Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Silva, J Clin Exp Cardiolog 2016, 7:5
DOI: 10.4172/2155-9880.1000441

Research Article Open Access

Renal Sympathetic Denervation in Mild to Moderate Chronic Kidney Disease Patients with Chronic Heart Failure Refractory to Cardiac Resynchronization Therapy: A Safety Evaluation Study

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Received date: March 19, 2016; **Accepted date:** May 02, 2016; **Published date:** May 12, 2016

Abstract

Background: Heart failure (HF) is a challenging disease to control. Chronic overactivation of the sympathetic nervous system occurs early in HF and chronic kidney disease (CKD). The aim of this study was to evaluate the safety and effects of renal sympathetic denervation (RSD) in reducing lesions on the heart and kidneys in patients with CKD and HF refractory to cardiac resynchronization therapy (CRT).

Methods and results: Twenty-one patients were included and treated with a standard irrigated cardiac ablation catheter. RSD was performed by a unique operator. All the patients included in the study had HF in functional New York Health Association (NYHA) class III, were refractory to CRT, and had mild-to-moderate CKD. Data were obtained at baseline, and at 6 and 12 months of follow-up. RSD was safe and feasible to perform in this population. No changes in blood pressure were observed during this period. At baseline, patients walked 172.4 ± 26.4 m during a 6-minute walk test, increasing to 209.4 ± 29.1 m at 12 months post RSD ($p<0.001$). All echocardiographic parameters evaluated improved at 6 ($p<0.001$) and 12 months ($p<0.001$) after RSD. Estimated glomerular filtration rate improved from 67.4 ± 20.5 mL/min/1.73 m^2 at baseline to 87.8 ± 17.9 mL/min/1.73 m^2 at 12 months post procedure ($p<0.001$). At 12 months after RSD, 42% of patients were in functional NYHA class I, 50% were in functional class II, and 8% remained in functional NYHA class III.

Conclusions: RSD seemed to be safe, feasible, and effective, resulting in an improvement in echocardiographic parameters, 6-minute walk test distance, renal function, and functional NYHA class in mild-to-moderate CKD patients with HF refractory to CRT.

Keywords: Chronic kidney disease; Refractory heart failure; Renal sympathetic denervation; Echocardiographic parameters; Cardiac resynchronization therapy

Introduction

Patients with heart failure (HF) are often refractory to pharmacologic treatment, including a combination of suppressive agents of the renin-angiotensin-aldosterone (RAA) system or after cardiac resynchronization therapy (CRT), remaining symptomatic and in an advanced functional New York Health Association (NYHA) class. They thus contribute to the highest number of hospitalizations and an increased mortality rate. Adequate control of HF and its progression is sometimes a difficult goal to achieve in this patient population, and in most cases, is only resolved after heart transplantation, which in turn is not easily accessible. Recently, Berukstis et al. [1] reported that renal sympathetic denervation (RSD) offers an innovative and safe catheter-based approach for selective reduction of the renal sympathetic drive. They demonstrated that selective denervation of sympathetic nerves in the renal arteries significantly reduced cardiac sympathetic overdrive, as assessed by 123I metaiodobenzylguanidine (MIBG) scintigraphy, thus positively affecting HF progression.

Chronic overactivation of the sympathetic nervous system is a major component of HF [2-4] and chronic kidney disease (CKD), occurring in the early clinical course of the disease [5], and involves both afferent and efferent pathways between the brain and numerous organs [6]. RSD has been shown to be effective in refractory hypertensive CKD patients [7]. Although in principle this intervention could help ameliorate the neurohormonal imbalance in chronic HF [8,9], in practice, there are concerns because patients with HF typically have normal or low blood pressure (BP), and therefore, may present with worse symptoms after RSD because their BP can subsequently fall. The aim of this study was to evaluate the safety and effects of RSD in reducing damage to the heart and kidneys in CKD patients with HF refractory to CRT.

