Kidney Research and Clinical Practice

KIDNEY RESEARCH
AND
CLINICAL PRACTICE

Original Article

Pulmonary vein isolation alone and combined with renal sympathetic denervation in chronic kidney disease patients with refractory atrial fibrillation

Márcio G. Kiuchi [1,2,*], Shaojie Chen [3], Gustavo R. e Silva [1], Luis M.R. Paz [1], Tetsuaki Kiuchi [1], Ary G. de Paula Filho [1], Gladyston L.L. Souto [1]

[1] Division of Cardiac Surgery and Artificial Cardiac Stimulation, Department of Medicine, Hospital e Clínica São Gonçalo, São Gonçalo, Rio de Janeiro, Brazil
[2] Electrophysiology Division, Department of Cardiology, Hospital e Clínica São Gonçalo, São Gonçalo, Rio de Janeiro, Brazil
[3] Department of Cardiology, Shanghai First People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

ABSTRACT

Background: Atrial fibrillation (AF) commonly occurs in association with chronic kidney disease (CKD), resulting in adverse outcomes. Combining pulmonary vein isolation (PVI) and renal sympathetic denervation (RSD) may reduce the recurrence of AF in patients with CKD and hypertension. We considered that RSD could reduce the recurrence of AF in patients with CKD by modulating sympathetic hyperactivity. Our goal was to compare the impact of PVI + RSD with that of PVI alone in patients with concurrent AF and CKD.

Methods: This was a single-center, prospective, longitudinal, randomized, double-blind study. Forty-five patients with controlled hypertension, symptomatic paroxysmal AF and/or persistent AF, stage 2 or 3 CKD, and a dual-chamber pacemaker were enrolled from January 2014 to January 2015. We assessed the 30-second recurrence of AF recorded by the pacemaker, 24-hour ambulatory blood pressure measurements, estimated glomerular filtration rate, albuminuria, echocardiographic parameters, and safety of RSD.

Results: No patient developed procedural or other complications. The ambulatory blood pressure measurements did not differ within the PVI + RSD group or between the PVI + RSD and PVI groups throughout the study. Significantly more patients in the PVI + RSD group than in the PVI group were free of AF at the 12-month follow-up evaluation. The PVI group had an unacceptable response to ablation with respect to changes in echocardiographic parameters, whereas these parameters improved in the PVI + RSD group.

Conclusion: PVI + RSD were associated with a lower AF recurrence rate than PVI alone; it also improved renal function and some echocardiographic parameters. These encouraging data will serve as baseline information for further long-term studies on larger patient populations.

* Corresponding author. Division of Cardiac Surgery and Artificial Cardiac Stimulation, Department of Medicine, Hospital e Clínica São Gonçalo, Rua Cel. Moreira César, 138 — Centro, São Gonçalo, Rio de Janeiro, 24440-400, Brazil.
E-mail address: marciokiuchi@gmail.com (MG Kiuchi).

Introduction

Atrial fibrillation (AF) affects approximately 2% of the population worldwide, and this percentage will increase in the next 50 years [1,2]. Progression of 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 the 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]. Pokushalov et al [5] recently reported that renal sympathetic denervation (RSD) diminishes systolic and diastolic blood pressure (BP) in drug-resistant hypertensive patients and reduces AF recurrences when combined with pulmonary vein isolation (PVI). Targeting of the pulmonary veins (PVs) and/or the PV antrum is the cornerstone for most AF ablation procedures. 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 end point. A strategy using percutaneous catheter-based delivery of radiofrequency (RF) energy was recently settled to interject the sympathetic innervation of the kidneys. This new procedure exposed no severe vascular or renal complications in the long term (up to 36 months). RSD is proving to be a worthwhile procedure in patients with CKD at different stages, improving the renal function, reducing the BP, the left ventricular (LV) mass and also the sympathetic nerve activity [6—9]. Our group believes that RSD can reduce AF recurrence in patients with CKD by modulation of the sympathetic hyperactivity present in this disease. The goal of this prospective, randomized, and double-blind study was to evaluate the impact of RSD associated with PVI in patients with a history of AF and mild-to-moderate CKD.

