

*Full Length Research Paper*

# Effects of supplementing qi and activating blood circulation herbs on expressions of basic fibroblast growth factor and platelet endothelial cell adhesion molecule-1 in ischemic myocardium of rats with acute myocardial infarction

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The objective of this study was to investigate the effects of supplementing qi and activating blood circulation herbs on the expressions of basic fibroblast growth factor (bFGF) and platelet endothelial cell adhesion molecule (PECAM-1) in ischemic myocardium of rats with acute myocardial infarction (AMI). Acute myocardial infarction (AMI control) of male Sprague-Dawley rats was established by ligating left anterior descending coronary artery. Rats with AMI were randomly divided into 6 groups, including AMI control, activating blood circulation herbs (blood group), supplementing qi herbs (qi group), supplementing qi herbs/activating blood circulation herbs 1:2 (1:2 group), supplementing qi herbs/activating blood circulation herbs 2:1 (2:1 group) and Tongxinluo capsule groups (TXL group), and a sham operation group was set up as negative control group. The herbs were administered on the second day after myocardial infarction with a therapeutic course of 4 weeks, and the bFGF and PECAM-1 expressions in the myocardial area were tested by immune histochemical methods at 1, 2 and 4 weeks. The supplementing qi and activating blood circulation herbs can promote the expression of bFGF and PECAM-1 in myocardial cells, thus promoting the formation of microvasculature in myocardial ischemia and improving blood supply to the ischemic myocardium. Supplementing qi and activating blood circulation herbs increase the expression of angiogenic factors; this may be their mechanism of angiogenesis.

**Key words:** Myocardial ischemia, supplementing qi and activating blood circulation herbs, basic fibroblast growth factor, platelet endothelial cell adhesion molecule, left ventricular mass index (LVMI).

## INTRODUCTION

Angiogenesis plays an important role in ischemic disease treatment and prognosis. In recent years, more studies confirm that the effective Chinese medicines to improve myocardial ischemia can promote coronary collateral

vessel growth; some research showed that supplementing qi and activating blood circulation herbs have a certain effect to promote angiogenesis (Gao and Chen, 2002). Since there is a direct relationship between vascular endothelial cells and angiogenesis, the experiments were conducted in acute myocardial infarction (AMI) control of left coronary vein ligated rats with acute myocardial infarction on the basis of

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preliminary studies (Huang et al., 2010). We further studied the impact of basic fibroblast growth factor (bFGF) and platelet endothelial cell adhesion molecule (PECAM-1) expressions in rats with myocardial infarction receiving the supplementing qi and activating blood circulation herbs. This study assesses the effect of the supplementing qi and activating blood circulation herbs on experimental ischemic myocardial angiogenesis and its possible mechanisms.

## MATERIALS AND METHODS

### Animals

Male Sprague-Dawley rats, purchased from Beijing Vital River Lab Animal Technology Co., Ltd. (Beijing, certificate No. SCXK 2007-0001), and initially weighing  $230 \pm 20$  g (aged 10 weeks) were used in this study. All rats were housed under constant conditions at the temperature of  $23 \pm 1^\circ\text{C}$ , humidity of  $40 \pm 5\%$ , and on a 12-h light/dark-cycle. The rats had free access to a standard diet and water. The animal experiments were performed in accordance with the standards established by the Guide for the Care and Use of Laboratory Animals of Beijing City, and approved by the local Ethics Committee. The whole laboratory process was carried out under the permission and surveillance of the Ethical Committee.

### Drugs and reagents

Supplementing qi herbs include *Astragalus* and *Ginseng*, and activating blood circulation herbs include *Chuanxiong*, *Panax* and *Pueraria* (provided by Pharmaceutical Factory of Beijing University of Chinese Medicine). The positive control drugs: Tongxinluo capsule (Yiling Pharmaceutical Company). bFGF and PECAM-1 antibody, Santa Cruz; 1% furosemide (Tianjin Jin Yao Amino Acid Co., Ltd.), production batch number: 0705093; 2% lidocaine injection (Beijing Yongkang Pharmaceutical Co., Ltd.), production batch number: 07,040,204; injection of penicillin sodium (North China Pharmaceutical Co., Ltd.), production batch number: Y0703113; 1% pentobarbital sodium injection, Anerdian domestic analytical reagents; CD34 antibody, Santa Cruz; endostatin antibodies (Wuhan Boster).

