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Different Strategies to Treat Paroxysmal AF in Patients with Moderate CKD and Severe OSA: a sub group analysis

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Highlights

Accentuated sympathetic nerve activity is a strong danger feature for cardiovascular major episodes, such as cerebral and myocardial ischemia/infarction. Peripheral sympathetic nerve activity is emphasized in the hypertensive state, congestive cardiac failure, OSA, heaviness, diabetes, and chronic kidney disease (CKD) subjects. At least a half of individuals with hypertension present augmented sympathetic nerve activity. Our group believes that RSD can reduce AF recurrence in patients with CKD and OSA by modulation of the sympathetic hyperactivity present in these diseases. The goal of this prospective study was to compare the impact of different treatments including CPAP, PVI, RSD, and some combination of them in controlled hypertensive patients with paroxysmal AF, moderate CKD, and severe OSA. Our data suggest that the patients underwent RSD associated to CPAP treatment or PVI, or both of them presented an improvement in the renal function, a decrease in AHI and a lower chance with present AF recurrence than the ones that did not suffer this intervention. Although encouraging, our data are preliminary and need long-term validation in a large population.

Keywords: Renal sympathetic nerve denervation; Atrial fibrillation

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Introduction

The ideal approach for the treatment of atrial fibrillation (AF) is rhythm control, but this is sometimes very hard to accomplish [1]. For such procedures, complete isolation of all pulmonary veins (PVs) is currently widely accepted as the best endpoint. Pokushalov and colleagues [2] recently reported that renal sympathetic denervation (RSD) reduces AF recurrences when combined with pulmonary vein isolation (PVI). RSD consists of a recent strategy using percutaneous catheter-based delivery of radiofrequency (RF) energy to interject the sympathetic innervation of the kidneys, and PVI is a well stablished ablation technique used to treat paroxysmal AF. RSD procedure exposed no severe vascular or renal complications in the long term (up to 36 months).

Obstructive sleep apnea (OSA) may trigger atrial fibrillation (AF), a common cardiac arrhythmia. In a previous study, AF appeared in 4.8% of individuals in the breathing sleep disorder group (N=228), but just in 0.9% of those without such conditions (P=0.003) [3]. Further, AF can be a causal factor for various syndromes such as cerebral or systemic embolism [4]. Thus, AF treatment is crucial to reduce cardiovascular morbidity and mortality [5,6]. Particularly, OSA is a risk factor for stroke and hypertension [7,8]. Further, continuous positive airway pressure (CPAP) decreases death and cardiovascular events and ameliorates hypertension control [9,10]. Moreover, OSA has been shown to be independently associated with AF development [9], with a prevalence rate as high as 50% [11]. Numerous primary mechanisms are attributable for OSA-induced AF. The main mechanism is intermittent nighttime desaturation [3,12]. Night time hypoxemia secondary to OSA may cause atrial remodeling and dilatation, conduction abnormalities, vagal tone hyperfunction, pulmonary vasoconstriction/hypertension, or increase in inflammatory markers [13-18].

Accentuated sympathetic nerve activity is a strong danger feature for cardiovascular major episodes, such as cerebral and myocardial ischemia/infarction [19]. Peripheral sympathetic nerve activity is emphasized in the hypertensive state,

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congestive cardiac failure, OSA, obesity, diabetes, and chronic kidney disease (CKD) subjects. At least a half of individuals with hypertension present augmented sympathetic nerve activity [20,21]. Our group believes that RSD can reduce AF recurrence in patients with CKD and OSA by modulation of the sympathetic hyperactivity present in these diseases. The goal of this prospective study was to compare the impact of different treatments including CPAP, PVI, RSD, and some combination of them in controlled hypertensive patients with paroxysmal AF, moderate CKD, and severe OSA.

This prospective, longitudinal study involved 200 patients with controlled hypertension, dual chamber pacemaker, moderate CKD, and severe OSA, all of them having a history of symptomatic paroxysmal AF (PAF). 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. This study was conducted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil. Patients were recruited from January 2012 till January 2016 from the Arrhythmias and Artificial Cardiac Pacing Service of the same hospital. Enrolled patients met the following criteria: (i) mean 24-h systolic ambulatory blood pressure measurement (ABPM) of ≥100 and <130 mmHg, (ii) essential hypertension for >1 year, (iii) a physically normal heart with an ejection fraction of >50% as measured by echocardiography (Simpson's method), (iv) PAF (defined as AF episodes lasting <7 days with spontaneous termination) recorded by the pacemaker, (v) aged 18 to 80 years, (v) treatment of PAF with amiodarone; (vi) severe obstructive sleep apnea syndrome, defined as AHI >30 events/hour, without previously treatment; (vii) have a dual chamber pacemaker implanted due a third degree or second degree Mobitz type 2 atrioventricular blockade, (viii) estimated glomerular filtration rate (eGFR) between 30 and 59 mL/min/1.73 m2, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22], and (ix) the capacity to read, comprehend and sign the informed consent form, and attend the study. Patients with any of the following were excluded: (i) pregnancy; (ii) valvular disease with significant adverse sequelae; (iii) unstable angina, myocardial infarction, transient ischemic attack or stroke within the preceding six months; (iv) renovascular abnormalities; (v) psychiatric disease; (vi) allergy to ionic contrast medium; (vii) the inability to be monitored clinically after the procedure; (viii) a known addiction to alcohol or drugs that affects the intellect; (ix) congestive heart failure (symptoms of functional class II to IV heart failure on the New York Heart Association scale); (x) and a previous AF ablation procedure.

