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Pulmonary vein isolation combined with spironolactone or renal sympathetic denervation in patients with chronic kidney disease, uncontrolled hypertension, paroxysmal atrial fibrillation, and a pacemaker

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Abstract

Background Atrial fibrillation (AF) commonly occurs in chronic kidney disease (CKD), occasioning adverse outcomes. Merging pulmonary vein isolation (PVI) and renal sympathetic denervation (RSD) may decrease the recurrence of AF in subjects with CKD and uncontrolled hypertension. We considered that RSD could reduce the recurrence of AF in patients with CKD by modulating sympathetic hyperactivity. We aimed to evaluate the impact of RSD or spironolactone 50 mg/day associated with PVI in reducing systolic blood pressure (BP), AF recurrence, and AF burden in patients with a history of paroxysmal AF and mild CKD.

Methods This was a single-center, prospective, longitudinal, randomized, double-blind study. The individuals were randomly divided into two groups (PVI + spironolactone, $n = 36$, and PVI + RSD, $n = 33$). All of them were followed for exactly 1 year to assess maintenance of sinus rhythm and to monitor the other variables.

Results Ambulatory BP measurements were reduced in both groups and at the 12th month also differed between groups. Significantly more patients in the PVI + RSD (61%) than in the PVI + spironolactone group (36%) were AF-free at the 12th month of follow-up, $P = 0.0242$. Toward the end of the study, the mean AF burden was lower in the PVI + RSD group as compared to PVI + spironolactone group, at the 9th month: $\Delta = -10\%$ ($P < 0.0001$), and at the 12th month: $\Delta = -12\%$ ($P < 0.0001$), respectively.

Conclusions PVI + RSD is safe and appears to be superior to PVI + spironolactone in BP reduction, augmentation of AF event-free rate, reduction of AF burden, and improvement of renal function.

Keywords Atrial fibrillation · Pulmonary vein isolation · Renal sympathetic denervation · Hypertension · Sympathetic hyperactivity · Chronic kidney disease · Pacemaker

1 Introduction

Atrial fibrillation (AF) affects approximately 2% of the population worldwide, and this percentage will increase in the next 50 years [1, 2]. Progression to end-stage renal disease is a major complication of chronic kidney disease (CKD), and the incidence of AF is associated with a higher risk of developing end-stage renal disease in patients with CKD [3]. The ideal approach for the treatment of AF is rhythm control, but this is sometimes very hard to accomplish [4]. AF ablation therapy can facilitate rhythm control through targeting of the pulmonary veins (PVs) and/or the PV antrum. If the PVs are targeted, complete electrical PVI should be the goal of the procedure. For such procedures, complete isolation of all PVs is currently widely accepted as the best endpoint.

A strategy using percutaneous catheter-based delivery of radiofrequency (RF) energy was recently developed to disrupt the sympathetic innervation of the kidneys. Renal sympathetic denervation (RSD) is proving to be a worthwhile procedure in patients with CKD, improving renal function and reducing blood pressure and sympathetic nerve activity [5–8].

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Pokushalov and colleagues [9] recently reported that RSD diminishes systolic and diastolic blood pressure in drug-resistant hypertensive patients and reduces AF recurrences when combined with pulmonary vein isolation (PVI).

The DENERHTN study confirmed the blood pressure (BP)-lowering efficacy of RSD added to a standardized stepped-care antihypertensive treatment for resistant hypertension. This stepwise antihypertensive regime included spironolactone, showing that its addition to denervation lowers ambulatory BP homogeneously over 24 h in patients with resistant hypertension and suggesting that night-time systolic BP and variability are predictors of the BP response to denervation [10].

The goal of this prospective, randomized, and double-blind study was therefore to evaluate the impact of RSD or spironolactone 50 mg/day associated with PVI in reducing systolic BP, AF recurrence, and AF burden in patients with a history of paroxysmal AF and mild CKD.

