

Blood pressure reduction in patients with accessory renal arteries and bilateral single renal arteries after catheter-based renal denervation

A prospective study with a 3-year follow-up

Krzysztof Bartus^{1*}, Jakub Podolec^{2*}, Jerzy Sadowski¹, Radosław Litwinowicz¹,
Wojciech Zajdel³, Magdalena Bartus⁴, Janusz Konstanty-Kalandyk¹, Artur Dziewierz⁵,
Rafał Trąbka¹, Stanisław Bartus⁵, Anna Chrapusta¹, Bogusław Kapelak¹

1 Department of Cardiovascular Surgery and Transplantology, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland

2 Department of Interventional Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland

3 Interventional Cardiology Clinic, John Paul II Hospital, Kraków, Poland

4 Department of Experimental Pharmacology, Jagiellonian University Medical College, Kraków, Poland

5 University Hospital, Jagiellonian University, Kraków, Poland

KEY WORDS

hypertension, renal
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ABSTRACT

INTRODUCTION Catheter-based renal denervation (RD) is an effective treatment leading to a significant reduction of systolic and diastolic blood pressure (BP) in patients with resistant hypertension.

OBJECTIVES The aim of this prospective study was to assess the BP-lowering and pulse pressure (PP)-lowering effects in patients with accessory and bilateral single renal arteries after catheter-based RD during a 3-year follow-up.

PATIENTS AND METHODS The study included 31 patients with diagnosed resistant hypertension. Patients were classified into 2 groups: group 1 included patients with accessory renal arteries, and group 2, with bilateral single renal arteries. The BP and PP reduction levels were measured before the procedure and at 6, 12, 24, and 36 months after the procedure.

RESULTS All procedures were successful. In group 1, mean systolic BP, diastolic BP, and PP at baseline were 172.7 mm Hg, 98.9 mm Hg, and 74.4 mm Hg, respectively. Systolic BP, diastolic BP, and PP reduction levels were, respectively, –26.9, 19.2, and 7.5 at 6 months; –33.3, 16.1, and 16.4 at 12 months; –29.2, 14, and 18.2 at 24 months; and –28.6, 13.6, and 13.7 at 36 months. In group 2, mean systolic BP, diastolic BP, and PP at baseline were 175.6 mm Hg, 100.1 mm Hg, and 75.5 mm Hg, respectively. Systolic BP, diastolic BP, and PP reduction levels were, respectively, –26, 10.5, and 15.5 at 6 months; –22, 8.9, and 13 at 12 months; –28, 12.4, and 15.6 at 24 months; and –24.6, 14.97, and 9.2 at 36 months. Significant reductions were observed for systolic BP in group 1 and for PP and systolic and diastolic BP in group 2.

CONCLUSIONS RD successfully reduced systolic BP in patients with resistant hypertension and accessory renal arteries. PP reduction after RD in patients with accessory renal arteries was less pronounced than in patients with bilateral single renal arteries.

INTRODUCTION Catheter-based renal denervation (RD) is an effective treatment method resulting in a significant reduction of systolic and diastolic blood pressure (BP) in patients with resistant hypertension.^{1,2} The first RD procedure was

performed by Krum et al³ in 2009. Recent studies have shown that 84% of patients who had undergone RD had significantly lower BP after treatment. The mean BP reduction was 30 mm Hg for systolic BP and 14 mm Hg for diastolic BP 2 years

Correspondence to:

Jakub Podolec, MD, PhD,
Oddział Kliniczny Kardiologii
Intensywnej z Pododdziałem
Intensywnej Nadzoru
Kardiologicznego, Uniwersytet
Jagielloński, Collegium Medicum,
Krakowski Szpital Specjalistyczny im.
Jana Pawła II, ul. Prądnicka 80,
31-202 Kraków, Poland,
phone: +48 12 614 35 01,
e-mail: jipodolec@gmail.com
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* KB and JP contributed equally to this work.

