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Original Article

Efficacy and safety of catheter-based renal sympathetic denervation in treatment of chronic heart failure

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Abstract: *Background and aim:* Chronic heart failure (CHF) is a disease with a relatively unsatisfactory prognosis. Sympathetic overactivity is an important factor for occurrence and development of heart failure. Catheter-based renal sympathetic denervation (RDN) can specifically remove renal afferent and efferent nerves, thus, reducing function of the sympathetic nervous system. This study aimed to investigate the efficacy and safety of catheter-based RDN in treatment of CHF. *Methods:* Twenty-four CHF patients were randomly divided into a control group (12 cases) and RDN group (12 cases). All patients received anti-heart failure therapy using drugs with maximum tolerated doses. In addition, the RDN group received catheter-based RDN based on medication. After 6 months of treatment, overall treatment efficacy was observed. Cardiac function indexes, heart rate variability indexes, and safety indexes were determined. *Results:* After treatment, overall treatment efficacy in the RDN group was significantly better than in the control group ($P < 0.05$). Left ventricular end-systolic dimension and left ventricular end-diastolic dimension in the RDN group were significantly lower than those in the control group ($P < 0.05$). Plasma N-terminal-pro-B-type natriuretic peptide levels and 6-minute walk distances in the RDN group were significantly higher than those in the control group ($P < 0.05$). In addition, standard deviation of NN intervals, standard deviation of average normal sinus R-R intervals for all 5-min segments, root mean square of successive normal sinus R-R interval difference, and percentage of successive normal sinus R-R interval longer than 50 minutes in RDN group were significantly higher than those in the control group ($P < 0.05$). During and after treatment, there were no obvious complications in the two groups. *Conclusion:* Catheter-based RDN can obviously improve cardiac function and heart rate variability for CHF patients. It is an effective and safe method for the treatment of CHF.

Keywords: Chronic heart failure, renal sympathetic denervation, efficacy, safety

Introduction

Chronic heart failure (CHF) is a complex clinical syndrome, due to a variety of factors, characterized by changes in cardiac structure and function caused by myocardial injury [1]. There are about 100 million people with CHF, worldwide. About 1 million CHF patients are hospitalized for treatment each year and over 3 million CHF patients receive treatment through outpatient services. Incidences of sudden death in heart failure patients are 6-9 times higher than in normal subjects. In the United States, about 300 thousand people die from CHF every year, accounting for about 1/8 of all deaths. Although medication can mitigate symptoms of heart failure, the 5-year survival rate is only 50% [2]. Sympathetic overactivity is an important factor for occurrence and development of heart failure. The activation degree of renal sympathetic nerves is directly related to degree of heart failure and is of great value for prediction of heart failure [3]. In recent years, studies have shown that catheter-based renal sympathetic denervation (RDN) can specifically remove renal afferent and efferent nerves, thus, reducing function of the sympathetic nervous system [4, 5]. Some studies have suggested that RDN can improve cardiac and renal function to a certain extent [6, 7]. In a study on hypertension, RDN was found to effectively reduce blood pressure in patients with refractory hypertension [8]. Our study investigated the efficacy and safety of catheter-based RDN in treatment of CHF. Our objective was to provide a reference for its further clinical application.

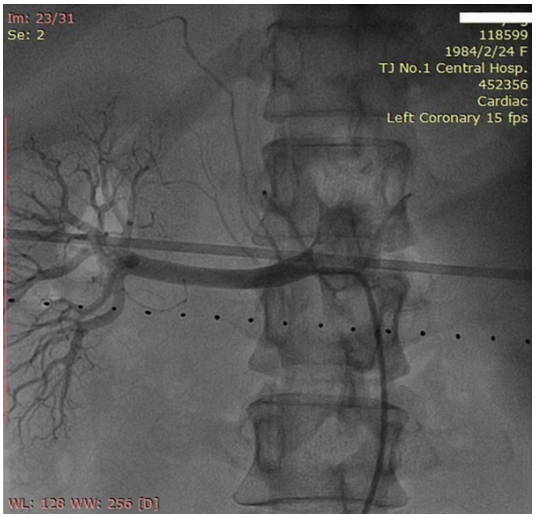

Figure 1. A non-fluoroscopic ruler was attached to the back of patients.