2 Methods

This prospective, longitudinal study involved 69 patients with uncontrolled hypertension, a history of symptomatic paroxysmal AF, CKD, and a dual-chamber pacemaker. The study was piloted in agreement with the Helsinki declaration and approved by the ethics committee of our institution. All patients signed the informed consent term before inclusion.

2.1 Study subjects

This study was conducted at the Cardiostim, Rio de Janeiro, Brazil. Patients were recruited from January 2014 until June 2015 from the Arrhythmias and Artificial Cardiac Pacing Office of the same institution. Patients with the combination of the following criteria were consecutively enrolled: (1) uncontrolled hypertension: mean 24-h systolic ambulatory blood pressure measurements (ABPMs) of ≥ 130 mmHg for systolic BP and/or ≥ 80 mmHg for diastolic BP values [11] despite using three or more antihypertensive agents at the maximum recommended or tolerated doses, (2) essential hypertension for >1 year, (3) a physically normal heart with an ejection fraction of > 50% as measured by echocardiography (Simpson's method), (4) a dual-chamber pacemaker implanted due to sinus node disease, (5) symptomatic drug-refractory AF (with a history of failure of two classes of antiarrhythmic drugs) in patients referred for catheter ablation of AF, (6) paroxysmal AF with one monthly episode registered by the pacemaker (paroxysmal AF was defined as AF episodes lasting < 7 days with spontaneous termination), (7) age of 18 to 70 years, (8) estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2 estimated by the Chronic Kidney Disease Epidemiology Collaboration equation [12] (necessarily having microalbuminuria), and (9) the capacity to read, comprehend, and sign the informed consent form and attend the clinical tests.

The patients who presented any of the subsequent criteria were excluded: (1) pregnancy; (2) valvular disease with significant adverse sequelae; (3) unstable angina, myocardial infarction, transient ischemic attack, or stroke within the 6 months before the procedure; (4) renovascular abnormalities; (5) psychiatric disease; (6) allergy to ionic contrast or spironolactone; (7) the inability to be monitored clinically after the procedure; (8) a known addiction to drugs or alcohol that affects the intellect; (9) a serious health condition that, in the investigator opinion's, may adversely affect the safety and/or efficacy of the participant or the study; (10) congestive heart failure presenting functional class II to IV symptoms according to New York Heart Association; (11) a previous AF ablation procedure; or (12) treatment with amiodarone.

The individuals were randomly divided into two groups (PVI + spironolactone 50 mg/day, $n = 36$, and PVI + RSD, $n = 33$). All of them were followed for exactly 1 year to assess maintenance of sinus rhythm and to monitor variations in BP and renal function. This study was double blind, and neither the patient nor the clinician responsible for follow-up of the pacemaker and other parameter assessments was aware of whether RSD had been performed; only the physician operator had this information.

The primary goal of this study was a 30-s recurrence of the arrhythmia and the AF burden recorded by the pacemaker as well as changes in BP. The blanking period (the first 3 months after ablation) was excluded from the analysis [13], and the pacemaker was evaluated at baseline and 3, 6, 9, and 12 months after RSD or spironolactone onset. The secondary endpoints were an evaluation of 24-h ABPM, eGFR, and albuminuria at baseline, 6, and 12 months after the beginning of the study. Additionally, safety was evaluated by a renal arterial duplex scan at baseline and 6 months after RSD or spironolactone onset.

2.2 Programming of pacemakers

The rate-adaptive function was activated in all of the pacemakers and programmed with a lower rate of 60 bpm and an upper rate of 120 bpm. In all of the pacemakers, we programmed the paced atrioventricular interval to 140 to 220 ms and activated the AV delay management algorithm that automatically searches for intrinsic conduction to prevent unnecessary right ventricular pacing in these cases of sinus node disease. The maximum tracking rate was individualized, and the auto mode switching function was activated. Auto mode switching occurred when the atrial rate exceeded 170 to 180 bpm for a specific number of beats or period of time. The atrial tachycardia/AF diagnostic suite provided detailed historical data, allowing us to identify and evaluate therapy for improved management of patients. Atrial sensitivity was programmed to 0.5 mV.