TABLE 1 Baseline characteristics of patients with accessory renal arteries (group 1) and single renal arteries (group 2)

Variable		Group 1	Group 2	P value
Sex, male/female, n		6/1	13/11	0.58
Age, y, mean (range)		57.7 (42–76)	55.8 (31–72)	0.84
Weight, kg, mean (range)		95.2 (77–122)	94.2 (74–145)	0.34
Height, cm, mean (range)		174.2 (167–184)	167.52 (159–178)	0.18
Body mass index, kg/m ² , mean (range)		30.9 (26.6–36.0)	33.6 (23–46.8)	0.22
Hypertension risk factors, n (%)	Hypercholesterolemia	4 (57.1)	15 (62.5)	0.25
	Type 2 diabetes	1 (14.3)	9 (37.5)	0.09
	Current smoking	0	2 (8.3)	0.79
Cardiovascular disease, n (%)	Angina pectoris	0	7 (29.2)	0.07
	Coronary artery disease	0	7 (29.2)	0.07
	Myocardial infarction	0	5 (20.8)	0.20
	Valvular disease	0	2 (8.3)	0.79
	Cardiomyopathy	0	2 (8.3)	0.79
	Ventricular arrhythmia	0	1 (4.2)	0.71
Other diseases, n (%)	Renal insufficiency	0	2 (8.3)	0.79
	Asthma	0	1 (4.2)	0.71
	Chronic obstructive pulmonary disease	0	1 (4.2)	0.71
	Gastric ulcer	0	4 (16.7)	0.33

after the procedure.^{3,4} In contrast, the Simplicity HTN-3 trial⁵ suggested that 6 months after RD there were no significant differences in the reduction of systolic BP in office or 24-hour ambulatory measurements as compared with a sham control. However, a 3-year follow-up in the Global Simplicity Registry showed a significant BP reduction after RD.⁶

A trial by Rosa et al⁷ showed that BP reduction after RD is comparable to intensified pharmacotherapy and that RD added to standardized stepped-care antihypertensive treatment additionally reduced BP compared with pharmacotherapy alone.⁸ In addition to BP reduction, RD seems to offer more therapeutic benefits for selected groups of patients such as those with sleep apnea,⁹ polycystic ovary syndrome,¹⁰ and end-stage renal failure.¹¹ The results of a Polish research group showed a significant reduction in systolic BP, diastolic BP, and pulse pressure (PP) after percutaneous RD. No vascular or renal complications in any of the patients were observed.¹²

However, the results of the above studies also showed that, despite proper implementation of the procedures, the BP-lowering effect varies among patients, with some of them showing no response to treatment. The reason for this remains unknown. Some authors postulate that the presence of an accessory renal artery may result in the lack of treatment effects after RD.^{13,14} Therefore, the aim of this prospective study was to assess the BP-lowering effect after catheter-based RD in patients with accessory renal arteries in comparison with that in patients with bilateral single renal arteries during a 3-year follow-up.

PATIENTS AND METHODS The study included 31 patients with diagnosed arterial hypertension resistant to pharmacological treatment who consented to therapeutic RD. Patients were assigned to 2 groups. Group 1 consisted of 7 patients (6 men and 1 woman) with accessory renal arteries. Accessory renal arteries were defined according to Id et al¹⁵ as the presence of more than 1 artery with a similar size arising directly from the aorta entering the kidney, or separation of a smaller artery from the main renal artery, or the presence of an additional smaller artery arising from the aorta and supplying a limited part of the kidney. Of the 7 patients, 5 had both the left and right accessory renal arteries, 1 had left accessory renal artery, and 1 had right accessory renal artery. Group 2 consisted of 24 patients (13 men and 11 women) with bilateral single renal arteries. In both groups, all arteries were patent. In group 2, 2 patients had arterial stenosis. The groups did not differ in terms of age, weight, height, or body mass index. The characteristics of patients are presented in [TABLE 1](#).

RD was performed with the Symplicity™ device (Medtronic Inc., Palo Alto, California, United States).^{1,3,4} After the procedure, patients were assessed during prospective follow-up visits at 6, 12, 24, and 36 months.

All patients were fully informed about the procedure and gave written informed consent to participate in the study. The study protocol was approved by an institutional review board (2 separate ethics committee approvals because the patients participated in the SYMPPLICITY HTN-1 and SYMPPLICITY HTN-2 trials).