Methods

This prospective longitudinal study involved 45 patients with controlled hypertension, a history of symptomatic paroxysmal AF (PAF) ($n = 27$) and/or persistent AF (PersAF) ($n = 18$), stage 2 or 3 CKD, and a dual-chamber pacemaker. The study was performed in agreement with the Declaration of Helsinki and approved by the ethics committee of our institution. All patients signed the informed consent terms before inclusion.

Study subjects

This study was conducted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil. Patients were recruited from January 2014 till January 2015 from the Arrhythmias and Artificial Cardiac Pacing Service of the same hospital. Patients with the combination of the following criteria were consecutively enrolled: (1) mean 24-hour systolic ambulatory BP measurements (ABPM) of ≥ 100 and < 130 mmHg; (2) essential hypertension for > 1 year (Hypertension was defined as office BP values ≥ 140 mmHg systolic BP and/or ≥ 90 mmHg diastolic BP, based on the evidence from randomized controlled trials that in patients with these BP values, treatment-induced BP reductions are beneficial or as mean 24-hour ABPM ≥ 130 mmHg for systolic BP and/or ≥ 80 mmHg for diastolic BP values [10]); (3) a physically normal heart with an ejection fraction of $> 50\%$ as measured by echocardiography (Simpson method); (4) a dual-chamber pacemaker; (5) symptomatic drug-refractory AF (with a history of failure of 2 classes of antiarrhythmic drugs) in patients referred for catheter ablation of AF; (6) PAF with 1 monthly episode or PersAF in patients who had already undergone 3 electrical cardioversions as registered by the pacemaker (PAF was defined as AF episodes lasting < 7 days with spontaneous termination, and PersAF was defined as AF lasting > 7 days before termination either pharmacologically or by electrical cardioversion); (7) age of 18—80 years; (8) estimated glomerular filtration rate (eGFR) of 30—89 mL/min/1.73 m^2 estimated by the Chronic Kidney Disease Epidemiology Collaboration equation [11] (patients presenting with eGFR > 60 mL/min/1.73 m^2 were considered to have microalbuminuria); and (9) the capacity to read, comprehend, and sign the informed consent form and attend the clinical tests.

The patients who met any of the following 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 medium; (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's opinion, may adversely affect the safety and/or efficacy of the participant or the study (e.g., abdominal aortic aneurysm, clinically significant peripheral vascular disease, diseases that may cause bleeding due to thrombocytopenia, hemophilia, or significant anemia); (10) congestive heart failure presenting functional class II—IV symptoms according to New York Heart Association; (11) a transverse left atrial diameter (LAD) > 50 mm on transthoracic echocardiography; (12) a previous AF ablation procedure; or (13) treatment with amiodarone.

The patients were randomly divided into 2 groups (PVI, $n = 24$, and PVI + RSD, $n = 21$). 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 end point of this study was a 30-second recurrence of AF recorded by the pacemaker. The blanking period (the first 3 months after ablation) was excluded from the analysis [12], and the pacemaker was evaluated at baseline and 3, 6, and 12 months after RSD. The secondary end points were an evaluation of 24-hour ABPM, eGFR, and albuminuria at baseline and 3, 6, and 12 months after the procedure. In addition, echocardiographic parameters and safety were evaluated by a renal arterial duplex scan at baseline and 12 months after RSD.

Implantation and programming of pacemakers

As a routine practice in our department, bipolar leads were implanted in the appendage of the right atrium and in the high septal region of the right ventricle. Dual chamber pacemakers (St. Jude Medical, St. Paul, MN, USA) were used. 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 140−220 ms and activated the atrioventricular delay management algorithm that automatically searches for intrinsic conduction to prevent unnecessary right ventricular pacing in the case 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 170−180 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.

Pacemaker follow-up

Patients were evaluated weekly after PVI or PVI + RSD to assess the pacemaker records. All of them were evaluated at 3, 6, and 12 months thereafter. 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 resetting of the memory. 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.

