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Changes in Plasma Renin Activity After Renal Artery Sympathetic Denervation

Felix Mahfoud, MD,[a] Raymond R. Townsend, MD,[b] David E. Kandzari, MD,[c] Kazuomi Kario, MD, PhD,[d] Roland E. Schmieder, MD,[e] Konstantinos Tsioufis, MD,[f] Stuart Pocock, PhD,[g] Shukri David, MD,[h] Kiritkumar Patel, MD,[i] Anjani Rao, MD,[i] Antony Walton, MD,[j] Jason E. Bloom, MD,[j] Thomas Weber, MD,[k] Markus Suppan, MD,[k] Lucas Lauder, MD,[a] Sidney A. Cohen, MD, PhD,[b,l] Pamela McKenna, MS,[l] Martin Fahy, MS,[l] Michael Böhm, MD,[a] Michael A. Weber, MD[m]

ABSTRACT

BACKGROUND The renin-angiotensin-aldosterone system plays a key role in blood pressure (BP) regulation and is the target of several antihypertensive medications. Renal denervation (RDN) is thought to interrupt the sympathetic-mediated neurohormonal pathway as part of its mechanism of action to reduce BP.

OBJECTIVES The purpose of this study was to evaluate plasma renin activity (PRA) and aldosterone before and after RDN and to assess whether these baseline neuroendocrine markers predict response to RDN.

METHODS Analyses were conducted in patients with confirmed absence of antihypertensive medication. Aldosterone and PRA levels were compared at baseline and 3 months post-procedure for RDN and sham control groups. Patients in the SPYRAL HTN-OFF MED Pivotal trial were separated into 2 groups, those with baseline PRA ≥0.65 ng/ml/h (n = 110) versus <0.65 ng/ml/h (n = 116). Follow-up treatment differences between RDN and sham control groups were adjusted for baseline values using multivariable linear regression models.

RESULTS Baseline PRA was similar between RDN and control groups (1.0 ± 1.1 ng/ml/h vs. 1.1 ± 1.1 ng/ml/h; p = 0.37). Change in PRA at 3 months from baseline was significantly greater for RDN compared with control subjects (−0.2 ± 1.0 ng/ml/h; p = 0.019 vs. 0.1 ± 0.9 ng/ml/h; p = 0.14), p = 0.001 for RDN versus control subjects, and similar differences were seen for aldosterone: RDN compared with control subjects (−1.2 ± 6.4 ng/dl; p = 0.04 vs. 0.4 ± 5.4 ng/dl; p = 0.40), p = 0.011. Treatment differences at 3 months in 24-h and office systolic blood pressure (SBP) for RDN versus control patients were significantly greater for patients with baseline PRA ≥0.65 ng/ml/h versus <0.65 ng/ml/h, despite similar baseline BP. Differences in office SBP changes according to baseline PRA were also observed earlier at 2 weeks post-RDN.

CONCLUSIONS Plasma renin activity and aldosterone levels for RDN patients were significantly reduced at 3 months when compared with baseline as well as when compared with sham control. Higher baseline PRA levels were associated with a significantly greater reduction in office and 24-h SBP. (SPYRAL PIVOTAL - SPYRAL HTN-OFF MED Study; NCT02439749) (J Am Coll Cardiol 2021;77:2909–19) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; [b]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [c]Department of Interventional Cardiology, Piedmont Heart Institute, Atlanta, Georgia, USA; [d]Department of Cardiovascular Medicine and Department of Sleep and Circadian Cardiology, Jichi Medical University School of Medicine, Tochigi, Japan; [e]Department of Nephrology and Hypertension, Universitätsklinikum Erlangen, Erlangen, Germany; [f]Department of Cardiology, University of Athens, Hippocratio Hospital, Athens, Greece; [g]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; [h]Department of Cardiology, Providence Hospital, Southfield, Michigan, USA; [i]Department of Cardiology, Saint Joseph Mercy Oakland, Bloomfield Hills, Michigan, USA; [j]Department of Cardiology, The Alfred Hospital, Melbourne, Victoria, Australia; [k]Department of Cardiology, Klinikum Wels-Grieskirchen, Wels, Austria; [l]Coronary and Renal Denervation Division, Medtronic PLC, Santa Rosa, California, USA; and the [m]Department of Medicine, SUNY Downstate College of Medicine, Brooklyn, New York, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

DBP = diastolic blood pressure

PRA = plasma renin activity

RAAS = renin-angiotensin-aldosterone system

RDN = renal denervation

SBP = systolic blood pressure

Blood pressure (BP) reduction after renal denervation (RDN) has been demonstrated in several randomized, sham-controlled trials (1–3). Given the variability in BP response following RDN, a practical, predictable, noninvasive, and pre-procedural measure to identify optimal candidates for RDN therapies remains a major unmet need (4). The renin-angiotensin-aldosterone system (RAAS) plays a key role in BP regulation and is the target of several antihypertensive medications. RDN is thought to interrupt sympathetic activity and reduce hormones of the RAAS as part of its mechanism of action to reduce BP (5). In certain animal models, RDN significantly reduced plasma renin activity (PRA) and renal tissue norepinephrine (6,7). However, effects of RDN on the human RAAS, and in particular on PRA, are elusive because in previous studies, patients were prescribed antihypertensive medications, which affected renin and aldosterone levels and confounded the results (8–13). The present prespecified analysis of the SPYRAL HTN-OFF MED Pivotal trial (14,15) aimed to: 1) evaluate changes in PRA and aldosterone after RDN; and 2) examine whether baseline PRA predicts response to RDN in hypertensive patients in the absence of antihypertensive medications.