TABLE 2 Antihypertensive medications at baseline in patients with accessory renal arteries (group 1) and single renal arteries (group 2)

Variable	Group 1	Group 2	P value
Number of antihypertensive drugs, mean (SD)	3.9 (0.4)	3.8 (0.8)	0.82
Patients on ≥ 5 antihypertensive drugs, n (%)	0	6 (25)	0.36
β -blockers, n (%)	5 (71.4)	20 (83.3)	0.87
Calcium channel blockers, n (%)	7 (100)	17 (71.0)	0.35
Angiotensin-converting enzyme inhibitors, n (%)	3 (42.9)	15 (62.5)	0.62
Angiotensin II receptor blockers, n (%)	5 (71.4)	14 (58.3)	0.83
Selective α_1 blocker, n (%)	1 (14.3)	2 (8.3)	0.80
α_2 adrenergic agonist, n (%)	0	1 (4.2)	0.50
Centrally acting sympatholytic agents, n (%)	0	2 (8.3)	0.93
Diuretics, n (%)	7 (100)	24 (100)	–

Statistical analysis Continuous variables were presented as mean \pm SD or median and quartiles as appropriate. Categorical variables were presented as number (percentage). The Shapiro–Wilk test was used to assess the normality of continuous variables. To examine the differences between the study groups, the analysis of variance (for normally distributed variables) and the Friedman test (for nonnormally distributed variables) were used. To examine the differences between the 2 dependent groups, the *t* test (for normally distributed variables) and the Wilcoxon test (for nonnormally distributed variables) were used. The analysis was performed using Statistica 10 (StatSoft Poland, Kraków). Statistical significance was set at a *P* level of less than 0.05.

RESULTS Changes in systolic BP, diastolic BP, and PP during the study for both patient groups are presented in **FIGURE 1**.

Before renal denervation (baseline) In group 1, mean systolic BP was 172.7 mm Hg (range, 163.7–186.7 mm Hg), diastolic BP was 98.9 mm Hg (range, 82.3–117.7 mm Hg), and PP was 74.4 mm Hg (range, 58.3–91.7 mm Hg). In group 2, mean systolic BP was 175.6 mm Hg (range, 162.3–211.6 mm Hg), diastolic BP was 100.1 mm Hg (range, 84.3–121.3 mm Hg), and PP was 75.6 mm Hg (range, 53.7–100 mm Hg). There were no significant differences in mean systolic BP, diastolic BP, and PP values between the groups.

Follow-up at 6 months after the procedure In group 1, mean systolic BP was 145.72 mm Hg (range, 132.7–181.7 mm Hg), and was 26.94 lower than the baseline. In group 2, mean systolic BP was 149.58 mm Hg (range, 120–188 mm Hg), and was 25.99 mm Hg lower than the baseline. In group 1, mean diastolic BP was 79.72 mm Hg (range, 65–91.7 mm Hg), and was 19.18 mm Hg lower than the baseline. In group 2, mean diastolic BP was 89.62 mm Hg (range, 73.3–110 mm Hg), and was 10.47 mm Hg lower than the baseline. Mean PP in group 1 was 66.9 mm Hg (range, 51–90 mm Hg), and was 7.5 mm Hg lower than the baseline. Mean PP in group 2 was 60 mm Hg

(range, 35–85 mm Hg), and was 15.5 mm Hg lower than the baseline.

Follow-up at 12 months after the procedure In group 1, mean systolic BP was 139.33 mm Hg (range, 115.67–163.67 mm Hg), and was 33.33 lower than the baseline. In group 2, mean systolic BP was 153.59 mm Hg (range, 111.3–203 mm Hg), and was 21.98 mm Hg lower than the baseline. Mean diastolic BP in group 1 was 82.76 mm Hg (range, 62.67–107 mm Hg), and was 16.14 mm Hg lower than the baseline. Mean diastolic BP in group 2 was 91.17 mm Hg (range, 64.67–116.7 mm Hg), and was 8.93 mm Hg lower than the baseline. Mean PP in group 1 was 57.9 mm Hg (range, 45–74 mm Hg), and was 16.4 mm Hg lower than the baseline. Mean PP in group 2 was 62.4 mm Hg (range, 37.7–111.7 mm Hg), and was 13 mm Hg lower than the baseline.

According to the study protocol, a computed tomography scan was performed at 6 months to 1 year during the postoperative follow-up. No significant lesions in renal arteries were diagnosed. Two patients had renal artery stenosis of up to 30%, but these lesions had been already diagnosed during the preprocedural angiography. No atherosclerosis progression in any of these lesions was found over the 1-year follow-up period.