Methods

This prospective, longitudinal study was conducted in 21 patients with refractory HF who underwent percutaneous RSD. The study was approved by the Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. All patients signed written informed consent prior to study inclusion. We evaluated the safety and effectiveness of RSD for improvement of clinical parameters and in reducing damage to the heart, through echocardiographic parameters, and kidneys, by assessing estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR), in patients with HF refractory to CRT.

Study subjects

This study was conducted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil, where patients were recruited from June 2013 through to January 2015 from the Artificial Cardiac Pacing Department. Patients meeting all the following criteria were consecutively enrolled: (i) office systolic BP ≥ 110 mmHg; (ii) aged between 18 and 75 years; (iii) HF due to systolic dysfunction and functional NYHA class III or IV; (iv) carrier of an implantable cardioverter defibrillator with CRT (ICD+CRT) without clinical improvement for at least 1 year of follow-up since implantation, and with biventricular pacing >99%; (v) optimized drug therapy for HF, including the maximum tolerated dose of recommended agents, e.g., beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), and spironolactone [10,11]; (vi) sinus rhythm; (vii) eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, eGFR11>45 mL/min/1.73 m^2 (patients with eGFR>60 mL/min/1.73 m^2 were required to have microalbuminuria); and (viii) able to read, understand and sign the informed consent form.

Patients with any of the following criteria were excluded: (i) pregnancy; (ii) acute HF; (iii) acute coronary syndrome; (iv) valvular disease with significant hemodynamic repercussions; (v) myocardial infarction, unstable angina, stroke or transient ischemic attack within the previous 6 months; (vi) renovascular abnormalities (including severe renal artery stenosis, and renal angioplasty with or without stenting); (vii) psychiatric disease; (viii) allergy to ionic contrast; (ix) unable to be followed clinically after the procedure; (x) known to have drug or alcohol addiction, which can affect the ability to understand or follow medical instructions; (xi) a serious disease, which in the opinion of the investigator, may adversely affect the safety and/or efficacy of the participant or the study (e.g., patients with clinically significant peripheral vascular disease, abdominal aortic aneurysm, diseases that may cause bleeding with thrombocytopenia, hemophilia, or significant anemia).

Transthoracic echocardiography

Transthoracic echocardiography was performed at baseline and at 6 months after RSD using a GE ultrasound system (Vivid I, General Electric, Frankfurt, Germany) equipped with a multi-frequency transducer and tissue Doppler imaging software according to the Guidelines of the American Society of Echocardiography [12]. Data were analyzed and interpreted by one experienced echocardiographer blinded to treatment status, HF stage, and the sequence of the images. Left ventricular (LV) mass was calculated from LV linear dimensions using the Devereux formula [12,13]. LV mass was indexed to body surface area [12,14], as indicated.

Study procedures and assessment

In total, 21 patients (12 men and nine women) with HF in functional NYHA class III with an ICD+CRT implant were treated in this study. All patients underwent a complete medical history and physical examination, and their HF medication was reviewed. BP was measured in the standing, sitting, and supine positions on at least two subsequent visits in both arms. Blood samples were collected to determine a complete blood count, biochemistry (including serum creatinine to estimate GFR), and brain natriuretic peptide (BNP). Urine samples were obtained to determine albuminuria, protein, and creatinine levels. Twenty-four hour ambulatory BP monitoring (ABPM), echocardiogram, 6-minute walk test, and Echo Doppler evaluation of the anatomy of the renal arteries of patients were also assessed.

To evaluate the true effects of RSD on HF and additional measures, baseline medication was unchanged for at least 6 months before RSD and treatment was maintained at follow-up. Patients were instructed not to change their medication and dosages after the procedure unless clinically indicated. For all patients, drug records and adherence were comprehensively reviewed and documented at each visit.

