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Original Article

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

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## 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.



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## 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 $\geq 100$ and $< 130$ mmHg; (2) essential hypertension for $> 1$ year (Hypertension was defined as office BP values $\geq 140$ mmHg systolic BP and/or $\geq 90$ 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 $\geq 130$ mmHg for systolic BP and/or $\geq 80$ 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