Influence of Renal Sympathetic Denervation in Patients with Early-Stage Heart Failure Versus Late-Stage Heart Failure

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Summary
Renal sympathetic denervation (RDN) is currently being investigated in multiple studies of heart failure (HF). Our aim was to assess the safety and effectiveness of RDN in patients with HF, and determine which patients could achieve more beneficial effects of RDN. A total of 17 consecutive patients with HF were enrolled in the study. Clinical symptoms, office blood pressure, and laboratory results were obtained and echocardiography was performed before and 12 months after RDN. Changes from baseline to 12 months were analyzed for all patients and for two subgroups based on HF duration (group 1: HF duration ≤ 3 years, n = 9; group 2: HF duration > 3 years, n = 8). The RDN procedure was successful in all patients and no procedure-related complications were documented. In comparison to baseline, there was a significant increase in left ventricular ejection fraction (LVEF) in all patients and group 1 (P < 0.05 for both), which did not happen in group 2. LAD, LVDs, and RVD also showed a significant reduction in group 1 (P < 0.05 for both). At 12 months, the reductions in TNF-α and CRP were significant for all patients and for patients in group 1 separately. No obvious changes in echocardiographic parameters, 6-minute walking distance, TNF-α, or CRP were recorded in group 2. No changes in BNP in either group were observed at the 12th month of follow-up. RDN could improve cardiac function and led to a significant drop in inflammatory markers in patients with HF. We also found that patients in early-stage HF could benefit more from RDN.

Key words: RDN, Cardiac function, Inflammatory markers

Heart failure (HF) is a global and growing public health problem because of its high frequency and mortality. Previous research suggests that sympathetic overactivity plays a key role in the development and progression of HF. Many studies have confirmed sympathetic nerve activity is increased in patients with HF. Therapeutic targeting to block excessive sympathetic activation in HF could reduce morbidity and mortality. While numerous types of inhibition of sympathetic activity are being investigated, renal sympathetic denervation (RDN) is an interventional treatment option for patients.

RDN first became known due to its effective reduction of blood pressure (BP) in patients with resistant hypertension without long-term complications. Recently, many clinical studies have verified that RDN is associated with a reduction in excessive sympathetic activity by measuring norepinephrine (NE) spillover, muscle sympathetic nerve activity (MSNA), and 123I-MIBG cardiac scintigraphy. A series of studies have been shown to significantly improve HF outcomes in both HF animal models and patients. Our previous study also showed that RDN can improve heart function, which may be associated with inhibiting cardio-renal fibrogenesis. All these studies have suggested that RDN is feasible, safe, and effective for the treatment of HF.

Despite previous clinical evidence on the benefits of RDN in improving symptoms of HF and cardiac parameters, the lack of clinical eligibility and patient selection for referral remains a major obstacle preventing wide clinical application. The aim of this study was to assess the effectiveness of RDN on cardiac function as reflected by laboratory tests, echocardiographic parameters, and 6-minute walking distance. Accordingly, the study was designed to select patients who could obtain more benefits from RDN.

Methods
Study design: This study was a multicenter, prospective, non-randomized clinical trial to evaluate the effects of RDN in HF patients. Between April 2012 and April 2016, a total of 17 consecutive patients who met all inclusion and exclusion criteria (Table I) underwent RDN. In order to evaluate which patients could benefit more from the procedure, these patients were divided into two groups according to the duration of HF: the early-stage of HF...
diofrequency (RF) ablation applied via an electrode procedure itself involved an endovascular catheter-based performed to localize and assess the renal arteries for abnormalities, Chicago, USA). Medical analyses were performed with SPSS statistical software (Version 17.0, Statistical Package for the Social Sciences, Chicago, USA).

**Results**

**Patient population:** A total of 17 consecutive patients with HF (15 patients had dilated cardiomyopathy, 2 patients had hypertensive cardiomyopathy) underwent RDN. The baseline characteristics of all patients are shown in Table II. The mean age of these patients was 47.6 ± 12.1 years and the majority were male (94.1%). The patients had a high proportion of comorbidities, including diabetes mellitus (29.4%), hypertension (52.9%), and atrial fibrillation (35.3%). Prior to RDN, all patients received routine anti-HF treatment; the most frequently used were angiotensin-converting enzyme inhibitors (ACEI) /
Baseline Characteristics for All Patients and All Patient Subgroups According to HF duration