TABLE 1 Patient Demographics and Baseline BP Measurements for Pooled RDN and Sham Control Patients

	Baseline PRA		
	<0.65 ng/ml/h (n = 110)	≥0.65 ng/ml/h (n = 116)	p Value
Age, yrs	54.0 ± 9.8	50.6 ± 11.1	0.015
Male	60.0 (66)	69.0 (80)	0.17
BMI, kg/m^2	31.2 ± 6.6	30.1 ± 5.1	0.15
Race			0.010
White	27.3 (30)	31.9 (37)	
Black/African American	27.3 (30)	10.3 (12)	
Asian	2.7 (3)	6.0 (7)	
Other	0.9 (1)	0.9 (1)	
Not reportable per local laws	41.8 (46)	50.9 (59)	
Diabetes (all type 2)	1.8 (2)	0 (0)	0.24
Current smoker	17.3 (19)	17.2 (20)	1.00
Obstructive sleep apnea	5.5 (6)	7.8 (9)	0.60
Peripheral artery disease	0.9 (1)	0 (0)	0.49
Coronary artery disease	0.9 (1)	1.7 (2)	1.00
Prior myocardial infarction/ACS	0 (0)	0.9 (1)	1.00
Prior stroke or transient ischemic attack	0 (0)	0.9 (1)	1.00
Mean 24-h SBP, mm Hg	150.9 ± 7.5	150.5 ± 7.9	0.69
Mean 24-h DBP, mm Hg	98.3 ± 7.5	99.0 ± 6.9	0.51
Office SBP, mm Hg	162.2 ± 7.4	162.5 ± 7.7	0.76
Office DBP, mm Hg	100.9 ± 6.6	102.2 ± 7.2	0.16
Mean 24-h heart rate, beats/min	73.2 ± 10.6	76.5 ± 10.7	0.020
Office heart rate, beats/min	71.7 ± 10.2	75.4 ± 10.8	0.009

Values are mean ± SD or % (n).

ACS = acute coronary syndrome; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity; RDN = renal denervation; SBP = systolic blood pressure.

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METHODS

STUDY DESIGN AND RANDOMIZATION. The data, analytic methods, and study materials are owned by the sponsor and will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

SPYRAL HTN-OFF MED Pivotal is a multicenter, single-blind, randomized, sham-controlled trial conducted at 44 sites in Australia, Canada, Germany, Greece, Ireland, Japan, the United Kingdom, and the United States, and has been previously described (14,15). Adult patients (age 20 to 80 years) with office systolic blood pressure (SBP) ≥150 and <180 mm Hg, office diastolic blood pressure (DBP) ≥90 mm Hg, and a mean 24-h ambulatory SBP ≥140 and <170 mm Hg were enrolled in the trial. The trial complied with the Declaration of Helsinki, all local ethics committees approved the research protocol, and all patients provided written informed consent.

Full details of the randomization strategy have been described previously (14,15). Briefly, patients were randomized 1:1 to RDN or sham procedure. Prior to randomization, patients were required to be off all antihypertensive medications. Tandem high-performance liquid chromatography and mass spectroscopy of urine and plasma by an independent laboratory were used to evaluate and confirm absence of antihypertensive medication usage (16).

PROCEDURES. Treatment with the Symplicity Spyral multielectrode catheter (Medtronic, Galway, Ireland) and the Symplicity G3 (Medtronic, Minneapolis, Minnesota) generator was performed using a standardized approach of targeting all accessible renal arterial vessels, including branch vessels and accessory arteries with a diameter >3 to <8 mm (14,15). The sham procedure consisted of a renal angiogram only.

Office BP was measured in all patients at 2-week intervals after randomization, and patients remained off antihypertensive medications unless there were safety concerns related to uncontrolled hypertension. Office BP measurements were obtained via automatic BP monitor (Omron, Omron Healthcare, Inc., Lake Forest, Illinois). The same arm and BP cuff size were used for all office BP measurements, and the patient was seated comfortably, with legs uncrossed, back supported, and upper arm bared with no clothing between the arm and BP cuff. Three

TABLE 2 Laboratory Values at Baseline and Changes at 3 Months Post-Procedure in Patients Without Antihypertensive Medications

	Baseline		3 Months		Change at 3 Months, p Value for Difference From Baseline		
Measurement	RDN	Sham Control	RDN	Sham Control	RDN	Sham Control	p Value* RDN vs. Sham
Plasma renin activity, ng/ml/h							
N	115	111	115	113	105	104	
Mean ± SD	1.0 ± 1.1	1.1 ± 1.1	0.8 ± 0.9	1.2 ± 1.2	−0.2 ± 1.0	0.1 ± 0.9	0.001*
Median (IQR)	0.6 (0.3 to 1.4)	0.7 (0.4 to 1.4)	0.5 (0.2 to 1.0)	0.8 (0.5 to 1.5)	−0.1 (−0.4 to −0.01)	0.02 (−0.2 to 0.3)	
p value					0.019†	0.14†	
Aldosterone, ng/dl							
N	119	118	120	119	115	115	
Mean ± SD	8.3 ± 6.4	8.1 ± 6.5	7.3 ± 4.6	8.6 ± 5.7	−1.2 ± 6.4	0.4 ± 5.4	0.011*
Median (IQR)	7.0 (5.0 to 10.0)	6.0 (3.0 to 11.0)	6.0 (4.0 to 10.0)	8.0 (5.0 to 11.0)	−1.0 (−3.0 to 2.0)	0.00 (−2.0 to 3.0)	
p value					0.04†	0.40†	
Aldosterone renin ratio							
N	113	111	112	113	101	104	
Mean ± SD	10.9 ± 8.4	9.6 ± 8.1	11.5 ± 9.5	10.0 ± 8.0	−0.1 ± 7.8	0.3 ± 6.6	0.92*
Median (IQR)	8.3 (4.2 to 16.0)	7.1 (4.0 to 12.0)	9.2 (4.4 to 16.0)	7.2 (4.0 to 13.8)	0.0 (−4.0 to 3.1)	−0.3 (−2.8 to 2.5)	
p value					0.88†	0.60†	
Serum creatinine, mg/dl							
N	126	122	126	121	126	121	
Mean ± SD	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	−0.01 ± 0.1	0.0 ± 0.1	0.87*
Median (IQR)	0.9 (0.8 to 1.0)	0.9 (0.8 to 1.0)	0.9 (0.8 to 1.0)	0.9 (0.8 to 1.0)	0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.1)	
p value					0.22†	0.71†	
eGFR, ml/min/1.73 m^2							
N	126	122	126	121	126	121	
Mean ± SD	85.3 ± 15.6	88.7 ± 16.9	86.0 ± 14.8	89.1 ± 15.6	0.7 ± 10.9	0.2 ± 11.6	0.70*
Median (IQR)	84.7 (74.2 to 93.6)	87.4 (77.6 to 97.9)	86.6 (76.4 to 96.3)	88.1 (77.2 to 100.8)	0.0 (−7.1 to 8.9)	0.0 (−6.2 to 7.4)	
p value					0.45†	0.86†	
Potassium, mmol/l							
N	126	122	126	121	126	121	
Mean ± SD	4.3 ± 0.4	4.2 ± 0.4	4.3 ± 0.4	4.2 ± 0.5	0.0 ± 0.4	0.03 ± 0.5	0.98*
Median (IQR)	4.2 (4.0 to 4.5)	4.2 (4.0 to 4.4)	4.3 (4.0 to 4.5)	4.2 (4.0 to 4.4)	0.0 (−0.2 to 0.2)	0.0 (−0.2 to 0.2)	
p value					0.89†	0.53†	
Sodium, mmol/l							
N	126	122	126	121	126	121	
Mean ± SD	139.7 ± 2.2	140.2 ± 2.2	139.9 ± 2.1	139.7 ± 2.1	0.2 ± 2.1	−0.5 ± 2.2	0.055*
Median (IQR)	140.0 (138.0 to 141.0)	140.0 (139.0 to 142.0)	140.0 (139.0 to 141.0)	140.0 (138.0 to 141.0)	0.0 (−1.0 to 1.0)	0.0 (−2.0 to 1.0)	
p value					0.24†	0.014†	