Subjects and methods

Subjects

Twenty-four CHF patients that received treatment in Tianjin First Central Hospital, from June 2015 to August 2016, were enrolled in this study. The age of patients was 48-72 years, with mean age of 54.33 ± 7.26 years. All patients were diagnosed with chronic systolic heart failure. Inclusion criteria were as follows: 1) Age ≥ 18 years; 2) Symptomatic heart failure; 3) New York Heart Association (NYHA) functional classification, III-IV grade; and 4) Left ventricular ejection fraction (LVEF) ≤ 40%; v) baseline systolic pressure > 100 mmHg. Exclusion criteria were as follows: Severe valvular heart disease; estimated glomerular filtration rate < 30 ml/min; anatomic abnormity of renal artery; cerebrovascular event occurrence within 6 months; chronic obstructive pulmonary disease; type 1 diabetes; secondary hypertension; pregnancy; lactation; cardiovascular surgery planned within next 6 months; and refusing follow up. This study was approved by the Ethics Committee of Tianjin First Central Hospital. Written informed consent was obtained from all participants.

Grouping and treatment

Twenty-four CHF patients were randomly divided into an RDN group and control group, with 12 cases in each group. All patients received anti-heart failure therapy using drugs with maximum tolerated doses, including β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, and spironolactone etc. Doses were adjusted according to patient blood pressure, heart rate, and other conditions. In addition, the RDN group received catheter-based RDN on the basis of medication.

RDN

Patients were in the supine position. Intravenous administration of midazolam was performed for anesthesia. The right femoral artery puncture was conducted, followed by bilateral renal arteriograph. After excluding anatomical abnormalities, RDN was conducted. A 6F radiofrequency catheter (Celsius, Biosense Webster Inc., MN, USA) was connected to the radio frequency ablation instrument (EP-SHUTTLE, Biosense Webster Inc., MN, USA). A non-fluoroscopic ruler was attached to the back of the patient (**Figure 1**). The tip of radiofrequency was sent to the distal segment of the renal artery and 4-6 spiral ablation points were made at the upper, lower, anterior, and posterior wall of the renal artery, from far to near. The distance of each two points was more than 5 mm. Ablation power was 8-12 w and ablation time was 2 minutes. During ablation, catheter tip temperature and impedance were monitored. Temperature fluctuation was controlled at 45-60°C and impedance attenuation was controlled at 10%-25%. After ablation was completed at one side of the renal artery, catheter was moved to the other side of the renal artery for ablation. After ablation, the catheter was removed and local compression was performed to stop the bleeding. Renal artery arteriography was performed to observe the presence of complications such as renal artery dissection. Patients were in the supine position for 12 hours. Blood pressure and heart rate changes were closely observed.

Determination of cardiac function and evaluation of curative effect

Before treatment and 6 months after treatment, cardiac function indexes of patients were evaluated. Left ventricular end-systolic dimension (LVESD) and left ventricular end-diastolic dimension (LVEDD) were detected using heart color Doppler ultrasound diagnostic instru-

Table 1. General conditions of patients in the two groups

Parameter	Intervention group	Control group	t/X^2	P
	12	12		
Age (years)	52.33 ± 6.78	50.40 ± 7.29	0.254	0.509
Marital status (n)			1.392	0.499
Divorced	2	1		
Remarried	1	3		
Married	9	8		
Education degree (n)			4.225	0.121
Junior high school and below	3	8		
High school	4	2		
College and above	5	2		
Occupation (n)				
Farmer	5	7	0.667	0.414
Non-farmer	7	5		
Annual income (ten thousand yuan)			1.511	0.219
≥ 5	5	8		
< 5	7	4		
Medical payment way (n)			1.551	0.460
Own expense	7	4		
Cooperative medical service	1	2		
Social insurance or public expense	4	6		

Table 2. Comparison of overall treatment efficacy between the two groups

Group	Remarkably effective (n)	Effective (n)	Ineffective (n)	Total effective rate [n (%)]
Control	0	9	3	9 (75.00)
Intervention	6	5	1	11 (97.62)
X^2		8.143		
P		0.017		

ment. In addition, 6-minute walk distances (6-MWD) were measured. Plasma levels of N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) were determined. Curative effect was evaluated as follows: 1) Remarkably effective: the symptoms and physical signs disappeared; NYHA cardiac function improvement was more than grade 2, and LVEF increase was more than 20%; 2) Effective: symptoms and physical signs were alleviated; NYHA cardiac function improvement was more than grade 1, and LVEF increase was more than 10%; 3) Ineffective: NYHA heart function was not improved and even worsened.

