Does the Presence of Accessory Renal Arteries Affect the Efficacy of Renal Denervation?

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Objectives This study sought to assess the efficacy of catheter-based renal sympathetic denervation in patients with accessory renal arteries and to compare the blood pressure (BP)-lowering effect with that observed in patients with bilateral single renal arteries after renal denervation.

Background Catheter-based renal sympathetic denervation causes significant BP reductions in patients with resistant hypertension.

Methods Seventy-four patients were included in this study. Patients were assigned to 2 main groups: a bilateral single renal arteries group I (n = 54) and an accessory renal arteries group II (n = 20). Group II consisted of 9 patients whose accessory renal arteries were all denervated (group IIa), and 11 patients whose accessory renal arteries were not, or only incompletely, denervated (group IIb). The primary endpoint was the change in office systolic BP after 6 months.

Results The procedure was successful in all patients. Group I: mean BP at baseline was 166.2/89.4 ± 20.5/14.6 mm Hg and decreased by −16.6 (p < 0.001)/−6.7 (p = 0.016) ± 16.4/11 mm Hg at 6-month follow-up. Group II: mean BP at baseline was 164.2/89.1 ± 19.9/15.4 mm Hg and decreased by −6.2 (p = 0.19)/−0.2 (p = 0.5) ± 19.7/11.3 mm Hg at 6-month follow-up. Patients in group IIa had an office BP reduction of −8.8 (p = 0.2)/1.1 ± 17.9/10.8 mm Hg and patients in group IIb of −4.1 (p = 0.55)/−1.3 ± 20.8/11.6 mm Hg. Similarly, significant improvements in 24-h mean systolic BP were seen in group I (−8.3 ± 17.4 mm Hg, p < 0.01), whereas none were seen in group II (−3.7 ± 8.3 mm Hg, p = 0.38).

Conclusions BP reduction achieved after renal denervation in patients with accessory renal arteries is less pronounced than in patients with bilateral single renal arteries.   (J Am Coll Cardiol Intv 2013;6:1085–91) © 2013 by the American College of Cardiology Foundation

Arterial hypertension is a major risk factor for cardiovascular, cerebrovascular, and renal morbidity and mortality (1). Approximately 30% to 40% of the adult population has arterial hypertension, and the prevalence is expected to increase (2). Despite maximal medical management, depending on the population studied, the blood pressure (BP) remains suboptimally controlled in approximately 10% of individuals (3,4). Under these circumstances, catheter-based renal sympathetic denervation has been shown to cause a significant BP reduction (5,6). Renal sympathetic nerves are located primarily in the adventitia of the arteries supplying the kidneys. The design of the most commonly used catheter allows denervation in arteries 4 mm or larger in diameter. However, accessory renal arteries, including dual renal

arteries and early separation of pole arteries (Fig. 1), are found in approximately 20% to 27% of patients (7–9). These arteries are frequently smaller than 4 mm and therefore not amenable to ablation with the currently approved device. Nonetheless, they supply the kidney with sympathetic nerve fibers. Therefore, due to concerns of incomplete denervation, patients with accessory renal arteries have traditionally been excluded from trial participation (5,10) or have not been analyzed as a separate subgroup (6). Moreover, a case report suggests a less pronounced BP reduction after incomplete denervation (11). A less pronounced or absent BP reduction is conceivable in patients with accessory renal arteries in whom only those arteries amenable to catheter ablation are treated. In addition, due to limitations in catheter manipulation in the typically smaller accessory renal arteries, even if all arteries are treated, a less pronounced BP reduction than reported in previous trials may be expected. Importantly, the efficacy of renal denervation in

**Abbreviations
and Acronyms**

BP = blood pressure

eGFR = estimated glomerular filtration rate

patients with accessory renal arteries has not been studied. Therefore, the purpose of the current study is to determine whether renal denervation in patients with accessory renal arteries (whether or not denervation in all renal arteries was feasible) reduces BP to a similar degree as in patients with bilateral single renal arteries.

Methods

Study design and patients. This is a single-center, non-randomized, uncontrolled retrospective analysis of hypertensive patients with special anatomic considerations. Patients age ≥18 years with a baseline systolic office BP of ≥140 mm Hg despite 3 or more antihypertensive agents were eligible for inclusion. Only patients with secondary causes of hypertension were excluded.

