A Randomized Comparison of Pulmonary Vein Isolation With Versus Without Concomitant Renal Artery Denervation in Patients With Refractory Symptomatic Atrial Fibrillation and Resistant Hypertension

Evgeny Pokushalov, MD, PhD,* Alexander Romanov, MD,* Giorgio Corbucci, PhD,† Sergey Artyomenko, MD,* Vera Baranova, MD,* Alex Turov, MD,* Natalya Shirokova, MD,* Alexander Karaskov, MD, PhD,* Suneet Mittal, MD,‡ Jonathan S. Steinberg, MD‡

Novosibirsk, Russia; Maastricht, the Netherlands; and New York, New York

Objectives
The aim of this prospective randomized study was to assess the impact of renal artery denervation in patients with a history of refractory atrial fibrillation (AF) and drug-resistant hypertension who were referred for pulmonary vein isolation (PVI).

Background
Hypertension is the most common cardiovascular condition responsible for the development and maintenance of AF. Treating drug-resistant hypertension with renal denervation has been reported to control blood pressure, but any effect on AF is unknown.

Methods
Patients with a history of symptomatic paroxysmal or persistent AF refractory to ≥2 antiarrhythmic drugs and drug-resistant hypertension (systolic blood pressure ≥160 mm Hg despite triple drug therapy) were eligible for enrollment. Consenting patients were randomized to PVI only or PVI with renal artery denervation. All patients were followed ≥1 year to assess maintenance of sinus rhythm and to monitor changes in blood pressure.

Results
Twenty-seven patients were enrolled, and 14 were randomized to PVI only, and 13 were randomized to PVI with renal artery denervation. At the end of the follow-up, significant reductions in systolic (from 181 ± 7 to 156 ± 5, p < 0.001) and diastolic blood pressure (from 97 ± 6 to 87 ± 4, p < 0.001) were observed in patients treated with PVI with renal denervation without significant change in the PVI only group. Nine of the 13 patients (69%) treated with PVI with renal denervation were AF-free at the 12-month post-ablation follow-up examination versus 4 (29%) of the 14 patients in the PVI-only group (p = 0.033).

Conclusions
Renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI. (Combined Treatment of Resistant Hypertension and Atrial Fibrillation; NCT01117025) (J Am Coll Cardiol 2012;60:1163–70) © 2012 by the American College of Cardiology Foundation

Activation of the sympathetic nervous system has been described in the development and progression of systemic hypertension (1). Sympathetic overdrive is also associated with target-organ damage related to chronic hypertension and has been detected in patients with heart failure, chronic kidney disease, and end-stage renal disease (2). Many of these comorbidities or consequences of hypertension can predispose patients to a treatment-resistant disease state (3,4). Preliminary data indicate that, by specifically targeting efferent sympathetic and afferent sensory renal nerve signaling, selective renal sympathetic nerve ablation improves
blood pressure control (5), at least in part by reducing central nervous system sympathetic out-put (6,7).

Hypertension is an important risk factor for developing atrial fibrillation (AF); the incidence of AF also increases with left ventricular (LV) hypertrophy, coronary heart disease, and heart failure (8–11), all consequences of poorly controlled hypertension.

We hypothesized that renal artery denervation could have a salutary effect on AF patterns in patients with poorly controlled hypertension by improving blood pressure control and by reduction in central sympathetic cardiac stimulation. The aim of this prospective randomized double-blind study was to assess the impact of renal artery denervation added to pulmonary vein isolation (PVI) in patients with a history of AF and drug-resistant hypertension.

**Methods**

The study protocol was approved by the local Ethics Committee and conducted in compliance with the protocol and in accordance with standard institutional operating procedures and the Declaration of Helsinki. All patients enrolled in the study provided written informed consent. **Study patients.** Patients with a history of symptomatic paroxysmal atrial fibrillation (PAF) and/or persistent atrial fibrillation (PersAF) and drug-resistant hypertension were eligible for this study.