The subjects were divided into 8 groups including 25 patients in each group as displayed in Table 1, including their baseline features. The patients that did not present AF were followed until 24 months to assess maintenance of sinus rhythm, to monitor variations in blood pressure and renal function. The primary endpoint of this study was to record a 30-s recurrence of AF by the dual chamber pacemaker. The blanking period (the first 3 months after ablation) was excluded from the analysis [23] in subjects underwent PVI, and a pacemaker was evaluated at baseline and quarterly after the performance of procedures forward. The secondary endpoints were an evaluation of mean 24-h ABPM, eGFR, albuminuria and apnea/hypopnea index (AHI) at baseline and 24 months after the procedures. Additionally, in the subjects who underwent RSD safety was evaluated by a renal arterial duplex scan at baseline and 6 months after this procedure.

The AF ablation procedure has been described in detail previously [24]. 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. And the RSD procedure has been described in detail previously [25]. The patients remained hospitalized in the ward for 24 h after the procedure.

The results are expressed as a mean and standard deviation for normally distributed data and as median with interquartile range otherwise. Comparisons between two-paired values were performed with the paired t-test in cases of a Gaussian distribution and by the Wilcoxon test otherwise. For normality of distribution, D'Agostino-Pearson test was used. 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 the post-hoc Tukey test. Categorical variables were compared with Fisher's exact test. A two-tailed P-value<0.05 was used as a criterion for statistical significance. Kaplan–Meier analysis was performed to determine the probability of success, estimated as the percentage of AF freedom. Differences in arrhythmia-free survival were assessed with the log-rank test. Cox regression analysis was applied to explore factors of AF recurrences. All statistical analyses were performed using the program Graphpad Prism v 7.0 (Graphpad Software, La Jolla, CA, USA).

No patient developed procedural complications related to PVI or RSD. Real-time renal artery images were performed at the end of the procedure to evaluate acute eventual structural moifications regarding the RSD. Six months after the procedure, all patients in the RSD groups underwent a Doppler scan of the renal arteries and showed no evidence of stenosis or flow limitation compared to the same exam at baseline. No significant change was observed on the mean 24-h ABPM from baseline to 24 months within the same group nor has there been significant differences between the groups. The effects of the procedures on the creatinine concentration, eGFR, and albumin:creatinine ratio during the first 24-month follow-up are shown in Table 2. As well, the changes in the AHI for the patients that achieved the 24th month of follow-up without present AF are presented in table 3.

During the follow-up period, AF recurrence was higher in some groups than in others, hazard ratio [HR], 95% confidence interval [CI] and P value by Log-rank test, are showed at table 4. There was difference related to AF reappearance in the comparison between groups submitted to different procedures by Log-rank test (P<0.0001), Figure 1.

Our data suggest that the patients who underwent RSD associated to CPAP treatment or PVI, or both of them presented an improvement in the renal function, a decrease in AHI and a lower chance to present AF recurrence than the ones that did not undergo any intervention. Although encouraging, our data are preliminary and need long-term validation in a large population.

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Table 1. General features of patients at baseline