Anticoagulation protocol

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

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 agreeing the guidelines of the American Society of Echocardiography [13]. Data were analyzed and interpreted by 1 experienced echocardiographer who was blinded to the treatment status and imaging sequence. The LV mass was calculated from the LV linear dimensions using the Devereux formula [13,14]. The LV mass was indexed to the body surface area [13,15]. LV hypertrophy was considered present when the LV mass exceeded 115 g/m^2 for men and 95 g/m^2 for women [13]. The LAD was measured in the parasternal long axis, perpendicularly to the LA walls. The LAD was measured in end-systole, from the leading border of the posterior aortic wall to the leading border of the posterior LA wall.

24-Hour ABPM

ABPM was performed for 24 hours with a clinically validated device (CardioMapa; Cardios, São Paulo, Brazil) before the procedure. The device was set to measure every 15 minutes during the day (from 6 AM to 10 PM) and every 30 minutes during sleep (from 10 PM to 6 AM). Patients were instructed to continue their regular activities during the recording and go to bed no later than 11 PM. The waking period ranged from 8 AM to 10 PM and the sleep period from midnight to 6 AM [16]. 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 [10].

Pulmonary vein isolation

The AF ablation procedure has been described in detail previously [17]. All patients underwent complete PVI using a 3-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.

Renal sympathetic denervation

All the patients received intravenous sodium bicarbonate (3 mL/kg) and 0.9% saline for 1 hour as prophylaxis for diminution of iodinated contrast media−associated nephrotoxicity [18,19]. The procedures were performed in the catheterization laboratory with direct visualization using fluoroscopy and radiopaque contrast. In several cases, we also used the aforementioned 3-dimensional mapping system (EnSite Velocity; St. Jude Medical) to anatomically construct the renal arteries and aorta and applied RF energy to the selected sites. 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. A 12F valved sheath was placed into this artery, and unfractionated heparin was managed as an intravenous bolus, targeting an activated coagulation time of > 250 seconds in the first 10 minutes. During the procedure, the target activated coagulation time ranged from 250 to 350 seconds. An aortography and selective renal arteriographies were obtained with an 11F steerable long sheath (Agilis; St. Jude Medical) using the standard "over-the-wire" technique, and a 7F ablation catheter with an open irrigated tip (Therapy Cool Path; St. Jude Medical) was put in the renal arteries, allowing the delivery of RF energy for innervation (Fig. 1). The RF ablation spots were performed at the main trunk of the bilateral renal arteries with a series of applications at 8-W power, duration of 60 seconds, and an irrigation flow rate of 17 mL/min, aiming for at least 4 RF applications per renal artery according to the length. Ablation was performed with a ≥ 5-mm distance between sites and by moving the catheter from distal to proximal helical. The number of lesions per artery was selected based on the artery length as measured by baseline angiography. A minimum of 4 lesions were applied for arteries shorter than 20 mm, and one additional lesion was applied for every 5-mm increase in length. After the procedure, the anatomy of the renal arteries was checked by angiography to identify any complications during the procedure. At the finish of the procedure, patients were given another infusion of sodium bicarbonate (1 mL/kg/h) for 6 hours [18,19]. The patients remained hospitalized in the ward for 24 hours after the procedure.
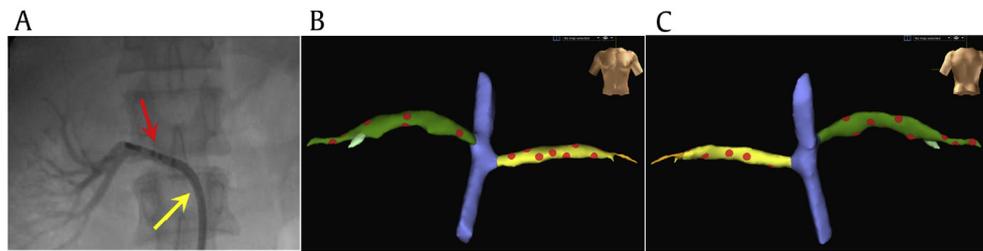
Figure 1. Renal artery mapping. Long steerable sheath (Agilis) anchored within the right renal artery with a steeper turn (yellow arrow); the ablation catheter is placed distally within the right artery with marked pressure at the upper aspect (red arrow) (A). Reconstruction of the anatomy of the renal arteries and abdominal aorta with the mapping system (EnSite Velocity) in anteroposterior projection (B) and posteroanterior projection (C). The red marks tag each ablation spot.