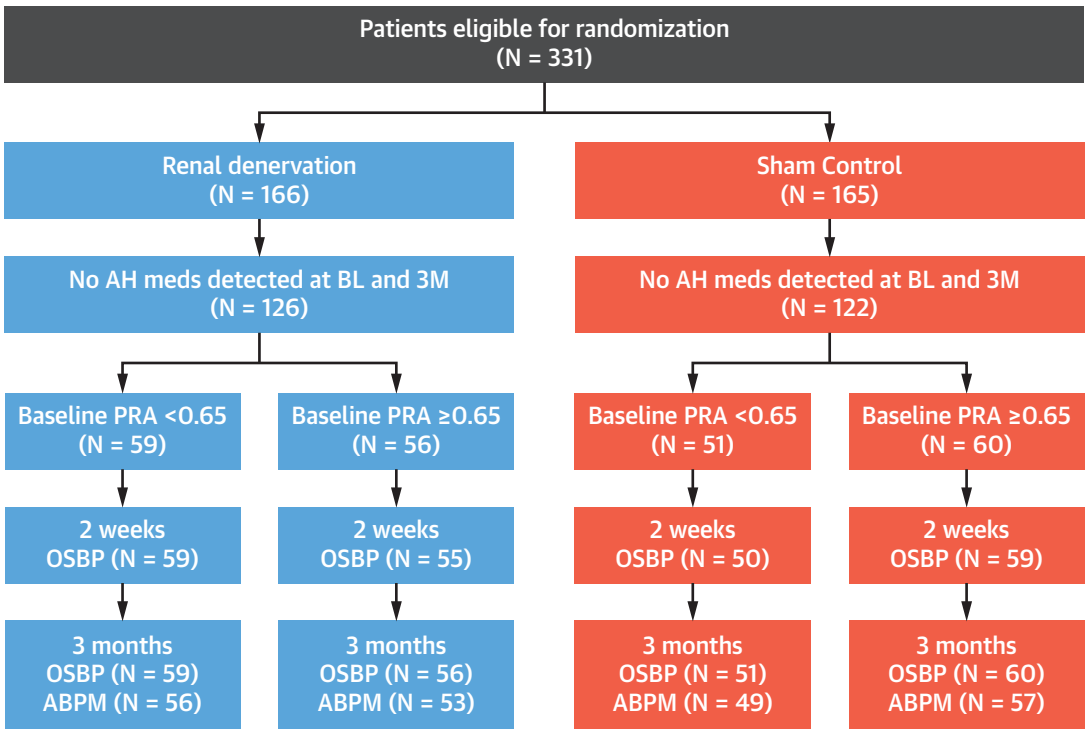
*p values from analysis of covariance regression model adjusting for baseline value. †p values from paired Student's *t*-tests.
eGFR = estimated glomerular filtration rate; IQR = interquartile range; RDN = renal denervation.

seated BP measurements were obtained, with at least 1 min between each measurement, to obtain an average measurement for the visit.

The 24-h BP measurements were obtained using an ambulatory BP monitor (Mobil-O-Graph, I.E.M GmbH, Stolberg, Germany). The same BP cuff size was used for all ambulatory measurements using the patient's nondominant arm. The 24-h BP measurements were considered valid if at least 21 daytime readings and 12 night-time readings were recorded.

Plasma renin activity, aldosterone, and aldosterone renin ratio levels were evaluated at a core laboratory (ACM Global Laboratories, Rochester, New York) at baseline and 3 months post-procedure. Patients abstained from all antihypertensive medications and were requested to fast prior to testing. Patients had to be out of bed for at least 2 h, after resting and quietly sitting for a minimum of 5 min but preferably 30 min before blood was sampled. The time of day and patient's position (standing, sitting, or lying down) during blood sampling was documented. The same time of day (± 2 h) and patient's position was used for collection of blood samples at later time points. All other laboratory values were

FIGURE 1 Patient Flow Diagram



Of the 331 patients eligible for randomization in the SPYRAL HTN-OFF MED Pivotal trial, 166 were randomized to renal denervation and 165 to sham control. Our analysis was restricted to patients free of antihypertensive medications at baseline and 3 months. Patients were then divided into 2 groups based on baseline plasma renin activity <0.65 or ≥0.65 ng/ml/h. Numbers of patients with available office and 24-h BP measurements at 2 weeks and 3 months are also shown. 3M = 3 months; ABPM = ambulatory blood pressure measurements; AH = antihypertensive; BL = baseline; OSBP = office systolic blood pressure; PRA = plasma renin activity.

