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ORIGINAL ARTICLE

Endothelial Factors after Selective Retrograde Coronary Venous Bypass under Different Pressures

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Abstract

Background. Selective retrograde coronary venous bypass (SRCVB) may be a promising treatment for patients with advanced coronary artery disease (CAD). The aim of this study is to investigate the effect of SRCVB on plasma endothelial factor levels in dog myocardial ischemic model, and explore the possible mechanisms. **Methods.** 24 crossbreed dogs were randomly divided into three groups: (1) control group; (2) SRCVB group with 60 mmHg perfusion pressure; (3) SRCVB group with 90 mmHg perfusion pressure. The posterior descending coronary artery (PDA) was ligated in all groups, and SRCVB was performed in the last two groups. The levels of plasma nitric oxide (NO) and endothelin (ET) at different time points were determined in each group. In SRCVB groups, ink and imaging agent were injected to the heart through SVG graft for assessment of vein perfusion. **Results.** At the acute period, there were significant increase in the plasma levels of NO and decrease in ET in SRCVB 90 mmHg group compared with the control ($P < 0.01$), and a further improvement were found in SRCVB 60 mmHg group ($P < 0.01$). The ink or imaging agent was found in the myocardial tissue and flowed back to right atrium through contralateral coronary vein. **Conclusions.** SRCVB with low level of perfusion pressure could provide effective perfusion for ischemic myocardium and alleviate the myocardial endothelial cell injury. It may be a new therapeutic strategy for severe CAD.

Key words: selective retrograde coronary venous bypass; endothelial factors; perfusion pressure

Introduction

With the extensive utilization of PCI, about 12%–30% of the patients with atherosclerosis suffered from diffuse stenosis and obstruction over the whole range. These patients are not eligible for traditional coronary artery bypass graft (CABG), whilst have no choice but to wait for cardiac transplantation [1], which has been significantly restricted by recent decline in organ donation [2], but consequently most of them may die during the waiting period. It has become a rather severe problem in cardiac surgery.

Selective retrograde coronary venous bypass (SRCVB) may provide a promising therapeutic option for patients with diffuse lesion and distal occlusion in the coronary artery. However, many mechanisms remain unclear, and the damage of veins during sudden exposure to arterial pressure is still

the major hurdle limiting its clinical application [3, 4]. The present study was set to investigate the effects of SRCVB with different perfusion pressure against ischemic myocardial and endothelial injury in dog model.

Material and methods

24 healthy crossbreed dogs, either male or female, weighing about 20–25 kg were purchased from the Experimental Animal Department, China Medical University, and received human care. The experiment was approved by Liaoning Administrative Committee for Laboratory Animals and the procedures were carried out strictly in compliance with the Guide for the care and use of laboratory animals published by the National Institutes of Health in 1996.

Abbreviations

ANOVA	Analysis of variance
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
ET	Endothelin
MCV	Middle cardiac vein
NO	Nitric oxide
PDA	Posterior descending coronary artery
SRCVB	Selective retrograde coronary venous bypass
SVG	Saphenous vein graft

Establishment of animal models

Dogs were anesthetized with intravenous injection of 3% pentobarbital sodium (50mg/kg), and were ventilated through a cuffed endotracheal tube with a Bird Mark 8 ventilator. Heparin sodium (1mg/kg) was intravenously injected to prevent coagulation. In the right lateral decubitus position, the left anterolateral thoracotomy was performed for exposure of the heart. A catheter was put into the ascending aorta to monitor the aortic pressure.

Thereafter, the animals were randomly divided into three groups: 1) control group; 2) SRCVB 60 mmHg group (SRCVB with 60 mmHg perfusion pressure); 3) SRCVB 90 mmHg group (SRCVB with 90 mmHg perfusion pressure). In the last two groups, SRCVB was performed from the descending aorta to the middle cardiac vein (MCV) with a great saphenous vein graft (SVG) harvested in advance, followed by ligation of the proximal part of MCV. Throughout the operation, the mean perfusion pressure measured through an artery-detaining needle set in the SVG was maintained at 60 mmHg and 90 mmHg respectively in SRCVB 60 mmHg group and SRCVB 90 mmHg group, by intravenous administration of dopamine and nitroglycerin. The initial segment of posterior descending coronary artery (PDA) was ligated, immediately after the SRCVB was completed in SRCVB groups or directly in the control.