### Main instruments

The RSP1002 small animal ventilator (Kent Scientific Corporation); BX-60 fluorescence/transmission microscope (Japan OLYMPUS Optical Co., Ltd.); Spot II digital imaging system (Diagnostic Instruments in USA); JA1003 electronic balance (Shanghai Precision & Scientific Instrument Co., Company); electrocardiogram (ECG) instrument XJJ-11 (Shanghai medical Electronic Instrument Factory); and MetaMorph image analysis system (Universal Imaging Corporation).

### Experimental myocardial infarction

Myocardial infarction (MI) was produced in rats by ligation of the left anterior descending coronary artery for 4 weeks. The surgical procedure was performed according to a previous study (Stanton et al., 2000) with minor modifications. Briefly, the rats were anesthetized with urethane (1.2 g/kg, interperitoneally, ip), and then underwent a left thoracotomy. The incised area was extended by forceps and the pericardium was opened. After tracheal intubation,

the rats were ventilated by a respirator with room air at a tidal volume of 25 ml/min and a respiratory rate of 70 cycles/min. The heart was exteriorized and ligated at the proximal left anterior descending coronary artery 2 to 3 mm from its origin between the pulmonary artery conus and the left atrium with a 4 to 0 prolene suture. The heart was returned to its normal position, and the thorax was closed. Sham operated rats underwent the identical surgical procedure as described earlier except that the suture was not tightened around the coronary artery.

### Experimental protocol

The surviving rats were divided randomly into 6 groups: AMI control, the supplementing qi herbs (referred to as Qi group), the activating blood circulation herbs (referred to as blood group), supplementing qi herbs/activating blood circulation herbs 1:2 (referred to as 1:2 group), supplementing qi herbs/activating blood circulation herbs 2:1 (referred to as 2:1 group) and Tongxinluo capsule groups (referred to as Tongxinluo (TXL) group). In addition to the sham operation group (referred to as sham group), which was only threatened from below the coronary artery with no ligation, there were 7 groups in total. AMI control group (were fed with the same volume of sterile distilled water daily, without drug intervention); Tongxinluo group (daily fed with 30 mg/kg/day Tongxinluo pills, consulting previous research (Chen et al., 2012)); Qi group (daily fed with 7 g/kg/day Qi herbs); blood group (daily fed with 7 g/kg/day blood herbs); 1:2 group (daily fed with formula prescribed in a proportion of 21 g/kg/day); 2:1 group (daily fed with formula prescribed in a proportion of 21 g/kg/day).

### Immunohistochemistry

The tissues were fixed with 10% neutral formalin at room temperature for 24 h. The paraffin-embedded specimens were cut into sections with a thickness of 5  $\mu\text{m}$ . The detection procedure was done as described in Kit protocol (Wuhan Boster Biological Technology Co. Ltd). Phosphate buffered saline (PBS) instead of the first antibodies was used in the negative control. bFGF and PECAM-1 positive cells were defined when there was an aggregation of brown particles in the cell. Immunoreactive score was determined by the sum of extension and intensity as previously reported (Schiller et al., 2007).

### Statistical analysis

All data were presented as mean  $\pm$  standard deviation (SD). Statistical analysis was performed with Statistical Package for Social Sciences (SPSS 17.0) for Windows. For comparison among multiple groups, data was analyzed by analysis of variance (ANOVA). When a statistical difference appeared, the least significant difference (LSD) procedure was applied. At the same time, the author consulted the methods in Chen's papers (Chen et al., 2007, 2012, 2010). A value of  $p < 0.05$  was considered statistically significant. A detailed description of the methodology has been provided in supplementary data.

