Therapeutical effect of *Radix Aconiti* and *Astragalus* extracts on models of experimental bradycardia animal

Lei Hong[1], Zhu Juanjuan[1], Zhang Xiaoxiang[1] and Wei Wei[2]
[1]School of Biology and Food Engineering, Hefei University of Technology, Hefei, China
[2]Hefei Hengxing Pharmaceutical Institute Hefei, China

Abstract: The antibradycardia effect of extract of RAE (Radix Aconiti and Astragalus) on bradycardia animal models were evaluated. Bradycardia rat model was induced by amiodarone or propranolol, and sick sinus syndrome (SSS) rabbit model was induced by chemical stimulation on surface of sinus node. The heart rates of the animal models were calculated according to ECG recording. The value of sino-atrial conduction time (SACT) and correcting sinus node recovery time (CSNRT) of SSS rabbit model were measured by multi-channel physiological recorder. The blood flow of aorta and coronary the diabolic pressure of normal rat hearts in vitro were measured. Treatment with RAE could increase the heart rate of bradycardia animals induced by amiodarone, propranolol, or SSS rabbit model significantly. Treatment with RAE could decrease in the value of SACT and CSNRT of SSS rabbit model. Moreover, treatment with RAE could increase the blood flow of aorta and coronary and could decrease diabolic pressure of normal rat hearts in vitro. RAE has heart-rate-increasing effect, which might be related to its ameliorating the autorhythmicity of sinus node and improving the sino-atrial conductive function. Moreover, RAE could ameliorate cardiac blood supply and enhance cardiac function.

Keywords: RAE; bradycardia; animal models; heart rate; hemodynamics

INTRODUCTION

Bradycardia is a kind of system disorder, which is characterized by slow heart rate induced by various cardiac diseases common in aged people. When heart rate decreases to a certain extent, blood supply of some important organs reduces resulting in dizziness, chest distress and debilitation (Sodeck *et al*., 2007). This often made cardiac pacemaker implantation necessary (Mann *et al*., 2000; Sweeney *et al*., 2007; Zhang *et al*., 2009). But as of expensive and harmful to body, fixing cardiac pacemaker is unable to be widely used. So patients commonly use drugs to increase the heart rate. Atropine is a kind of chemical drugs which is widely used and shows rapid and obvious effect. But its effect is short and has some side effects, such as dry mouth, facial fever and dysuria in aged men (Brady *et al*., 1999). Therefore, searching for more effective and safer anti-bradycardia agents is very important.

Some natural products possess the ability to increase heart rate, and utilization of natural products over a long period of time should be safer than chemical drugs. RAE had been extracted from Chinese tonic herbs radix aconiti and astragalus. Radix aconiti is a kind of traditional Chinese medicines commonly used to treat joint pain and arthritis, which has analgesia and anti-inflammation effects. Astragalus is a kind of Chinese tonic herbs. Its active part is astragalosides (AST) and polysaccharides extracted from the root of Astragalus membranceus (Fisch.) Bge, which possesses anti-aging effect, anti-oxidative properties, anticancer effect, immunomodulatory effect and heart-benefiting effect. The broth of radix aconiti and astragalus has been used in China for hundred years which is a traditional tonic formula (Dong *et al*., 1999). Recent years it has been used in Anhui Medical University Affiliated Hospital to treat bradycardia, including drug (amiodarone, digoxin, verapamil and propafenone)-induced and various of bradycardia induced by cardiac diseases such as coronary disease, myocarditis, myocardiopathy and conducting system diseases of heart. Initial clinical practice results show that it is effective and has no obvious side effects. So exploiting RAE as a kind of new anti-bradycardia drugs has the important clinical value. But there had no reports of pharmacological research on broth of radix aconiti and astragalus in treating bradycardia. Therefore, the present study was designed to investigate the anti-bradycadia effect of RAE and its mechanism of action, exploiting drugs (amiodarone and Propranolol)-induced bradycardia rats and sick sinus syndrome (SSS) rabbit models . Moreover, hemodynamic effect of RAE on normal isolated perfused rat hearts in vitro was also investigated.