**INCLUSION CRITERIA**

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. Paroxysmal AF with ≥1 monthly episodes or PersAF in patients who had already undergone ≥3 electrical cardioversions. Paroxysmal AF was defined as episodes lasting <7 days with spontaneous termination. Persistent AF was defined as lasting more than 7 days before being terminated pharmacologically or by electrical cardioversion.
3. Office-based systolic blood pressure of ≥160 mm Hg, despite treatment with ≥3 antihypertensive drugs (including 1 diuretic)
4. A glomerular filtration rate ≥45 ml/min/1.73 m², with modification of diet with a renal disease formula

**EXCLUSION CRITERIA**

1. Secondary causes of hypertension
2. Severe renal artery stenosis or dual renal arteries
3. Congestive heart failure with New York Heart Association functional class II to 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

Patients were randomized to PVI only (n = 14) or PVI with renal artery denervation (n = 13) with a coded envelope system opened on the day of the procedure. All patients were followed for 1 year to assess maintenance of sinus rhythm and to monitor variations in blood pressure (Fig. 1).

The primary endpoint of the study was recurrence of ≥30 s 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 (12). The secondary endpoints were office blood pressure and safety data before and at 3, 6, 9, and 12 months after procedure. This study was double-blind, and neither the patient nor the clinician responsible for follow-up of AF and blood pressure assessments was aware of whether renal artery ablation had been performed or not.

**PVI.** The ablation procedure has been defined in detail previously (13). All patients underwent complete PVI by encircling ipsilateral pulmonary veins without additional ablation lesion sets or lines. If still in AF at the end of the procedure, patients were converted to sinus rhythm electrically.

**Renal artery denervation.** All patients in the PVI with renal artery ablation group also underwent bilateral renal denervation directly after PVI during the same procedure. We used a technique of renal denervation recently described by Krum et al. (14). Real-time 3-dimensional aorta-renal artery maps were reconstructed with the use of the same navigation system and catheter used for PVI (Figs. 2A and 2B) via femoral artery access. Both mapping and ablation were performed under modified sedation with a propofol infusion. Radiofrequency (RF) ablations of 8 to 10 watts were applied discretely from the first distal main renal artery bifurcation all the way back to the ostium. The duration of each RF delivery was 2 min, and up to 6 lesions (separated by >5 mm) were performed both longitudinally and rotationally within each renal artery. To confirm renal denervation, we used high-frequency stimulation (HFS) before the initial and after each RF delivery within the renal artery. Rectangular electrical stimuli were delivered at the ostium of the targeted renal artery at a frequency of 20 Hz, with an amplitude of 15 V and pulse duration of 10 ms (Stimulator B-53, Biotok, Inc., St. Petersburg, Russia) for 10 s. Renal sympathetic denervation was considered to have been achieved when the sudden increase of blood pressure (>15 mm Hg from invasive arterial monitoring) was eliminated in the presence of HFS.
Follow-up. Weekly electrocardiograms (ECGs) were obtained for the first month, and 24-h Holter recordings were performed at 3, 6, 9, and 12 months. Holter and ECG interpretation was by consensus of 2 physicians blinded to the phase of the study (i.e., baseline or follow-up) and assigned study treatment. Patients were instructed to report symptoms suggestive of AF and to undergo prompt ECG recording. Office blood pressure measurements (averages of the triplicate measures) were taken according to the standard Joint National Committee VII guidelines (15), and clinicians assessing blood pressure were unaware of the study assignment. All patients were maintained on their baseline antihypertensive medication after ablation, without any changes except when medically required. All patients were treated with antiarrhythmic drugs (propafenone or flecainide) for 6 weeks after PVI; these drugs were subsequently withdrawn, regardless of the cardiac rhythm, to prevent their influence after the blanking period. To exclude post-procedural renal complications, we performed magnetic resonance angiography and measured glomerular filtration rate at the 6-month follow-up examination.

Statistical analysis. The primary endpoint of the study was the recurrence of any atrial tachyarrhythmia >30 s after a single ablation procedure after the first 3 months after ablation had elapsed (12,13). Results are expressed as mean ± SD or as absolute values and percentages, as appropriate. Continuous variables were compared by Student t test. Chi-square analysis for categorical variables was used for comparisons between characteristics of patients. For antihypertensive...
drugs statistical significance was calculated with the Wilcoxon Mann-Whitney test. 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.