Eligible patients were allocated to 2 groups: single renal arteries only supplying both kidneys (group I) and accessory renal arteries including those with more than 1 renal artery supplying either kidney (group II). Importantly, patients were considered to have accessory renal arteries if 1 or both kidneys were supplied by dual main renal arteries of similar size, 1 main and 1 or more additional renal arteries supplying either the upper or lower pole, or a very early separation of a pole artery from the main renal artery (Fig. 1). Group II was further divided into 2 subgroups, group IIa including patients with accessory renal arteries with denervation of all arteries, and group IIb including patients with accessory renal arteries with denervation of only the main renal artery or some, but not all, accessory renal arteries.

The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent for the procedure, follow-up, and data analysis.

Procedure. Renal denervation was performed with the Symplicity catheter system (Medtronic, Mountain View, California), including a radiofrequency catheter and a radiofrequency generator. Before the treatment, patients received a sedative, for example, midazolam, and an analgesic, for
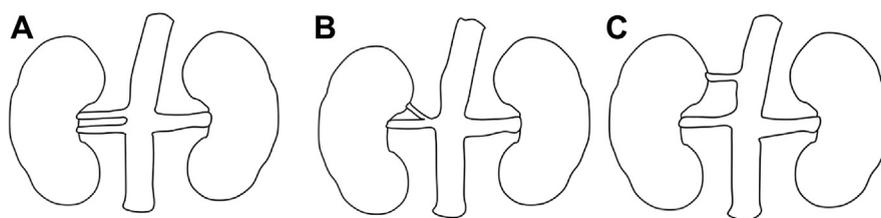
Figure 1. Anatomic Variations of ARAs

(A) Demonstrates dual renal artery supply to the right kidney with similarly sized renal arteries. **(B)** Shows a very early separation of a right pole artery. **(C)** Illustrates a separate right upper pole renal artery. ARA = accessory renal artery.

example, morphine, and appropriate systemic anticoagulation with unfractionated intravenous heparin with a target activated clotting time >250 s. Femoral arterial access was obtained with a 6-F sheath. First, nonselective angiography of the abdominal aorta was performed to outline the anatomy and to assess for the presence of accessory renal arteries. Subsequently, selective angiography of all renal arteries was performed with a 6-F guide catheter (typically internal mammary or renal double curve). Common treatment strategy in the main renal arteries includes the application of radiofrequency energy in a circumferential manner, aiming at a minimum of 4 ablation points at 8 W, as previously described (5,6). In the case of multiple renal arteries, ablation was performed in all arteries with a suitable diameter (>3.5 mm). To avoid vessel injury, accessory arteries measuring ≤3.5 mm were not treated. Final angiography was performed to rule out acute renal artery injury.

Outcome analysis. Baseline data collection included a detailed medical history, vital signs including heart rate, 3 office BP measurements according to The Joint National Committee guidelines for accurate office BP measurements (the average of which was used for data analysis), 24-h ambulatory BP measurement and serum creatinine. At 6-month follow-up, baseline examination was repeated with an accepted time window of ±2 weeks. In addition, bilateral renal artery duplex imaging was performed to rule out renal artery stenosis. If duplex ultrasound detected questionable findings, especially in accessory renal arteries, computed tomography angiography or magnetic resonance angiography was performed.

Medication history and adverse events were reported at baseline and at 6-month follow up.

The primary endpoint was the change in average office BP at 6-month follow-up compared with baseline. The BP changes between the groups and subgroups were compared. Secondary endpoints were the change in mean systolic 24-h ambulatory BP and the number of antihypertensive medications at 6-month follow-up compared with baseline. Safety endpoints included procedural complications and renal artery stenosis at follow-up, as well as renal function assessed by estimated glomerular filtration rate (eGFR).

Statistical analysis. The values of all test parameters are presented as the mean ± SD. Within-group analyses were performed with paired 2-tailed *t* tests comparing baseline and 6-month values. Of note, there was no correction for multiple comparisons. To compare BP reductions between groups, an unpaired *t* test (group I vs. group II) and a 1-way analysis of variance with the Dunnett post hoc test for multiple comparisons (group I vs. IIa, and group I vs. group IIb) were used. A 2-tailed p value of <0.05 was considered statistically significant. The statistical analyses were performed with GraphPad InStat for Windows (version 3.10, GraphPad Software, La Jolla, California).