| Patient characteristics | All Patients (n = 17) | Group 1 (n = 9) | Group 2 (n = 8) | P G1 versus G2 |
|-------------------------|----------------------|----------------|----------------|----------------|
| Age, years              | 47.6 ± 12.1          | 45.0 ± 8.3     | 50.5 ± 15.5    | 0.228          |
| Male sex, n (%)         | 16                   | 9              | 7              | 0.317          |
| BMI, kg/m²              | 26.8 ± 2.5           | 27.1 ± 2.5     | 26.4 ± 2.6     | 0.531          |
| Diabetes mellitus, n    | 5                    | 3              | 2              | 0.317          |
| Hypertension, n         | 9                    | 5              | 4              | 0.317          |
| Atrial fibrillation, n  | 6                    | 2              | 4              | 0.157          |
| NYHA class medication, n| 2.8 ± 0.7            | 2.7 ± 0.7      | 2.9 ± 0.6      | 0.487          |
| ACEI/ARB                | 14                   | 7              | 7              | 1.000          |
| β-Blockers              | 15                   | 8              | 7              | 0.317          |
| Diuretics               | 16                   | 8              | 8              | 1.000          |
| Aldosterone antagonists | 16                   | 8              | 8              | 1.000          |
| Office blood pressure, mm Hg |                |                |                |                |
| Systolic blood pressure baseline | 113.4 ± 10.8 | 113.6 ± 11.5 | 113.3 ± 10.6 | 0.961          |
| Diastolic blood pressure baseline | 73.4 ± 8.5  | 75.4 ± 8.0    | 71.1 ± 8.9    | 0.287          |

Procedural Characteristics

| Ablation characteristics | All Patients (n = 17) | Group 1 (n = 9) | Group 2 (n = 8) |
|-------------------------|----------------------|----------------|----------------|
| Lesions                  |                      |                |                |
| R                       | 8.6 ± 1.7            | 9.0 ± 1.5      | 8.2 ± 1.9      |
| L                       | 8.6 ± 1.4            | 8.7 ± 1.5      | 8.6 ± 1.1      |
| Avg. lesion duration (s) |                      |                |                |
| R                       | 68.7 ± 9.0           | 68.0 ± 8.9     | 71.2 ± 9.8     |
| L                       | 67.3 ± 7.8           | 65.5 ± 4.7     | 71.6 ± 11.4    |
| Avg. temp. (C°)         |                      |                |                |
| R                       | 39.0 ± 1.3           | 39.0 ± 1.2     | 39.1 ± 1.5     |
| L                       | 39.1 ± 1.3           | 39.2 ± 1.1     | 38.8 ± 1.6     |
| Avg. power (W)          |                      |                |                |
| R                       | 9.5 ± 0.7            | 9.7 ± 0.7      | 9.2 ± 0.7**    |
| L                       | 9.6 ± 0.7            | 9.9 ± 0.4*     | 9.1 ± 0.8**    |
| Avg. impedance (Ω)      |                      |                |                |
| R                       | 184.4 ± 32.8         | 192.2 ± 35.5   | 170.4 ± 20.2   |
| L                       | 192.9 ± 31.8         | 197.4 ± 32.4   | 185.1 ± 29.2   |

Echocardiographic Parameters

| All Patients (n = 17) | Group 1 (n = 9) | Group 2 (n = 8) |
|----------------------|----------------|----------------|
| LVEF (%)             | 29.8 ± 6.4     | 35.5 ± 12.0    | 0.013          |
|                      | 31.3 ± 6.8     | 42.0 ± 12.2    | 0.004          |
|                      | 31.1 ± 6.8     | 42.0 ± 12.2    | 0.004          |
|                      | 28.1 ± 5.8     | 28.1 ± 6.5     | 0.980          |
| LAD (mm)             | 49.8 ± 5.8     | 48.0 ± 8.7     | 0.283          |
|                      | 49.2 ± 6.8     | 43.9 ± 6.1     | 0.001          |
|                      | 50.5 ± 4.9     | 52.6 ± 9.3     | 0.468          |
| LVDd (mm)            | 72.2 ± 6.6     | 69.6 ± 9.1     | 0.114          |
|                      | 70.9 ± 6.8     | 65.6 ± 10.1    | 0.075          |
|                      | 73.8 ± 6.5     | 74.1 ± 5.5     | 0.723          |
| LVDs (mm)            | 61.7 ± 7.5     | 57.7 ± 11.2    | 0.051          |
|                      | 59.9 ± 8.2     | 52.1 ± 12.2    | 0.028          |
|                      | 63.8 ± 6.6     | 64.0 ± 5.4     | 0.854          |
| RAD (mm)             | 43.2 ± 6.5     | 42.1 ± 8.0     | 0.479          |
|                      | 41.7 ± 6.3     | 38.4 ± 6.0     | 0.155          |
|                      | 45.0 ± 6.7     | 46.1 ± 8.4     | 0.658          |
| RVD (mm)             | 42.1 ± 7.3     | 39.1 ± 7.9     | 0.139          |
|                      | 43.1 ± 8.8     | 37.7 ± 6.7     | 0.044          |
|                      | 41.0 ± 5.4     | 40.6 ± 9.2     | 0.909          |