The secondary endpoint was pattern of office blood pressure readings relative to baseline. Results are presented as mean ± SD.

All reported p values were based on 2-sided tests, and a p value of <0.05 was considered significant. All statistical calculations were performed with the SPSS (version 13.0, SPSS, Inc., Chicago, Illinois).

**Results**

**Clinical characteristics of study patients.** We enrolled 27 patients (14 randomized to PVI only, and 13 randomized to PVI with renal artery denervation), all of whom were followed for 12 months after ablation. All had a history of PAF, and 18 (67%) also had a history of PersAF. Table 1 shows the baseline characteristics of the patient population; the clinical characteristics of patients in the 2 groups did not differ significantly.

**Ablation procedures.** Complete disconnection of the pulmonary veins from the left atrium was successfully achieved in all 27 patients. Cavo-tricuspid isthmus ablation was successfully performed in all 12 patients with a history of atrial flutter—7 in the PVI only group, and 5 in the PVI with renal artery denervation group.

All patients showed a sudden increase in blood pressure >15 mm Hg in response to HFS. Renal denervation was successfully obtained in all 13 patients, obliterating the blood pressure response to HFS.

**Figure 2** Imaging of Renal Arteries Before and After Ablation

(A, B) Three-dimensional reconstructions with sites of radiofrequency ablation represented in red; (C, D) magnetic resonance imaging scans performed 6 months after ablation, demonstrating no evidence of renal artery stenosis.

<table>
<thead>
<tr>
<th></th>
<th>PVI</th>
<th>PVI + Renal</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56 ± 9</td>
<td>57 ± 8</td>
<td>0.41</td>
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<tr>
<td>Male/female</td>
<td>10/4</td>
<td>11/2</td>
<td>0.47</td>
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<td>PAF/PersAF</td>
<td>5/9</td>
<td>4/9</td>
<td>0.72</td>
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<tr>
<td>AF history, yes</td>
<td>5.3 ± 2</td>
<td>5.7 ± 4.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>2 (14.2%)</td>
<td>1 (7.7%)</td>
<td>0.32</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66 ± 4</td>
<td>65 ± 5</td>
<td>0.39</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>50 ± 6</td>
<td>49 ± 7</td>
<td>0.62</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>80.2 ± 4.6</td>
<td>78 ± 6.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>178 ± 8</td>
<td>181 ± 7</td>
<td>0.61</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>96 ± 4</td>
<td>97 ± 6</td>
<td>0.58</td>
</tr>
<tr>
<td>CAD</td>
<td>2 (14.2%)</td>
<td>2 (15.3%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3 (21%)</td>
<td>3 (23%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28 ± 5</td>
<td>28 ± 6</td>
<td>0.83</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (21%)</td>
<td>4 (30%)</td>
<td>0.22</td>
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<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
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<tr>
<td>Diuretics</td>
<td>13 (92%)</td>
<td>13 (100%)</td>
<td>0.73</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>14 (100%)</td>
<td>12 (92%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>11 (78%)</td>
<td>10 (77%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>10 (71%)</td>
<td>10 (76%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>3.6 (2–5)</td>
<td>3.8 (2–5)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%), or n (range).

**Table 1** Baseline Characteristics of Patient Population

**PersAF** = persistent atrial fibrillation; **PVI** = pulmonary vein isolation; **SD** = standard deviation.
pressure response to HFS. A total of 4.4 ± 0.8 RF applications (median = 4, range = 4 to 6) were delivered within each renal artery. Figure 3 shows the immediate response of blood pressure to HFS: a significantly and substantially lower blood pressure response was observed after renal ablation than in the pre-ablation state (p < 0.001).

The mean total duration of the procedure was 154 ± 28 min for the PVI-only group compared with 192 ± 36 min for the PVI with renal artery ablation group (including 31 ± 9 min for renal ablation; p = 0.18). The mean total fluoroscopy times were 21 ± 16 min for the PVI-only group, compared with 29 ± 14 min for the PVI with renal artery ablation group (including 8 ± 4 min for renal ablation; p = 0.21).