Results

All consecutive patients who underwent renal denervation between February 2009 and January 2012 and completed the 6-month follow-up were screened for eligibility. Seventy-four patients were enrolled, of whom 24 patients were treated within a therapeutic renal denervation trial. Fifty-four patients had single renal arteries only (group I), and in 20 patients (group II), accessory renal arteries were present. Of the patients with accessory renal arteries, 17 patients had unilateral and 3 patients bilateral accessory renal arteries (Table 1). In 9 patients, all renal arteries, including accessory arteries, were denervated (group IIa), whereas in 11 patients, none or only some of the accessory renal arteries were denervated (group IIb). Baseline characteristics are outlined in Table 2.

Mean office BP at baseline was 166.2/89.4 ± 20.5/14.6 mm Hg in group I and 164.2/89.1 ± 19.9/15.35 mm Hg in group II (group IIa: 163.6/93.8 ± 27/18.4 mm Hg; IIb: 164.6/85.3 ± 13.1/11.9 mm Hg). Baseline ambulatory BP was available in 54 patients in group I and in 18 patients in group II (IIa: 8; IIb: 10). Ambulatory BP at baseline was 156.0/85.6 ± 16.3/12.6 mm Hg (group I) and 151.9/86.4 ± 16.3/14.6 mm Hg (group II). Heart rate at baseline was 66.9 ± 12.6 beats/min in group I and 67.6 ± 11.5 beats/min in group II. Mean number of antihypertensive medications at baseline was 4.2 ± 1.4 (group I) and 4.4 ± 1.4 (group II). Details regarding antihypertensive medications are shown in Table 3. Baseline eGFR was 81.6 ± 22.4 ml/min/1.73 m^2 (group I) and 84.7 ± 23.2 ml/min/1.73 m^2 (group II).

During the procedure, there were no serious adverse events related to the device or procedure. Two patients

Table 1. Characteristics of Renal Artery Anatomy in Patients With ARA (Group II)

Characteristics of Renal Artery Anatomy	Group IIa (ARA): Completely Denervated (n = 9)	Group IIb (ARA): Incompletely Denervated (n = 11)
Unilateral accessory arteries	8	9
Left side	2	2
Right side	6	7
Separate renal artery	0	3
Early bifurcation with pole artery	1	6
Dual main arteries	7	0
Bilateral accessory arteries	1	2
Separate renal artery	0	0
Early bifurcation with pole artery	1	2
Dual main arteries	1	2

Values are n.
ARA = accessory renal artery.

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Table 2. Baseline Characteristics of All Treated Patients

	Group I (BSRA) (n = 54)	Group II (ARA) (n = 20)	Group IIa (Complete) (n = 9)	Group IIb (Incomplete) (n = 11)
Mean age, yrs	64.5	59.1	54.1	63.8
Female, %	38.9	35	22.3	45.5
Mean office BP, mm Hg	166.2/89.5	164.2/89.1	163.6/93.8	164.6/85.3
Mean 24-h BP, mm Hg	156.0/85.6	151.9/86.5	151.9/90.9	152/83
Mean heart rate, beats/min	66.9	67.6	66.8	68.4
Mean eGFR, ml/min/1.73 m^2	81.6	84.7	92.4	78.3
Diabetes mellitus type 2, n	12	7	3	4
CAD, n	19	6	4	2
PAD, n	11	3	1	2
Hyperlipidemia, n	9	6	2	4

ARA = accessory renal artery; BP = blood pressure; BSRA = bilateral single renal artery; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; PAD = peripheral artery disease.

experienced transient renal artery spasm during the procedure (1 patient from group I, and 1 from group IIb). Mean number of ablations in group I was 5.8 ± 1.4 on the right side and 5.7 ± 1.7 on the left side, and 6.0 ± 1.6 on the right side and 6.2 ± 2.9 on the left side in group II. Mean number of ablations in patients of group IIa was 6.6 ± 1.7 on the right side and 7.3 ± 3.8 on the left side, with an additional 6.3 ± 3.5 ablations in the accessory renal arteries. In group IIb, 5.4 ± 1.3 and 5.2 ± 1.5 ablations were performed on the right and left side, respectively.