Determination of heart rate variability

Heart rate variability was determined using a 24-h dynamic electrocardiogram instrument. Observation indexes included standard deviation of NN intervals (SDNN), standard deviation of average normal sinus R-R intervals for all 5-min segments (SDANN), root mean square of successive normal sinus R-R interval difference (RMSSD), and percentage of successive normal sinus R-R interval longer than 50 minutes (PNN50).

Statistical analysis

All statistical analysis was carried out using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Enumeration data are presented as number and rate and were compared using X^2 test. Measurement data are presented as mean ± SD and were compared using t-test. $P < 0.05$ was considered as statistically significant.

Results

General conditions of patients in the two groups

General conditions of patients in the two groups are shown in **Table 1**. There were no significant differences in age, marital status, education degree, occupation, annual income, or medical payment way between RDN and control groups ($P > 0.05$).

Comparison of overall treatment efficacy between the two groups

After 6 months of treatment, there were 0, 9 and 3 cases with remarkably effective, effective, and ineffective treatment outcomes in the control group. There were 6, 5 and 1 cases with remarkably effective, effective, and ineffective treatment outcomes in RDN group. There was

Table 3. Comparison of LVESD and LVEDD between the two groups

Group	LVESD (mm)	LVEDD (mm)
Control		
Before treatment	44.23 ± 3.12	70.32 ± 5.33
After treatment	38.03 ± 2.44*	59.37 ± 5.01*
Intervention		
Before treatment	43.22 ± 3.64	69.71 ± 6.55
After treatment	36.81 ± 1.82*,#	53.02 ± 3.92*,#

*P < 0.05 compared with before treatment; #P < 0.05 compared with control group. LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension.

Table 4. Comparison of plasma NT-pro-BNP and 6-MWD between the two groups

Group	NT-pro-BNP (pg/ml)	6-MWD (m)
Control		
Before treatment	2988.56 ± 334.51	284.73 ± 25.37
After treatment	538.29 ± 140.46*	402.12 ± 33.17*
Intervention		
Before treatment	3053.03 ± 382.97	291.29 ± 26.61
After treatment	405.38 ± 114.29*,#	493.46 ± 41.79*,#

*P < 0.05 compared with before treatment; #P < 0.05 compared with control group. NT-pro-BNP, N-terminal-pro-B-type natriuretic peptide; 6-MWD, 6-minute walk distance.

significant difference between the two groups (P < 0.05). Total effective rates in control and RDN groups were 97.62% and 75.00%, respectively (**Table 2**).

Comparison of cardiac function indexes between the two groups

After treatment, LVESD and LVEDD in each group were significantly lower than those before treatment (P < 0.05). Plasma NT-pro-BNP levels and 6-MWD in each group were significantly higher than before treatment (P < 0.05). In addition, after treatment, LVESD and LVEDD in RDN group were significantly lower than in the control group (P < 0.05) and plasma NT-pro-BNP levels and 6-MWD in RDN group were significantly higher than in the control group (P < 0.05, **Tables 3** and **4**).

Comparison of heart rate variability indexes between the two groups

As shown in **Table 5**, after treatment, SDNN, SDANN, RMSSD, and PNN50, in each group, were significantly higher than those before treatment (P < 0.05). In addition, after treatment, each index in RDN group was significantly higher than in control group (P < 0.05).

Comparison of complications between the two groups

During and after treatment, there were no obvious complications including renal artery dissection, oliguria, arrhythmia, hypotension, or syncope in the two groups.

Discussion

Ventricular remodeling after myocardial injury is the pathophysiological mechanism of CHF. It refers to various reactions after myocardial injury or load increase including changes in myocardial cell size, geometry, mass, and function. The scope of ventricular remodeling is related to severity of heart failure. Neurohormonal changes in the ventricular remodeling process include obviously increased activity of the sympathetic nervous system. These are the basis of neuroendocrine antagonizing therapy for CHF [9]. Overactivity of sympathetic nerves plays an important role in occurrence and development of heart failure. With activation of sympathetic nerves, release of norepinephrine is increased. This causes peripheral vasoconstriction, reduced blood flow, and decreased renal water and sodium excretion, thus, promoting the heart failure process [10]. In addition, this can change the cardiac phenotype and induce hypertrophy and fibrosis, leading to cardiac systolic and diastolic dysfunction [11].