## RESULTS

### Comparison of left ventricular mass index (LVMI)

There were significant differences between sham group and AMI control group ( $p < 0.01$ ). Compared with AMI

**Table 1.** Comparison of LVMI ( $\bar{x} \pm SD$ , mg/g).

Group	No.	LVMI		
		7 days	14 days	28 days
Sham group	19	2.13 ± 0.24	2.18 ± 0.35	2.21 ± 0.11
AMI control group	28	2.71 ± 0.11*	2.90 ± 0.36*	3.10 ± 0.31*
Blood group	27	2.61 ± 0.17	2.78 ± 0.14	2.91 ± 0.22
Qi group	25	2.62 ± 0.17	2.76 ± 0.14	2.89 ± 0.19
1:2 group	27	2.30 ± 0.11 <sup>#</sup>	2.42 ± 0.15 <sup>#</sup>	2.53 ± 0.16 <sup>#</sup>
2:1 group	28	2.20 ± 0.26 <sup>#</sup>	2.27 ± 0.28 <sup>#</sup>	2.31 ± 0.27 <sup>#</sup>
TXL group	25	2.21 ± 0.24 <sup>#</sup>	2.30 ± 0.44 <sup>#</sup>	2.37 ± 0.17 <sup>#</sup>

Compared with sham group, \*p < 0.05; Compared with AMI control group, <sup>#</sup>p < 0.05.

**Table 2.** Comparison of bFGF expression ( $\bar{x} \pm SD$ ).

Group	No.	bFGF (IOD)		
		7 days	14 days	28 days
Sham group	19	11.74 ± 0.95	11.83 ± 0.97	11.76 ± 0.89
AMI control group	28	21.47 ± 1.25**	18.50 ± 1.12**	12.68 ± 1.01*
Blood group	27	22.37 ± 1.35	24.74 ± 1.30 <sup>##</sup>	23.76 ± 1.38 <sup>##</sup>
Qi group	25	23.76 ± 1.25	26.76 ± 1.14 <sup>##</sup>	19.99 ± 1.30 <sup>##</sup>
1:2 group	27	24.47 ± 1.30 <sup>#</sup>	29.54 ± 1.40 <sup>##</sup>	25.13 ± 1.42 <sup>##</sup>
2:1 group	28	27.74 ± 1.48 <sup>##</sup>	32.58 ± 1.59 <sup>##</sup>	29.56 ± 1.52 <sup>##</sup>
Tongxinluo group	25	27.62 ± 1.60 <sup>##</sup>	33.58 ± 1.52 <sup>##</sup>	29.95 ± 1.65 <sup>##</sup>

Compared with sham group, \*p < 0.05, \*\* p < 0.01; Compared with AMI control group, <sup>#</sup>p < 0.05, <sup>##</sup>p < 0.01. IOD: Integrated optical density.

control, the LVMI of every time point of qi and blood groups were lower, while the 1:2, 2:1 and TXL groups were significantly lower (p < 0.05) which indicated that the supplementing qi and activating blood circulation herbs significantly reduced the LVMI, especially in the 2:1 group (Table 1).

### Comparison of bFGF expression

#### Comparison between the two groups

**7 days:** Compared with sham group, the bFGF expression of AMI control group was significantly higher (p < 0.01). Compared with AMI control group, the bFGF expression of qi and blood groups were higher, and the 1:2, 2:1 and TXL groups were significantly higher (p < 0.05 or p < 0.01) which indicated that the supplementing qi and activating blood circulation herbs could promote the bFGF expression of ischemic myocardium, especially in the 2:1 group (Table 2).

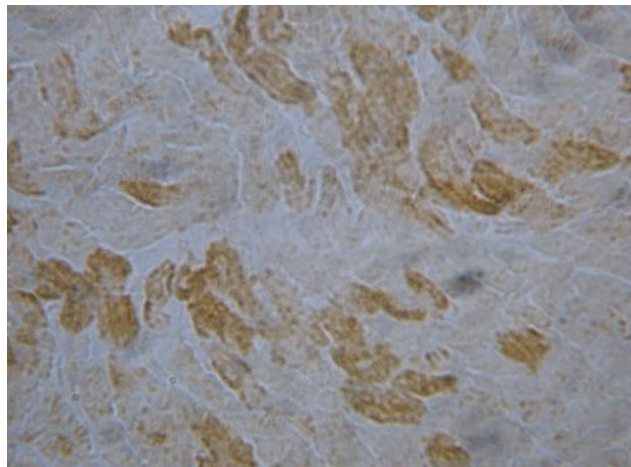
**14 days:** The bFGF expression of AMI control group was significantly higher than sham group (p < 0.01) compared with AMI control group; there were significant differences

in the blood, qi, 1:2, 2:1 and TXL groups (p < 0.01) which indicate that the supplementing qi and activating blood circulation herbs could promote the bFGF expression of ischemic myocardium, especially in the 2:1 group (Table 2).