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 2 sided. Comparisons between 2-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 2-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 the Fisher's exact test. A *P* value of < 0.05 was considered significant. Correlations between 2 variables were performed by the Pearson 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 freedom from AF. 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).

Results

Baseline characteristics of patients

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

Safety evaluation of RSD

No patient developed procedural complications. No hypotensive or syncopal episodes were reported after β-blocker onset or RSD. Real-time renal artery imaging was performed to evaluate eventual structural changes after the procedure. Some small foci of irregularities of the renal arteries that were existent during the procedure (maybe because of edema or minor

Table 1. Patients' baseline characteristics

Parameters	PVI	PVI + RSD	P
N	24	21	−
Age (y)	66 ± 9	68 ± 9	0.508
Body mass index (kg/m^2)	25 ± 3	27 ± 3	0.112
Male sex	16 (67)	13 (62)	0.765
White ethnicity	17 (71)	13 (62)	0.546
Hypertension	24 (100)	21 (100)	> 0.999
Type 2 diabetes mellitus	13 (54)	16 (76)	0.212
Coronary artery disease	14 (58)	12 (57)	> 0.999
Stroke/transient ischemic attack	7 (29)	9 (43)	0.369
Paroxysmal atrial fibrillation	15 (63)	12 (57)	0.767
Persistent atrial fibrillation	9 (37)	9 (43)	0.767
CHA$_2$DS$_2$-VASc	3.7 ± 1.3	4.7 ± 1.7	0.026
eGFR (mL/min/1.73 m^2)	60.5 ± 15.9	59.3 ± 13.3	0.799
CKD stage			
2	12 (50)	8 (38)	0.550
3	12 (50)	13 (62)	0.550
Left ventricular ejection fraction (%)	63.5 ± 6.8	62.7 ± 6.6	> 0.999
Left atrial diameter (mm)	44.9 ± 3.9	45.1 ± 3.2	> 0.999
Antihypertensives	3.3 ± 0.5	3.41 ± 0.6	0.393
ACE inhibitors/ARBs	24 (100)	21 (100)	> 0.999
β blockers	15 (63)	14 (67)	> 0.999
Diuretics	16 (67)	16 (76)	0.528
DHP calcium channel blockers	24 (100)	21 (100)	> 0.999
24-h ABPM (mmHg)	$117 \pm 8/79 \pm 3$	$119 \pm 7/80 \pm 3$	0.999/> 0.999
Mean volume of contrast used during RSD (mL)	23.8 ± 8.5	25.2 ± 7.9	0.572

Data are presented as mean $\pm$ SD or *n* (%).
ABPM, ambulatory blood pressure measurement; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.

spasm) were no longer observed postoperatively. Twelve months after the procedure, all patients in the RSD group underwent a Doppler scan of the renal arteries and showed no evidence of stenosis or flow limitation.

Effects on BP

No significant change was observed on mean 24-hour ABPM from baseline to 3, 6, and 12 months within the same group. Nor have there been significant differences between the 2 groups at the same time points, as shown in Table 2. At baseline, the mean number of antihypertensive agents used by the PVI group was 3.1 ± 0.4 vs. 3.2 ± 0.3 used by the PVI + RSD group ($P = 0.7062$), and at the 12th month of follow-up, the PVI group used 3.0 ± 0.3 antihypertensive agents vs. 3.0 ± 0.2 used by the PVI + RSD group ($P > 0.0999$). Comparisons between baseline and 12 months after RSD for PVI and PVI + RSD groups were not significant ($P = 0.6833$ and $P = 0.1679$, respectively).

Effects on renal function

The effects of PVI alone or PVI + RSD on the creatinine concentration, eGFR, and albumin:creatinine ratio during the 12-month follow-up are shown in Table 3.

Effects on echocardiographic parameters

Changes in the LV ejection fraction, LAD, end-diastolic LV internal dimension, and LV mass index 12 months after PVI or PVI + RSD versus the respective baseline values, as well as comparisons between both groups at the same time points, are shown in Table 4.