Mean office BP at 6-month follow-up was 149.6/82.7 ± 21.4/14.5 mm Hg in group I and 158.0/88.9 ± 25.9/16.0 mm Hg in group II (group IIa: 154.8/94.9 ± 26.2/16.7 mm Hg; IIb: 160.5/84.0 ± 26.6/14.2 mm Hg) (Figs. 2A to 2C). In group I, there was an office BP reduction of −16.6 ± 16.4 mm Hg systolic (p < 0.001) and −6.7 ± 11 mm Hg diastolic (p = 0.016) 6 months after treatment, whereas in group II, the office systolic and diastolic BP reductions were −6.2 ± 19.7 mm Hg and −0.2 ± 11.3 mm Hg,

respectively (p = 0.19 for systolic values, p = 0.5 for diastolic values). Group IIa had an office BP reduction of −8.8/1.1 ± 17.9/10.8 mm Hg (p = 0.2 for systolic values), and group IIb of −4.1/−1.3 ± 20.8/11.6 mm Hg (p = 0.55 for systolic values) (Fig. 3).

There was a significant difference in systolic and diastolic office BP reductions between patients with bilateral single renal arteries (group I) and those with accessory renal arteries (group II) (p = 0.027 and p = 0.016 for systolic and diastolic BP, respectively). There was also a significant difference in systolic office BP changes between patients with bilateral single renal arteries and those with accessory renal arteries and incomplete or no denervation of the accessory arteries (group IIb) (p = 0.036); however, there was no significant difference in systolic BP changes between patients with bilateral single renal arteries (group I) and those with accessory renal arteries and complete denervation of all arteries (group IIa) (p = 0.14).

There was no significant change in the mean number of antihypertensive medications from baseline to 6-month follow-up (group I: 4.2 ± 1.5, p = 0.9; group II: 4.4 ± 1.5, p = 0.99). In 6 patients (group I: 3; group II: 3), the number of medications was reduced, whereas in 3 patients (group I: 1; group II: 2), the number of antihypertensive medications was increased before the 6-month follow-up.

Ambulatory 24-h BP 6 months after the procedure was 147.7/80.5 ± 16.4/11.3 mm Hg in group I. The reduction in ambulatory BP compared with baseline (systolic −8.3 ± 17.4 mm Hg and diastolic −5.1 ± 10.2 mm Hg) was statistically significant (p = 0.01 and p = 0.028 for systolic and diastolic, respectively). Group II had a nonsignificant ambulatory BP change of systolic −3.7 ± 8.3 mm Hg and diastolic 0.3 ± 9 mm Hg (p = 0.38 for systolic values). In both group IIa and IIb, there were no significant ambulatory BP reductions. Ambulatory BP follow-up was available for only 6 and 8 patients,

Table 3. Baseline Antihypertensive Medications in Group I and Group II

Antihypertensive Medications	Group I (BSRA) (n = 54)	Group II (ARA) (n = 20)
Patients on ≥5 antihypertensive drugs	46.3	60
Mean number of antihypertensive drugs	4.2 ± 1.4	4.4 ± 1.4
Diuretic	81.5	90
Beta-blocker	81.5	85
Calcium channel blocker	59.3	60
ACE inhibitor	35.2	35
Angiotensin receptor blocker	57.4	70
Renin inhibitor	35.2	25
Centrally acting sympatholytic agent	48.1	77.8
Vasodilator	7.4	5
Alpha1-blocker	16.7	5