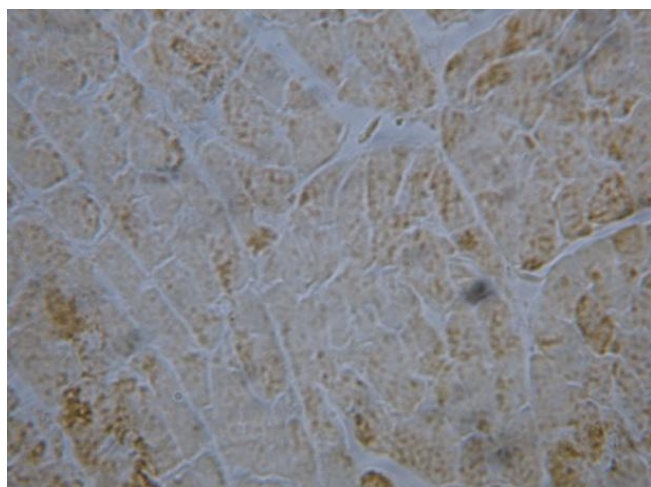
**28 days:** There were differences between the AMI control and sham groups (p < 0.05) when compared with the AMI control group; there were significant differences in the blood, qi, 1:2, 2:1 and TXL groups (p < 0.01) which indicate that the supplementing qi and activating blood circulation herbs could promote the bFGF expression of ischemic myocardium (Table 2).

#### Comparisons of different times

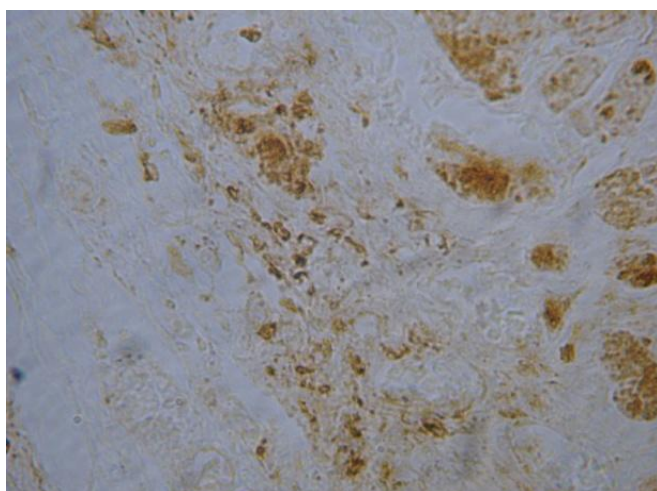
There were no significant differences in the sham group (P > 0.05) compared with 7 and 14 days; there were significant differences in the AMI control, 1:2, 2:1 and TXL groups (p < 0.05) and compared with 14 and 28 days, there were significant differences in the AMI control, qi and 1:2 groups (p < 0.05) (Table 2). The pictures of the bFGF expressions at the 28th day are shown in Figures 1 to 4.



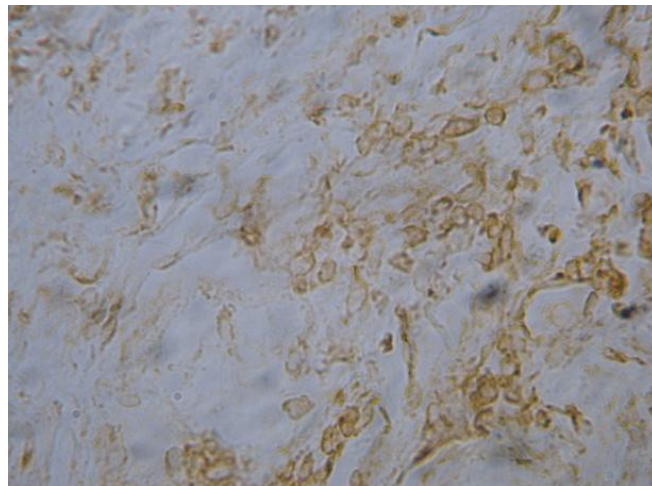
**Figure 1.** Sham group (28 days).