No procedure-related complications occurred with regard to either PVI or renal ablation. There were no cases of renal artery stenosis observed at 6 months on repeat magnetic resonance imaging (Figs. 2C and 2D). Baseline and 6-month follow-up glomerular filtration rate data were unchanged: 78.0 ± 6.1 ml/min/1.73 m² and 81 ± 4.6 ml/min/1.73 m², respectively (p = 0.42).

AF freedom at 1-year visit. At the 12-month follow-up examination, 9 (69%) of the 13 PVI with renal artery ablation group patients were AF-free. In contrast, in the PVI-only group, only 4 (29%) of the 14 patients were AF-free on no antiarrhythmic drugs (p = 0.033) (Fig. 4). At the end of 1-year follow-up, 8 of the patients with AF recurrences (6 in the PVI-only group and 2 from the PVI...
with renal artery ablation group) required treatment with amiodarone; the remaining 6 patients with AF recurrences (4 PVI only and 2 PVI with renal artery ablation) underwent a second procedure.

**Blood pressure control during follow-up.** Patients who underwent PVI only did not show any significant variation in systolic or diastolic blood pressures. By contrast, patients treated with renal denervation displayed a significant decrease in systolic and diastolic blood pressure at each of the visits at 3, 6, 9, and 12 months.

All 13 patients in the PVI with renal artery ablation group responded with systolic blood pressure reduction of $\pm 10$ mm Hg after the procedure and until 1-year follow-up. The diastolic blood pressure followed a similar pattern with reduction of $\pm 5$ mm Hg. The detailed trend in blood pressure reduction from 3 to 12 months after the procedure is shown in Figure 5. At 12 months, the reductions in systolic and diastolic blood pressures were successfully and significantly maintained ($p < 0.001$ vs. PVI only) resulting in a fall from baseline of $25 \pm 5$ mm Hg and $10 \pm 2$ mm Hg, respectively.

Patients and physicians were instructed not to change antihypertensive medications unless adverse effects occurred. In 3 patients in the PVI with renal artery ablation group, antihypertensive medication had to be reduced, owing to hypotension associated with symptoms. In 2 patients in the PVI only group, antihypertensive medication had to be further increased for symptomatic sustained hypertension. Patients received $3.6 \pm 0.6$ (median = 4, range = 3 to 5) antihypertensive drugs in the PVI only group and $3.8 \pm 0.4$ (median = 4, range = 3 to 5) in the PVI with renal artery ablation group at baseline; at the end of the 12-month follow-up, the figures were $3.8 \pm 0.4$ (median = 4, range = 3 to 5) and $3.3 \pm 0.7$ (median = 4, range = 2 to 4) ($p = 0.21$), respectively.

**Change in LV dimensions and mass.** As shown in Table 2, mean LV mass was reduced in the PVI with renal artery ablation group during follow-up by approximately 10%. The reduction of LV mass was due to reduction of interventricular septal, posterior wall, and relative wall thicknesses.

**Discussion**

The main findings of this prospective double-blind randomized study are: 1) renal artery denervation had a positive impact on AF recurrences in hypertensive patients with refractory AF who also underwent PVI; and 2) renal artery ablation resulted in sustained improvement in systolic and diastolic blood pressure control over 1 year of follow-up.

Hypertension is a well-known risk factor for AF, and elevated blood pressure can play a major role in developing and maintaining AF. The ARIC (Atherosclerosis Risk in

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean Changes From Baseline of LV Dimensions and Mass</th>
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<tbody>
<tr>
<td><strong>Mean Change</strong></td>
<td></td>
</tr>
<tr>
<td>PVI (n = 14)</td>
<td>PVI + Renal (n = 13)</td>
</tr>
<tr>
<td>ST, cm</td>
<td>$0.01 \pm 0.03$</td>
</tr>
<tr>
<td>LVID, cm</td>
<td>$0.04 \pm 0.09$</td>
</tr>
<tr>
<td>PWT, cm</td>
<td>$−0.01 \pm 0.03$</td>
</tr>
<tr>
<td>LVMI, g/m</td>
<td>$2.0 \pm 3.4$</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
LV = left ventricular diameter; LVID = left ventricular diameter; LVMI = left ventricular mass index; PVI = pulmonary vein isolation; PWT = posterior wall thickness; ST = septal thickness.
Communities) study recently found that 57% of incident AF could be attributed to elevated or borderline levels of risk factors for AF—namely, elevated blood pressure, overweight/obesity, diabetes mellitus, smoking, and prior cardiac disease (16).