2.3 Pacemaker follow-up

All of them were evaluated at baseline (24 h after PVI or PVI + RSD), 3, 6, 9, and 12 months after PVI to assess the pacemaker records. At each follow-up visit, we obtained a record (stored on a USB stick and then transferred to a computer) of the pacemaker memory data that had accumulated since the previous memory reset. The occurrence and duration of auto mode switching events were recorded. The onset of the first episode of AF was also registered in each patient's data record.

2.4 Anticoagulation protocol

All patients were using dabigatran at 110 or 150 mg twice a day, according to their condition. The patients were considered anticoagulated owing to the profile and mechanism of action of this new anticoagulant.

2.5 Transthoracic echocardiography

The transthoracic echocardiography was performed at baseline and 6 months after RSD using a Vivid I ultrasound system (General Electric, Frankfurt, Germany) equipped with a multifrequency transducer and tissue Doppler imaging software according to the Guidelines of the American Society of Echocardiography [14]. Data were analyzed and interpreted by one experienced echocardiographer who was blinded to the treatment status and imaging sequence. The left ventricular (LV) mass was calculated from the LV linear dimensions using the Devereux formula [14, 15]. The LV mass was indexed to the body surface area [14, 16]. LV hypertrophy was considered present when the LV mass exceeded 115 g/m^2 for men and 95 g/m^2 for women [14]. The left atrium (LA) volume was measured using the disk sum algorithm similar to that used to measure LV volume [17, 18] and indexed according to body surface area. The LA size depends on sex. However, differences in LA size related to sex are generally recognized when fitted to the body surface area [19]. Several indexing methods have been proposed [20, 21], but by indexing, the body surface area produced the most available data and was recommended by the committee. The indexing by body surface area compensates for differences between the sexes in LA size, so only the indexed value should be reported. The recommended value of the higher limit of the LA is 34 ml/m^2. [21–24]

2.6 24-h ABPM

ABPM was performed for 24 h with a clinically validated device (CardioMapa; Cardios, São Paulo, Brazil) before the procedure. The device was set to measure every 15 min during the day period (for 6 to 22 h) and every 30 min during sleep (from 22 to 6 h). Patients were instructed to continue their regular activities during the recording and go to bed no later than 23:00 h. The waking period ranged from 8 to 22 h and the sleep period from midnight to 6:00 h [25]. All individuals were trained to record in a diary the hours during which they were asleep and awake, meals, intake of medications, and symptoms and events that could influence BP during this period. Measurements were transferred to a computer for analysis. Monitoring was repeated as necessary until ≥ 70% of the daytime and nighttime measured values were satisfactory [11]. The mean 24-h ABPM was the parameter evaluated in this study.

2.7 PVI

The AF ablation procedure has been described in detail previously [26]. All patients underwent complete PVI using a three-dimensional mapping system (EnSite Velocity; St. Jude Medical) without additional ablation lesion sets or lines. Patients still in AF at the end of the procedure were converted to sinus rhythm by cardioversion.

2.8 RSD

All the patients received intravenous sodium bicarbonate (3 ml/kg) and 0.9% saline for 1 h as prophylaxis for diminution of iodinated contrast media-associated nephrotoxicity [27, 28]. The patients were pretreated with diazepam or midazolam under the supervision of an anesthesiologist. Catheterization of the femoral artery by the standard Seldinger technique was performed after subcutaneous injection of a local anesthetic in the inguinal site. An 8-Fr valved sheath was placed into this artery, and unfractionated heparin was managed as an intravenous bolus, targeting an activated coagulation time of > 250 s in the first 10 min. During the procedure, the target activated coagulation time ranged from 250 to 350 s. An aortography and selective renal arteriographies were obtained with an EnligHTN™ guide catheter (St. Jude Medical, St. Paul, MN, USA) using the standard "over-the-wire" technique, and the EnligHTN™ multi-electrode renal denervation ablation catheter (St. Jude Medical, St. Paul, MN, USA) was inserted, alternately, inside the left and right renal arteries, respectively, allowing the delivery of RF energy to the renal artery innervation. The RF spots were performed at the main trunk of the bilateral renal arteries with a series of applications at 8-W power, duration of 60 s, and at least eight RF applications per renal artery according to length. After the procedure, the anatomy of the renal arteries was checked by angiography to identify any complications during the procedure. At the end of the procedure, patients were given another infusion of sodium bicarbonate (1 ml/kg/h) for 6 h [27, 28]. The patients remained hospitalized in the ward for 24 h after the procedure.