Values are % or mean ± SD.
ACE = angiotensin-converting enzyme; other abbreviations as in Table 2.
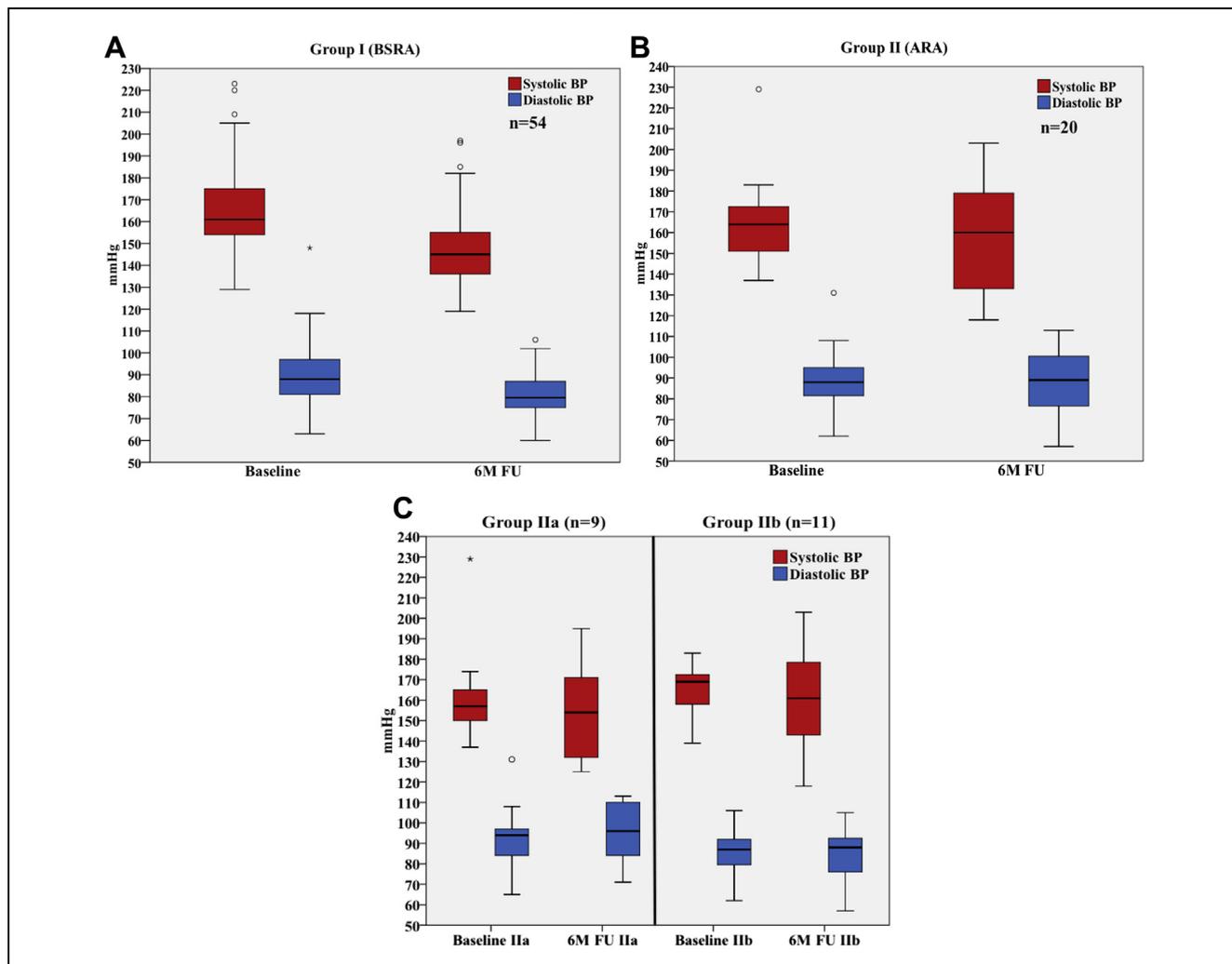
Figure 2. Office BP Changes in Groups I, II, and IIa and IIb

Boxplots of office (BP) blood pressure values at baseline and 6-month follow-up (6M FU) are shown. The boxplots show maximum and minimum values, and medians with upper and lower quartiles. **(A)** Office blood pressure (BP) change in group I (bilateral single renal arteries [BSRA]). **(B)** Office BP change in group II (accessory renal arteries [ARA]). **(C)** Office blood pressure change in group IIa and IIb.

respectively. Three patients in each subgroup were lost to ambulatory BP follow-up because of missed visits.

