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Effects of warming *yang* and invigorating *qi* prescription on renin-angiotensin-aldosterone system in rats with heart failure after myocardial infarction

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Abstract

This study investigated the effects of warming *yang* and invigorating *qi* prescription on renin-angiotensin-aldosterone system (RAAS) in rats with heart failure after myocardial infarction. 126 rats were randomly divided into model group, sham operation, warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi*, digoxin and captopril group for respective treatment. After intervention for 6, 8 and 10 weeks, the left ventricular ejection fraction (LVEF) was calculated, and the plasma renin, angiotensin II and aldosterone levels were measured. Results showed that, after 6, 8 and 10 weeks, LVEF in warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi* and captopril group was significantly higher than model group ($P < 0.05$), and the plasma renin, angiotensin II and aldosterone levels in warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups were significantly lower than model group ($P < 0.05$). Renin angiotensin II and aldosterone levels in invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups after 10 weeks was significantly lower than after 6 weeks ($P < 0.05$); aldosterone level in captopril groups after 10 weeks was significantly lower than after 6 weeks ($P < 0.05$). Warming *yang* and invigorating *qi* prescription can improve LVEF in rats with heart failure after myocardial infarction, which may be related with the inhibition of RAAS activation.

Keywords: warming *yang*; invigorating *qi*; heart failure; renin-angiotensin-aldosterone system.

Practical Application: Traditional Chinese medicine warming *yang* and invigorating *qi* prescription can be used for treating heart failure after myocardial infarction.

1 Introduction

Chronic congestive heart failure is the common endpoint of various heart diseases (Zhang et al., 2015). It is mainly caused by the pathological changes due to left ventricular remodeling, which leads to ventricular expanding and left ventricular ejection fraction decreasing (Kunishige et al., 2006). At present, it is thought that activation of neuroendocrine is the most important cause of ventricular remodeling in chronic heart failure, and is also an important reason for the development and deterioration of heart failure, and the activation of renin-angiotensin-aldosterone system (RAAS) is the most important (Lin et al., 2008). Therefore, blocking the activation of the neuroendocrine system to achieve the blocking of ventricular remodeling has become the key for treatment of heart failure. In traditional Chinese medicine, it is believed that the heart failure is due to weakness of heart *qi* and *yang*, blood stasis, and retained fluid (Li et al., 2012). Invigorating *qi*, warming *yang*, promoting blood circulation and clearing damp are the four basic methods in traditional Chinese medicine, and have obtained certain curative effect in clinic (Liu et al., 2014; Guo et al., 2015). At present, it is generally thought that, the traditional Chinese medicine with heart strengthening function can be used for warming *yang* and invigorating *qi* (Li et al., 2009; Yu et al., 2012). *Radix aconiti carmichaeli*, *Cinnamomum cassia Presl*, *Panax ginseng* and *Astragalus* were the common used traditional Chinese herbs. This study investigated the effects of traditional Chinese medicine warming *yang* prescription and invigorating *qi* prescription on heart failure after myocardial infarction in rats and its actions on the RAAS. The objective was to provide a basis for their further clinical applications to treating heart failure.

2 Material and methods

2.1 Preparation of Chinese medicinal prescriptions

Warming *yang* prescription and invigorating *qi* prescription were prepared by the Manufacturing Department of Henan Province Hospital of Traditional Chinese Medicine (Zhengzhou, China) according to the standard production process. The main components of warming *yang* prescription were *Radix aconiti carmichaeli* and *Cinnamomum cassia Presl*, with mass ratio of 1: 1. One gram of dry extract was equal to 1.76 g crude drug. The main components of invigorating *qi* prescription were

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Panax ginseng and *Astragalus*, with mass ratio of 1: 1. One gram of dry extract was equal to 2.82 g crude drug.