**Figure 2.** AMI control group (28 days).



**Figure 3.** TXL group (28 days).



**Figure 4.** 2:1 group (28 days).

### Comparisons of PECAM-1 expressions

#### *Comparisons between the two groups*

**7 days:** Compared with sham group, the PECAM-1 expression of AMI control group was significantly higher ( $p < 0.01$ ). Compared with AMI control group, the PECAM-1 expression of the 1:2, 2:1 and TXL groups were significantly higher ( $P < 0.05$  or  $P < 0.01$ ), which indicated that the supplementing qi and activating blood circulation herbs could promote the PECAM-1 expression of ischemic myocardium, especially in the 2:1 group (Table 3).

**14 days:** The PECAM-1 expression of AMI control group was significantly higher than the sham group ( $P < 0.01$ ) when compared with AMI control group; the PECAM-1 expression of qi and blood groups were higher and there were significant differences in the 1:2, 2:1 and TXL groups ( $p < 0.01$ ) which indicated that the supplementing qi and activating blood circulation herbs could promote the PECAM-1 expression of ischemic myocardium, especially in the 2:1 group (Table 3).

**28 days:** There were differences between the AMI control group and sham group ( $p < 0.05$ ) compared with AMI control group; the PECAM-1 expression of other groups were higher and showed significant differences ( $P < 0.01$ ) which indicated that the supplementing qi and activating blood circulation herbs could promote the PECAM-1 expression of ischemic myocardium (Table 3).

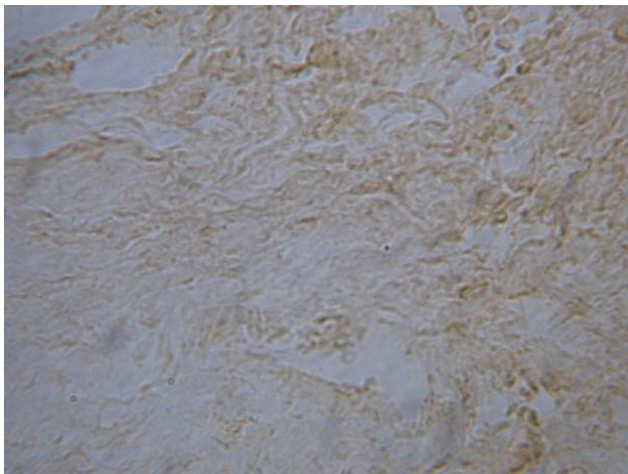
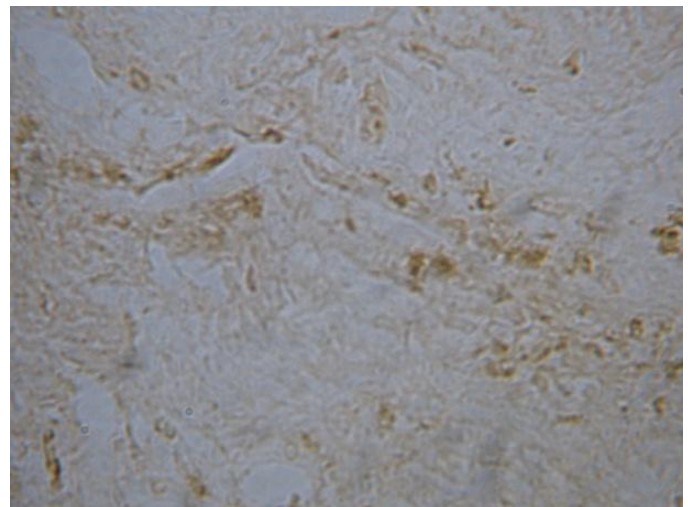
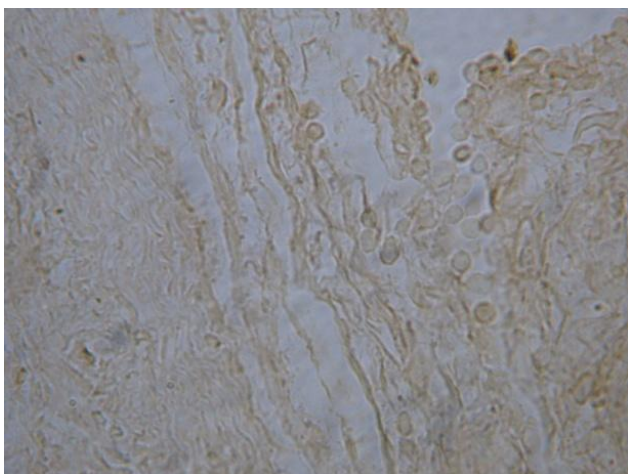
#### *Comparisons at different times*