2.9 Double-blinding procedure

The renal denervation was performed directly after completion of PVI under deep sedation. All patients underwent femoral artery puncture, so they had no way of knowing whether or not they were submitted to RSD. When not submitted to RSD, a pigtail catheter was positioned in the aorta, serving as a reference for performing the transseptal puncture before the PVI. Only the anesthesiologist and the electrophysiologist who performed the procedures knew which patients had undergone PVI or PVI + RSD. All other physicians who accompanied the patients in the office or who performed the complementary examinations and the laboratory tests did not have access to such information. Regarding the patients who were in the RSD group, they did not use spironolactone but rather placebo pills. In addition, the patients had no contact with each other.

2.10 Statistical analysis

The results are expressed as a mean and standard deviation for normally distributed data and as median with interquartile range otherwise. All statistical tests were two-sided. Comparisons between two-paired values were performed with the paired *t* test in cases of a Gaussian distribution and by the Wilcoxon test otherwise. Comparisons between more than two-paired values were made by repeated-measures analysis of variance or by Kruskal–Wallis analysis of variance as appropriate, complemented by a post hoc test. Categorical variables were compared with Fisher's exact test. A P value < 0.05 was considered significant. Correlations between two variables were performed by Pearson's chi-square test in case of a Gaussian distribution and with the Spearman correlation test otherwise. Kaplan–Meier analysis was performed to determine the probability of success, estimated as the percentage of AF event-free rate. Differences in arrhythmia-free survival were assessed with the log-rank test. All statistical analyses were performed using the program GraphPad Prism v 7.0 (GraphPad Software, La Jolla, CA, USA).

3 Results

3.1 Baseline characteristics of patients

The general features of both groups of patients are listed in Table 1.

3.2 Safety evaluation of RSD

No patient developed procedural complications. No hypotensive or syncopal episodes were reported after spironolactone onset or RSD. Real-time renal artery imaging was performed to evaluate eventual structural changes regarding the procedure. Some small foci of irregularities of the renal arteries that

Table 1 General features of the patients

Parameters	PVI + spironolactone 50 mg	PVI + RSD	*P* value
N	36	33	–
Uncontrolled hypertension (%)	36 (100%)	33 (100%)	> 0.9999
Paroxysmal atrial fibrillation (%)	36 (100%)	33 (100%)	> 0.9999
Sinus node disease (%)	36 (100%)	33 (100%)	> 0.9999
Dual-chamber pacemaker (%)	36 (100%)	33 (100%)	> 0.9999
Pacemaker mode AAI ↔ DDD (%)	36 (100%)	33 (100%)	> 0.9999
Atrial pacing (%)	69.7 ± 9.7	66.4 ± 12.3	0.2184
Ventricular pacing (%)	3.5 ± 1.9	4.2 ± 2.1	0.1793
Age, years	58.4 ± 5.1	56.8 ± 6.5	0.2679
Body mass index (kg/m^2)	26.4 ± 1.8	27.1 ± 1.9	0.1046
Male gender (%)	30 (83%)	25 (76%)	0.5526
White ethnicity (%)	25 (69%)	20 (61%)	0.4610
Coronary artery disease (%)	9 (25%)	5 (15%)	0.3776
Type 2 diabetes mellitus (%)	10 (28%)	8 (24%)	0.7893
Echocardiographic parameters			
Left ventricular ejection fraction (%)	61.2 ± 5.7	62.2 ± 7.2	0.4920
Indexed left atrial volume (ml/m^2)	34.6 ± 6.8	36.6 ± 7.4	0.2272
Antihypertensive			
ACE inhibitor/ARB (%)	36 (100%)	33 (100%)	> 0.9999
Diuretic (%)	36 (100%)	33 (100%)	> 0.9999
DHP Ca^{++} channel blocker (%)	36 (100%)	33 (100%)	> 0.9999
β blocker (%)	25 (69%)	18 (55%)	0.2240
Number of antihypertensives	3.7 ± 0.4	3.5 ± 0.5	0.2077