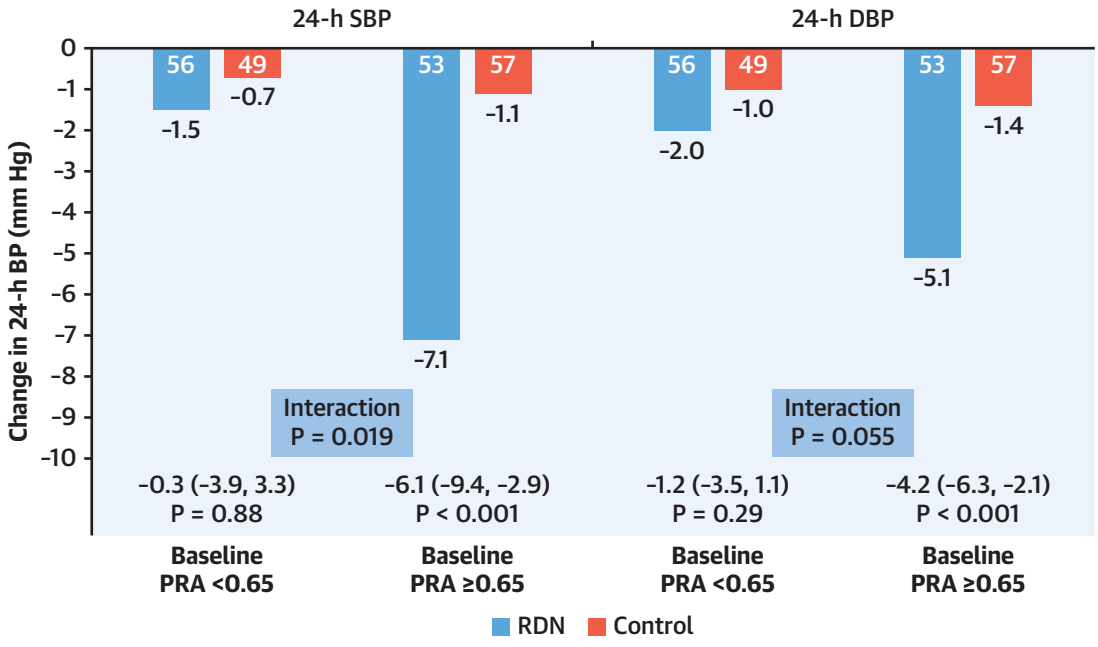
measured at local laboratories. As suggested in previous studies (17,18), patients were graded into low versus normal PRA using a cut-off of 0.65 ng/ml/h.

STATISTICAL ANALYSIS. The aim of this pre-specified subgroup analysis of the SPYRAL HTN-OFF MED Pivotal trial was to compare BP changes in patients with baseline PRA ≥0.65 ng/ml/h and <0.65 ng/ml/h (18). Enrollment was not stratified per baseline PRA. Only patients with no antihypertensive medications at baseline or 3 months were included in the analysis. Multivariable linear regression models were used to test for a significant interaction between patients with baseline PRA <0.65 ng/ml/h versus ≥0.65 ng/ml/h and the treatment group. Patients were also divided into 4 groups based on quartiles of baseline PRA, and treatment differences between the quartiles were compared using interaction tests for trend. Baseline continuous variables are summarized as mean ± SD and were compared using Student's *t*-tests. Within each treatment arm, paired Student's *t*-tests were used to compare changes in continuous variables from baseline to follow-up. Categorical variables were summarized as counts and percentages and were compared between groups using chi-square or Fisher exact tests for categorical variables. For continuous measures, follow-up treatment differences between RDN and sham control groups were determined using analysis of covariance models adjusting for baseline values. Statistical analyses were performed using SAS for Windows version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

For patients with no antihypertensive medications measured in urine or plasma at baseline or at 3 months, there were 110 patients with baseline PRA <0.65 ng/ml/h and 116 patients with baseline PRA ≥0.65 ng/ml/h. Patients with baseline PRA ≥0.65 ng/ml/h were younger and had higher baseline HR (Table 1). Importantly, office and ambulatory BP values were similar for patients with baseline PRA <0.65 ng/ml/h versus ≥0.65 ng/ml/h:

FIGURE 2 Changes in 24-h BP for Baseline PRA <0.65 and ≥0.65 ng/ml/h



Changes in 24-h SBP and DBP at 3 months are compared for RDN and sham control patients with baseline PRA <0.65 and ≥0.65 ng/ml/h. Follow-up treatment differences between RDN and sham control groups were determined using analysis of covariance models adjusting for baseline values. Changes in 24-h SBP and DBP for patients with baseline PRA ≥0.65 ng/ml/h were significantly greater for RDN compared with sham control patients ($p < 0.001$ for both). The interaction p value was significant for 24-h SBP ($p = 0.019$) suggesting that the effect of RDN on 24-h SBP reduction differs based on baseline PRA. BP = blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity; RDN = renal denervation; SBP = systolic blood pressure.