2.2 Establishment of rat model with heart failure after myocardial infarction

According to the reported method (Song et al., 2011), clean grade male Wistar rats (200-250 g, provided by Shandong Lukang Pharmaceutical Co., Ltd., Jining, China) were selected for establishment of rat model with heart failure after myocardial infarction. After weighing, the rats were anesthetized by intraperitoneal injection of 1% pelltobarbitalum natricum (50 mg/kg). The rats were fixed on the rat experiment board at supine position. The skin on the left front chest was shaved, followed by disinfection with iodine. After tracheal intubation via larynx, and the rats were connected with ventilator and electrocardiograph machine. The assisted respiration was conducted, with frequency of 80 /min and tidal volume of 0.7-0.8 mL. The skin between third and fourth ribs was laterally cut open (length ca. 1.5 cm), and muscular layer is bluntly dissected. A 1.5 cm skin incision was made between the third and fourth ribs, and the muscular layer was bluntly isolated. The chest cavity was opened, and the visual field was expanded using retractor. The heart was exposed and the left coronary artery between the arterial cone and left auricle was ligated using 6/0 line. When the electrocardiogram showed that the ST segment was significantly elevated, the heart was placed in the chest cavity, and the chest wall is immediately stratified. In sham operation group, the procedure was the same with above, but the coronary artery was not ligated. After surgery, penicillin (400 thousand units per rat) was injected for anti-infection. On the second day, the rats are examined by echocardiography. Left ventricular ejection fraction (LVEF) ≤ 50% was considered as the standard of the success of modeling. All animals were handled according to the guidelines of the Animal Research Committee of Henan University of Chinese Medicine. The protocols were approved by the Committee on the Ethics of Animal Experiments of Henan University of Chinese Medicine.

2.3 Intervention experiment

One hundred and twenty-six qualified rats were randomly divided into model group, sham operation, warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi*, digoxin and captopril groups, with 18 rats in each group. In warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi*, digoxin and captopril groups, on the second day after modeling, the rats were intragastrically administrated with warming *yang* prescription, invigorating *qi* prescription, warming *yang*+invigorating *qi* prescription, digoxin and captopril, respectively. The drugs were dissolved with demineralized water. The dosage in rats was 6.35 times to that in the adult. The model group and sham operation group were treated with demineralized water with volume as the same as treatment groups. The intervention period was 6, 8 and 10 weeks, respectively, with 6 rats for each intervention period.

2.4 Observation indexes

After intervention, the rats were examined by echocardiography, and the LVEF was calculated. The blood was taken from the abdominal aorta (Hasić et al., 2013). The blood plasma was separated by centrifuging at low temperature, and was store at –25 °C. The plasma renin, angiotensin II and aldosterone levels were measured by radioimmunoassay (Langer et al., 1998). The kits were provided by Beijing North Institute of Biological Technology (Beijing, China).

2.5 Statistical analysis

Data were expressed as mean ± SD. Statistical analysis was performed using SPSS 17.0 statistical software. A t-test was used to analyze the differences between two groups. $P < 0.05$ was considered as statistically significant.

3 Results

3.1 Comparison of LVEF among different groups

As shown in Table 1, after 6, 8 and 10 weeks from intervention, the LVEF in model group was significantly lower than that in sham operation group ($P < 0.05$), and those in warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi* and captopril group were significantly higher than model group ($P < 0.05$). The LVEF in warming *yang*, warming *yang*+invigorating *qi* and captopril groups after 10 weeks was significantly higher than from 6 weeks ($P < 0.05$).

3.2 Comparison of renin level among different groups

As shown in Table 2, after 6, 8 and 10 weeks from intervention, the renin levels in model group were significantly higher than sham operation group ($P < 0.05$), and those in warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups were significantly lower than model group ($P < 0.05$). The renin level in model group after 10 weeks from intervention was significantly higher than from 6 weeks ($P < 0.05$), and that in invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups after 10 weeks was significantly lower than from 6 weeks ($P < 0.05$).

3.3 Comparison of angiotensin II level among different groups

After 6, 8 and 10 weeks from intervention, the angiotensin II levels in model group were significantly higher than sham operation group ($P < 0.05$), and those in warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups were

Table 1. Comparison of LEEF among different groups.