MATERIALS AND METHODS

Preparation of RAE

RAE was prepared by Hefei Hengxing Pharmaceutical Institute (Anhui, China). RAE was extracted from radix aconiti (Aconitum carmichaelii Debx.) and astragalus (Astragalus membranaceus (Fisch.) Bge), whose dose of proportion of the two herbs was 1:1. The process of extraction of RAE mainly included water decoction, filtration, alcohol precipitation, concentration and spray drying. The active parts containing in the extract were

*Corresponding author: e-mail: leihong56@163.com

astragalosides 1mg/g and aconitine 0.75 mg/g. The content of astragalosides was determined by thin-layer chromatography (TLC) and the content of aconitine was determined by spectrophotometric method according to China pharmacopeia. The extract was dissolved in distilled water and diluted to the concentration needed.

Animals

Healthy Wistar strain rats (150-200g) and rabbits (2.5-3.0 kg) were supplied by Experimental Animal Center of Anhui Medical University (Anhui,China). They were housed in plastic cages and maintained under standard conditions (12h light/dark cycle; 23-25°C; 35-60% humidity). Before and during the experiment, rats and rabbits were fed with a normal laboratory pellet diet and water was freely available. After randomization into various groups, the animals were acclimatized in the new environment for two days before initiation of the experiment. The study complied with the current ethical regulations for animal research of this institute, and the animal experimental protocol complied with the regulation of animal administration and ethical commission of Hefei University of Technology, and all animals used in the experiment received human care.

Main reagents

Amiodarone hydrochloride tablets were from Shanghai jiufu Pharmaceutical Co.,Ltd (Shanghai, China). Propranolol tablets were from Jiangsu Wujin Pharmaceutical Co.,Ltd (Shanghai, China). Xinbao pills (XBP) were from Guangdong Pharmaceutical Institute (Guangdong, China). Formaldehyde solution was from Chemical Reagents Factory of Hefei University of Technology (Anhui, China). Chloride hydrate was from Shanghai Wulian Chemical Reagents Factory (Shanghai, China). All the other biochemicals and chemicals used in the experiment were of analytical grade.

Induction of two experimental sinus bradycardia models and experimental protocol

One sinus bradycardia animal model was induced in rats by orally given amiodarone at a dose of 120 mg/kg every day for two weeks. A total of 60 rats were used and were divided into six groups, each containing 10 animals as follows: normal control; bradycardia model control; four treatment groups (given RAE 600, 300, 150 mg.kg-1 or XBP 32 mg.kg-1). Rats were given drugs or dissolvent 1 mL/100 g orally by gavage once a day for two weeks, followed by body weight measured each week.

The other sinus bradycardia animal model was induced in rats by orally given propranolol at a dose of 7.5 mg/kg every day for seven days (Li *et al*., 2010; Wang, 2006). Two weeks before given propranolol, rats were orally given drugs or dissolvent once a day for three weeks. A total of 60 rats were used and were divided into six groups, each containing 10 animals as follows: normal control; bradycardia model control; four treatment groups (given RAE 600, 300, 150 mg.kg-1 or XBP 32 mg.kg-1).

Before treatment and at the end of the treatment, rats were anaesthetized with 10% Chloral Hydrate (0.3 ml.100 g-1) intraperitoneally and fixed in supine position. The surface electrocardiogram (ECG) was recorded using bipolar lead Ⅱ (Wang and Wang, 1998). According to ECG recording, heart rate (HR) was calculated and expressed as beats per minute (bpm). The result was expressed by the percentage change of HR: change of HR = (HR before treatment- HR after treatment)/ HR before treatment x 100%.