Monitoring of AF by pacemaker records

At the 12-month follow-up evaluation, only 6 (25%) of the 24 patients in the PVI group were free of AF. However, 16 (76%) of the 21 patients in the PVI + RSD group were free of AF on no antiarrhythmic drugs ($P = 0.0007$), as shown in Fig. 2. At the end of the 1-year follow-up, AF recurrence was observed in both groups. In the PVI group, 6 (25%) patients were in stage 2 CKD and 12 (50%) were in stage 3 CKD. In the PVI + RSD group, however, only 5 (24%) patients had AF recurrence, and all of them had stage 3 CKD.

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 versus PVI + RSD, only the CHA_2DS_2-VASc score differed, being more severe in the PVI + RSD group.

The effect of RSD on the mean 24-hour systolic and diastolic ABPM did not differ during the follow-up or in comparison with the PVI group at the same time points. The 3-, 6-, and 12-month results showed a change in the mean 24-hour systolic ABPM of $-3.6/-1.0$, $-4.8/-1.7$, and $-4.4/-2.0$ mmHg in the PVI + RSD and PVI groups, respectively, which is not very different from the effects reported by other studies [20,21]. As reported in the SYMPLICITY HTN-3 trial [22], no significant differences in the 24-hour ABPM were observed between 6 and 12 months in the denervation and crossover subjects. Ambulatory data were available for only 20 of 70 (29%) noncrossover subjects at 12 months, given that ABPM was not protocol mandated for these subjects at this time point. However, in these 20 subjects, a pattern similar to that of office readings was observed, showing a larger 24-hour ABPM reduction at 6 than 12 months (-11.0 ± 19.5 vs. -6.1 ± 14.4 mmHg at 6 and 12 months, respectively; $P = 0.272$) [22]. Moreover, no change in 24-hour ABPM was expected in our study because the patients had controlled hypertension, and one predictor of success is a baseline office systolic BP of ≥ 180 mmHg [23].

This study had as one of the objectives to analyze the temporal changes in renal function after RSD. We enrolled patients with controlled hypertension and stage 2 or 3 CKD and used the eGFR to accurately evaluate the renal function, which is the standard of care in the clinical evaluation of glomerular filtration. We calculated the eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation, which is known to perform better for a larger range of glomerular filtration rate values [10]. The adopted protocol [24] for denervation involved the delivery of a higher number of ablative lesions per artery than in previous studies [25,26] and an irrigated catheter with a more wide contact area. Recent data suggest that the combined number of complete and incomplete ablation runs (i.e., the overall number of ablation attempts) is related to greater BP reductions [23]. Sympathetic activation is a hallmark of the essential hypertensive state occurring early in the clinical course of the disease [27–29]. In CKD, the sympathetic overactivity looks to be expressed at the earliest clinical phase of this condition, being directly related to the severity of the renal failure [30–33]. In both hypertension and renal failure, the mechanisms of the hyperadrenergic state are manifold and include reflex and neurohumoral pathways [27,28,32]. The adrenergic activation has an adverse impact on cardiovascular morbidity and, in the case of renal failure, also on cardiovascular mortality [27,28,33,34]. We believe that this overactivity from the essential hypertensive state is in part controlled by antihypertensive drugs because patients maintain a normotensive state, leaving only sympathetic hyperactivity due to

Table 2. 24-Hour ABPM during the follow-up period

Procedures	Mean 24-h ABPM (mmHg)			
	Baseline	3rd mo	6th mo	12th mo
PVI	$117 \pm 8/79 \pm 3$	$113 \pm 8/78 \pm 3$	$112 \pm 8/78 \pm 4$	$112 \pm 8/77 \pm 4$
PVI + RSD	$119 \pm 8/80 \pm 3$	$115 \pm 7/79 \pm 3$	$114 \pm 7/78 \pm 3$	$114 \pm 7/77 \pm 3$

Data are presented as mean $\pm$ SD.
ABPM, ambulatory blood pressures measurements; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.