All patients received i.v. sodium bicarbonate (3 mL/kg) and 0.9% saline for 1 h, as prophylaxis for attenuation of iodinated contrast media-associated nephrotoxicity [15,16]. Procedures were performed in the catheterization laboratory with direct visualization using fluoroscopy and radiopaque contrast. In all cases, a three-dimensional mapping system, EnSite Velocity (St. Jude Medical, St. Paul, MN, USA), was also used to visualize the anatomy of the renal arteries and aorta for radiofrequency (RF) application at the selected sites. Under the supervision of an anesthesiologist, patients were pretreated with diazepam or midazolam. Catheterization of the femoral artery by the standard Seldinger technique was performed after subcutaneous injection of the local anesthetic in the inguinal region. A 12-Fr valved sheath was introduced into this artery and unfractionated heparin was administered as an intravenous bolus, targeting an activated coagulation time (ACT) >250 s in the first 10 min. During the procedure, the ACT targeted range was 250–350 s. Subsequently, using an 11-F steerable long sheath (Agilis®, St. Jude Medical, St. Paul, Minnesota, USA) by the standard "over the wire" technique, an angiogram of the aorta and renal arteries was performed, and a 7-Fr standard irrigated cardiac ablation catheter (Therapy™ Cool Path™, St. Jude Medical) was inserted into the renal artery, allowing the delivery of RF energy to the renal artery for innervation (Figure 1). Because the RF application is usually very painful, fentanyl was administered intravenously before the procedure. RF applications were performed within the main stem of the renal arteries, bilaterally, with a series of applications of 8 W power, 60 s duration each, with an irrigation flow rate of 17 mL/min, aiming for >4 RF applications per renal artery, according to their length. These ablated points were made with at least 5 mm distance between them and by moving along the catheter from the distal to the proximal end in a circumferential manner. The number of lesions per artery was chosen based on the artery length measured by baseline angiography. For arteries<20 mm, a minimum of four lesions was applied, and for every increase in length of 5 mm, one additional lesion was applied. After the procedure, the anatomy of the renal arteries was checked by angiography to assess whether any complications had occurred during the procedure. At the end of procedure, patients were given another infusion of sodium bicarbonate (1 mL/kg/h) for 6 h [15,16].

After the procedure, patients remained hospitalized for a period of 24 h in a ward. Follow-up was performed weekly for the first month and monthly from the second to the sixth month. At each visit to the office, ICD+CRT was evaluated, the medication was revised, and BP was measured after standing for 10 min in both upper limbs, and in the sitting and supine positions. There was a pause of 5 min between every change in patient position (standing, sitting, and supine). The mean of four BP measurements was considered for the study. Samples were collected for blood and urine tests to monitor variables and BNP. In addition, 24-hour ABPM, 6-minute walk test, and echocardiogram were performed at 6 and 12 months after RSD. Echo Doppler was also

performed to evaluate the anatomy of the renal arteries of patients at 6 months after RSD. The following variables were monitored during the follow-up period: echocardiographic parameters, systolic and diastolic BP, number and dose of medication, eGFR, albuminuria, BNP, and 6-minute walk test.

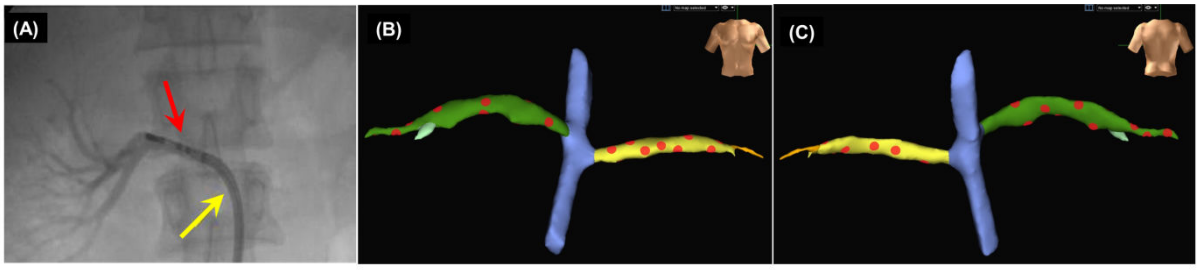

Figure 1: (A) Long steerable sheath (Agilis) anchored within the right renal artery with a steeper turn (yellow arrow); the ablation catheter is placed distally within the right artery with marked pressure at the upper aspect (red arrow). (B) Anatomic reconstruction of renal arteries and abdominal aorta segment with the mapping system (EnSite Velocity®) in antero-posterior projection and (C) in postero-anterior projection. The red marks tag each ablation spot.