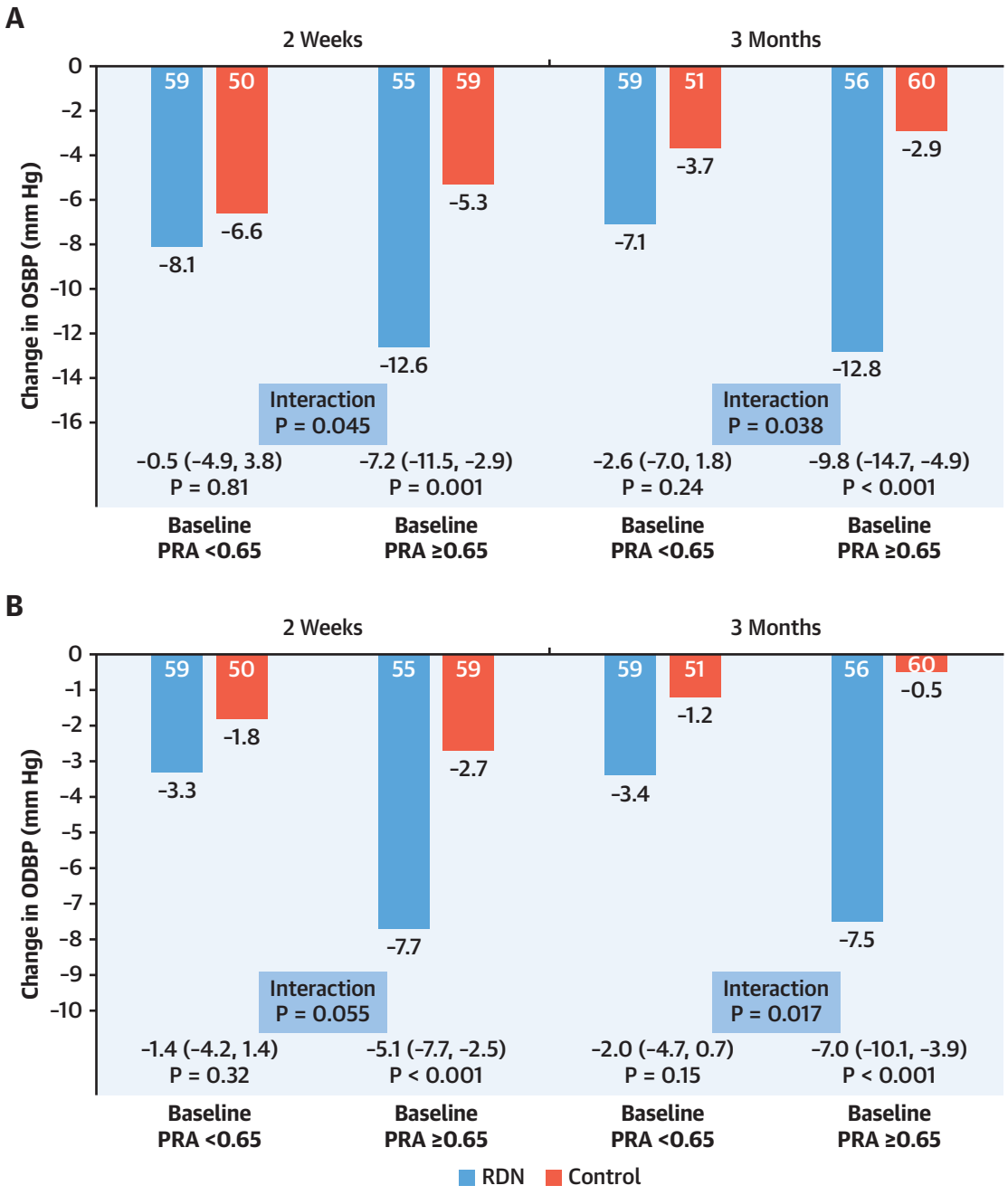
baseline 24-h SBP was 150.9 ± 7.5 mm Hg versus 150.5 ± 7.9 mm Hg; $p = 0.69$, and baseline office SBP was 162.2 ± 7.4 mm Hg versus 162.5 ± 7.7 mm Hg; $p = 0.76$.

Mean baseline PRA was similar between RDN and sham control groups (1.0 ± 1.1 ng/ml/h vs. 1.1 ± 1.1 ng/ml/h; $p = 0.37$) (Table 2). Change in PRA from baseline to 3 months was significantly greater for RDN (−0.2 ± 1.0 ng/ml/h; $p = 0.019$) compared with the sham control group (0.1 ± 0.9 ng/ml/h; $p = 0.14$); $p = 0.001$ for RDN versus sham control group. Similarly, change in aldosterone from baseline to 3 months was significantly greater for RDN (−1.2 ± 6.4 ng/dl; $p = 0.04$) compared with the sham control group (0.4 ± 5.4 ng/dl; $p = 0.40$); $p = 0.011$ for RDN versus sham control group.

Changes in BP at 2 weeks and 3 months were compared for RDN and sham control group based on baseline PRA (Figure 1). For 24-h SBP, treatment difference at 3 months was −0.3 mm Hg (95% confidence interval [CI]: −3.9 to 3.3 mm Hg); $p = 0.88$ for baseline PRA <0.65 ng/ml/h and −6.1 mm Hg (95% CI: −9.4 to −2.9 mm Hg); $p < 0.001$ for baseline PRA ≥0.65 ng/ml/h (interaction $p = 0.019$) (Figure 2). For 24-h DBP, treatment difference at 3 months was −1.2 mm Hg (95% CI: −3.5 to 1.1); $p = 0.29$ for baseline PRA <0.65 ng/ml/h and −4.2 mm Hg (95% CI: −6.3 to −2.1); $p < 0.001$ for baseline PRA ≥0.65 ng/ml/h (interaction $p = 0.055$) (Figure 2).