There were no significant differences in the sham group ( $P > 0.05$ ) compared with 14 and 28 days; there were

**Table 3.** Comparisons of PECAM-1 ( $\bar{X} \pm SD$ ).

Group	No.	PECAM-1 (IOD)		
		7 days	14 days	28 days
Sham group	19	11.97 ± 1.15	12.14 ± 1.20	12.05 ± 1.23
AMI control group	28	20.76 ± 1.27**	20.32 ± 1.48**	13.75 ± 1.36*
Blood group	27	21.00 ± 1.26	20.97 ± 1.37	23.25 ± 1.32 <sup>##</sup>
Qi group	25	20.53 ± 1.41	21.07 ± 1.50	23.65 ± 1.66 <sup>##</sup>
1:2 group	27	23.17 ± 1.37 <sup>#</sup>	23.94 ± 1.45 <sup>#</sup>	24.99 ± 1.52 <sup>##</sup>
2:1 group	28	24.57 ± 1.55 <sup>##</sup>	26.74 ± 1.52 <sup>##</sup>	27.02 ± 1.47 <sup>##</sup>
Tongxinluo group	25	25.16 ± 1.42 <sup>##</sup>	26.94 ± 1.53 <sup>##</sup>	28.43 ± 1.37 <sup>##</sup>

Compared with sham group, \* $p < 0.05$ , \*\*  $p < 0.01$ ; Compared with AMI control group, <sup>#</sup> $p < 0.05$ , <sup>##</sup> $p < 0.01$ . IOD: Integrated optical density.

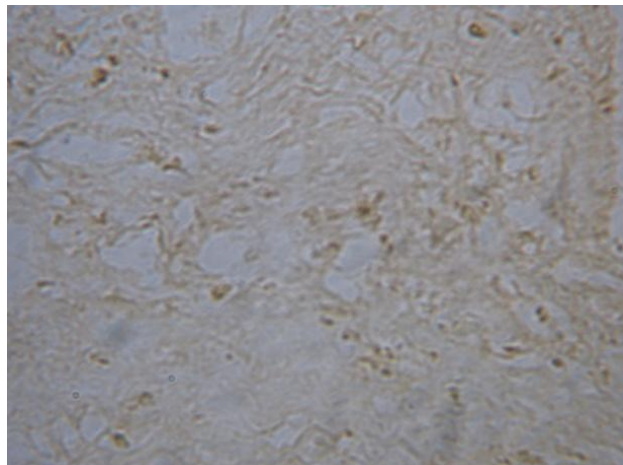
**Figure 5.** Sham group (28 days).**Figure 7.** TXL group (28 days).**Figure 6.** AMI control group (28 days).

days and 14 days, there were significant differences in the 2:1 and TXL groups ( $P < 0.05$ ) (Table 3). The pictures of the PECAM-1 expressions at 28th days are shown in Figures 5 to 8.

