

Heart, Lung and Circulation (2016) xx, 1–7
1443-9506/04/\$36.00
<http://dx.doi.org/10.1016/j.hlc.2016.06.1208>

Efficacy and Safety of Renal Sympathetic Denervation on Dogs with Pressure Overload-Induced Heart Failure

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Received 19 November 2015; received in revised form 15 March 2016; accepted 10 June 2016; online published-ahead-of-print xxx

Background

In dogs with heart failure (HF) induced by overload pressure, the role of renal sympathetic denervation (RSD) on heart failure and in the renal artery is unclear. Therefore, we investigated the efficacy and safety of RSD in dogs with pressure overload-induced heart failure.

Methods

Twenty mongrel dogs were divided into a sham-operated group, an HF group and an HF + RSD group. In the sham-operated group, the abdominal aorta was located but was not constricted, in the HF group, the abdominal aorta was constricted without RSD, and the HF + RSD group underwent RSD with constriction of the abdominal aorta after 10 weeks. Blood sampling assays, echocardiography, intravascular ultrasound (IVUS) measurement and histopathological examination were performed.

Results

Renal sympathetic denervation caused a significant reduction in the levels of noradrenaline (166.62 ± 6.84 vs. 183.48 ± 13.66 pg/ml, $P < 0.05$), plasma renin activity (1.93 ± 0.12 vs. 2.10 ± 0.13 ng/mlh, $P < 0.05$) and B-type natriuretic peptide (71.14 ± 3.86 vs. 83.15 ± 5.73 pg/ml, $P < 0.05$) at eight weeks after RSD in the HF + RSD group. Compared with the HF group at eight weeks, the left ventricular internal dimension at end-diastole and end-systole were lower and the left ventricular ejection fraction was higher (all $P < 0.05$) at eight weeks after RSD in the HF+RSD group. Intravenous ultrasound images showed no changes in the renal artery lumen, and intimal hyperplasia and vascular lumen stenosis were not observed after RSD.

Conclusions

Renal sympathetic denervation could improve cardiac function in dogs with HF induced by pressure overload; RSD had no adverse influence on the renal artery.

Keywords

Heart failure • Renal sympathetic denervation • Pressure overload

Introduction

The sympathetic nerve plays an important role in regulating cardiac function, and afferent renal nerve activation is thought to have central effects on reflexes involving the modulation of

systemic sympathetic activity [1]. Furthermore, renal sympathetic nerve activity significantly increases in rats with chronic heart failure [2]. Thus, the interaction between the renal sympathetic nerve and the heart is thought to be of critical importance to the development of heart failure (HF).

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Recently, renal sympathetic denervation (RSD), a catheter-based strategy for modulating sympathetic nerve activity, was developed for the treatment of refractory and drug-resistant hypertension [3,4], and it may also be effective in some other conditions that are driven by sympathetic overactivity, such as left ventricular hypertrophy [5], heart failure [6] and arrhythmias [7]. The roles of RSD on heart failure were explored in several animal experiments, and the results showed the beneficial effect of RSD on cardiac function improvement [8,9]. However, the model of heart failure that was used in these studies was induced by rapid ventricular pacing or left coronary artery ligation. Differences in pathophysiological mechanisms in variant aetiologies of heart failure could exist. Whether the beneficial effect of RSD will be altered according to different aetiologies of heart failure remains poorly understood.

Abdominal aortic constriction is able to induce pressure overload, resulting in significant left ventricular hypertrophy and heart failure. Considering the effective roles of RSD on left ventricular hypertrophy [5], we hypothesised that RSD can also improve cardiac function in dogs with heart failure induced by abdominal aortic constriction. Moreover, in previous studies, after RSD, the renal artery was examined by angiography, ultrasound or pathology; thus, information regarding the renal artery lumen and intima after RSD was not obtained. Intravascular ultrasound (IVUS) is an efficient way of detecting both the artery lumen and vessel dimensions. Therefore, it can provide more accurate knowledge of the renal artery after RSD. The purpose of this work was to assess the safety and efficacy of RSD in the treatment of dogs with heart failure induced by abdominal aortic constriction.

Materials and Methods

Animals

Twenty healthy adult mongrel dogs, provided by Guangzhou Medical University (Guangzhou, China), of both sexes weighing 19.8 ± 2.9 kg were distributed randomly into three groups: the sham-operated group (n=6), HF group (n=7) and HF+RSD group (n=7). All of the dogs were anaesthetised intraperitoneally with 3% pentobarbital sodium (30 mg/kg), followed by additional maintenance doses of 2 mg/kg when required to maintain a surgical level of anaesthesia. Penicillin (800,000 IU once a day) was administered intramuscularly before and three days after surgical procedures. All animals received standard care. The experimental protocol was approved by the institutional ethics committee of Guangzhou First People's Hospital, and all animal handling was performed in strict accordance with the Guidelines for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Establishment of Heart Failure in Dogs

The dog heart failure model was established by abdominal aortic constriction. Dogs were anaesthetised and placed in a

supine position. Under sterile conditions, the abdominal aorta above the bilateral renal arterial bifurcation was dissected free of surrounding adipose tissues and muscles and was constricted at suprarenal level with 2.0 silk suture tied around both the abdominal aorta and a 6F radial artery sheath. The sheath was promptly removed after constriction, and the arterial diameter was reduced by at least 50% [10,11]. Operative incisions were sutured, and dogs were allowed to recover in their cages. In the sham-operated group dogs, the abdominal aorta was located but was not constricted. Ten weeks following surgery, the dogs were used for studies.

Renal Sympathetic Denervation

After intravenous heparin was administered (60 U/kg) for anticoagulation, bilateral renal angiography was performed using a 6F JR4 Cordis catheter (Cordis Corporation Miami, Florida, USA) to exclude the renal artery abnormalities, including renal artery stenosis and malformations. The dogs in the HF+RSD group underwent a double renal artery ablation with a saline irrigated catheter (Celsius, Johnson & Johnson Inc., Diamond Bar, California, USA). The catheter was introduced into each renal artery via the femoral artery and was applied to the wall of the renal artery; six total ablations were performed both longitudinally and circumferentially from the inside of each main stem of the proximal renal artery. The average impedance was $130 \pm 9.5 \Omega$, and the rate of impedance decrease was approximately 9.4%. Eight watts of radiofrequency energy was applied to the renal artery for two minutes, and the average temperature measured from the electrode was 60°C . The procedure for RSD was similar to the experiment of Henegar JR *et al.* [12]. In the HF group dogs, the ablation catheter was inserted into each renal artery without ablation.

Intravascular Ultrasound

Eight weeks after RSD, the dogs in the HF+RSD group and sham-operated group underwent renal angiography and IVUS. Intravenous ultrasound imaging was performed using Atlantis SR Pro 40-MHz catheters (Boston Scientific, Fremont, California). Imaging was carried out with a motorised pullback at 0.5 mm/s to include the ostial renal artery and the segment that was proximal and distal to the renal artery [13]. Quantitative analysis of the IVUS images was performed by a skilled interpreter using the iLab system (Boston Scientific, Fremont, California, USA).

Echocardiography

Transthoracic Doppler echocardiography was performed in dogs with Vivid 7 (GE Vingmed Ultrasound, Horten, Norway). Images of the long-axis, short-axis and apical four-chamber views were obtained. The left atrial dimension (LAD), left ventricular internal dimension at end-diastole (LVIDd), left ventricular internal dimension at end-systole (LVIDs), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured.

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