Heart rate at 6-month follow-up was 65.6 ± 9.8 beats/min in group I, and 64.2 ± 8.1 beats/min in group II. Both reductions (group I: 1.3 ± 9.6 beats/min; group II: 3.4 ± 8.9 beats/min) were considered as statistically not significant (p = 0.55 and p = 0.29, respectively).
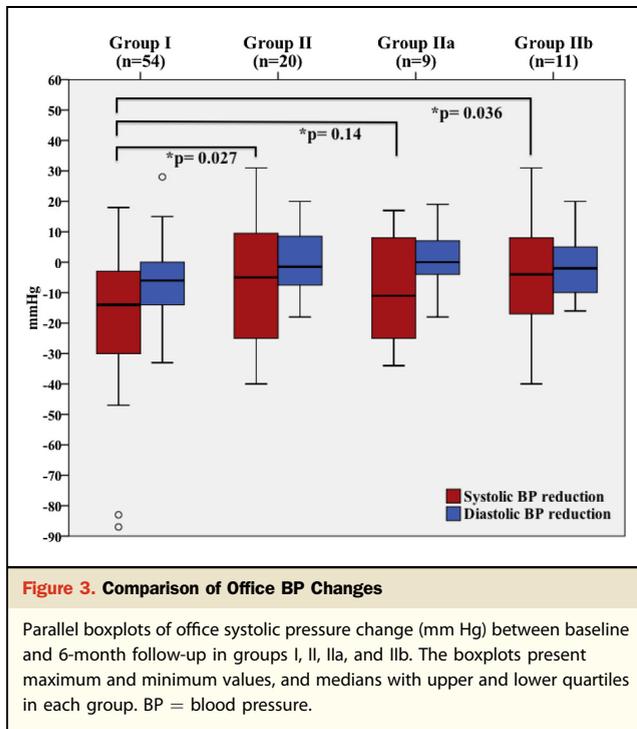
In all groups, renal function, as assessed by serum creatinine and eGFR, was unchanged from baseline to 6-month follow-up (group I: p = 0.31, group IIa: p = 0.14, group IIb: p = 0.5).

During 6-month follow-up, adverse events were observed in 4 patients (7.4%): 2 patients underwent a coronary intervention. One patient had an ST-segment elevation myocardial infarction treated with percutaneous revascularization. One patient was hospitalized for inpatient analgesic

therapy of spinal disc herniation. The named adverse events were classified as not related to the device or the procedure.

Discussion

Our findings demonstrate a BP reduction after catheter-based renal denervation in patients with bilateral single renal arteries. The magnitude of the 6-month office BP reduction (17/7 mm Hg) was slightly less than that reported in previous studies. Nevertheless, both office and ambulatory BP reductions were statistically significant. In the Symplicity HTN-1 trial including registry patients and the randomized Symplicity HTN-2 trial, both of which excluded patients with accessory renal arteries, 6-month BP reductions were 25/11 mm Hg and 32/12 mm Hg, respectively (5,6). It has been shown that baseline systolic office BP is a significant predictor

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Figure 3. Comparison of Office BP Changes

Parallel boxplots of office systolic pressure change (mm Hg) between baseline and 6-month follow-up in groups I, II, IIa, and IIb. The boxplots present maximum and minimum values, and medians with upper and lower quartiles in each group. BP = blood pressure.

of efficacy, with the highest BP reduction in patients with a baseline systolic BP of >175 mm Hg (10,12). Therefore, the more pronounced BP reduction might be related to the higher baseline office BP with 176/98 mm Hg in the Simplicity HTN-1 trial as well as 178/97 mm Hg in the Simplicity HTN-2 trial. This may also explain the slightly lower reduction in ambulatory BP in patients with bilateral single renal arteries in our study (−8.3/−5.1 mm Hg, p < 0.01) compared with Simplicity HTN-2 (−11/−7 mm Hg, p = 0.006). Of note, there was no significant reduction in ambulatory BP in patients with accessory renal arteries at 6-month follow-up. Importantly, office systolic and diastolic BP reductions in patients with accessory renal arteries (including those with complete or incomplete denervation) were significantly less than in patients with bilateral single renal arteries. Moreover, systolic office BP reductions in patients with incompletely (including no) denervated accessory renal arteries were significantly less than in patients with bilateral single renal arteries. Though reductions in systolic office BP in those with completely denervated accessory renal arteries were also numerically less pronounced than in patients with bilateral single renal arteries, this difference did not reach statistical significance. This may be related to a true absence of a difference in BP reductions or to the small number of patients in the latter subgroup with insufficient power to demonstrate a small difference.