Sample collection

Six milliliters of blood sample were collected from aortic catheter before ligation and 240 min after the ligation of PDA. Thereafter, 10 mL ink was injected

into the vein graft on the beating heart at a steady speed in SRCVB groups. And then, the animals were sacrificed with an overdose of potassium chloride and the hearts were harvested for *in vitro* angiography and histological analysis. *In vitro* angiography was performed using a C-Arm Cardiac Angiography System (Siemens AG, Healthcare Sector, Erlangen, Germany), with imaging agent injected into the vein graft.

Serum nitric oxide (NO) generation was analysed by the Griess reaction. Serum levels of endothelin (ET) were measured using a commercially available ELISA-Kit (Immundiagnostik, Bensheim, Germany) as previously described [5].

The heart samples were immersed into 10% formaldehyde in phosphate-buffered saline of PH 7.4 at 4°C for 24 hours. After fixation, the samples were embedded in paraffin and sectioned to 5- μ m-thick slices. Routine staining was performed with hematoxylin-eosin.

Statistical analysis

All offline measurements were made by investigators blinded to the treatment. Quantitative data were presented as mean \pm SD. SPSS 13.0 software package (SPSS Inc, Chicago, USA) was used for statistical analysis. Experimental measurements in each group were compared by one-way analysis of variance (ANOVA) with Bonferroni post hoc correction. A value of $P < 0.05$ was regarded as statistically significant.

Results

It was detected in control group, but not in SRCVB groups, that the corresponding myocardium became purple color and ST segment was significantly elevated in lead II of the electrocardiogram monitor.

Changes of NO and ET levels

As shown in Table I, no significant differences in the plasma levels of NO and ET were found among the three groups before PDA ligation ($P > 0.05$). Compared with control group, the plasma concentration of NO and ET respectively increased and decreased in both SRCVB groups 240 min after treatment

Table I. Changes of endothelial factors in each group.

	Time	Control Group	60 mmHg Group	90 mmHg Group
NO (μ mol/L)	before	97.52 \pm 6.65	93.79 \pm 5.13	96.21 \pm 5.52
	240 min	28.75 \pm 4.05	57.43 \pm 4.23 Δ	47.70 \pm 2.87 Δ
ET (pg/L)	before	58.32 \pm 2.44	58.20 \pm 2.21	57.42 \pm 2.98
	240 min	251.15 \pm 8.29	102.23 \pm 7.30 Δ	155.75 \pm 7.87 Δ

ET: Endothelin. NO: Nitric oxide. $\Delta P < 0.001$ compared with control group; $\Delta P < 0.001$ compared with 60 mmHg group.

($P < 0.001$). Importantly, there was a more significant improvement in SRCVB 60 mmHg group than in the 90 mmHg ($P < 0.001$).

Histological analysis

In SRCVB 60 mmHg group, it was revealed by HE staining myocardium sections that the ink distributed in myocardial sinuses (Figure 1A), capillaries and even arterioles (Figure 1B), without angiorrhexis or ink efflux. Although there were similar results in SRCVB 90 mmHg group, significant myocardial tissue edema was detected in this group at the same time (Figures 1C and 1D).

Angiography

The angiography showed that imaging agent could be perfused into the PDA region, and ultimately flowed back to right atrium through contralateral coronary vein (Figures 2 A–D).

Discussion

Our study has demonstrated that SRCVB with low perfusion pressure brought little pressure related

cardiac injury, protected endothelial cells against ischemic injury, and provided effective perfusion for ischemic myocardium, at least for the acute period.

As an effective method of myocardial preservation, coronary venous retroperfusion has been widely used for delivering cardioplegic solutions during cardiac surgery [6], which can nourish the myocardium through myocardial sinusoids. In addition, it has been widely accepted that coronary venous system is barely affected by atherosclerosis [7], which is an alternative pathway for myocardium perfusion when the coronary arteries are impaired with diffuse atherosclerosis. Therefore, the coronary veins-derived revascularization is expected to become an effective therapeutic strategy for patients with advanced diffuse lesion in coronary arteries [8].