Values are presented as mean ± SD or *n* (%)

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *DHP* dihydropyridine, *PVI* pulmonary vein isolation, *RSD* renal sympathetic denervation

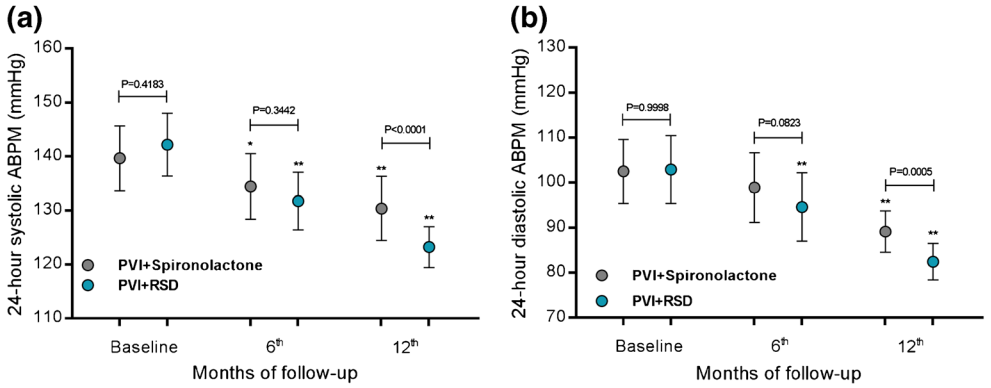

Fig. 1 **a** In the PVI + spironolactone group ($n = 36$), significant changes were observed on the mean 24-h systolic ABPM from baseline to 6 and 12 months. The same effect was observed in the PVI + RSD group ($n = 33$) regarding the mean 24-h systolic ABPM from baseline to 6 and 12 months. **b** About the mean 24-h diastolic ABPM in the PVI + spironolactone group, the change was only noted from baseline to 12 months. However, in the PVI + RSD group, a different effect was noted in the mean 24-h diastolic ABPM from baseline to 6 and 12 months. *$P < 0.05$ and **$P < 0.0001$ for values at 6th and 12th months versus baseline values. ABPM, ambulatory blood pressure measurement; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation

were existent during the procedure (maybe because of edema or minor spasm) were no longer observed postoperatively. Six months after the procedure, all patients underwent a Doppler scan of the renal arteries and showed no evidence of stenosis or flow limitation.

3.3 Effects on blood pressure

In the PVI + spironolactone group, significant changes were observed in the mean 24-h systolic ABPM. The baseline of 140 ± 6 mmHg decreased to 135 ± 6 ($P = 0.0013$) and 130 ± 6 ($P < 0.0001$) mmHg at 6 and 12 months, respectively. The same effect was observed in the PVI + RSD group regarding the mean 24-h systolic ABPM. The baseline of 142 ± 6 mmHg decreased to 132 ± 5 ($P < 0.0001$) and 123 ± 4 ($P < 0.0001$) mmHg at 6 and 12 months, respectively. Comparisons between groups at the same time point just showed a difference at the 12th month ($\Delta = 7$ mmHg, $P < 0.0001$), as shown in Fig. 1a. Regarding the mean 24-h diastolic ABPM in the PVI + spironolactone group, the baseline of 103 ± 7 mmHg decreased to 99 ± 8 ($P = 0.1916$) and 89 ± 5 ($P < 0.0001$) mmHg at 6 and 12 months, respectively. However, in the PVI + RSD group, a more substantial effect was noted in the mean 24-h diastolic ABPM from baseline, 103 ± 8 mmHg to 6 and 12 months, and 95 ± 8 ($P < 0.0001$) and 82 ± 4 ($P < 0.0001$) mmHg, respectively. Comparisons between groups at the same time point just showed a difference at the 12th month ($\Delta = 6$ mmHg, $P = 0.0005$), as displayed in Fig. 1b.