Group	LVEF		
	6 weeks	8 weeks	10 weeks
Model group	38 ± 9	36 ± 10	35 ± 14
Sham operation	87 ± 9*	88 ± 14*	87 ± 21*
Warming *yang*	50 ± 10*	50 ± 5*	55 ± 5*▲
Invigorating *qi*	48 ± 10#	48 ± 14*	46 ± 14*
Warming *yang*+invigorating *qi*	55 ± 11*	56 ± 10*	59 ± 10*▲
Digoxin	41 ± 8	43 ± 12	41 ± 12
Captopril	45 ± 11*	46 ± 7*	49 ± 7*▲

*$P < 0.05$ compared with model group; #$P < 0.05$ compared with sham operation group; ▲$P < 0.05$ compared with 6 weeks. LVEF, left ventricular ejection fraction.

Table 2. Comparison of renin level among different groups.

Group	Renin (ng/ml)		
	6 weeks	8 weeks	10 weeks
Model group	4 ± 0$^{\#}$	5 ± 1$^{\#}$	5 ± 2$^{\#\blacktriangle}$
Sham operation	2 ± 0*	2 ± 0*	2 ± 1*
Warming *yang*	3 ± 0*	3 ± 1$^{*\#}$	3 ± 1$^{*\#}$
Invigorating *qi*	3 ± 0*	3 ± 0$^{*\#}$	3 ± 0$^{*\#\blacktriangle}$
Warming *yang*+invigorating *qi*	3 ± 0*	3 ± 1$^{*\#}$	3 ± 1$^{*\#\blacktriangle}$
Digoxin	4 ± 1	4 ± 1$^{\#}$	4 ± 1$^{\#}$
Captopril	3 ± 0$^{*\#}$	3 ± 1$^{*\#}$	3 ± 1$^{*\#\blacktriangle}$

$^{*}P < 0.05$ compared with model group; $^{\#}P < 0.05$ compared with sham operation group; $^{\blacktriangle}P < 0.05$ compared with 6 weeks.

Table 3. Comparison of Angiotensin II level among different groups.

Group	Angiotensin II (ng/ml)		
	6 weeks	8weeks	10weeks
Model group	1170 ± 96$^{\#}$	1194 ± 76$^{\#}$	1254 ± 77$^{\#\blacktriangle}$
Sham operation	592 ± 81*	660 ± 160*	600 ± 79*
Warming *yang*	996 ± 110$^{*\#}$	969 ± 93$^{*\#}$	909 ± 96$^{*\#}$
Invigorating *qi*	1023 ± 120$^{*\#}$	956 ± 53$^{*\#}$	907 ± 35$^{*\#\blacktriangle}$
Warming *yang*+invigorating *qi*	931 ± 121$^{*\#}$	836 ± 105$^{*\#}$	790 ± 58$^{*\#\blacktriangle}$
Digoxin	1084 ± 111$^{\#}$	1071 ± 127$^{\#}$	1177 ± 25$^{\#}$
Captopril	1004 ± 104$^{*\#}$	894 ± 158$^{*\#}$	800 ± 80$^{*\#\blacktriangle}$

$^{*}P < 0.05$ compared with model group; $^{\#}P < 0.05$ compared with sham operation group; $^{\blacktriangle}P < 0.05$ compared with 6 weeks.

significantly lower than model group (P < 0.05). The angiotensin II level in model group after 10 weeks from intervention was significantly higher than from 6 weeks (P < 0.05), and that in invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups after 10 weeks was significantly lower than from 6 weeks (P < 0.05) (Table 3).

3.4 Comparison of aldosterone level among different groups

After 6, 8 and 10 weeks from intervention, the aldosterone levels in model group were significantly higher than sham operation group (P < 0.05), and those in warming *yang*, invigorating *qi*, warming *yang*+invigorating *qi* and captopril groups were significantly lower than model group (P < 0.05). The aldosterone level in model group after 10 weeks from intervention was significantly higher than from 6 weeks (P < 0.05), and that in captopril group after 10 weeks was significantly lower than from 6 weeks (P < 0.05) (Table 4).