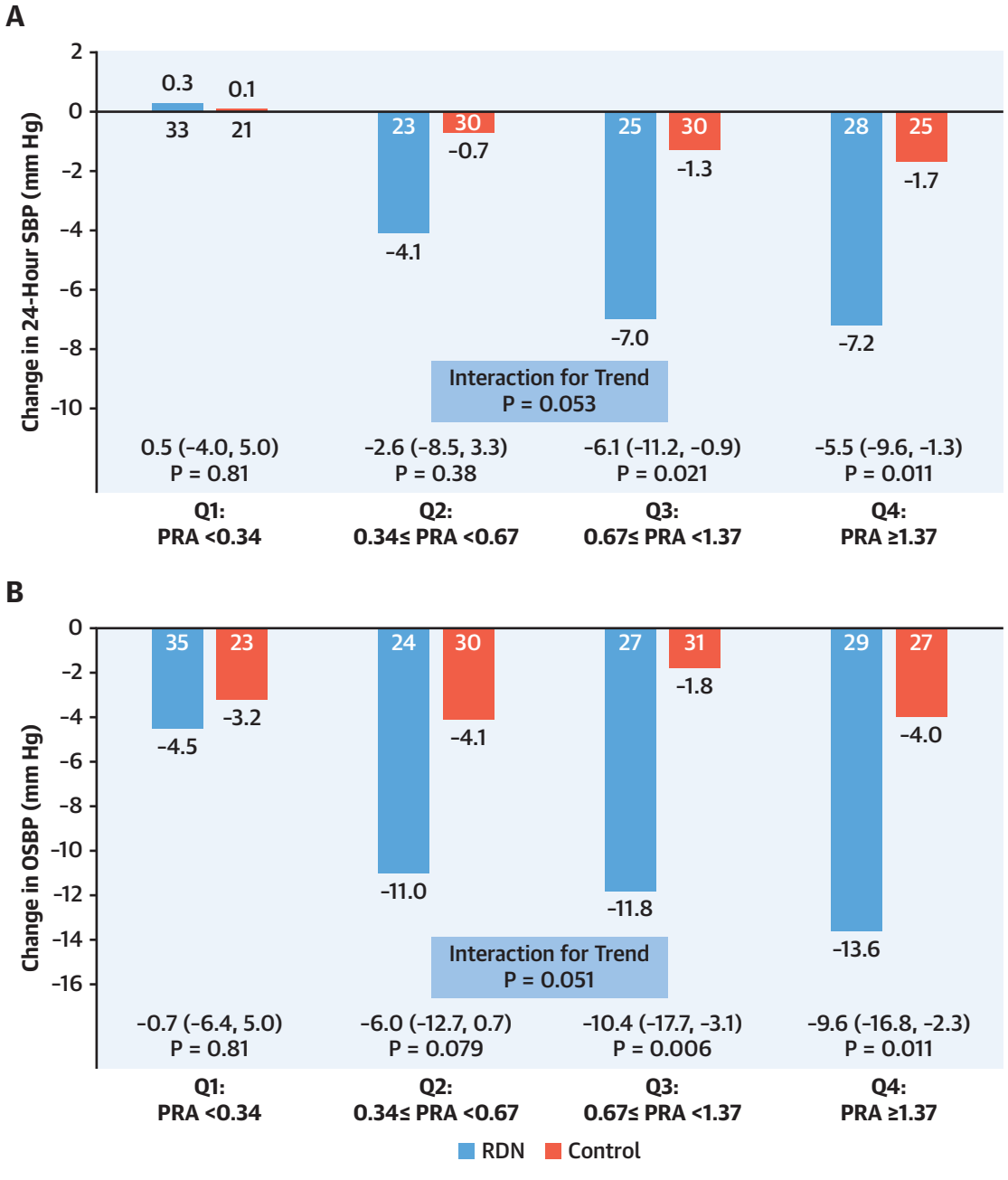
Similarly, treatment differences for RDN versus sham control group at 3 months for office SBP (Figure 3A) and office DBP (Figure 3B) were greater for patients with baseline PRA ≥0.65 ng/ml/h. For office SBP, treatment difference at 3 months was −2.6 mm Hg (95% CI: −7.0 to 1.8 mm Hg); $p = 0.24$ for baseline PRA <0.65 ng/ml/h and −9.8 mm Hg (95% CI: −14.7 to −4.9 mm Hg); $p < 0.001$ for baseline PRA ≥0.65 ng/ml/h (interaction $p = 0.038$). For office DBP, treatment difference at 3 months was −2.0 mm Hg (95% CI: −4.7 to 0.7 mm Hg); $p = 0.15$ for baseline PRA <0.65 ng/ml/h and −7.0 mm Hg (95% CI: −10.1 to −3.9 mm Hg); $p < 0.001$ for baseline PRA ≥0.65 ng/ml/h (interaction $p = 0.017$). Treatment differences in office SBP and DBP at 2 weeks post-procedure were also examined, and consistently greater BP reduction in the baseline PRA ≥0.65 ng/ml/h group was seen.

FIGURE 3 Changes in Office BP for Baseline PRA <0.65 and ≥0.65 ng/ml/h



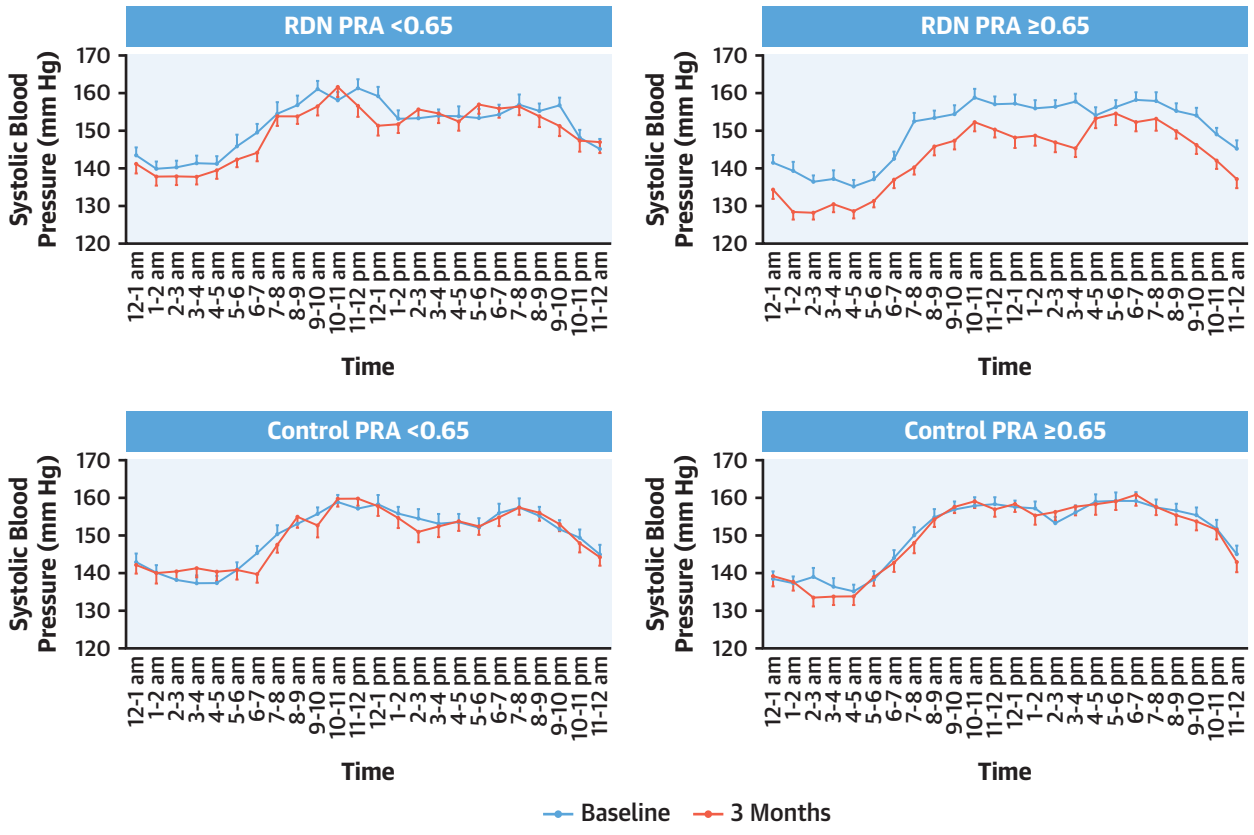
Changes in office SBP and DBP at 2 weeks and 3 months are compared for RDN and sham control patients with baseline PRA <0.65 and ≥0.65 ng/ml/h. Follow-up treatment differences between RDN and sham control groups were determined using analysis of covariance models adjusting for baseline values. Changes in office SBP and DBP at 2 weeks and 3 months for patients with baseline PRA ≥0.65 ng/ml/h were significantly greater for RDN compared with sham control patients ($p < 0.001$ for all). Interaction p values were significant for office SBP at 2 weeks ($p = 0.045$) and 3 months ($p = 0.038$), as well as office DBP at 3 months ($p = 0.017$), suggesting that the effect of RDN on BP reduction differs based on baseline PRA in these cases. OSBP = office systolic blood pressure; other abbreviations as in Figure 2.