## DISCUSSION

Coronary artery disease is the main cause of death in both the developed and developing countries, while acute myocardial infarction is the most critical type of coronary heart disease. Ventricular remodeling is an important pathophysiological process of myocardial infarction (Tan and Hua, 2012), and LVMI is an indirect indicator which can evaluate ventricular remodeling after acute myocardial infarction. The results suggested that the LVMI of the 1:2, 2:1 and TXL groups were significantly lower than the AMI control group, especially the 2:1 group which indicated that the supplementing qi and activating blood circulation herbs could reduce ventricular

significant differences in the AMI control, qi, blood, 1:2, 2:1 and TXL groups ( $P < 0.05$ ), and compared with 7



**Figure 8.** 2:1 group (28 days).

dilatation and ventricular remodeling to improve cardiac function, especially the 2:1 group. bFGF stimulates angiogenesis, including the migration and proliferation of endothelial cells, vascular tube formation, and linkage to the preexisting vascular network (Thau-Zuchman et al., 2012; Jeong et al., 2010). Some medicine like JingZhiNing (Chen et al., 2012, 2011) may have effects on it. A previous study showed that bFGF could be used *in vivo* to facilitate the mobilization and differentiation of resident cardiac precursors in the treatment of cardiac diseases (Oka et al., 2000). The expression levels of bFGF in normal myocardial cells are low which increases during myocardial ischemia and hypoxia. It was also found that the bFGF expression in AMI control group was significantly higher than the sham group, but this high expression of hypoxia-inducible ischemia is far from sufficient to meet the body's needs of angiogenesis. The bFGF expression significantly increased after the application of activating blood circulation herbs, supplementing qi herbs and its compatibility, especially the 2:1 group which was almost the same as Tongxinluo capsule.

PECAM-1 is of the immunoglobulin (Ig)-superfamily with wide variety of functions in platelet activation, inflammation, cell survival and the immune response and is involved in transendothelial migration of monocytes (TEM) (Wee et al., 2005; McCormick et al., 2011; Sachs et al., 2007). Thus, it has a role in atherosclerotic plaque formation. It also has a role in thrombus formation subsequent to plaque rupture leading to MI. Since it has high expression in all vascular endothelial cells, it is often used as a marker of vascular endothelial cells. After the application of activating blood circulation herbs, supplementing qi herbs and their compatibility, PECAM-1 expression of rats with ischemic myocardium was significantly increased showing active angiogenesis, especially the 2:1 group, equal to Tongxinluo capsule.

By the observation of bFGF and PECAM-1 expression

of rats with myocardial infarction at different times, it showed that the bFGF and PECAM-1 expression gradually reduced as time passed. It indicated that myocardial ischemia could induce the increase of bFGF and PECAM-1 expression which may be a compensatory reaction elicited by body tissue hypoxia. However, as time passed, the expression of bFGF and PECAM-1 increased by causing myocardial ischemia which indicated that the body's own compensatory establishment was difficult to restore without treatment. The bFGF expression of each group showed that the 14 days was higher than the 7 days and the 28 days was higher than the 14 days, suggesting that the promoting of angiogenesis in the ischemic myocardium may be an important mechanism to improve myocardial ischemia. The proangiogenic factor control of the supplementing qi and activating blood circulation herbs was not unlimited, and there may be a two-way adjustment in the safe range. The PECAM-1 expression was different. As time passed, the expression of PECAM-1 increased in a sustained manner. The mechanism of sustained increase of PECAM-1 may be a negative feedback regulation of the body. It transmitted inhibitory signals and inhibited platelet adhesion, aggregation, secretion and the platelet activation around thrombus. It finally limits the expansion of the volume of thrombus.

Traditional Chinese medicine theory propounds that "the heart dominates the blood". Heart qi promotes blood to flow smoothly in the vessels. Deficiency of qi is the start of the initiating factor and promoter throughout the whole process. The composition of the supplementing qi and activating blood circulation herbs is based on the classic prescription, Danggui Buxue Tang, and at the same time, modern researches (Chen et al., 2011) has offered some support. The results showed that the effect of the combination of supplementing qi herbs and activating blood circulation herbs is better than single supplementing qi herbs or activating blood circulation herbs and the 2:1 group is better than the 1:2 group. It can be suggested that a large dose of supplementing qi herbs with small dose of activating blood circulation herbs is better than the small dose of supplementing qi herbs and large dose of activating blood circulation herbs. The improvement has a higher correlation with the combined ratio with the supplementing qi and activating blood circulation herbs and their intervention time, and the longer the treatment time was, the better the angiogenesis. The supplementing qi and activating blood circulation herbs might have produced the observed beneficial effect through increased expression of angiogenic factors. This can be suggested as mechanism of angiogenesis.

#### ACKNOWLEDGEMENT

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