RDN can selectively damage renal sympathetic nerve fibers at the renal artery adventitia, thus, reducing renal sympathetic nerve activity inhibiting the overactivity of systemic sympathetic nerves and reducing overflow of norepinephrine. This has become a hotspot in hypertension and other diseases with excessively increased sympathetic activity including heart failure, arrhythmia, sleep apnea syndrome, type 2 diabetes, and end-stage renal disease [12-15]. Recent studies have shown that RDN can lower blood pressure and reduce myocardial hypertrophy, thus, improving heart function

Table 5. Comparison of SDNN, SDANN, RMSSD and PNN50 between the two groups

Group	SDNN (ms)	SDANN (ms)	RMSSD (ms)	PNN50 (%)
Control				
Before treatment	81.45 ± 12.67	33.41 ± 6.28	20.72 ± 3.04	7.72 ± 2.06
After treatment	100.71 ± 18.58*	45.93 ± 8.26*	23.42 ± 4.12*	12.47 ± 3.21*
Intervention				
Before treatment	82.34 ± 11.38	32.67 ± 5.33	21.37 ± 3.16	7.28 ± 3.13
After treatment	123.04 ± 19.02*,#	52.16 ± 7.27*,#	25.21 ± 3.59*,#	15.73 ± 3.86*,#

*P < 0.05 compared with before treatment; #P < 0.05 compared with control group. SDNN, standard deviation of NN intervals; SDANN, standard deviation of the average normal sinus R-R intervals for all 5-min segments; RMSSD, root mean square of the successive normal sinus R-R interval difference; PNN50, percentage of successive normal sinus R-R interval longer than 50 mins.

[16]. Therefore, RDN can provide a new way for treatment of heart failure. The results of our study confirmed that, after 6 months of treatment, overall treatment efficacy in the intervention group was better than control group. In addition, during and after treatment, there were no obvious complications such as renal artery dissection, oliguria, arrhythmia, hypotension, or syncope. This indicates that catheter-based RDN is an effective and safe method in the treatment of CHF.

Kidneys are innervated by extensive sympathetic efferent and afferent nerves [17]. Activation of sympathetic afferent nerves can increase the number of sympathetic pathways, affect vasoactive activity, and cause inappropriate cardiac hypertrophy, myocardial damage, and arrhythmias. Efferent nerves are terminated in various parts of the kidneys and independently affect renal tubular reabsorption of sodium, renin secretion, and renal blood flow. With low-frequency stimulation, reabsorption of sodium is increased. At high-frequency stimulation, renin is released and renal blood flow is decreased. Mild sympathetic nerve activity can increase sodium reabsorption and blood flow. Drastic sympathetic nerve activity can further strengthen sodium reabsorption due to release of angiotensin II (Ang II) and aldosterone [18]. At the same time, blood vessels contract due to the effects of norepinephrine and Ang II on blood vessels. Thus, renal efferent sympathetic activity can increase blood flow and arterial pressure, while reducing renal blood flow. Sustaining or overcompensation can lead to pathophysiological changes such as hypertension and CHF. RDN can inhibit excessive activation of sympathetic nerves in CHF patients, thus, exerting the function of treating CHF and improving prognosis [19].

Recent studies have shown that RND can significantly reduce levels of blood pressure and left ventricular mass index, increase LVEF, and improve ventricular systolic function for patients with refractory hypertension [20]. At present, some scholars have studied the effects of RDN on myocardial remodeling of heart failure. Dai et al. [21] suggested that RDN can significantly reduce serum concentrations of Ang II and aldosterone in canines with heart failure induced by rapid pacing, thus, inhibiting atrial remodeling. Clayton et al. [22] confirmed that RDN can inhibit expression of myocardial Ang II receptors in heart failure rabbits, increase urinary sodium excretion, and reduce plasma BNP levels, improving cardiac function. A study by Hu et al. [23] found that RDN can alleviate myocardial remodeling in rats with myocardial infarction and increase the amount of urine, thus, improving heart function. The results of our study showed that, after treatment, LVESD and LVEDD in the intervention group were significantly lower than control group ($P < 0.05$) and plasma NT-pro-BNP and 6-MWD in the intervention group were significantly higher than control group. These results further confirm the action mechanism of RDN for CHF.

In conclusion, catheter-based RDN can obviously improve cardiac function and heart rate variability for CHF patients. It is an effective and safe method in the treatment of CHF. This study provides a reference for further clinical application of catheter-based RDN. Our study was limited by a relatively small sample size. In future studies, sample sizes should be increased, providing more convincing results. In addition, we did not detect Ang II and aldosterone levels in patients. These are important indexes in the study of heart failure which should be considered in future studies.

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Disclosure of conflict of interest

None.

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