Statistical analysis

Results are expressed as the mean and standard deviation (mean ± SD), in the case of normal distribution, or as the median with inter-quartile range. Statistical tests were all two sided. Comparisons between two-paired values were performed by the paired t-test in the case of Gaussian distribution or, alternatively, by the Wilcoxon test. Comparisons between more than two-paired values were performed by ANOVA for repeated measures or with Kruskal–Wallis ANOVA as appropriate, complemented by a post hoc test. Frequencies were compared with x^2 test. P-values<0.05 were considered statistically significant. Correlations between two variables were performed by the Pearson method in the case of Gaussian distribution or, alternatively, with the Spearman correlation test. All statistical analyses was performed using Graphpad Prism version 6.0 (Graphpad software, La Jolla, CA, USA).

N	21
Age (years)	57.2 ± 11.3[a]
Body mass index, kg/m^2	24.7 ± 2.8[a]
Male sex (%)	12 (57%)
Ethnicity (white) (%)	21 (100%)
Cardiomyopathy of non-ischemic etiology (%)	11 (52%)
Type 2 diabetes mellitus (%)	12 (57%)
eGFR, mL/min/1.73 m^2 (CKD-EPI)	67.4 ± 20.5[a]
Functional class (NYHA III)	21 (100%)
LVEF (Simpson),%	28.0 ± 4.5[a]
ICD+CRT	21 (100%)
Office blood pressure, mmHg	126 ± 8/83 ± 3[a]
24-hour ABPM, mmHg	125 ± 7/81 ± 3[a]

ABPM: Ambulatory Blood Pressure Measurements; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimated Glomerular Filtration Rate; ICD +CRT: Implantable Cardioverter-Defibrillator with Cardiac Resynchronization Therapy; LVEF: Left Ventricular Ejection Fraction; N: Number of Patients; NYHA: New York Heart Association. Data are presented as the amean ± SD or number (percentage).

Table 1: General characteristics of patients at baseline.

Results

Baseline patient characteristics

General baseline characteristics of the 21 HF patients are listed in Table 1; all patients were in functional NYHA class III. Mean office systolic/diastolic BP was 126 ± 8/83 ± 3 mmHg. Mean LV ejection fraction (LVEF) was 28.0 ± 4.5%.

Safety evaluation of renal sympathetic denervation in heart failure

No patient was re-admitted for HF symptoms or procedural complications during follow-up. No hypotensive (systolic BP<90 mmHg) [10] or syncopal episodes were reported. Real-time renal artery imaging was performed to assess potential structural changes related to the procedure. Some small focal irregularities of the renal arteries that were present during the procedure (possibly due to minor spasm or edema) were no longer seen postoperatively. At 6 months post-procedure, all patients underwent a Doppler scan of renal arteries and there was no evidence of stenosis or flow limitation.

Post-procedure effects on blood pressure, QRS complex width, brain natriuretic peptide, renal function, and heart failure medications

At 6 and 12 months after RSD, there was a nonsignificant change in office BP and 24-hour ABPM, as shown in Table 2. Effects of RSD on creatinine values, eGFR, albumin:creatinine ratio, BNP and QRS complex width in all patients are also shown in Table 2. Changes in the use of each class of HF medication post-RSD are shown in Table 3.