FIGURE 4 Quartile Analysis of Changes in 24-h and Office SBP Based on Baseline PRA (ng/ml/h)



Changes in **(A)** 24-h and **(B)** office SBP at 3 months are compared for RDN and sham control patients according to quartiles of baseline PRA. Follow-up treatment differences between RDN and sham control groups were determined using analysis of covariance models adjusting for baseline values. Changes in 24-h and office SBP for patients in the 2 largest quartiles of baseline PRA were significantly greater for RDN compared with sham control patients. Changes in 24-h and office SBP for patients in the 2 smallest quartiles of baseline PRA were similar for RDN compared with sham control. However, interaction p values were not significant. Abbreviations as in Figures 2 and 3.

FIGURE 5 Hourly Ambulatory SBP Measurements for Baseline PRA <0.65 and ≥0.65 ng/ml/h



Changes in ambulatory SBP from baseline to 3 months were examined for RDN and sham control patients with baseline PRA <0.65 and ≥0.65 ng/ml/h. Control patients with baseline PRA <65 and ≥0.65 ng/ml/h had similar hourly SBP measurements at baseline and 3 months. Hourly blood pressure plots for RDN patients with baseline PRA ≥0.65 ng/ml/h show reduction in hourly SBP measurements at 3 months compared to baseline, but less difference in hourly SBP measurements for RDN patients with baseline PRA <0.65 ng/ml/h. Abbreviations as in Figure 2.

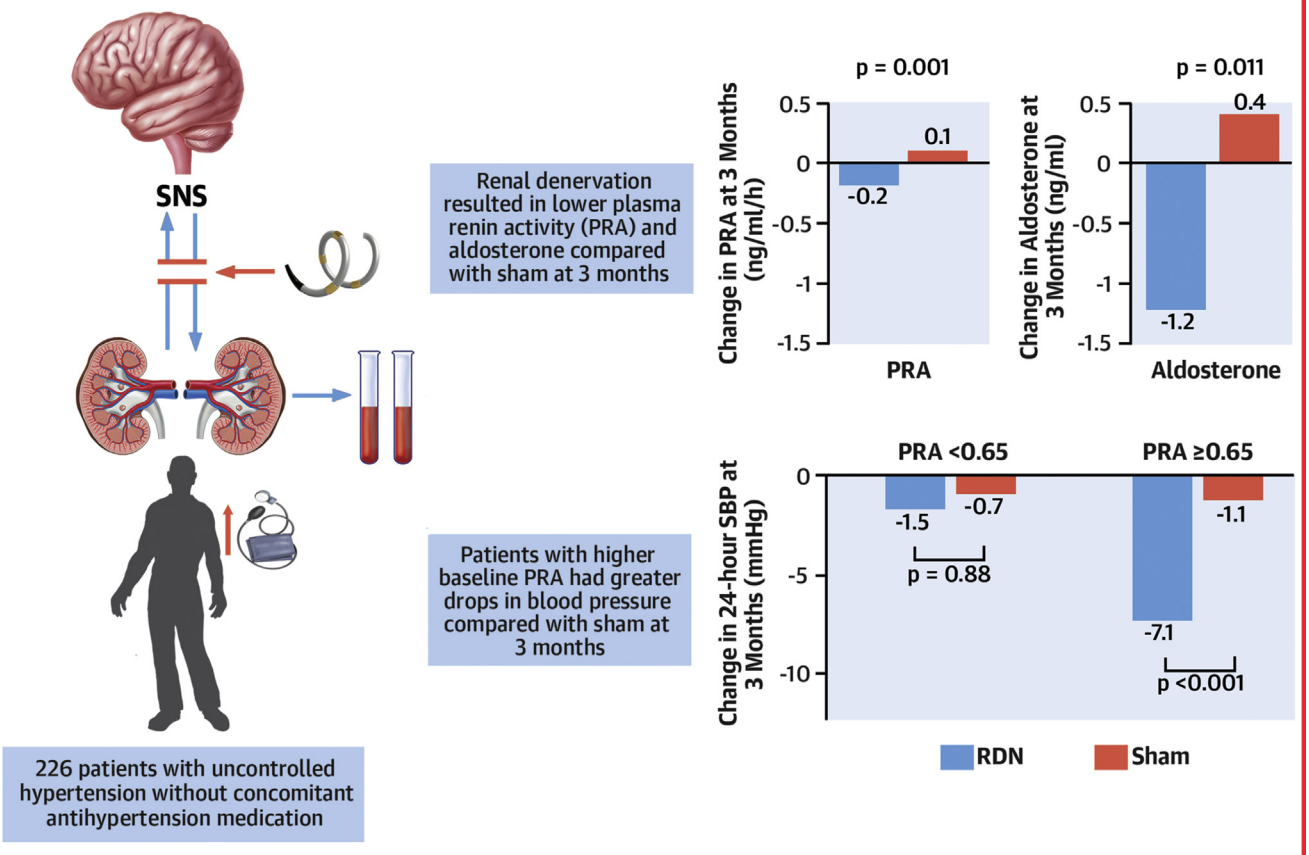
Quartile analysis of changes in office and 24-h SBP at 3 months showed greater reduction in BP for RDN patients in the highest 2 quartiles of baseline PRA, although the trends did not reach statistical significance (trend $p = 0.051$ for office SBP and $p = 0.053$ for 24-h SBP) (Figure 4). A similar evaluation by tertiles of aldosterone demonstrated no significant relationship of baseline aldosterone levels with office or 24-h systolic BP changes at 3 months (Supplemental Figure 1).

The 3-month changes in 24-h SBP also showed greater BP reduction for the RDN group with baseline PRA ≥0.65 compared with baseline PRA <0.65 ng/ml/h (Figure 5).