Table 3. Renal function during the follow-up period

Variables	Pulmonary vein isolation				Pulmonary vein isolation + renal sympathetic denervation			
	Baseline	3rd mo	6th mo	12th mo	Baseline	3rd mo	6th mo	12th mo
Cr (mg/dL)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2*†	1.3 ± 0.2	1.1 ± 0.2*	1.1 ± 0.2**	1.1 ± 0.2**
eGFR (mL/min/1.73 m^2)	60.5 ± 15.9	59.1 ± 15.4	58.3 ± 14.0	56.6 ± 14.7†	59.3 ± 13.3	62.5 ± 12.2*	64.9 ± 13.4**	65.7 ± 14.0**
ACR (mg/g)	77.5 (62.3–82.8)	82.5† (66.3–87.8)	84.5†† (68.3–89.8)	86.5†† (69.3–91.8)	85.0 (66.0–116.0)	44.0* (31.0–74.0)	31.0** (21.0–53.0)	19.0** (11.5–32.5)

Data are presented as mean ± SD or median (interquartile range).
*$P < 0.05$ and **$P < 0.001$ for values at 3rd, 6th, and 12th months versus baseline. †$P < 0.05$ and ††$P < 0.0001$ for comparisons between pulmonary vein isolation and pulmonary vein isolation + renal sympathetic denervation at the same time point.
ACR, albumin:creatinine ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate.

CKD. The interruption of this vicious feedback cycle, which reduces this sympathetic overactivity and the feedback loop of the renin–angiotensin–aldosterone system [35], may at least in part account for our findings regarding eGFR improvement and albuminuria reduction after RSD, even lower than previously reported results [24,7].

The association of RSD with PVI had a positive impact on AF recurrence. Once PVI was achieved, the dominant initiating source was eliminated. However, in patients with substantial pathology in the atrial substrate, additional intervention might be required to maximize the antiarrhythmic response. The PVI-only group did not have an acceptable response to ablation regarding echocardiographic parameters (LV ejection fraction, LAD, LV internal dimension, and LV mass index), and these parameters worsened during the follow-up. In contrast, the PVI + RSD [36,8] group showed improvement in these parameters, which were significantly higher than those in the PVI group at 12 months. In addition, ablation of afferent renal nervous input decreases central sympathetic output [30], which might attenuate autonomic triggers of AF and offer the potential for an antiarrhythmic effect superior to medications. Owing to sympathetic hyperactivity inherent to CKD, we believe that AF recurred more readily in patients with stage 2 (25%) and 3 (50%) CKD in the PVI group. However, AF recurred in 24% of patients with stage 3 CKD in the PVI + RSD group, suggesting that RSD can suppress sympathetic overactivity and consequently suppress arrhythmogenic foci triggered by this.

Study limitations

Although our data show an independent contribution of RSD to eliminating AF recurrence in patients with controlled hypertension and CKD, our patient cohort was small. This relatively small sample can be seen as a limitation. To our knowledge, however, the present series is the first to address percutaneous renal artery denervation in patients with concurrently controlled hypertension, CKD, and AF.

The type of AF can have conceivable effects on the outcome (i.e., PAF can be more prone to cure by PVI + RSD than PersAF). The inclusion of different types of AF did not allow us to analyze them separately. 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 3-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. The neuromuscular sympathetic activity can also be measured, which would contribute greatly to the assessment of the degree of sympathetic blockade.

Table 4. Echocardiographic parameters during the follow-up period

Echocardiographic parameters	PVI ($n = 24$)		PVI + RSD ($n = 21$)		P at 12th mo (PVI vs. PVI + RSD)
	Baseline	12th month	Baseline	12th month	
LVEF (Simpson %)	63.5 ± 6.8	59.0 ± 6.4*	62.7 ± 6.6	65.8 ± 7.0*	0.0016
LAD (mm)	44.9 ± 3.0	46.5 ± 3.9*	45.1 ± 3.2	42.9 ± 3.4*	0.0018
LVIDd (mm)	53.6 ± 2.9	55.3 ± 3.3*	54.0 ± 3.0	51.6 ± 2.6*	0.0001
LV mass index (g/m²)	102.7 ± 14.1	109.0 ± 14.8*	107.0 ± 13.5	97.9 ± 12.3*	0.0097