It has been reported by many investigators that SRCVB could rescue ischemic myocardium, restore myocardial contractile force, and improve cardiac function after myocardial ischemia [3, 4, 9]. And as shown by angiography and histological analysis in our experiment, blood was perfused into the PDA region through the venous graft and MCV (the ink was distributed in myocardial sinuses, capillaries and even arterioles, without angiorrhexis), and ultimately flowed back to right atrium through contralateral coronary vein, indicating the feasibility of SRCVB again.

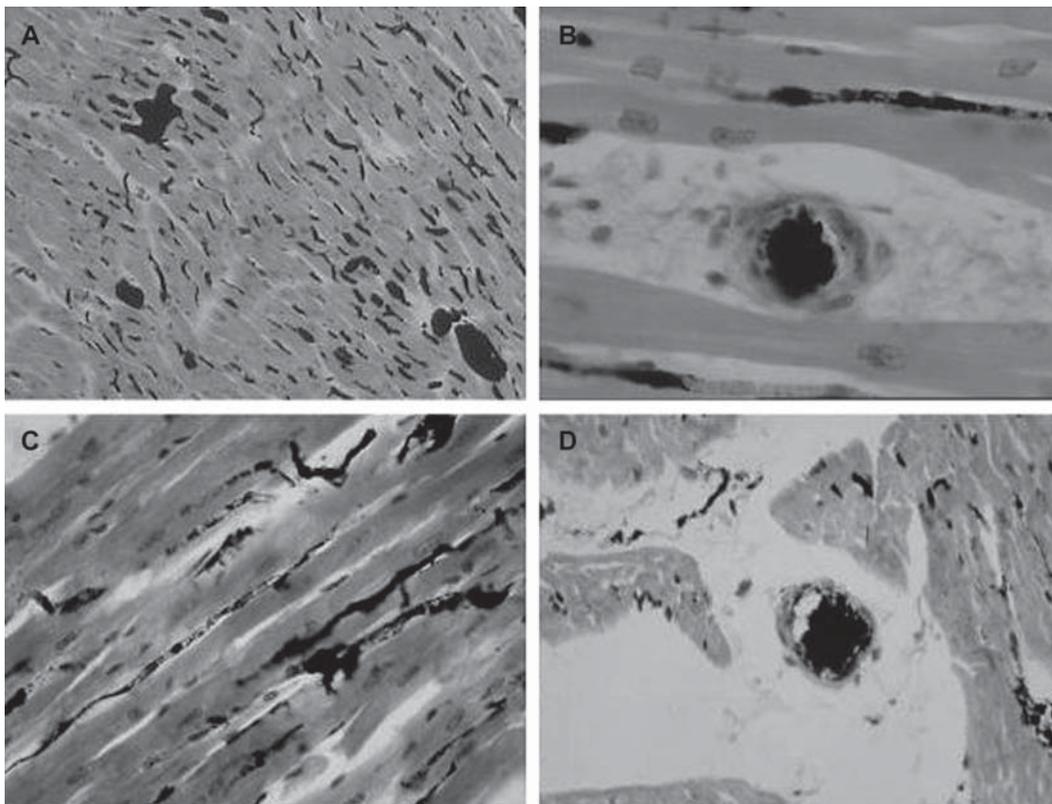


Figure 1. Pathological analysis (A) The ink was distributed in myocardial sinuses and no angiorrhexis in SRCVB 60mmHg group; (B) the ink was distributed in capillaries and no angiorrhexis or ink efflux in SRCVB 60 mmHg group; (C) and (D) though ink could be distributed to PDA region, significant myocardial tissue edema was observed in SRCVB 90 mmHg group.