LVEF indicates left ventricular ejection fraction; LAD, left atrial diameter; LVDd, left ventricular end diastolic diameter; LVDs, left ventricular end systolic diameter; RAD, right atrial diameter; RVD, right ventricular diameter; and M, months. P means Baseline versus 12 M in each group.

Angiotensin-1 receptor blockers (ARB) (82.4%), beta-blockers (82.2%), and diuretics (94.1%). During the 12-month follow-up period, the dosage of diuretic was reduced in 6 patients because of an improvement of HF symptoms. Four patients switched their medication from metoprolol to carvedilol or sotalol by themselves. Baseline office BP was 113.4 ± 10.8 / 73.4 ± 8.5 mmHg. Nine patients were classified as group 1, with the duration of HF (from first onset of HF symptoms) ≤ 3 years. Accordingly, 8 patients were classified as group 2, with HF duration > 3 years. There was no statistically significant difference in baseline characteristics between group 1 and group 2. Ablation procedural characteristics: The RDN procedure was successful in all 17 patients. A detailed account of the ablation parameters are presented in Table III. These subjects received an average of 8.6 ± 1.7 ablation.
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Figure 1. Effect of RDN on 6-min walk test. The 6-min walk distance was significantly increased by RDN, particularly in early-stage HF patients.

Figure 2. Change from baseline in TNF-α (A) and CRP (B) by RDN. Both TNF-α and CRP were reduced significantly in all patients by RDN, and the reductions were greater in patients at an early stage of HF.

Effect of RDN on cardiac function: The echocardiographic parameters evaluated at baseline and 12-month follow-up are summarized in Table IV. Significant improvements in LVEF were observed in all patients after the RDN procedure (baseline: 29.8 ± 6.4% versus 12-month follow-up: 35.5 ± 12.0%, P = 0.013), while LAD, LVDd, LVDs, RAD, and RVD did not significantly change. The LVEF of group 1 was: baseline, 31.3 ± 6.8% versus follow-up, 42.0 ± 12.2% (P = 0.001) and of group 2: baseline, 28.1 ± 5.8% versus follow-up, 28.1 ± 6.5% (P = 0.980). Also, there were significant differences in LAD, LVDs, and RVD in group 1, while all characteristics of group 2 were similar between baseline and follow-up.

Effect of RDN on TNF-α and CRP: TNF-α and CRP were tested in 11 of 17 patients, 7 of which were in group 1. Both TNF-α and CRP were reduced significantly in all patients by RDN, and were greater in patients at an early stage of HF (Figure 2). At 12-months follow-up, TNF-α was reduced by 365.7 ± 299.6 pg/mL (P = 0.001), 440.8 ± 314.1 pg/mL (P = 0.010), and 234.5 ± 256.7 pg/mL (P = 0.165), and CRP was reduced by 800.9 ± 870.1 ng/mL (P = 0.012), 998.3 ± 1036.6 ng/mL (P = 0.044) and 455.5 ± 552.8 ng/mL (P = 0.082) in all patients, group 1, and group 2, respectively.

Safety of RDN: Office blood pressure did not change between baseline and 12 months for all patients, group 1, and group 2 (all patients: from 113.4 ± 10.8/73.4 ± 8.5 mmHg to 113.2 ± 12.7/74.3 ± 10.9 mmHg, P = NS, group 1: from 113.6 ± 11.5/75.4 ± 8.0 mmHg to 112.2 ± 13.7/73.6 ± 11.6 mmHg, P = NS, group 2: from 113.3 ± 10.6/71.1 ± 8.9 mmHg to 114.4 ± 12.3/75.1 ± 10.8 mmHg, P = NS). No procedural complications were documented in this study, such as renal function injury, renal artery stenosis/dissection, or orthostatic hypotension.