Induction of experimental sick sinus syndrome (SSS) model and experimental protocol

The SSS animal model was induced in rabbit by destruction of sinus node function using 10% formaldehyde solution (Jiang and Ma, 1996; Xi *et al*., 1999). Rabbit was anaesthetized with 20% urethane (1g.kg-1) intraveneously and fixed in supine position. Then the trachea was isolated and the artificial breathing machine was connected if necessary. The jugular vein was cannulated by pacing catheter of grade 4 to right atrium region. The cardiac electrophysiological stimulator and multichannel physiological recorder were connected to the rabbit. The chest of rabbit was dissected along the middle of the sternum and then the cardiac pericardium was opened. The right atrium and superior vena was exposed. The filter paper (diameter 0.8 cm) soaked in 10% formaldehyde solution was applied on the region of sinus node for three to five minutes. When the heart rate decreased 50% and /or nodal escape beat appeared, SSS model were established successfully.

After the animal model stabilized for thirty minutes, a number of electrophysiological parameters stated below were measured. Then drugs were given by duodenum. 30, 60, 120 minutes after treatment, the parameters were measured again. The electrophysiological parameters were sino-atrial conduction time (SACT), sinus node recovery time (SNRT) and correcting sinus node recovery time (CSNRT). SACT and SNRT were measured by multi-channel physiological recorder, while the value of CSNRT is SNRT minus mean sinus rhythm.

A total of 45 rabbits were used and were divided into five groups, each containing 9 animals as follows: SSS model; four treatment groups (given RAE 75, 150, 300 mg.kg-1 or XBP 16 mg.kg-1 by duodenum.

Hemodynamic studies on normal isolated perfused rat hearts

The procedure of preparing isolated perfused rat hearts was similar to that previously described (Shi *et al*., 1995). Briefly, ten rats were anesthetized with an i.p. injection of 20% urethane (1.2 g.kg-1) and heparin (10 mg.kg-1) was i.v. injected as the anticoagulant. The rat heart was rapidly excised and immersed in cold KHB buffer. The aorta was

rapidly cannulated for retrograde perfusion connected to a perfusion system. The perfusion solution was lukewarm KHB buffer equilibrated with 95% O2 and 5% CO2. The perfusion pressure was 70 cmH2O and the temperature of prefusate maintained at 36.5°C. Pulmonary artery and left atrium were also cannulated. The perfusion pressure of the left atrium was 12 cmH2O. The heart stabilized for at least 30 min after attached to the perfusion system. Then each hemodynamic parameter was measured. After the equilibration period, RAE (0.15 g/ml, 1ml) was added to the KHB solution. 30 min after administration of the drug, each hemodynamic parameter was measured again. The hemodynamic parameters were as follows: heart rate (HR), aorta flow (AF), coronary flow (CF), systolic pressure (SP), diabolic pressure (DP). The value of cardiac output (CO) was AF value plus CF value.

STATISTICAL ANALYSIS

Data were expressed as means±s.d. Statistical analysis was evaluated by one-way analysis of variance, followed by the Student-Newman-Keuls test for multiple comparisons, which was used to evaluate the difference between two groups. $P<0.05$ was considered significant.

RESULTS

Effect of RAE on the heart rate of amiodarone-induced-bradycardia rats

ECG recordings showed that amiodarone induced arrhythmia was sinus bradycardia. table 1 shows the effect of RAE on heart rate of amiodarone-treated-rats. Results showed that amiodarone (120 mg.kg-1) markedly decreased the heart rate of rats ($P<0.01$). RAE (300, 600 mg.kg-1) and XBP (32 mg.kg-1) markedly increased the heart rate of amiodarone treated rats ($P<0.01$). This suggested that RAE has anti-bradycardia effect on amiodarone-treated rats.

Effect of RAE on the heart rate of propranolol-induced-bradycardia rats

ECG recordings showed that propranolol induced arrhythmia was also sinus bradycardia. table 2 shows the effect of RAE on heart rate of propranolol-treated-rats. Propranolol (7.5 mg.kg-1) decreased the heart rate of rats significantly ($P<0.01$). RAE (600 mg.kg-1) and XBP (32 mg.kg-1) markedly increased the heart rate of propranolol- treated rats ($P<0.01$ or $P<0.05$). This suggested that RAE also has anti-bradycardia effect induced by propranolol.