Follow-up at 24 months after the procedure In group 1, mean systolic BP was 143.47 mm Hg (range, 122.67–157.33 mm Hg), and was 28.04 lower than the baseline. In group 2, mean systolic BP was 147.53 mm Hg (range, 117–192 mm Hg), and was 28.04 mm Hg lower than the baseline. Mean diastolic BP in group 1 was 84 mm Hg (range, 70.67–93.67 mm Hg), and was 14.04 mm Hg lower than the baseline. Mean diastolic BP in group 2 was 87.65 mm Hg (range, 71.33–110.3 mm Hg), and was 12.54 mm Hg lower than the baseline. Mean PP in group 1 was 56.2 mm Hg (range, 48.3–68.3 mm Hg), and was 18.2 mm Hg lower than the baseline. Mean PP in group 2 was 59.9 mm Hg (range, 40–98 mm Hg), and was 15.6 mm Hg lower than the baseline.

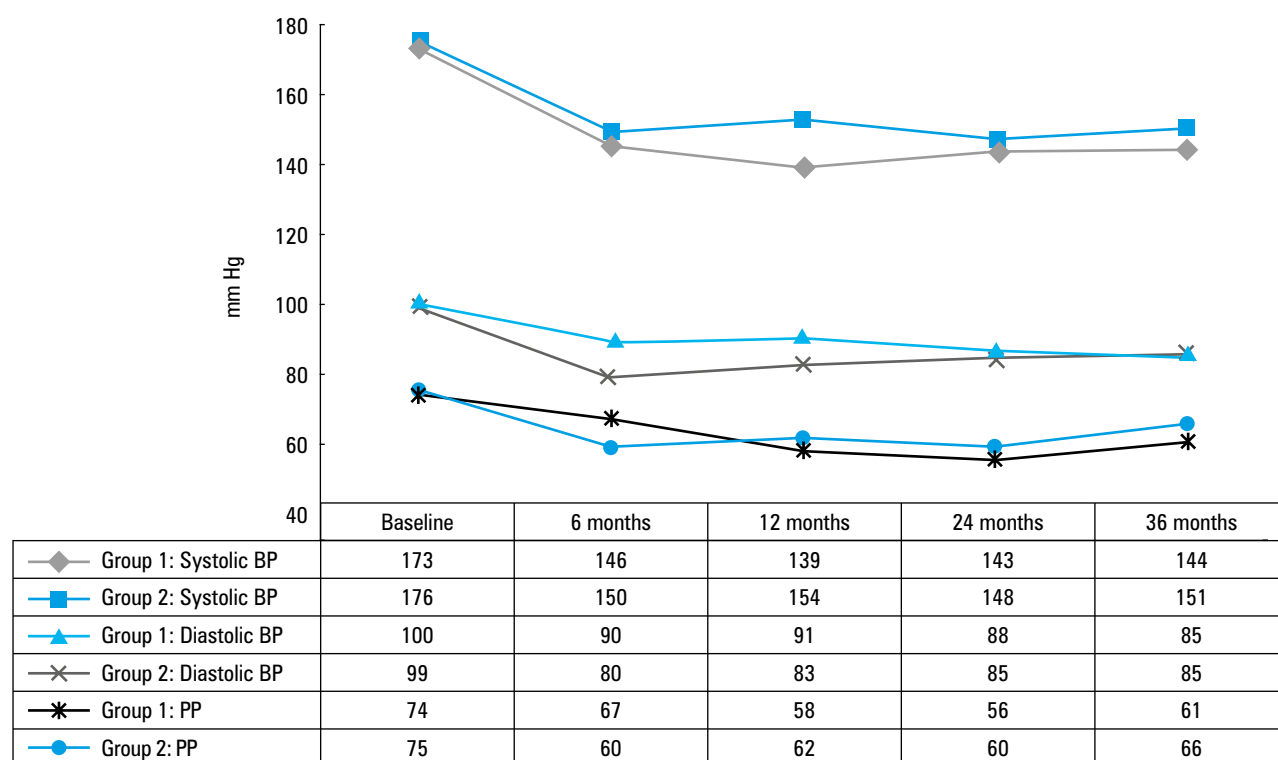


FIGURE 1 Reduction in mean systolic blood pressure (BP), diastolic BP, and pulse pressure (PP) during the study

Follow-up at 36 months after the procedure In group 1, mean systolic BP was 144.05 mm Hg (range, 118–162.67 mm Hg), and was 28.62 mm Hg lower than the baseline. In group 2, mean systolic BP was 150.92 mm Hg (range, 109.67–210.67 mm Hg), and was 24.65 mm Hg lower than the baseline.

