Renal denervation for improving outcomes of catheter ablation in patients with atrial fibrillation and hypertension: Early experience

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BACKGROUND The potential role of renal denervation (RD) in patients with AF and less severe hypertension is unknown.

OBJECTIVE The purpose of this study was to assess the potential role of RD as an adjunct to pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF) and moderate resistant or severe resistant hypertension.

METHODS The data for this study were obtained from 2 different prospective randomized studies, analyzed by meta-analysis. Patients with paroxysmal AF or persistent AF and moderate resistant hypertension (office blood pressure BP $\geq$140/90 mm Hg and $<$160/100 mm Hg; first study; n = 48) or severe resistant hypertension ($\geq$160/100 mm Hg; second study; n = 38) were randomized to PVI or PVI with RD.

RESULTS At 12 months, 26 of the 41 PVI with RD patients (63%) were AF-free vs 16 of the 39 patients (41%) in the PVI-only group ($P = .014$). In patients with severe hypertension, 11 of the 18 PVI with RD patients (61%) vs 5 of the 18 PVI-only patients (28%) were AF-free ($P = .03$). For moderate hypertension, the differences were less dramatic: 11 of 21 (52%) vs 15 of 23 (65%) when RD added ($P = .19$). The superior efficacy of adding RD was most apparent in persistent AF and severe hypertension (hazard ratio 0.25, confidence interval 0.09–0.72, $P = .01$). Duration of the procedure and fluoroscopy were nonsignificantly longer in the RD group.

CONCLUSION RD may improve the results of PVI in patients with persistent AF and/or severe resistant hypertension.

KEYWORDS Atrial fibrillation; Ablation; Renal denervation; Resistant hypertension

ABBREVIATIONS **AF** = atrial fibrillation; **CI** = confidence interval; **ECG** = electrocardiography; **HR** = hazard ratio; **HFS** = high-frequency stimulation; **PAF** = paroxysmal atrial fibrillation; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **RF** = radiofrequency

(Heart Rhythm 2014;11:1131–1138)

Introduction

Renal sympathetic denervation is a new method that may be effective for controlling resistant hypertension.[1] Apart from its antihypertensive effects, renal denervation also may exert antiarrhythmic effects, with reports suggesting a potential role for both atrial fibrillation (AF)[2] and ventricular tachyarrhythmias.[3] Hypertension is an established risk factor for AF,[4,5] and many cases of apparently "lone" AF can be attributed to latent hypertension.[6] The sympathetic nervous system also appears to play an important role in the initiation and maintenance of AF.[7,8] Increases in sympathetic tone frequently precede the onset of AF,[9] and excessive sympathetic activation can predict recurrences of AF after catheter ablation.[10] Autonomic denervation, which inevitably affects both the parasympathetic and sympathetic components of the autonomic innervation of the atria, has also been found beneficial in patients subjected to pulmonary vein isolation (PVI) for AF.[11,12]

We previously showed in a randomized controlled pilot study that renal artery denervation provided incremental AF suppression after PVI in patients with symptomatic and refractory AF in the setting of drug-resistant hypertension.[2] However, that study enrolled only patients with severe resistant hypertension; thus, the potential role of renal denervation in patients with less severe (or even no) hypertension has not been investigated. Renal denervation, by affecting the sympathetic nervous system, may exert antiarrhythmic actions independent from its antihypertensive

Dr. Katritsis has received research grants from Medtronic and Boston Scientific. Dr. Steinberg has served as a consultant with Boston-Scientific, Medtronic, Sanofi-Aventis, Janssen, Bristol-Myers-Squibb, Pfizer, and Biosense-Webster, and has received research grants from Medtronic and Biosense-Webster. ClinicalTrials.gov Unique Identifiers: NCT01117025 and NCT01897545. **Address reprint requests and correspondence:** Dr. Evgeny Pokushalov, Rechkunovskaya 15, 630055 Novosibirsk 55, Russia. E-mail address: E.Pokushalov@gmail.com.

effects, but whether this translates into clinically significant benefits in patients subjected to PVI for AF is not known.

The present study aimed to confirm our earlier findings of the value of renal denervation as an adjunct to PVI[2] but in a larger and more diverse cohort of patients with moderate resistant as well as severe resistant hypertension.