DISCUSSION

The major findings from this pre-specified analysis are: 1) PRA and aldosterone were significantly reduced in the RDN group compared with the sham control group at 3 months; and 2) treatment differences at 3 months between RDN and sham control groups for office and 24-h SBP were significantly greater for patients with baseline PRA ≥0.65 ng/ml/h (Central Illustration). To our knowledge, this is the first report of significant reductions in PRA and aldosterone in a randomized trial comparing RDN with sham control in patients not treated with concomitant antihypertensive medication. The data also identified PRA as a potential predictor of response to RDN when antihypertensive drugs are not present, although further confirmatory studies are warranted, and it would likely be one of several predictive factors. Of interest is that differences in office SBP reduction for patients with baseline PRA <0.65 ng/ml/h versus ≥0.65 ng/ml/h were seen as early as 2 weeks post-procedure. However, the effect could have occurred far sooner, but first BP measurements were obtained only 2 weeks post-procedure. These findings are consistent with drug studies

CENTRAL ILLUSTRATION **Impact of Renal Denervation on Plasma Renin Activity, Aldosterone, and Blood Pressure Reduction at 3 Months**



Mahfoud, F. et al. J Am Coll Cardiol. 2021;77(23):2909–19.

Renal denervation (RDN) targets the renal nerves to reduce sympathetic nervous system activity with the goal of lowering blood pressure. Laboratory measurements at 3 months show significantly greater reductions in plasma renin activity (PRA) and aldosterone in the RDN group compared to sham control. Treatment difference for change in mean 24-h systolic blood pressure for RDN versus sham control at 3 months was greater for patients with baseline PRA ≥0.65 ng/ml/h, compared with those with baseline PRA <0.65 ng/ml/h. SBP = systolic blood pressure; SNS = sympathetic nervous system.

(including beta-blockers and angiotensin-converting enzyme inhibitors) in which BP reductions were greater in patients with high or normal renin levels than in low-renin patients (19,20).

The enzyme renin is secreted by the kidneys in response to efferent sympathetic stimulation and increases BP primarily by producing arterial vasoconstriction through angiotensin II activation (21). RDN is hypothesized to lower BP by interrupting both afferent and efferent renal nerve signaling (22). Renal efferent nerve ablation has been associated with reduced PRA levels in multiple animal models of hypertension (6,7,23–25). The results in humans are inconsistent with an early human case report in which catheter-based RDN reduced PRA (9), whereas several clinical trials have reported no change in PRA following RDN (10–13). Invariably, these trials included patients with uncontrolled hypertension prescribed several antihypertensive drugs, many of them affecting RAAS activity. Consistent with the reduction in renin levels, a difference in aldosterone levels between groups at 3 months was found in this study. The absence of a relationship of aldosterone levels with BP response following RDN, however, likely reflects the impact of factors other than PRA on aldosterone secretion, including potassium and sodium levels, volume status, and ACTH.

Recent sham-controlled trials have proven the BP-lowering efficacy of RDN in patients with uncontrolled hypertension (1–3,14). A common feature of all RDN trials is the variability of the treatment effect among patients (26). Thus, the identification of patients with a high likelihood of a relevant BP lowering by using a practical, predictable, noninvasive, and pre-

procedural measure remains a major unmet need (4). The most commonly identified predictor of response to RDN is high baseline SBP (27–31), which in part also relates to the statistical phenomenon of regression to the mean (32). Arterial stiffness measured by invasive pulse wave velocity has also been proposed (33), as well as noninvasive surrogates as determined by pulse wave analysis (34) or total arterial compliance (35), all of which may be markers of sympathetic activity. In the present study, baseline PRA ≥0.65 ng/ml/h was associated with significantly greater BP reduction after RDN for 24-h SBP, office SBP, and DBP at 3 months in patients without antihypertensive medications. It is likely that RDN affects PRA levels as part of its mechanism of action; thus, higher baseline PRA levels could predict a greater BP reduction. Herein, we used a cut-off of 0.65 ng/ml/h, as used in a comparison of responders and nonresponders of BP reduction to angiotensin-converting enzyme inhibitors (18). For use as a predictor of response, the optimal PRA cut-off will need to be determined prospectively after prospectively powered studies in patients with and without antihypertensive medications, and baseline PRA may be only one of several predictive factors.

STUDY LIMITATIONS. Not all patients were adherent to the protocol requirement to abstain from all antihypertensive medications, but we restricted the analysis to patients who were determined medication-free by plasma and urine drug testing. Alterations in sodium intake may have influenced the results. However, sodium intake and urinary sodium excretion were not systematically assessed in this randomized, sham-controlled trial, but are unlikely to be imbalanced between the groups. Furthermore, the influence of baseline PRA levels on response to RDN will be more complex to interpret in the presence of antihypertensive medications in a real-world setting. Although statistically significant changes were documented, and the trial design allowed robust comparisons between treated and sham-controlled patient groups, this pre-specified analysis was not powered to detect differences in BP reduction for different levels of baseline PRA or aldosterone. No statistical adjustments were made for multiple comparisons.

CONCLUSIONS

Radio-frequency RDN with the multielectrode Symplicity Spyral system in patients with hypertension who were not taking antihypertensive medications was associated with decreased PRA and aldosterone levels at 3 months compared with a blinded sham-controlled group. In addition, patients with baseline PRA ≥0.65 ng/ml/h had greater 24-h and office SBP reduction at 3 months compared with patients with baseline PRA <0.65 ng/ml/h. These differences emerged by 2 weeks following RDN, indicating that the procedure affects renal physiology as early as 2 weeks following treatment.

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ADDRESS FOR CORRESPONDENCE: Prof. Felix Mahfoud, Saarland University Hospital, Department of Cardiology, Angiology and Intensive Care Medicine, Kirrberger Str. 100, IMED 66421 Homburg/Saar, Germany. E-mail: Felix.Mahfoud@uks.eu. Twitter: @FelixMahfoud.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Plasma renin activity and aldosterone levels are significantly reduced 3 months after renal artery sympathetic denervation.

TRANSLATIONAL OUTLOOK: Additional studies are needed to elucidate the relationship between renal sympathetic activity and the RAAS in patients with hypertension.

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APPENDIX For a supplemental figure, please see the online version of this paper.