Discussion

The excessive activation of sympathetic nerves is a critical factor in the development and progression of HF. Previous research has shown that beta-blockade, which is
the blocking of excessive sympathetic activation in patients with HF could be beneficial. Different studies have shown that RDN is associated with a reduction in overall sympathetic activity. Davies et al observed that RDN significantly improved the symptoms and exercise capacity in patients with HF without complications. Furthermore, RDN reduced LV mass and increased LVEF in hypertensive patients with cardiomyopathy, independent of lowering BP. In order to determine who would benefit the most from RDN, all patients undergoing RDN were divided into two subgroups according to the concomitant disease (diabetes mellitus, hypertension and atrial fibrillation) or the duration of HF (group 1: HF duration ≤ 3 years; group 2: HF duration > 3 years). Finally, we determined that the duration of HF was an important factor that influences the effect of RDN. However, these outcomes of RDN on HF were unrelated to the concomitant diseases. The effects of RDN on HF patients were independent of hypertension. Our results showed significant improvements in LVEF and the 6-minute walk distance in the 12th month post RDN in comparison to baseline (29.8 ± 6.4% versus 35.5 ± 12.0%, P = 0.013; 410.1 ± 87.7 m versus 464.0 ± 92.9 m, P = 0.001). In addition to classical sympathetic overstimulation, inflammation also plays a key role in the progression of HF. High levels of inflammatory markers such as CRP and TNF-α were reported to be independent risk factors for HF, which were also correlated with cardiac events. Among our study patients, there were dramatic reductions in the concentrations of TNF-α and CRP at 12-months follow-up. Previous research has shown RDN can significantly delay the progression of left ventricular hypertrophy in spontaneously hypertensive rats, which may be associated with decreasing expression of inflammatory factors. The effects of RDN on improvement of cardiac function may be potentially related to reductions of CRP and TNF-α.

In contrast to earlier studies on RDN, we found no significant decrease in BNP at 1 year after the procedure in all patients and two other subgroups, in spite of a downward trend. As previously noted, some studies have examined the role of RDN in cardiac function of heart failure; however, we still lack the ability to accurately predict which patients will respond to RDN. As a result, echocardiographic parameters (LVEF, LAD, LVDs, and RVD) as well as other markers of cardiac function such as 6-minute walk distance and inflammatory markers in group 1 were found to improve more remarkably than in all the patients. Conversely, the results of group 2 showed no dramatic improvement. These results indicate that early RDN is more conducive to improving cardiac function and reducing inflammatory markers.

In early studies, the oversuppression of sympathetic tone could facilitate the progression of cardiac remodeling and accelerate the process of HF. Therefore, lowering sympathetic nerve activity is important for the treatment of advanced HF. Early and timely blockage of excessive sympathetic activity may result in a better therapeutic consequence. Our animal experimentation and current studies showed RDN could reduce sympathetic hyperactivity and improve cardiac function. At the same time, fibrosis is a common pathway to HF. Inflammation can trigger fibrosis. Cardiac fibrosis contributes to both systolic and diastolic dysfunction, which gradually leads to structural heart damage. It was better to slow progression of the inflammatory response (TNF-α and CRP) sooner than later because it was involved in cardiac fibrogenesis. In our previous study showed that RDN can reduce inflammatory markers and inhibit cardio-renal fibrogenesis. In this study, we found that RDN also reduces the inflammatory response. RDN promotes heart function perhaps through the abrogation of inflammatory responses. Sympathetic nerve over-activation and cardiac fibrosis are key factors in the development and progression of HF. As HF progresses, many of the structural changes of LV remodeling may contribute to worsening HF. Therefore, RDN that interferes with excessive activation of the sympathetic nervous system and cardiac fibrosis can improve heart function by stabilizing and/or reversing cardiac remodeling.

In our research, we found that cardiac function improvement and inflammatory marker reduction were dramatic in group 1, while there were almost no changes in group 2. This may be related to the early modulation of sympathetic nervous system (SNS) activation and cardiac fibrosis. The results of this study suggest that the earlier RDN begins in HF patients, the better the outcome, although further randomised, blinded, sham-controlled clinical trials are required to determine the impact of RDN on the early and late stages of heart failure.

**Conclusion**

RDN improved cardiac function and led to a significant drop in inflammatory markers in patients with HF. These effects might be more obvious in early-stage HF. We also observed patients in early-stage HF could benefit more from RDN. Our data are preliminary and need to be validated in a larger population over a longer period of time.

**Limitations**

The present study has several limitations, namely it only included a small number of patients, it was an observational study, and no control group was implemented. All results were based on a pre- and post-RDN. Furthermore, randomized, controlled studies are required to confirm the results of the present study.

**Disclosures**

**Conflicts of interest:** None.

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