Effect of RAE on the heart rate of SSS rabbit model

Table 3 shows the effect of RAE on heart rate of SSS rabbit model. The heart rate of SSS model was significantly lower as compared with the pre-model ($P<0.01$). 60, 120 minutes after treatment, RAE (75, 150, 300 mg.kg-1) and XBP (16 mg.kg-1) could increase the low heart rate significantly as compared with the pre-treatment and compared with the model given normal saline ($P<0.05$ or $P<0.01$).

Effect of RAE on SACT of SSS rabbit model

The changes of the values of SCAT in normal, SSS rabbits and experimental groups are shown in table 4. The electrophysiological study revealed that the value of SACT in SSS rabbit model markedly increased. RAE (75,150,300 mg.kg-1) and XBP (16 mg.kg-1) could decrease the value of SACT significantly. This suggests that RAE could improve the sino-atrial conductive function of SSS animal model.

Effect of RAE on CSNRT of SSS rabbit model

The values of CSNRT in normal, SSS rabbits and experimental groups are shown in table 5. The electrophysiological study revealed that the value of CSNRT in SSS model markedly increased. RAE (75,150,300 mg.kg-1) and XBP (16 mg.kg-1) could decrease the value of CSART significantly. This suggests that RAE could improve the autorhythmicity of the sinus node in SSS animal model.

Effect of RAE on hemodynamics parameters of normal isolated rat hearts

Table 6 shows the effect of RAE on hemodynamics parameters of normal isolated rat hearts. Results showed that after administration of RAE, the value of AF, CF and CO increased and the value of DP decreased significantly ($P<0.01$), while the value of HR and SP did not change markedly. This suggested that treatment with RAE could increase the blood flow of aorta and coronary, and thus, cardiac output increased. Decreased DP was mainly due to dilation of aorta and coronary. Treatment with RAE had no effect on heart rate and systolic pressure of normal rat hearts.

DISCUSSION

In the present study we used three animal models. One is amiodarone-induced- bradycardia rat model, the second is propranolol-induced-bradycardia rat model, and the third is sick sinus syndrome (SSS) rabbit model. Xinbao pills (XBP) were used as positive control drugs which were widely used in China in treating bradycardia induced by various of cardiac diseases, including chronic congestive heart failure, sino-atrial dysfunction and sick sinus syndrome (Wong, 1985). Other similar Chinese tonic herbs had beneficial effects on the bradycardia animals. The influence of Shenfu injection (composed of Ginseng and Radix Aconiti extracts) on bradycardia model in dogs induced by propranolol was investigated, and results showed that Shenfu injection could raise the heart rate of propranolol-induced-bradycardia (Yang *et al*., 2001). The anti-bradycardic mechanism of Ganfu granule (composed of Licorice and Radix Aconiti extracts) was studied in

Table 1: Effect of RAE on heart rate of amiodarone-induced-bradycardia rats

Group	Dose ($mg \cdot kg^{-1}$)	Heart rate (HR, bpm)		% change of HR
		Pre-treatment	Post-treatment	
Normal	-	445±23	446±24	0.61±7.3
Model	-	432±18	308±35	28.6±8.47**
RAE	600	429±24	370±26	13.4±7.6$^{**\#\#}$
	300	432±35	367±37	15.0±6.7$^{**\#\#}$
	150	431±19	307±62	28.7±14.4**
XBP	32	429±26	378±41	12.0±7.1$^{**\#\#}$

Data are the mean ± s.d. (n=10). Analysis of variance followed by the Student-Newman-Keuls test. In each vertical column, $^{*}P<0.05$ and $^{**}P<0.01$ compared with normal group; $^{\#}P<0.05$, $^{\#\#}P<0.01$, compared with model group.