3.4 Effects on renal function

The effects of PVI + spironolactone or PVI + RSD on the creatinine concentration, eGFR, and albumin/creatinine ratio during the 12-month follow-up are meticulously demonstrated in Table 2.

3.5 Monitoring of AF by pacemaker records

At the 12-month follow-up evaluation, only 13 (36%) of the 36 patients in the PVI + spironolactone group were AF event-

Table 2 Renal function at baseline and during follow-up

Parameters	Baseline	6th month	12th month
Pulmonary vein isolation + spironolactone 50 mg ($n = 36$)			
Creatinine (mg/dl)	1.13 ± 0.11	1.16 ± 0.12†	1.19 ± 0.13†
eGFR (ml/min/1.73 m^2)	66.7 ± 7.7	66.4 ± 8.6†	64.8 ± 9.9†
Albumin/creatinine ratio (mg/g)	69.9 ± 23.6	70.6 ± 24.7	76.4 ± 25.0†
Pulmonary vein isolation + renal sympathetic denervation ($n = 33$)			
Creatinine (mg/dl)	1.11 ± 0.12	1.03 ± 0.12*	0.97 ± 0.09**
eGFR (ml/min/1.73 m^2)	69.2 ± 6.7	76.2 ± 7.2*	81.8 ± 6.8**
Albumin/creatinine ratio (mg/g)	75.0 ± 23.4	62.1 ± 21.3	39.5 ± 15.5**

Values are presented as mean ± SD

eGFR estimated glomerular filtration rate

* $P < 0.05$ and ** $P < 0.0001$ for values at 6th and 12th months of follow-up vs. baseline values; † $P < 0.0001$ for comparison between values into different groups at the same time point

free. However, 20 (61%) of the 33 patients in the PVI + RSD group were AF event-free on no antiarrhythmic drugs ($P = 0.0242$) by log-rank test, as shown in Fig. 2. In the PVI + spironolactone group, some augmentations were observed in the mean AF burden from the third month, 3.4 ± 1.0% to 6, 9, and 12 months, 6.7 ± 3.7 ($P = 0.8930$), 14.5 ± 5.2 ($P < 0.0001$), and 19.4 ± 6.6% ($P < 0.0001$), respectively. However, in the PVI + RSD group, no changes were noted in the mean AF burden from the third month, 3.8 ± 0.6% to 6, 9, and 12 months, 6.1 ± 3.4 ($P = 0.9985$), 4.9 ± 2.0 ($P > 0.9999$), and 7.4 ± 3.6% ($P = 0.9667$), respectively. Toward the end of the study, the mean AF burden was lower in the PVI + RSD group as compared to the PVI + spironolactone group; at the 9th month: Δ = − 10% ($P < 0.0001$), and at the 12th month: Δ = − 12% ($P < 0.0001$), as demonstrated in Fig. 3.

3.6 Correlation

3.6.1 AF burden and Δ mean 24-h systolic ABPM

In the PVI + spironolactone group, there was no association between the degree of mean systolic BP reduction and mean AF burden at the 12th month: $r = 0.0231$ (95% CI = − 0.3929 to 0.4312), $P = 0.9168$. However, in the PVI + RSD group, there was a strong negative association between the degree of mean systolic BP reduction and mean AF burden at the 12th month: $r = -0.7426$ (95% CI = − 0.9180 to − 0.3243), $P = 0.0036$.

3.6.2 PVI + RSD group: AF burden, Δ mean 24-h systolic ABPM, and number of ablated spots

The significant correlations between these three parameters are demonstrated in Table 3.