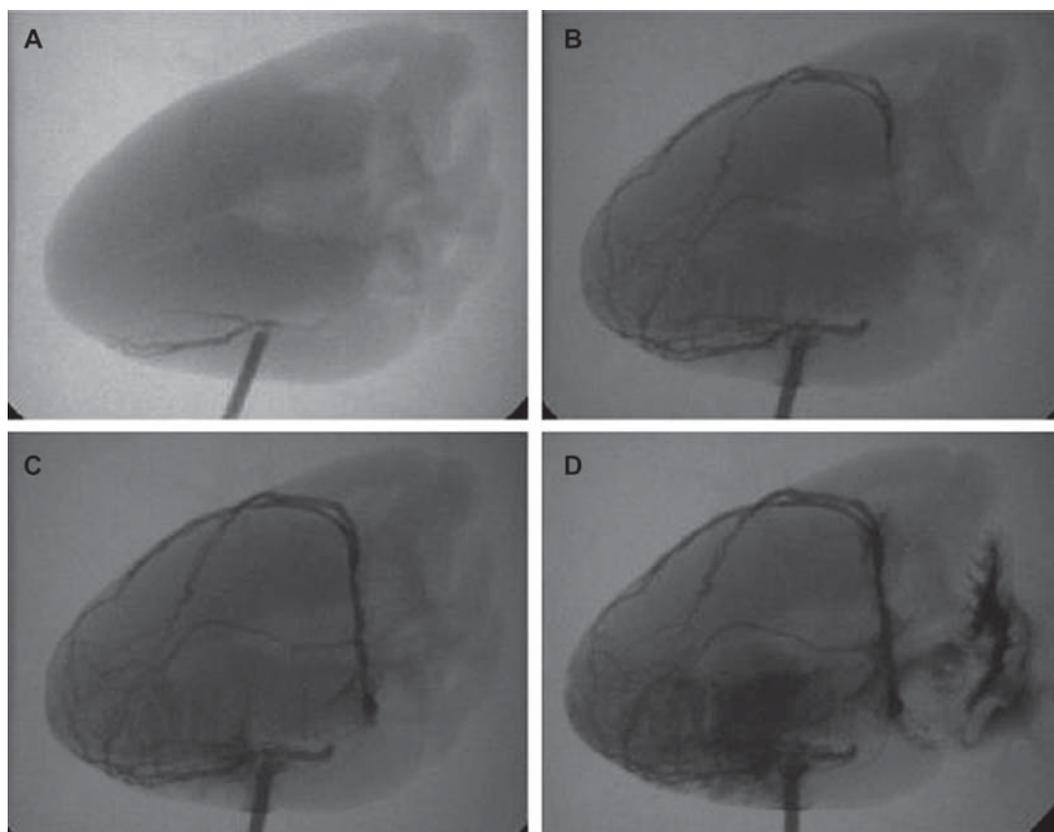


Figure 2. **Blood vessel imaging.** The imaging agent could diffuse into the myocardial tissue through middle cardiac vein, and flow back to right atrium through contralateral coronary vein.

NO/ET, a biochemical maker indicating the degree of endothelial injury [10, 11], was used in this study to assess the effect of SRCVB on endothelial protection. Compared with control group, there were significant increase in plasma levels of NO and decrease in ET in both SRCVB groups, indicating that this revascularization therapy may alleviate myocardial ischemia and endothelial cell injury. It has been demonstrated that both NO and ET are involved in the pathological process of myocardial ischemia [12–14]. The underlined mechanism may be that myocardial ischemia induces endothelial cells to synthesize and release ET, whilst reduce NO level, which breaks the balance of NO/ET [11]. The disbalance leads to further contraction of peripheral vessels, resulting in severer myocardial ischemia and hypoxia.

Fitzgerald et al. [15] found that blood pressure higher than 60 mmHg could lead to harmful changes such as insufficient venous drainage, myocardial edema and intramyocardial hemorrhage. Our results have also demonstrated that higher perfusion pressure induced larger endothelial injury and more significant myocardial tissue edema, rather than more effective perfusion, and effective control of perfusion pressure could significantly attenuate pressure related cardiac injury. Therefore, it is suggested that the perfusion pressure, on the premise that adequate tissue

perfusion is guaranteed, should be maintained as low as possible after SRCVB operation, which may be a decisive factor for the success in SRCVB therapy, although a certain blood pressure is required after coronary arteriovenous anastomosis to ensure the retrograde perfusion.

Despite encouraging results, there are still questions and considerations that need to be further addressed. For instance, only postoperative 4 hours results were investigated in the study, the long-term effects should be further assessed. In addition, the present experiment was performed on the dog model of acute myocardial ischemia, the differences between human and animal hearts has not been taken into account.

In summary, SRCVB may provide effective perfusion for ischemic myocardium, and prevent acute ischemic endothelial cells injury. It is suggested that the mean perfusion pressure should be maintained at low level, at least for the acute period of SRCVB therapy, to avoid high perfusion pressure-induced cardiac injury. Therefore, this study may provide an effective therapeutic strategy for severe CAD.

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