Table 2: Effect of RAE on heart rate of propranolol--induced-bradycardia rats

Group	Dose ($mg \cdot kg^{-1}$)	Heart rate (HR, bpm)		% change of HR
		Pre-treatment	Post-treatment	
Normal	-	400±37	388±20	2.5±10.4
Model	-	427±28	336±44	22.3±6.6**
RAE	600	418±28	370±31	11.4±5.3$^{**\#\#}$
	300	433±21	345±24	20.2±5.8**
	150	448±30	339±52	24.1±9.3**
XBP	32	398±62	343±68	14.09±6.59$^{**\#}$

Data are the mean ± s.d. (n=10). Analysis of variance followed by the Student-Newman-Keuls test. In each vertical column, $^{*}P<0.05$ and $^{**}P<0.01$ compared with normal group; $^{\#}P<0.05$, $^{\#\#}P<0.01$, compared with model group.

Table 3: Effect of RAE on heart rate (bpm) of SSS rabbit model

Group	Dose ($mg.kg^{-1}$)	Pre-model	Post-model	Post-treatment		
			30min	30min	60min	120min
N.S	-	300.22±21.35	164.88±18.50$^{\#\#}$	169.88±16.74$^{\#\#}$	172.33±13.01$^{\#\#}$	170.88±16.86$^{\#\#}$
RAE	75	297.78±15.99	163.11±14.47$^{\#\#}$	179.00±16.45$^{\#\#}$	187.66±10.37$^{*\#\#\Delta\Delta}$	188.22±11.67$^{*\#\#\Delta\Delta}$
	150	299.56±17.99	166.78±9.15$^{\#\#}$	180.56±17.71$^{\#\#}$	188.33±10.92$^{*\#\#\Delta\Delta}$	189.33±12.06$^{*\#\#\Delta\Delta}$
	300	293.22±17.33	162.33±20.91$^{\#\#}$	180.22±16.74$^{\#\#}$	189.22±16.42$^{*\#\#\Delta}$	190.33±18.68$^{*\#\#\Delta}$
XBP	16	296.22±16.41	165.22±13.83$^{\#\#}$	174.44±13.83$^{\#\#}$	186.67±10.52$^{*\#\#\Delta\Delta}$	190.44±17.77$^{*\#\#\Delta}$

Data are the mean ± s.d. (n=9). Analysis of variance followed by the Student-Newman-Keuls test. In each vertical column, $^{*}P<0.05$ and $^{**}P<0.01$ compared with N.S group. In each horizontal column, $^{\#}P<0.05$, $^{\#\#}P<0.01$, compared with pre-model group; $^{\Delta}P<0.05$, $^{\Delta\Delta}P<0.01$, compared with post-model group

Table 4: Effect of RAE on SACT (ms) of SSS rabbit model

Group	Dose ($mg.kg^{-1}$)	Pre-model	Post-model	Post-treatment		
			30min	30min	60min	120min
N.S	-	26.44±2.75	63.00±7.59$^{\#\#}$	62.67±8.79$^{\#\#}$	63.22±8.93$^{\#\#}$	62.44±8.87$^{\#\#}$
RAE	75	27.11±2.51	65.33±5.87$^{\#\#}$	51.33±6.04$^{*\#\#\Delta\Delta}$	52.21±6.63$^{*\#\#\Delta\Delta}$	48.10±4.07$^{**\#\#\Delta\Delta}$
	150	28.00±3.97	67.00±9.13$^{\#\#}$	44.44±4.76$^{**\#\#\Delta\Delta}$	45.14±3.37$^{**\#\#\Delta\Delta}$	41.32±3.77$^{**\#\#\Delta\Delta}$
	300	27.33±3.74	69.56±11.36$^{\#\#}$	42.78±5.18$^{**\#\#\Delta\Delta}$	38.78±7.07$^{**\#\#\Delta\Delta}$	37.22±7.15$^{**\#\#\Delta\Delta}$
XBP	16	27.00±3.12	70.56±10.12$^{\#\#}$	54.00±9.38$^{\#\#\Delta\Delta}$	40.00±6.11$^{**\#\#\Delta\Delta}$	36.22±7.90$^{**\#\Delta\Delta}$