Parameters	No Treatment	CPAP	PVI	RSD	CPAP + PVI	CPAP + RSD	PVI + RSD	CPAP + PVI + RSD	Overall P value
N	25	25	25	25	25	25	25	25	---
Age, years	59±15	63±12	55±15	62±9	57±13	60±10	58±11	56±14	0.2735
Body mass index, kg/m^2	27±6	25±10	26±8	29±8	26±10	26±6	27±9	27±5	0.7439
Male gender (%)	20 (80%)	10 (40%)	13 (52%)	14 (56%)	15 (60%)	16 (64%)	13 (52%)	17 (68%)	0.1620
White ethnicity (%)	14 (56%)	10 (40%)	12 (48%)	8 (32%)	15 (60%)	15 (60%)	10 (40%)	11 (44%)	0.3769
Paroxysmal AF	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
Controlled hypertension	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
Severe obstructive sleep apnea	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
Dual chamber pacemaker	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
Type 2 Diabetes Mellitus	10 (40%)	10 (40%)	14 (56%)	16 (64%)	11 (44%)	10 (40%)	15 (60%)	12 (48%)	0.4670
Creatinine, mg/dL	1.60±0.08	1.67±0.02	1.55±0.05	1.61±0.09	1.70±0.08	1.77±0.05	1.80±1.00	1.82±1.10	0.5120
eGFR, mL/min/1.73 m^2	46.0±6.4	43.4±6.9	48.0±11.5	45.5±7.0	44.2±8.3	45.1±7.0	42.0±8.4	43.3±9.6	0.2645
Albumin:creatinine ratio, mg/g	99±21	90±29	89±27	100±34	82±22	90±33	102±31	86±27	0.1307
Amiodarone	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
Antihypertensive agents									
ACE-inhibitors/ARB	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
Diuretics	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
DHP Ca++ channel blockers	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	25 (100%)	1.0000
β-blockers	15 (60%)	12 (48%)	16 (64%)	16 (64%)	10 (40%)	10 (40%)	12 (48%)	15 (60%)	0.3977
Mean 24-hour ABPM, mmHg									
Systolic	122.0±4.3	119.5±7.0	118.8±9.0	121.2±5.7	123.5±6.0	122.7±6.5	120.4±8.2	122.1±7.9	0.2335
Diastolic	70.5±5.5	73.4±3.6	74.1±5.0	73.8±5.0	71.2±8.0	70.0±8.5	72.9±7.7	74.2±5.1	0.0855
Echocardiographic parameters									
Indexed LA volume (mL/m^2)	41.0±8.7	39.9±10.0	41.9±7.7	38.7±8.0	42.1±10.5	39.4±8.5	40.4±11.1	41.8±10.6	0.8745
IST (mm)	9.8±2.5	9.0±2.9	8.8±3.0	8.5±2.8	10.0±2.7	9.5±2.4	10.0±2.6	9.7±3.0	0.3687
LVPWT (mm)	10.0±2.0	9.5±2.1	9.8±1.7	10.0±1.9	8.8±3.1	9.0±2.2	9.5±2.0	10.0±1.9	0.3124
LVEF, Simpson (%)	65.2±10.0	66.5±12.0	66.0±12.5	70.6±10.5	67.5±13.2	68.3±9.5	67.4±9.0	70.0±12.8	0.6772
LVEDD (mm)	46.2±6.0	47.1±5.4	48.0±5.5	47.8±4.2	45.9±8.4	46.7±9.9	47.5±8.0	49.5±8.3	0.7285
LVESD (mm)	32.0±8.0	31.5±6.4	32.5±7.7	33.3±8.1	34.0±9.6	34.9±8.8	33.6±10.0	32.5±10.0	0.8895
LV mass index (g/m^2)	98.0±18.5	94.3±22.1	103.3±18.4	99.0±17.2	106.0±20.8	93.2±21.0	104.0±25.2	96.3±22.2	0.2594

Values are expressed as Mean±SD; ABPM, ambulatory blood pressure measurements; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CPAP, continuous positive airway pressure; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; LA, left atrium; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.

Table 2. Effects on blood pressure and renal function at the 24th month.

Parameters	No Treatment	CPAP	PVI	RSD	CPAP + PVI	CPAP + RSD	PVI + RSD	CPAP + PVI + RSD	Overall P value
Number of patients that achieved the 24th month without AF	0	0	0	0	6	6	11	20	<0.0001
Mean systolic 24-hour ABPM, mmHg	---	---	---	---	121.0±6.8	124.0±3.9	120.0±9.3	121.5±8.2	0.2642
Mean diastolic 24-hour ABPM, mmHg	---	---	---	---	70.0±6.5	71.2±8.0	71.8±8.7	72.5±7.6	0.7051
Creatinine, mg/dL	---	---	---	---	1.90±1.00	1.65±0.05	1.60±0.03	1.69±0.06	0.4364
eGFR, mL/min/1.73 m^2	---	---	---	---	37.2±3.3	45.4±3.2	46.1±4.2	46.0±4.5	<0.05*
ACR, mg/g	---	---	---	---	99.0±15.6	58.0±18.0	60.5±20.2†	55.0±16.3†	<0.05*

Values presented as Mean±SD. ABPM, ambulatory blood pressure measurements; AF, atrial fibrillation; ACR, albumin:creatinine ratio; CKD, chronic kidney disease; CPAP, continuous positive airway pressure; eGFR, estimated glomerular filtration rate; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation. *P<0.05 for CPAP+PVI vs. CPAP+RSD, PVI+RSD, and CPAP+PVI+RSD at the 24th month; †P<0.05 for value at the 24th month vs. respective baseline value.