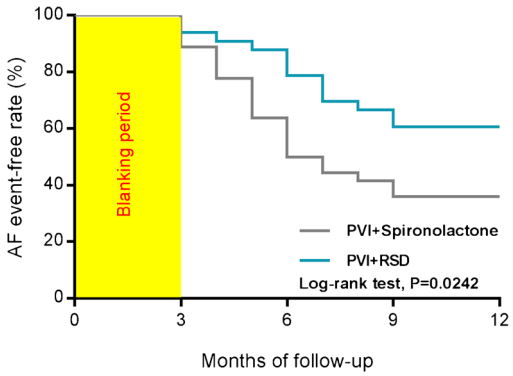

Fig. 2 At the 12-month follow-up evaluation, only 13 (36%) of the 36 patients in the PVI + spironolactone group (gray line) had been AF event-free. However, 20 (61%) of the 33 patients in the PVI + RSD group (blue line) were AF event-free on no antiarrhythmic drugs ($P = 0.0242$) by log-rank test. AF, atrial fibrillation; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation

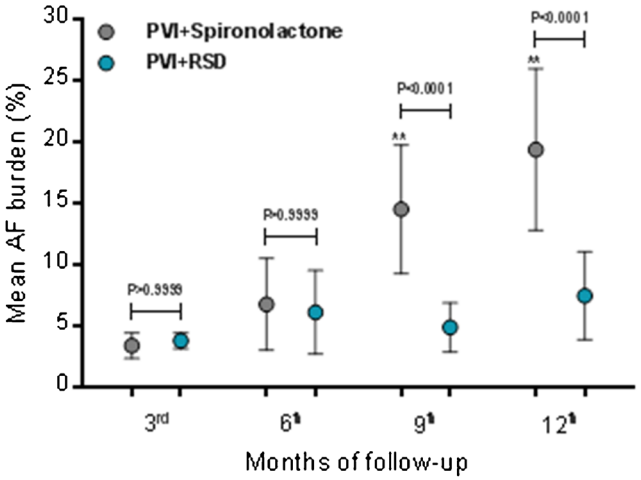

Fig. 3 In the PVI + spironolactone group ($n = 36$), some augmentations were observed on the mean AF burden from the 3rd month to 9 and 12 months. However, in the PVI + RSD group ($n = 33$), no changes were noted on the mean AF burden from the third month to the rest of the follow-up period. $^{**}P < 0.0001$ for values at 9th and 12th months versus 3rd-month values. AF, atrial fibrillation; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation

4 Discussion

We chose patients with pacemakers because they are more compliant when undergoing pacemaker evaluation and clinical monitoring. Furthermore, detection of AF is more reliable because the heart rhythm is continuously monitored. Of the baseline characteristics of patients undergoing PVI + spironolactone versus PVI + RSD, none of them was significantly different. Our main results show that PVI + RSD is safe and appears to be superior to PVI + spironolactone in BP reduction, augmentation of AF event-free rate, reduction of AF burden, and improvement of renal function.

In CKD, sympathetic overactivity is expressed at the earliest clinical phase of this condition, being directly related to the severity of the renal failure [29–32]. In both hypertension and renal failure, the mechanisms of the hyperadrenergic state are manifold and include reflex and neurohumoral pathways [32–34]. The adrenergic activation has an adverse impact on cardiovascular morbidity and, in the case of renal failure, also on cardiovascular mortality [32–35]. The interruption of this vicious feedback cycle, by reducing sympathetic overactivity and the feedback loop of the renin–angiotensin–aldosterone system [36], may at least in part account for our findings regarding eGFR improvement and albuminuria reduction after RSD, findings that are even lower than previously reported results [6]. Several previous studies have demonstrated that the autonomic nervous system (ANS) is a key sponsor to AF deployment and advancement. High ANS activity is involved in both initiating and maintaining AF [37–41]. Consequently, central sympathetic inhibition by RSD [42–44] might be the major tool of benefit for AF cessation. Uncontrolled hypertension brings cardiac structural modifications leading to