Data are the mean ± s.d. (n=9). Analysis of variance followed by the Student-Newman-Keuls test. In each vertical column, *P<0.05 and **P<0.01 compared with N.S group. In each horizontal column, #P<0.05, ##P<0.01, compared with pre-model group; ΔP<0.05, ΔΔP<0.01, compared with post-model group

bradycardia rats induced by propranolol and acetylcholine, and results showed that Ganfu granule significantly inhibited the propranolol-induced decrease of heart rate and shortened the time of bradycardia induced by acetylcholine (Li *et al*., 2010).

Table 5: Effect of RAE on CSART (ms) of SSS rabbit model

Group	Dose ($mg.kg^{-1}$)	Pre-model	Post-model	Post-treatment		
			30min	30min	60min	120min
N.S	-	61.00±5.83	115.56±8.53$^{\#\#}$	113.22±7.80$^{\#\#}$	114.00±6.96$^{\#\#}$	113.56±6.45$^{\#\#}$
RAE	75	64.78±8.38	111.33±10.18$^{\#\#}$	102.00±12.81$^{\#\#}$	80.44±11.79$^{**\#\#\Delta\Delta}$	74.44±8.35$^{**\#\#\Delta\Delta}$
	150	63.78±6.12	115.78±12.56$^{\#\#}$	97.33±9.03$^{**\#\#\Delta\Delta}$	82.78±8.87$^{**\#\#\Delta\Delta}$	65.66±7.57$^{**\#\#\Delta\Delta}$
	300	62.22±7.21	113.67±11.25$^{\#\#}$	96.56±9.80$^{**\#\#\Delta\Delta}$	81.22±13.44$^{**\#\#\Delta\Delta}$	76.22±12.48$^{**\#\#\Delta\Delta}$
XBP	16	62.88±7.16	116.11±9.48$^{\#\#}$	97.00±12.30$^{*\#\#\Delta\Delta}$	86.33±11.39$^{**\#\#\Delta\Delta}$	80.33±10.68$^{**\#\#\Delta\Delta}$

Data are the mean ± s.d. (n=9). Analysis of variance followed by the Student-Newman-Keuls test. In each vertical column, *P<0.05 and **P<0.01 compared with N.S group. In each horizontal column, #P<0.05, ##P<0.01, compared with pre-model group; ΔP<0.05, ΔΔP<0.01, compared with post-model group.

Table 6: Effect of RAE (0.15 g/ml, 1ml) on hemodynamics parameters of isolated rat hearts

parameters	HR (bpm)	AF (ml/min)	CF (ml/min)	CO (ml/min)	SP (kPa)	DP (kPa)
Pre-treatment	276.0±35.32	22.80±1.94	5.43±1.12	28.23±3.07	6.13±0.76	2.58±0.68
Post-treatment	268.7±16.43	25.03±3.32**	5.87±1.08**	31.23±4.52**	6.45±0.49	2.10±0.48**

Data are the mean ± s.d. (n=10). Analysis of variance followed by the Student-Newman-Keuls test. In each vertical column, $^{*}P<0.05$ and $^{**}P<0.01$ compared with pre-treatment group.

The experimental animal models are common in vivo studies of bradycardia. It has been reported that bradycardia model in dogs (Yang *et al*., 2001) and in rats (Li *et al*., 2010) could be induced by propranolol. The bradycardia model in rats and mice were also induced by propranolol, acetylcholine or verapamil (Wang, 2006; Wan *et al*., 2007). Therefore, propranolol was commonly used in replicating bradycardia animal models. We established two kinds of sinus bradycardia animal models, exploiting amiodarone and propranolol which could induce bradycardia in clinical application (Bramah, 1996; Love, 1998). The doses of these two drugs applied in rats were designed according to their dosage used in clinical practice, conversion to dosage used in rats (Xu *et al*., 1991). Results of our studies showed that amiodarone and propranolol-induced arrhythmia were all sinus bradycardia according to ECG recordings. RAE could counteract the sinus bradycardia induced by some antiarrhythic drugs.