Variable	Baseline (n=21)	6 months (n=21)	P-value*	12 months (n=12)	P-value**
Office BP, mmHg	126 ± 8/83 ± 3	125 ± 7/82 ± 3	0.654/0.267	123 ± 4/81 ± 3	0.300/0.223
24-hour ABPM, mmHg	125 ± 7/81 ± 3	123 ± 6/80 ± 3	0.483/0.182	122 ± 5/79 ± 3	0.216/0.148
QRS complex, ms	132.7 ± 6.2	132.4 ± 6.3	0.988	132.8 ± 5.4	0.999
BNP, pg/mL	240.1 ± 53.8	204.2 ± 49.8	0.036	195.7 ± 30.8	0.026
Creatinine, mg/dL	1.1 ± 0.2	1.0 ± 0.1	<0.001	0.9 ± 0.1	<0.001
eGFR, mL/min/1.73 m^2	67.4 ± 20.5	75.3 ± 18.3	<0.001	87.8 ± 17.9	<0.001
ACR, mg/g	44.9 (38.4 – 50.2)	26.7 (24.5 – 28.6)	<0.001	21.8 (19.1 – 24.6)	<0.001

ABPM: Ambulatory Blood Pressure Measurement; ACR: Albumin:Creatinine Ratio; BP: Blood Pressure; BNP: Brain Natriuretic Peptide; eGFR: Estimated Glomerular Filtration Rate. Data are presented as the amean ± SD or bmedian (interquartile range). P-value* = baseline vs. 6th month; P-value** = baseline vs. 12th month.

Table 2: Parameters at baseline vs. 6 and 12 months after renal sympathetic denervation.

Patient	Baseline (n=21)	6 months (n=21)	12 months (n=12)
ACE-inhibitor	11 (52)	11 (52)	5 (42)
Angiotensin II receptor blocker	10 (48)	10 (48)	7 (58)
β-blocker	21 (100)	21 (100)	12 (100)
Loop diuretic	21 (100)	21* (100)	7 (58)
Aldosterone antagonist	21 (100)	21 (100)	12 (100)
Digoxin	21 (100)	17 (81)	7 (58)

ACE: Angiotensin-Converting Enzyme. Data are expressed as number (percentage); *Reduction to half the dose in four patients.

Table 3: Medication use by class before, 6, and 12 months after denervation sympathetic denervation.

Changes in exercise parameters

During the 6-minute walk test, patients walked 172.4 ± 26.4 meters at baseline; however, at 6 and 12 months post RSD, the distance walked during 6 minutes was 192.1 ± 24.8 meters (p=0.035) and 209.4 ± 29.1 meters (p<0.001), respectively, as shown in Figure 2A. Individual changes in the 6-minute walk test are depicted in Figure 2B.

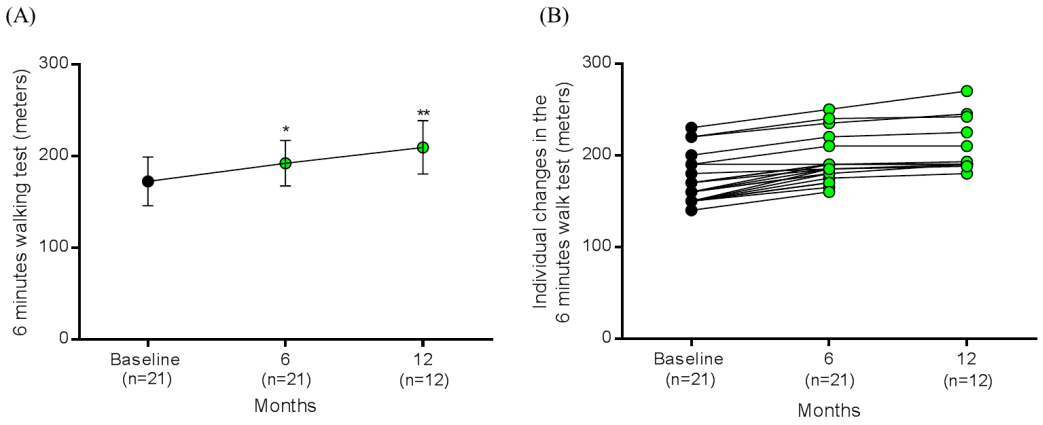

Figure 2: (A) Increase in 6-minute walk test distance over 12 months after renal sympathetic denervation. (B) Individual changes in the 6-minute walk test during the follow-up period post procedure. Values are presented as mean ± SD; *p<0.05; **p<0.001.