Renal denervation is a newly available therapeutic option for drug-resistant hypertension. Resistant hypertension is recognized as an important subset of patients for whom pharmacologic control is elusive. The Symplicity trials reported positive long-term results of renal denervation (17,18). Post-procedure office systolic/diastolic pressures were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively, without significant adverse events. In this study we had similar reductions of 27/12, 28/10, 25/10, and 25/10 mm Hg at 3, 6, 9, and 12 months, respectively. However, it is not known whether lowering blood pressure also has an impact on arrhythmia burden in patients with a history of AF. Although several prior studies of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy for hypertension suggested that the inhibition of the renin-angiotensin-aldosterone system as antihypertensive therapy might reduce AF occurrence, recent studies focusing on AF patients have shown that lowering blood pressure alone is not enough to prevent AF recurrences (19,20).

The hypothesis of our study was that blood pressure control via renal artery denervation added to PVI might also have a positive impact on arrhythmia recurrences. Both acute and chronic blood pressure elevation can increase atrial stretching and dilation (i.e., atrial substrate), resulting in deleterious atrial electrical consequences that promote AF. However, it is less likely that sustained blood pressure elevation will have an impact on the triggers that arise from the pulmonary veins. Once PVI has been achieved, the dominant initiating source has been eliminated. However, in patients with substantial pathology in the atrial substrate, additional intervention might be required to maximize antiarrhythmic response. Indeed, the PVI only group in our study did not have an acceptable response to ablation (likely due to advance atrial remodeling due to resistant and persistent AF and hypertension). Because optimized blood pressure control might play a considerable role at the substrate level of the atria in preventing the development or recurrence of AF, it was reasoned that renal artery ablation could influence the recurrence rate of AF after PVI. In addition, the ablation of afferent renal nervous input will decrease central sympathetic output (7), which might attenuate autonomic triggers of AF in addition to improved blood pressure control and offer the potential for an antiarrhythmic effect superior to medications.

Atrial fibrillation ablation is a well-known and accepted therapy for symptomatic patients with PAF or PersAF. Our data, albeit from a small patient cohort, show an independent contribution of renal denervation to eliminating AF recurrences in hypertensive and drug-resistant patients. The high risk of arrhythmia recurrence post-PVI in drug-resistant hypertensive patients is not surprising (21,22). Recently, Lau et al. (23) showed in an animal model that the hypertensive group developed a progressive increase in mean arterial pressure, longer mean effective atrial refractory periods, progressive bi-atrial hypertrophy, atrial inflammation, left atrial dysfunction, and greater AF inducibility. On the basis of this evidence, our results underline the partially reversible impact of elevated blood pressure on AF burden if patients also undergo PVI.

This was the “first-in-man” study of combined renal denervation and AF ablation; thus a limited number of patients were enrolled. Although the study was randomized and both the AF and blood pressure double-blind outcomes were markedly improved in the combined ablation group, the results will require validation in additional and larger trials. Because our data refer to a follow-up period of 1 year after the ablation procedure, we cannot extrapolate our results to the long-term maintenance of sinus rhythm or blood pressure control. Furthermore, the use of an implantable monitor might allow more accurate detection of AF recurrences than office ECG and 24-h Holter monitoring (13).

Renal artery denervation provided incremental AF suppression after PVI in patients with symptomatic and refractory AF in the setting of drug-resistant hypertension.

Reprint requests and correspondence: Dr. Evgeny Pokushalov, State Research Institute of Circulation Pathology, Arrhythmia Department, Rechkuhosnaya 15, 30055 Novosibirsk 55, Russia. E-mail: E.Pokushalov@gmail.com.

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