Amiodarone and propranolol are widely used in clinical practice as antiarrhythic drugs. But they have several side effects including lowering heart rate. Atropine, which is widely used as an anti-bradycardia drug in clinical practice, is ineffective in treating bradycardia induced by amiodarone. In such case, amiodarone must be withdrawn or cardiac pacemaker must be fixed. Other drugs widely used in treating arrhythmia such as digoxin and Verapamil have the same circumstance. Treatment with RAE could counteract bradycardia induced by these drugs and stabilize the heart rate at a certain range. This could avoid withdrawing these drugs and fixing cardiac pacemaker. RAE had no effect on systolic blood pressure, and thus, RAE could be used in patients with hypertension. Therefore, this kind of extract is of much value in clinical practice.

The sick sinus syndrome (SSS) is the result of an intrinsic inability of the sinus node and is usually associated with a number of cardiac diseases (Kim *et al*., 2011). SSS was assumed to progress slowly, over > 10 years, from sinus bradycardia to various forms of exit block, until no sinus beats appeared or chronic atria1 fibrillation occurred (Menozzi *et al*., 1998). Cardiac pacing was widely used for the treatment of SSS. The drugs used in treating SSS were β-adrenergic and vagolytic agents, which gave disappointing results both in terms of efficacy and in the high incidence of side effects during long-term treatment (Verza *et al*., 1996). In the present study we developed an experimental animal model induced by chemical stimulation on the surface of sinus node using 10% formaldehyde solution. Treatment with RAE could increase the heart rate of SSS model.

Sino-atrial conduction time (SACT) is indicative of the sino-atrial conductive function. Correcting sinus node recovery time (CSNRT) is sinus node recovery time (SNRT) minus mean sinus rhythm, which is indicative of the autorhythmicity of the sinus node (Xi *et al*., 1999; Lee *et al*., 2010). Results of this study showed that the sino-atrial conductive function and the autorhythmicity of the sinus node of SSS model markedly decreased. The sinus node function and the sino-atrial conductive function of SSS model markedly improved. This suggested that the heart-rate-increasing effect of RAE might be related to its ameliorating the autorhythmicity of the sinus node and improving the sino-atrial conductive function.

The present study was also to elucidate whether RAE exerted direct hemodynamic effect on the heart. We investigated the effects of RAE on isolated perfused rat hearts. The hemodynamic parameters were heart rate (HR), aorta flow (AF), coronary flow (CF), systolic

pressure (SP), diabolic pressure (DP), cardiac output (CO). Treatment with RAE could increase the blood flow of aorta and coronary, and thus, cardiac output increased. The decreased DP value was mainly due to dilation of aorta and coronary. Results of this study further indicated that RAE had no effect on heart rate and blood pressure of normal rats. Therefore, treatment with RAE could ameliorate cardiac blood supply and enhance cardiac function, which may be part responsible for its heart rate-increasing effect. RAE had no effect on systolic pressure and could decrease diabolic pressure, which suggested that it could be safely used in hypertensive patients.

In conclusion, treatment with RAE could increase the heart rate of sinus bradycardia rat models which were induced by amiodarone and propranolol and the heart rate of SSS rabbit model induced by chemical stimulation on the surface of sinus node. These effects of RAE might be related to its ameliorating the autorhythmicity of the sinus node and improving the sino-atrial conductive function. Moreover, RAE exerted well hemodynamic effect on the heart, which could ameliorate cardiac blood supply and enhance cardiac function. All these results indicated that RAE would be a potential anti-bradycardia agent. At present, phase 3 clinical study of RAE are carried out in China. Initial results showed that it is effective and safe used in clinical application.

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