Table 4. Comparison of aldosterone level among different groups.

Group	Aldosterone (pg/ml)		
	6 weeks	8 weeks	10 weeks
Model group	894 ± 147$^{\#}$	911 ± 106$^{\#}$	994 ± 156$^{\#\blacktriangle}$
Sham operation	386 ± 58*	401 ± 79*	392 ± 29*
Warming *yang*	682 ± 204$^{*\#}$	642 ± 97$^{*\#}$	577 ± 56$^{*\#}$
Invigorating *qi*	661 ± 203$^{*\#}$	655 ± 102$^{*\#}$	600 ± 46$^{*\#}$
Warming *yang*+invigorating *qi*	643 ± 188$^{*\#}$	561 ± 46$^{*\#}$	488 ± 73$^{*\#}$
Digoxin	706 ± 153$^{\#}$	859 ± 108$^{\#}$	759 ± 157$^{\#}$
Captopril	677 ± 212$^{*\#}$	582 ± 123$^{*\#}$	425 ± 35$^{*\#\blacktriangle}$

$^{*}P < 0.05$ compared with model group; $^{\#}P < 0.05$ compared with sham operation group; $^{\blacktriangle}P < 0.05$ compared with 6 weeks.

4 Discussion

Chronic congestive heart failure is not clearly documented in traditional Chinese medicine. According to the symptoms, it is attributed to the palpitation, edema, phlegm, dyspnea and chest pain (Alikhassi et al., 2014). Its basic pathology belongs to deficiency in origin and excess in superficiality. The deficiency in origin mainly is the lack of vital energy and the deficiency of vital energy. The excess in superficiality mainly is blood stasis and water retention. The lack of vital energy and the deficiency of vital energy is the main pathogenesis of heart failure (Huss & Kelly, 2005). Warming *yang* and invigorating *qi* are most fundamental method to treat heart failure (Wan et al., 2007). A lot of Chinese herbal medicine of invigorating *qi* and warming *yang* have effect in strengthening heart. *Radix aconiti carmichaeli*, *Cinnamomum cassia Presl*, *Panax ginseng* and *Astragalus* have the function to ameliorate the symptoms of heart failure (Li et al., 2009; Yu et al., 2012). This study applied traditional Chinese medicine warming *yang* prescription and invigorating *qi* prescription to treat heart failure rats after myocardial infarction. Results find that, warming *yang*+invigorating *qi* prescription can significantly improve LVEF in heart failure rats after myocardial infarction.

At present, it is considered that the activation of neuroendocrine factors such as RAAS is the most important cause of ventricular remodeling after myocardial infarction (Wan et al., 2007; Ma et al., 2010). This study investigated the effects of warming *yang* prescription and invigorating *qi* prescription on RAAS in treatment of heart failure rats after myocardial infarction. The results show that, the invigorating *qi* and warming *yang* prescriptions have different effect on RAAS at different time points. At the same time point, the levels of renin, angiotensin and aldosterone in warming *yang* group, invigorating *qi* group, warming *yang*+invigorating *qi* group are significantly lower than model group. The decrease of these indexes in invigorating *qi*+warming *yang* group is more than invigorating *qi* group and warming *yang* group, respectively. This indicates that, the warming *yang* medicine and invigorating *qi* medicine can inhibit the activation of RAAS in the blood circulation, and the effect of warming *yang*+invigorating *qi* group is the best. Comparisons of different time in each group show that, with the prolongation of the treatment time, the level of each index in the RAAS has a downward trend. Above results indicate that, the improvement of LVEF in heart failure after myocardial infarction by warming *yang* prescription and invigorating *qi* prescription may be related to its the inhibition of RAAS activation.

5 Conclusion

Warming *yang* and invigorating *qi* prescription can improve LVEF in rats with heart failure after myocardial infarction, which may be related with the inhibition of RAAS activation. However, the sample size of this study is relatively small. In our next studies, the sample size should be further increased to make the results more convincing.

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