Changes in echocardiographic parameters

Table 4 shows the effects of RSD at baseline, 6, and 12 months of follow-up on echocardiographic parameters: LVEF, end diastolic left ventricular diameter (EDLVD), end diastolic left ventricular volume (EDLVV), end systolic left ventricular diameter (ESLVD), end systolic left ventricular volume (ESLVV), left ventricular mass, end diastolic posterior wall thickness (EDPWT), and end diastolic inter ventricular septum thickness (EDIVST). Compared with baseline, all parameters were statistically significantly changed at both 6 and 12 months after RSD (p<0.001).

Variable	Baseline (n=21)	6th month (n=21)	P-value*	12th month (n=12)	P-value**
LVEF (Simpson), %	28.0 ± 4.5	33.9 ± 6.7	<0.001	36.3 ± 6.8	<0.001
EDLVD, mm	67.1 ± 5.3	64.3 ± 5.6	<0.001	63.0 ± 6.1	<0.001
EDLVV, mL	193.7 ± 16.3	178.7 ± 16.4	<0.001	173.4 ± 18.6	<0.001
ESLVD, mm	57.1 ± 4.4	54.6 ± 4.4	<0.001	53.3 ± 5.1	<0.001
ESLVV, mL	161.4 ± 11.8	150.5 ± 12.5	<0.001	142.7 ± 12.0	<0.001
LV mass, g/m^2	215.5 ± 27.4	194.6 ± 26.2	<0.001	180.0 ± 32.3	<0.001
EDPWT, mm	11.5 ± 0.7	10.6 ± 0.8	<0.001	10.3 ± 0.8	<0.001
EDIVST, mm	11.3 ± 0.7	10.4 ± 0.7	<0.001	10.0 ± 0.7	<0.001

EDIVST: End Diastolic Inter Ventricular Septum Thickness; EDLVD: End Diastolic Left Ventricular Diameter; EDLVV: End Diastolic Left Ventricular Volume; EDPWT: End Diastolic Posterior Wall Thickness; ESLVD: End Systolic Left Ventricular Diameter; ESLVV: End Systolic Left Ventricular Volume; LV: Left Ventricular; LVEF: Left Ventricular Ejection Fraction. Data are presented as the mean ± SD; P-value* = baseline vs. 6 months; P-value** = baseline vs. 12 months.

Table 4: Echocardiographic parameters at baseline vs. 6 and 12 months after renal sympathetic denervation.

Changes in functional class of heart failure

At baseline, all the HF patients were in functional NYHA class III; however, 6 months after RSD 19% were in functional class I, 67% were in functional class II, and 14% remained in functional class III. At 12 months post procedure, 42% of the patients were in functional NYHA class I, 50% were in functional class II, and 8% remained in functional class III (Figure 3).