Data are presented as mean ± SD.
*$P < 0.0001$ for values at 12 months versus baseline.
LAD, left atrial diameter; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, end-diastolic left ventricular internal dimension; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.
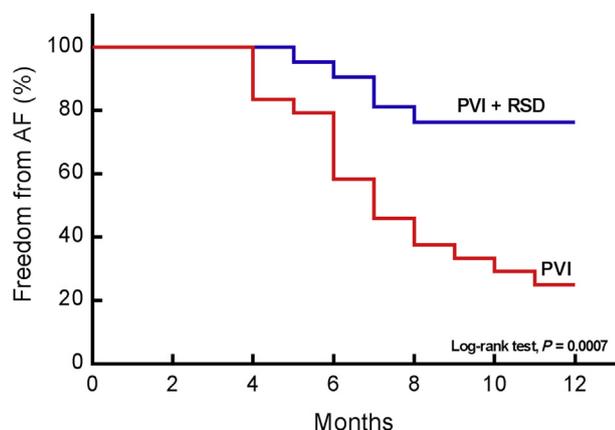

Figure 2. Incidence of AF recurrence in the PVI group (red line) and PVI +RSD group (blue line). Patients in the PVI + RSD group had a significantly lower rate of AF recurrence during the 12-month follow-up than did patients in the PVI group ($P = 0.0007$).
AF, atrial fibrillation; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.

Conclusions

PVI + RSD is safe and appears to be superior to PVI in the treatment of AF; it can also improve renal function and some cardiac parameters as assessed by echocardiography. Although encouraging, our data are preliminary and need long-term validation in a large population. PVI + RSD is a potential tool for incorporation into future clinical practice.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

[1] Stewart S, Hart CL, Hole DJ, McMurray J: Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/ Paisley study. *Heart* 86:516–521, 2001

[2] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE: Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 285:2370–2375, 2001

[3] Bansal N, Xie D, Tao K, Chen J, Deo R, Horwitz E, Hsu CY, Kallem RK, Keane MG, Lora CM, Raj D, Soliman EZ, Strauss L, Wolf M, Go AS, CRIC Study: Atrial fibrillation and risk of ESRD in adults with CKD. *Clin J Am Soc Nephrol* 11:1189–1196, 2016

[4] European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH: Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 31:2369–2429, 2010

[5] Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS: A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 60:1163–1170, 2012

[6] Kiuchi MG, Chen S, Andrea BR, Kiuchi T, Carreira MA, Graciano ML, Lugon JR: Renal sympathetic denervation in patients with hypertension and chronic kidney disease: does improvement in renal function follow blood pressure control? *J Clin Hypertens (Greenwich)* 16:794–800, 2014

[7] Kiuchi MG, Graciano ML, Carreira MA, Kiuchi T, Chen S, Lugon JR: Long-term effects of renal sympathetic denervation on hypertensive patients with mild to moderate chronic kidney disease. *J Clin Hypertens (Greenwich)* 18:190–196, 2016

[8] Kiuchi MG, Mion Jr D, Graciano ML, de Queiroz Carreira MA, Kiuchi T, Chen S, Lugon JR: Proof of concept study: improvement of echocardiographic parameters after renal sympathetic denervation in CKD refractory hypertensive patients. *Int J Cardiol* 207:6–12, 2016

[9] Schlaich MP, Bart B, Hering D, Walton A, Marusic P, Mahfoud F, Böhm M, Lambert EA, Krum H, Sobotka PA, Schmieder RE, Ika-Sari C, Eikelis N, Straznicky N, Lambert GW, Esler MD: Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with the end-stage renal disease. *Int J Cardiol* 168:2214–2220, 2013

[10] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D,

Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA: 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 34:2159—2219, 2013

[11] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150:604—612, 2009

[12] Joshi S, Choi AD, Kamath GS, Raiszadeh F, Marrero D, Badheka A, Mittal S, Steinberg JS: Prevalence, predictors, and prognosis of atrial fibrillation early after pulmonary vein isolation: findings from 3 months of continuous automatic ECG loop recordings. *J Cardiovasc Electrophysiol* 20:1089—1094, 2009

[13] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440—1463, 2005

[14] Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 57: 450—458, 1986

[15] Mosteller RD: Simplified calculation of body-surface area. *N Engl J Med* 317:1098, 1987 [Correspondence]