Mean diastolic BP in group 1 was 85.33 mm Hg (range, 71–97.67 mm Hg), and was 13.57 mm Hg lower than the baseline. Mean diastolic BP in group 2 was 85.13 mm Hg (range, 64.33–119 mm Hg), and was 14.97 mm Hg lower than the baseline. Mean PP in group 1 was 60.6 mm Hg (range, 47–63 mm Hg), and was 13.7 mm Hg lower than the baseline. Mean PP in group 2 was 66.2 mm Hg (range, 45.3–91.2 mm Hg), and was 9.3 mm Hg lower than the baseline.

In group 1, there was a significant difference in systolic BP reduction ($P = 0.025$), while there were no significant differences in diastolic BP and PP reductions ($P = 0.09$ for both comparisons). In group 2, there were significant differences in systolic BP, diastolic BP, and PP reductions ($P < 0.001$ for all comparisons). There were no significant differences in mean systolic BP, diastolic BP, and PP values between the study groups at 36 months after RD.

There were no significant changes in the mean number of antihypertensive medications or their doses during the follow-up (TABLE 2). In group 1, a reduction in medication doses was observed in 2 patients, and the number of antihypertensive medications was reduced in 1 patient. In group 2, a reduction of medication doses was observed in 2 patients, an increased dose was observed in 1

patient, and the number of antihypertensive medications was increased in 1 patient.

DISCUSSION The results of this study show that RD is a successful treatment in long-term follow-up in patients with resistant hypertension with accessory renal arteries. However, a significant reduction was observed only for systolic BP.

Resistant hypertension, in contrast to pseudo-resistance hypertension in which there are several other reasons for uncontrolled hypertension,¹⁶ is defined as BP that remains above the treatment goal despite the concomitant use of 3 antihypertensive medications of different classes (of which one should be a diuretic) in optimal doses.¹⁷ Resistant hypertension is present in about 10% to 25% of treated hypertensive patients and is associated with a higher risk of cardiovascular morbidity, mortality, and worse prognosis compared with easily controlled hypertension.^{18–21}

RD is a novel therapeutic option for drug-resistant hypertension, initially performed by Krum et al³ in 2009. The Symplicity I and Symplicity II trials (1-year follow-up) have shown that 84% of the patients had durable lower BP. In Symplicity I, a reduction in systolic and diastolic BP was 25 and 11 mm Hg, respectively, and in Symplicity II, 28.1 and 9.7 mm Hg, respectively ($P < 0.001$).^{3,4} Two years after the procedure, a reduction in systolic and diastolic BP was 32 and 14 mm Hg, respectively, without serious events. In contrast to the previous studies, the Symplicity HTN-3 trial suggested that 6 months after RD there were no significant differences in the reduction of systolic BP in office or

24-hour ambulatory measurements as compared with a sham control.⁵ However, there are several limitations of the study design that might have influenced the clinical outcomes.^{22,23} Importantly, the long-term results of the Global Symplicity Registry trial confirmed that RD significantly reduced BP 3 years after the procedure,⁶ which was also corroborated by our study.

In both groups, no modification of antihypertensive treatment was observed. The DENERHTN study⁸ showed that RD in combination with standardized stepped-care antihypertensive treatment results in a greater decrease in ambulatory BP than the standardized treatment alone at 6 months. The 6-month results of the Prague-15 Study showed that RD led to a reduction of BP comparable to intensified pharmacotherapy.⁷

Unfortunately, in some patients, the BP-lowering effect was insufficient, and, according to study results, 10% to 13% of the patients did not respond to treatment.^{2,3} The reason for this remains unknown; however, some authors suspect that the nonresponse to treatment is related to the renal vascular anatomy.^{13,14} It has been hypothesized that accessory renal arteries, which are seen in 25% to 50% of the population (according to autopsy data), are related to the risk of hypertension via activation of the renin-angiotensin-aldosterone system.^{23,24} Isolated stenosis or occlusion of accessory renal arteries with a patent main renal trunk can result in renovascular hypertension. However, Kuczera et al²⁵ showed that stenosis of the accessory artery is rare (0.8%).²⁵ Their magnetic resonance imaging study revealed no significant differences in the prevalence of renal artery stenosis between patients with and those without accessory renal arteries, which seems to refute the previous hypotheses.