Methods

The data for this study were obtained from 2 different prospective randomized studies (Unique identifiers NCT01117025 and NCT01897545; Figure 1). The first study included patients with moderate drug-resistant hypertension, defined by the Joint National Committee VII and ESH/ESC guidelines as office blood pressure ≥140/90 mm Hg and <160/100 mm Hg. The second study included patients with severe drug-resistant hypertension, defined as office blood pressure ≥160/100 mm Hg.[13–16] This cohort of 80 patients includes the 27 patients previously reported as pilot data.[2]

Study patients

Patients with a history of symptomatic paroxysmal atrial fibrillation (PAF) and/or persistent AF and resistant hypertension (≥3 antihypertensive drugs) were eligible for this study.

Inclusion criteria were similar in both studies, except for the blood pressure levels:

1. Symptomatic drug-refractory AF (with history of failure of ≥2 class I or III antiarrhythmic drugs) in patients referred for catheter ablation of AF.
2. PAF with ≥1 monthly episodes or persistent AF in patients who had already undergone ≥3 electrical cardioversions. PAF was defined as episodes lasting <7 days with spontaneous termination. Persistent AF was defined as lasting >7 days before being terminated pharmacologically or by electrical cardioversion.
3. Office-based systolic blood pressure ≥140/90 mm Hg and <160/100 mm Hg (first study, moderate resistant hypertension) or ≥160/100 mm Hg (second study, severe resistant hypertension), despite treatment with 3 antihypertensive drugs (including a diuretic).
4. Glomerular filtration rate ≥45 mL/min/1·73 m^2, with modification of diet using a renal disease formula.

Exclusion criteria were similar in both studies:

1. Secondary causes of hypertension
2. Severe renal artery stenosis or dual renal arteries
3. Congestive heart failure with New York Heart Association class II–IV symptoms
4. Left ventricular ejection fraction <35%
5. Transverse left atrial diameter >60 mm on transthoracic echocardiography
6. Previous AF ablation procedure
7. Treatment with amiodarone
8. Previous renal artery stenting or angioplasty
9. Type 1 diabetes mellitus

Both studies were randomized and double-blind, and neither the patient nor the clinician responsible for follow-up of AF and blood pressure assessments was aware of treatment assignment. The study protocols were approved by the local Ethics Committees and were conducted in compliance with the protocol and in accordance with standard institutional operating procedures and the Declaration of Helsinki. All patients enrolled provided written informed consent.

The primary end-point of the studies was recurrence of >30 seconds of atrial tachyarrhythmia, including AF and left atrial flutter/tachycardia, after a single ablation procedure on no antiarrhythmic drug. The blanking period (the first 3 months after ablation) was excluded from the analysis.[17,18] The secondary end-points were office blood pressure and safety data at 3, 6, 9, and 12 months after the procedure. Office blood pressure was measured according to protocol-specified guidelines based on Standard Joint National Committee VII, European Society of Cardiology, and European Society of Hypertension recommendations.[13,14] Investigators used averages of triplicate measurements in our analysis.

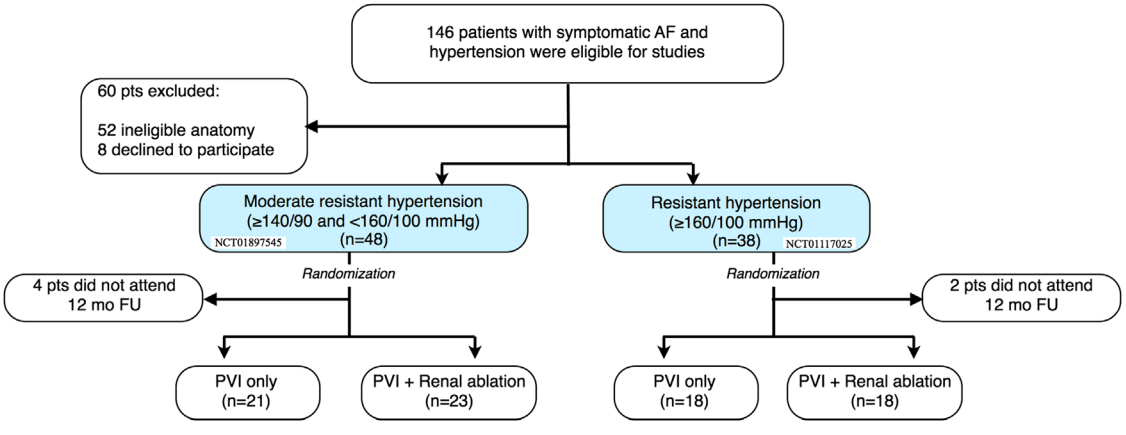

Figure 1 Study design and patient flow. AF = atrial fibrillation; FU = follow-up; PVI = pulmonary vein isolation.