The reason for the more modest BP reduction seen in patients with accessory renal arteries is not clear. However, renal sympathetic fibers are found in all arteries supplying the kidneys, regardless of whether these are accessory renal arteries or bilateral single renal arteries.

Therefore, the most plausible explanation is a more incomplete interruption of the renal sympathetic fibers in patients with accessory renal arteries, either due to an inability to denervate all accessory renal arteries or due to a more conservative approach in smaller arteries because circumferential catheter manipulation is not always safe. Along these lines, absence of a BP reduction has been reported in a patient with incomplete denervation (in whom only 1 renal artery was denervated), emphasizing the importance of complete denervation (11). To date, however, data regarding the BP lowering effect in patients with incompletely denervated renal arteries or accessory renal arteries have not been reported.

There were no periprocedural complications. Specifically, renal artery injury (e.g., dissection, occlusion, or renal artery stenosis at follow-up) was not observed by renal artery duplex imaging after 6 months. Furthermore, there were no adverse events related to renal denervation at follow-up. The renal function remained unchanged in all groups and subgroups. Hence, denervation of accessory renal arteries of adequate size is safe with the currently available Symplicity catheter.

Our findings have important implications. First, sympathetic fibers surrounding all arteries supplying the kidneys appear to have an important role in BP regulation. Ablation of accessory renal arteries of adequate size (>3.5 mm) appears to be safe, and hence, a strategy aiming for complete denervation should be pursued. Second, the BP reduction even after complete denervation in patients with accessory renal arteries appear to be lower than that seen in patients with bilateral single renal arteries.

Study limitations. Our study is a nonrandomized single-center study in which neither the investigators nor the patients were blinded to the treatment. Selection and observer bias and a placebo effect cannot be ruled out. The numbers of patients in the subgroups were limited and do not allow definitive statements regarding the importance of complete versus incomplete denervation in patients with accessory renal arteries. Likewise, the number of patients with 6-month ambulatory BP measurements in both subgroups of accessory renal arteries (n = 14) was too small to allow any conclusions regarding the effect of renal denervation on 24-h ambulatory BP.

It is important to mention that our patients did not undergo routine invasive imaging at follow-up, and all noninvasive imaging strategies have limited utility in the visualization of and detection of stenosis in accessory renal arteries. Hence, it is conceivable that accessory renal artery stenosis was missed at follow-up.

Conclusions

BP reduction after renal denervation appears to be less pronounced in patients with accessory renal arteries than in

patients with bilateral single renal arteries, particularly if they are incompletely denervated. The number of patients in our study was limited; therefore, further studies are needed before definitive conclusions can be made. If our findings are confirmed, this could have important implications for patient selection and device technology. Future device generations should allow safe and complete denervation of all, including accessory renal arteries.

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REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217–23.
2. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480–6.
3. Garg JP, Elliott WJ, Folker A, Izhar M, Black HR. Resistant hypertension revisited: a comparison of two university-based cohorts. Am J Hypertens 2005;18:619–26.
4. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension 2011;57:1076–80.
5. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373:1275–81.
6. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. Lancet 2010;376:1903–9.
7. Ozkan U, Oguzkurt L, Tercan F, Kizilkilic O, Koc Z, Koca N. Renal artery origins and variations: angiographic evaluation of 855 consecutive patients. Diagn Interv Radiol 2006;12:183–6.
8. Satyapal KS, Haffejee AA, Singh B, Ramsaroop L, Robbs JV, Kalideen JM. Additional renal arteries: incidence and morphometry. Surg Radiol Anat 2001;23:33–8.
9. Dhar P, Lal K. Main and accessory renal arteries—a morphological study. Ital J Anat Embryol 2005;110:101–10.
10. Krum H, Sobotka P, Esler M, et al. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 hours. Hypertension 2011;57:911–7.
11. Vaclavik J, Taborsky M, Richter D. Unilateral catheter-based renal sympathetic denervation in resistant arterial hypertension shows no blood pressure-lowering effect. Clin Exp Hypertens 2013;35:192–4.
12. Mahfoud F, Cremers B, Janker J, et al. Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. Hypertension 2012;60:419–24.