Following Id et al,¹⁵ renal sympathetic nerves are located primarily in the adventitia of 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. Moreover, accessory renal arteries, including dual renal arteries and early separation of pole arteries, are frequently smaller than 4 mm. Therefore, these arteries are mostly not available to ablation with currently approved devices. Due to incomplete denervation, BP reduction may be less effective compared with single renal artery denervation.¹⁵

Id et al¹⁵ first compared the BP-lowering effect after RD in patients with accessory renal arteries and in patients with bilateral single arteries (54 patients).¹² After a 6-month follow-up, BP reduction was more effective in patients with bilateral single renal arteries.²⁰ Our long-term results support this observation.

The outcomes of our study suggest that BP reduction is observed only in systolic BP in patients with accessory renal arteries. However, the lowering effect was also observed in diastolic BP and PP, but the results were not significant. In the group with bilateral arteries, the lowering effect was observed in systolic BP, diastolic BP, and PP ($P < 0.001$). However, when we compared mean systolic BP, diastolic BP, and PP between the 2 groups 36 months after RD, no significant differences were observed. These differences may be explained by a small number of patients in group 1. The population in the study by Id et al¹⁵ was larger (74 patients) than in our study (31 patients). However, the percentage of patients with accessory renal arteries was similar: 27% in the study by Id et al¹⁵ and 23% in our study.

Additional differences between the studies were observed in the levels of baseline BP. In our study, baseline systolic and diastolic BP was higher than that in the study by Id et al¹⁵: in patients with accessory renal arteries, the values were 172.67 and 98.9 mm Hg, respectively, compared with 164.2 and 89.1 mm Hg, respectively; and in patients with bilateral single renal arteries, they were 175.57 and 100.1 mm Hg, respectively, compared with 166.2 and 89.4 mm Hg, respectively. When comparing the levels of BP reduction at 6 months between the studies, higher BP reduction was observed in our study than in the study by Id et al¹⁵ both in patients with accessory renal arteries (systolic and diastolic BP, 26.94 and 19.18 mm Hg, respectively, compared with 6.2 and 0.2 mm Hg, respectively) and in patients with bilateral single renal artery (systolic and diastolic BP, 25.99 and 10.47 mm Hg, respectively, compared with 16.6 and 6.7 mm Hg, respectively). Of note, in the study by Id et al,¹⁵ the decrease in BP levels in patients with accessory renal arteries was statistically significant. Thus, a smaller sample size and higher BP values at baseline probably explain the discrepancies between the results. It should also be noted that our study had a much longer follow-up (36 months) than the study by Id et al¹⁵ (6 months), which might be another reason for the observed differences.

To our knowledge, our study was the first to compare the PP-lowering effects in patients with accessory renal arteries and in those with bilateral single renal arteries. Importantly, the first clinical RD trials (Symplicity I and Symplicity II) did not include patients with accessory renal arteries. The presence of more than 1 main renal artery was one of the exclusion criteria for the trials. For this reason, further randomized controlled trials on a large number of patients are needed.

As shown by numerous clinical studies, any new pharmacological drugs should be introduced carefully to avoid adverse events or interactions with other drugs or diseases.²⁶ Therefore, alternative treatment options, including RD, are considered to be promising for patients with resistant hypertension.

Conclusions RD successfully reduced systolic BP in patients with resistant hypertension and accessory renal artery. PP reduction achieved after RD in patients with accessory renal arteries is less pronounced than that in patients with bilateral single renal arteries. At primary endpoint of the study and at 36 months, the difference in BP-lowering effects between the groups was only 3.97 mm Hg, and the results had no statistical significance.

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Contribution statement KB conceived the idea for the study and wrote the manuscript. JP contributed to the design of the research, writing and editing of the manuscript, and data analysis and collection. JS contributed to the design of the research. All authors were involved in data collection. RL, MB, and JK-K analyzed the data. JS coordinated funding for the project. All authors edited and approved the final version of the manuscript. KB and JP contributed equally to the content of this manuscript and both are the first authors of this work.

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