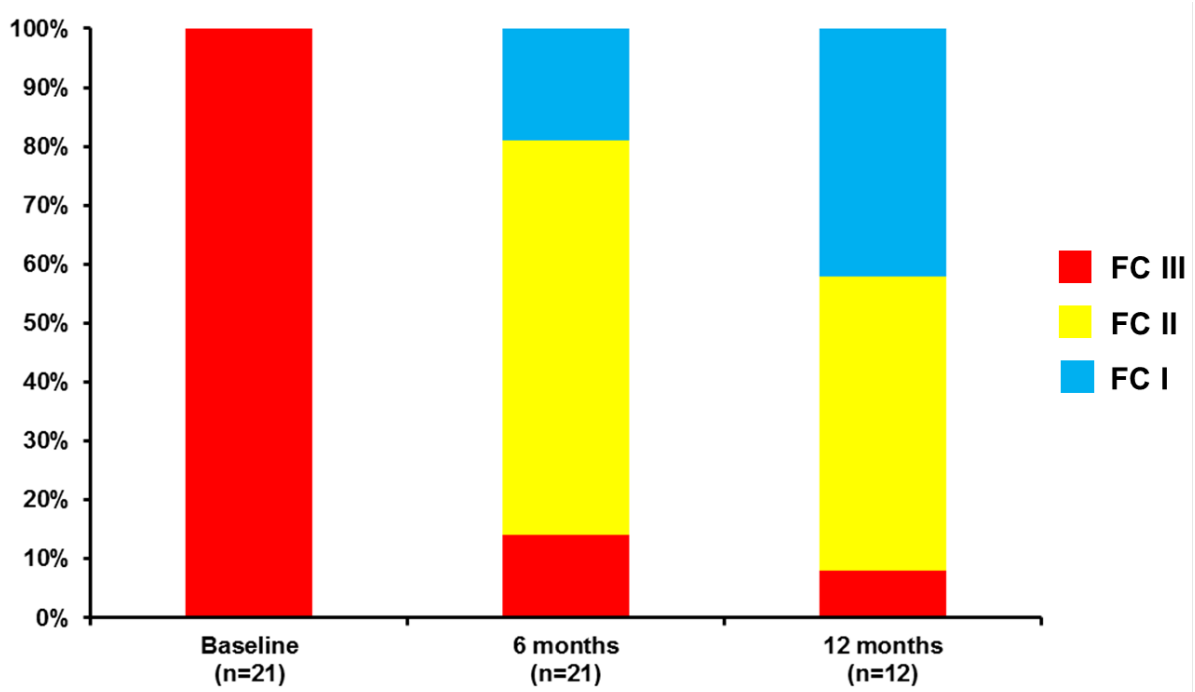

Figure 3: Functional New York Health Association (NYHA) class (FC) of heart failure at baseline, 6, and 12 months after renal sympathetic denervation.

Number of events registered by implantable cardioverter defibrillator

The number of anti-tachycardia pacing (ATP) events and shocks registered by each ICD during follow-up are shown in Table 5.

Event	Baseline (n=21)	6th month (n=21)	P value baseline vs. 6th month	12th month (n=12)	P value baseline vs. 12th month	P value 6th vs. 12th month
ATP	7.3 ± 5.5	1.4 ± 1.3	<0.0001	0.3 ± 0.4	<0.0001	0.6296
Shock	1.5 ± 1.4	0.2 ± 0.4	<0.0001	0	0.0001	0.8331
ATP: Anti-Tachycardia Pacing; ICD: Implantable Cardioverter Defibrillator. Data are presented as the mean ± SD.						

Table 5: Number of anti-tachycardia pacing and shocks registered by ICD during follow-up.

Discussion

Our study results show a reduction from baseline in creatinine levels (0.19 mg/dL), a consequent increase in eGFR (14.4 mL/min/1.73 m^2), and a reduction in ACR (35.0 mg/g) at 12 months after the RSD procedure. These data are in concordance with our findings obtained in a long-term study in hypertensive patients with mild-to-moderate CKD [17]. This improvement in renal function cannot be attributed to the reduction/removal of the diuretic or increasing LVEF, as there was no correlation between these parameters. These results suggest that in mild-to-moderate CKD, an improvement in echocardiographic cardiac parameters occurs, which benefits these patients and reduces the severity of HF. We attribute this improvement in HF as most likely due to reversal of sympathetic hyperactivity resulting in reverse cardiac remodeling, and not due to changes in electrical properties because both ventricles are consistently being paced and resynchronized.

HF is a very common condition in our country, Brazil. CRT (atrium-biventricular pacing) is an alternative therapy for patients with advanced refractory HF. Their pathophysiological basis is reverse remodeling of the left ventricle and its direct implications, such as reduction of mitral regurgitation, improvement in cardiovascular and peripheral autonomic control, in addition to neuro-humoral factors.

When HF is completely refractory to therapy, cardiac assist devices and heart transplantation are needed [10].

