocardial ischemia and hypoxia cause a decline in cardiac function and are the main causes of death from heart failure caused by myocardial infarction. The size of the myocardial infarction area is the key to affecting cardiac function, and myocardial oxygen consumption and myocardial oxygen utilization are also important indices that reflect the balance of cardiac oxygen supply and demand. In the pathological process of ischemic heart disease, due to coronary artery spasm or infarction causing relative or absolute insufficiency of myocardial blood supply and an increase in myocardial oxygen demand leading to the imbalance of oxygen supply and demand in myocardial tissue, oxygen supply mainly depends on coronary blood flow, coronary perfusion pressure and diastolic time. In the state of myocardial ischemia, improving coronary blood flow and improving the utilization of oxygen in myocardial tissue is an important measure to reduce the damage of myocardial ischemia and hypoxia [37, 38]. The effects of SAFE on HR, SBP, DBP, MAP, LVSP, LVEDP, +dp/dt max and -dp/dt max were observed by cardiac catheterization in anesthetized dogs. The results showed that low and medium doses of SAFE slightly and temporarily reduced LVEDP, +dp/dt max and -dp/dt max, and the other indices of HR, SBP, DBP, MAP, and LVSP were not significantly affected. The effects of SAFE on myocardial oxygen consumption, myocardial oxygen uptake rate, coronary flow, coronary resistance, cardiac output, and vascular resistance were also observed. The results showed that SAFE significantly decreased myocardial oxygen consumption and the myocardial oxygen uptake rate, and there were no significant effects on coronary flow, coronary resistance, cardiac output, and vascular resistance. Xingling granule is a new generation of ginkgo preparation, and its function and indications are promoting blood circulation and removing blood stasis. Clinical application is for blood stasis-type chest pain and mild arteriosclerosis vertigo, coronary heart disease, and angina pectoris. Our study results indicate that SAFE has the same effect on prevention of myocardial ischemia as Xinling granule.

Conclusions

SAFE had no significant effects on hemodynamic indices but had significant effects on myocardial oxygen consumption. This suggests that SAFE had a significant effect on the prevention of myocardial ischemia and improved the function of the ischemic heart.

Declarations

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Author contributions

ZC and DD carried out the study and performed the statistical analysis. WQ participated in the design of the study. WS supervised the entire study. ZJ collected important background information and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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None.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committee of Second Affiliated Hospital of Naval Medical University.

Consent for publication

All authors agree to publish this article.

Competing interests

The authors declare no competing interests..

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Figures

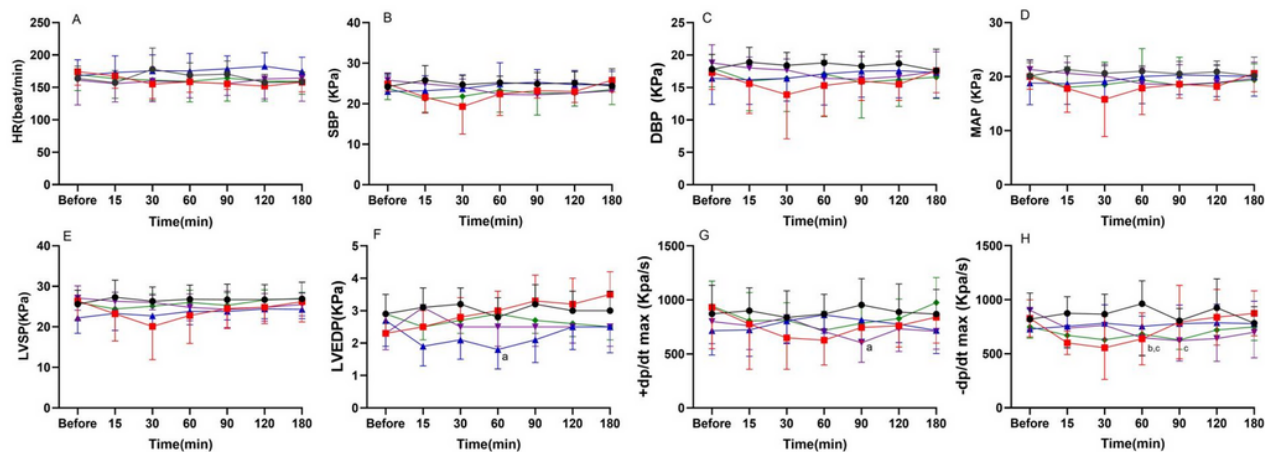


Figure 1. The effects of SAFE on hemodynamics in anesthetized dogs.

(●), control, normal saline 2 mLkg⁻¹; (▲), SAFE-L, n=5; (▼), SAFE-M, n=5; (◆), SAFE-H, n=5; (■), XLKL, n=5. ^a*P*< 0.05 compared to control group, ^b*P*< 0.05, SAFE-M compared to control group, ^c*P*< 0.05, SAFE-M compared to before administration.

Figure 1

See image above for figure legend