[16] Stergiou GS, Kollias A, Destounis A, Tzamouranis D: Automated blood pressure measurement in atrial fibrillation: a systematic review and meta-analysis. *J Hypertens* 30:2074—2082, 2012

[17] Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Turov A, Shirokova N, Karaskov A: Ablation of paroxysmal and persistent atrial fibrillation: 1-year follow-up through continuous subcutaneous monitoring. *J Cardiovasc Electrophysiol* 22:369—375, 2011

[18] Merten GJ, Burgess WP, Rittase RA, Kennedy TP: Prevention of contrast-induced nephropathy with sodium bicarbonate: an evidence-based protocol. *Crit Pathw Cardiol* 3:138—143, 2004

[19] ten Dam MA, Wetzels JF: Toxicity of contrast media: an update. *Neth J Med* 66:416—422, 2008

[20] Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Véhier C, Courand PY, Lantelme P, Denolle T, Dourmap-Collas C, Trillaud H, Pereira H, Plouin PF, Chatellier G; Renal Denervation for Hypertension (DENERHTN) investigators: Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 385:1957—1965, 2015

[21] De Jager RL, Sanders MF, Bots ML, Lobo MD, Ewen S, Beeftink MM, Böhm M, Daemen J, Dörr O, Hering D, Mahfoud F, Nef H, Ott C, Saxena M, Schmieder RE, Schlaich MP, Spiering W, Tonino PA, Verloop WL, Vink EE, Vonken EJ, Voskuil M, Worthley SG, Blankestijn PJ: Renal denervation in hypertensive patients not on blood pressure lowering drugs. *Clin Res Cardiol* 105:755—762, 2016

[22] Bakris GL, Townsend RR, Flack JM, Brar S, Cohen SA, D'Agostino R, Kandzari DE, Katzen BT, Leon MB, Mauri L, Negoita M, O'Neill WW, Oparil S, Rocha-Singh K, Bhatt DL, SYMPLICITY HTN-3 Investigators: 12-month blood pressure results of catheter-based renal artery denervation for resistant hypertension: the SYMPLICITY HTN-3 trial. *J Am Coll Cardiol* 65:1314—1321, 2015

[23] Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL: Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 36: 219—227, 2015

[24] Kiuchi MG, Maia GL, de Queiroz Carreira MA, Kiuchi T, Chen S, Andrea BR, Graciano ML, Lugon JR: Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood pressure and renal function in patients with chronic kidney disease and resistant hypertension. *Eur Heart J* 34:2114—2121, 2013

[25] Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M: Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 373:1275—1281, 2009

[26] Symplicity HTN-1 Investigators: Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 57:911—917, 2011

[27] Grassi G: Sympathetic neural activity in hypertension and related diseases. *Am J Hypertens* 23:1052—1060, 2010

[28] Grassi G: Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. *Hypertension* 54:690—697, 2009

[29] Paton JF, Raizada MK: Neurogenic hypertension. *Exp Physiol* 95: 569—571, 2010

[30] Schlaich MP, Socratous F, Hennebry S, Eikelis N, Lambert EA, Straznicky N, Esler MD, Lambert GW: Sympathetic activation in chronic renal failure. *J Am Soc Nephrol* 20:933—939, 2009

[31] Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ: Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 65:1568—1576, 2004

[32] McGrath BP, Ledingham JG, Benedict CR: Catecholamines in peripheral venous plasma in patients on chronic haemodialysis. *Clin Sci Mol Med* 55:89—96, 1978

[33] Grassi G, Bertolli S, Seravalle G: Sympathetic nervous system: role in hypertension and in chronic kidney disease. *Curr Opin Nephrol Hypertens* 21:46—51, 2012

[34] Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, Bonanno G, Rapisarda F, Fatuzzo P, Seminara G, Cataliotti A, Stancanelli B, Malatino LS: Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 105:1354—1359, 2002

[35] Wang L, Lu CZ, Zhang X, Luo D, Zhao B, Yu X, Xia DS, Chen X, Zhao XD: The effect of catheter based renal sympathetic denervation on renin-angiotensin-aldosterone system in patients with resistant hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi* 41:3—7, 2013

[36] Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC: Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 59:901—909, 2012