Table 3. Apnea/Hypopnea index at baseline and at the 24th month.

Parameters	No Treatment	CPAP	PVI	RSD	CPAP + PVI	CPAP + RSD	PVI + RSD	CPAP + PVI + RSD	Overall P value
Number of patients that achieved the 24th month without AF	0	0	0	0	6	6	11	20	<0.0001
AHI, events/hour at baseline	45.7±5.8	47.5±7.2	50.2±11.0	48.2±7.5	51.3±12.2	49.4±13.0	47.6±9.5	52.2±10.7	0.3069
AHI, events/hour at 24th month	---	---	---	---	22.5±6.0†	8.1±5.6†	9.0±4.5†	6.6±5.0†	<0.0001*

Values presented as Mean±SD. AF, atrial fibrillation; AHI, apnea/hypopnea index; CPAP, continuous positive airway pressure; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation. *P<0.0001 for CPAP+PVI vs. CPAP+RSD, PVI+RSD, and CPAP+PVI+RSD at the 24th month; †P<0.0001 for value at the 24th month vs. respective baseline value.

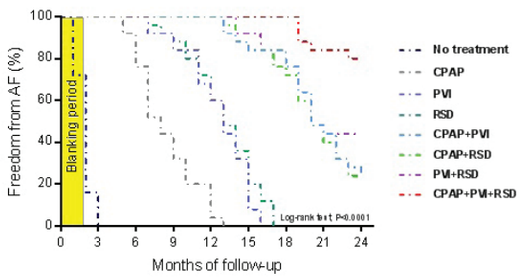

Figure 1. Kaplan-Meier curves depicting recurrences of paroxysmal atrial fibrillation in patients with controlled hypertension, dual chamber pacemakers, moderate chronic kidney disease, and severe obstructive sleep apnea. N=25 into each group; AF, atrial fibrillation; CPAP, continuous positive airway pressure; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.

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Table 4. Hazard ratio for AF occurrence/recurrence between patients with CKD and OSA evaluated by Log-rank test.

AF occurrence/recurrence	Hazard ratio	95% Confidence Interval	P value
No treatment			
vs. CPAP	4.044	2.018 – 8.106	<0.0001
vs. PVI	4.044	2.018 – 8.106	<0.0001
vs. RSD	4.044	2.018 – 8.106	<0.0001
vs. CPAP+PVI	4.525	2.231 – 9.179	<0.0001
vs. CPAP+RSD	4.525	2.231 – 9.179	<0.0001
vs. PVI+RSD	5.240	2.549 – 10.770	<0.0001
vs. CPAP+PVI+RSD	10.130	4.735 – 21.680	<0.0001
CPAP			
vs. PVI	3.172	1.657 – 6.072	<0.0001
vs. RSD	3.240	1.686 – 6.224	<0.0001
vs. CPAP+PVI	5.402	2.566 – 11.370	<0.0001
vs. CPAP+RSD	5.432	2.577 – 11.450	<0.0001
vs. PVI+RSD	6.386	2.982 – 13.600	<0.0001
vs. CPAP+PVI+RSD	12.560	5.685 – 27.760	<0.0001
PVI			
vs. RSD	1.254	1.261 – 4.128	0.3382
vs. CPAP+PVI	4.372	2.170 – 8.811	<0.0001
vs. CPAP+RSD	4.427	2.192 – 8.943	<0.0001
vs. PVI+RSD	5.553	2.672 – 11.540	<0.0001
vs. CPAP+PVI+RSD	12.410	5.629 – 27.380	<0.0001
RSD			
vs. CPAP+PVI	4.469	2.209 – 9.044	<0.0001
vs. CPAP+RSD	4.373	2.170 – 8.812	<0.0001
vs. PVI+RSD	5.537	2.667 – 11.500	<0.0001
vs. CPAP+PVI+RSD	12.940	5.825 – 28.740	<0.0001
CPAP+PVI			
vs. CPAP+RSD	0.959	0.508 – 1.812	0.8917
vs. PVI+RSD	1.376	0.696 – 2.723	0.3364
vs. CPAP+PVI+RSD	5.542	2.454 – 12.510	<0.0001
CPAP+RSD			
vs. PVI+RSD	1.425	0.720 – 2.820	0.2885
vs. CPAP+PVI+RSD	5.675	2.508 – 12.840	<0.0001
PVI+RSD			
vs. CPAP+PVI+RSD	3.713	1.497 – 9.208	0.0050

AF, atrial fibrillation; CKD, chronic kidney disease; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation.

Declarations of interest

The authors report no relationships that could be construed as a conflict of interest.

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The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals" [26].

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