Activation of renal nerves in chronic HF can cause a reflex increase in sympathetic tone, leading to a sympathetic hyperactivity state, which contributes to high peripheral vascular resistance, vascular remodeling, as well as remodeling and LV dysfunction [18-21]. Sympathetic hyperactivity is well known to increase cardiovascular risk in CKD patients and the sympathetic hyperactivity in CKD patients appears to be expressed at the initial clinical stage of the disease, showing a direct relationship with the severity of renal impairment [5,22-24]. Interruption of sympathetic hyperactivity and feedback from the RAA system can at least partly be beneficial for this population. Based on these pathophysiological mechanisms, RSD in patients with CKD and chronic HF refractory to optimized treatment may be effective in reducing damage to the heart and kidneys.

In a small study, 'the first performed in humans', in seven normotensive patients with chronic severe HF, 6 months after receiving RSD, the distance walked by patients in their 6-minute walk test increased significantly, and their evaluation of self-wellness was also improved [25]. Recently, Dai and colleagues also reported improvements in symptoms of chronic severe HF after RSD in 10 patients, and no complications were recorded in this study [26]. These data corroborate our findings 12 months after RSD. Compared with baseline, BNP levels were reduced (44.4 pg/mL), 6-minute walk test distance was increased (37.0 m), and the HF functional NYHA class was improved in 92% of the patients. Moreover, no complications occurred, and BP, both office and 24-hour ABPM, remained stable. This is similar to the results described by Davies et al., even in normotensive patients [25]. Although Dai et al. [26] described an improvement in LVEF, we did not expect to see the same because of the severity of HF of our patients, who already had ICD+CRT implanted with biventricular pacing >99%. However, we observed improvements in all echocardiographic parameters evaluated 12-months post RSD. Recently, Berukstis et al. [1] reported that RSD offers an innovative and safe catheter-based approach for selective reduction of renal sympathetic drive, which may explain, in part, our results. Previously, we described improvements in these parameters in 45 patients at 6 months post RSD, but these patients had resistant hypertension, LV hypertrophy and CKD [27].

Study limitations

This study was a safety evaluation and was therefore neither blinded nor powered to assess clinical efficacy. Whilst there was self-reported improvement in symptoms (functional NYHA class), echocardiographic parameters, BNP levels, renal function, and an observed increase in 6-minute walk distance, these findings should be interpreted with caution given the unblinded non-randomized nature of the study. A randomized trial with appropriate blinding of treatment is required to address the potential benefits of RSD in chronic HF refractory to ICD+CRT treatment.

In future studies, neuromuscular sympathetic activity may be measured, which could benefit in assessing the degree of sympathetic block.

The use of echo Doppler to assess damage in the renal arteries is in some way a limitation. However, early complications caused by the RF applications were excluded by angiography performed at the end of the procedure. Any other method, such as computed tomography angiography or a new angiography of the renal arteries, could expose patients to additional undesirable toxic insults. Angiography using CO_2 is not available at our center.

The evaluation of heart rate was compromised in this study, primarily because of the use of maximum dose beta-blockers and digoxin. Hence, the activity of the sinus node was suppressed most of the time by atrial electrical stimulation of the anti-bradycardia function of the ICD+CRT.

In addition, more precise methods for the assessment of GFR, such as cystatin C or iothalamate, should be used in future studies to confirm our findings regarding the effects of RSD upon eGFR, especially considering that only one measurement of serum creatinine was performed at each time point in our study.

Conclusion

Many of the factors reported above can lead to cardiac transplantation and sudden cardiac death in this population, particularly if these patients reach the end stage of renal disease or remain in a stage of HF refractory to optimized medication, even with ICD+CRT. However, these factors appear to be modified by RSD, as reported in the studies discussed above, which leads us to consider this new tool to modify such risk factors, which until now have not been modifiable. Although encouraging, our data are preliminary and need to be validated in a large population and in long-term studies, and then, RSD can become a potential tool for incorporation in clinical practice.

Funding

This study was funded by Pacemed (USD$500,000).

Conflict of Interest

None declared.

Acknowledgements

The authors would like to thank all the participants in this study, and also Pacemed for stimulating the development of this research and for technical support.

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