Table 3 Correlations for PVI + RSD group at the 12th month of follow-up

Parameters	Correlation	*r* value	95% CI	*P* value
(A) Total number of ablated spots	A vs. B	− 0.9419	− 0.9712 to − 0.8846	< 0.0001
(B) Δ 24-h systolic ABPM (mmHg)	A vs. C	− 0.6744	− 0.8264 to − 0.4309	< 0.0001
(C) AF burden (%)	B vs. C	0.7759	0.5896 to 0.8838	< 0.0001

Values are presented after Pearson correlation. $N = 33$

ABPM ambulatory blood pressure measurement, *AF* atrial fibrillation, *CI* confidence interval, *PVI* pulmonary vein isolation, *r* coefficient of correlation, *RSD* renal sympathetic denervation

impairment of LV diastolic function, which can be in theory linked with a growing risk of AF [45]. The AF events sustain the high BP levels, forming a pathological feedback loop in which hypertension leads to AF and AF causes hypertension. Renal denervation provokes a fall in arterial BP and consequently reverses LV and LA remodeling [41]. More recently, Romanov and colleagues reported that RSD, when added to PVI, reduces AF recurrences, AF burden, and mean BP. The decrease of mean BP is associated with both AF burden and recurrences [46]. Pokushalov and colleagues also demonstrated that RSD had a positive influence on AF recurrences in a blend of hypertensive subjects with refractory AF who also underwent PVI [9], having more benefit in those with severe drug-resistant hypertension and those with persistent AF.

We believe that BP decreases post-RSD result in a considerably reduced rate of AF evolution when matched with PVI alone. Thus, reduction of BP with ablation of afferent kidney nerve input, hypothetically, can decrease central sympathetic output and may trigger the cascade effects that positively control the arrhythmia recurrences and advancement. This observation does not eliminate a decrease of ANS activity as the major driver of these beneficial reactions, however, proposes that the decline in AF recurrence is powerfully connected with improved BP control, either directly or indirectly. Due to sympathetic hyperactivity inherent to CKD, we believe that AF recurred more readily in patients in the PVI + spironolactone group. Nonetheless, AF recurred in 29% of subjects in the PVI + RSD group, suggesting that RSD can at least suppress sympathetic overactivity and consequently suppress arrhythmogenic foci triggered by this.

4.1 Study limitations

Although our data show a contribution of RSD to diminishing paroxysmal AF recurrence in patients with uncontrolled hypertension and CKD, our patient cohort was small. This relatively small sample can be seen as a limitation. The presence of AF introduces a problem in LV ejection fraction measurement because of tachycardia and beat-to-beat (i.e., R-to-R) LV filling variability. Because we did not use a three-dimensional single-beat ultrasound system, this should be considered a limitation.

The use of Doppler echocardiography to assess damage in the renal arteries can also be seen as a restriction. However, early complications due to the RF applications were excluded by angiography performed at the end of the procedure. Any other method, such as magnetic resonance angiography, computed tomographic angiography, or a new angiography of the renal arteries, could expose patients to extra undesirable toxic insults. Carbon dioxide angiography is not available in our service.

More precise methods of eGFR assessment, such as cystatin C or iothalamate measurement, should be used in future studies to endorse our findings concerning the effects of RSD on the eGFR, especially considering that only one serum creatinine measurement was performed at each time point of the study. Neuromuscular sympathetic activity can also be measured, which would contribute greatly to the assessment of the degree of sympathetic blockade.

5 Conclusions

PVI + RSD is safe and appears to be superior to PVI + spironolactone in BP reduction, augmentation of AF event-free rate, reduction of AF burden, and improvement of renal function. Although encouraging, our data are preliminary and need long-term validation in a large population.

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Procedures: M.G.K.
Acquisition of data: T.K.
Analysis and interpretation of the data: S.C. and M.G.K.
Statistical analysis: M.G.K.
Obtaining funding: M.G.K.
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Compliance with ethical standards

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Abbreviations ABPM, ambulatory blood pressure measurements; AF, atrial fibrillation; ANS, autonomic nervous system; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; PVs, pulmonary veins; RF, radiofrequency; RSD, renal sympathetic denervation

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