Role of Adding Spironolactone and Renal Denervation in True Resistant Hypertension

One-Year Outcomes of Randomized PRAGUE-15 Study

Ján Rosa, Petr Widimský, Petr Waldauf, Lukáš Lambert, Tomáš Zelinka, Miloš Táborský, Marian Branny, Petr Toušek, Ondřej Petrák, Karol Čurila, František Bednář, Robert Holaj, Branislav Štrauch, Jan Václavík, Igor Nykl, Zuzana Krátká, Eva Kociánová, Otakar Jiravský, Gabriela Rappová, Tomáš Indra, Jiří Widimský Jr

See Editorial Commentary, pp 278–280

Abstract—This randomized, multicenter study compared the relative efficacy of renal denervation (RDN) versus pharmacotherapy alone in patients with true resistant hypertension and assessed the effect of spironolactone addition. We present here the 12-month data. A total of 106 patients with true resistant hypertension were enrolled in this study: 52 patients were randomized to RDN and 54 patients to the spironolactone addition, with baseline systolic blood pressure of 159±17 and 155±17 mm Hg and average number of drugs 5.1 and 5.4, respectively. Twelve-month results are available in 101 patients. The intention-to-treat analysis found a comparable mean 24-hour systolic blood pressure decline of 6.4 mm Hg, *P*=0.001 in RDN versus 8.2 mm Hg, *P*=0.002 in the pharmacotherapy group. Per-protocol analysis revealed a significant difference of 24-hour systolic blood pressure decline between complete RDN (6.3 mm Hg, *P*=0.004) and the subgroup where spironolactone was added, and this continued within the 12 months (15 mm Hg, *P*= 0.003). Renal artery computed tomography angiograms before and after 1 year post-RDN did not reveal any relevant changes. This study shows that over a period of 12 months, RDN is safe, with no serious side effects and no major changes in the renal arteries. RDN in the settings of true resistant hypertension with confirmed compliance is not superior to intensified pharmacological treatment. Spironolactone addition (if tolerated) seems to be more effective in blood pressure reduction. (***Hypertension*****. 2016;67:397-403. DOI: 10.1161/HYPERTENSIONAHA.115.06526.)** ● **Online Data Supplement**

Key Words: ambulatory blood pressure monitoring ■ blood pressure ■ renal denervation ■ resistant hypertension ■ spironolactone

Catheter-based renal denervation (RDN) has been considered as a new hope for patients with resistant hypertension (RH). The first studies published by the same pioneering group of experts[1,2] triggered widespread enthusiasm, and the new method was quickly promulgated. However, this was slowed down in 2014 by publication of trials with negative results for RDN.[3–6] Apart from exceptions,[7] most of these studies failed to prove the satisfactory efficacy of RDN.[3–6] Based on these results, the Czech Society for Hypertension does not recommend implementation of RDN in routine practice.[8]

This study seeks to evaluate the efficacy of RDN in a prospective multicenter randomized trial with the acronym PRAGUE-15 in patients with true RH. Twenty-four-hour ambulatory blood pressure monitoring, exclusion of secondary hypertension, and evaluation of treatment compliance served as confirmation of true resistance. The efficacy of RDN was compared with intensified antihypertensive treatment, including the use of spironolactone. The 6-month results of the PRAGUE-15 study were previously published.[6] To date, only 1 properly designed study has published 12-month results[9] where RDN was compared with a sham procedure. Here we present the 1-year data, including the evaluation of renal artery changes after RDN and hormonal and hemodynamic parameters.

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From the 3rd Department of Medicine, Center for Hypertension, General University Hospital and First Faculty of Medicine (J.R., T.Z., O.P., R.H., B.Š., Z.K., T.I., J.W. Jr), Cardiocentre, University Hospital Královské Vinohrady and Third Faculty of Medicine (J.R., P. Widimský, P. Toušek, K.Č., F.B.), Department of Anesthesiology, University Hospital Královské Vinohrady and Third Faculty of Medicine (P. Waldauf), and Department of Radiology, General University Hospital and First Faculty of Medicine (L.L.), Charles University, Prague, Czech Republic; Department of Internal Medicine I, University Hospital Olomouc, Czech Republic (M.T., J.V., E.K.); and Cardiocentre, Nemocnice Podlesí, Třinec, Czech Republic (M.B., I.N., O.J., G.R.).

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Correspondence to Ján Rosa, 3rd Department of Medicine, Center for Hypertension, General University Hospital, U Nemocnice 2, 128 08 Prague, Czech Republic. E-mail jan.rosa@lf1.cuni.cz

Methods

Study Design

The PRAGUE-15 study was designed as an academic investigator–initiated, open-label, prospective, multicenter randomized trial (clinicaltrials.gov identifier: NCT 01560312). Patients with true RH were randomized (in a 1:1 ratio) to either (A) a catheter-based RDN (using the Symplicity Renal Denervation System [Medtronic Inc, Mountain View, CA]) plus optimal antihypertensive treatment group or to (B) an intensified pharmacological treatment group (PHAR) including spironolactone.

The exact study design (see Figure S1 in the online-only Data Supplement), including power and sample-size analysis and 6-month results, were previously reported.[6,10] The entry criteria included office systolic blood pressure (BP) over 140 mm Hg, ambulatory 24-hour mean systolic BP over 130 mm Hg, treatment with at least 3 antihypertensive drugs, including a diuretic, exclusion of secondary hypertension, and excluding drug noncompliance.[11,12] Renal anatomy was evaluated during screening using computed tomographic or magnetic resonance angiography.

Three tertiary high-volume centers in the Czech Republic enrolled 106 patients. After randomization, patients selected for RDN were maintained on baseline medical therapy for 1 year unless changes were considered clinically necessary. Patients selected for intensified medical treatment received baseline medical therapy plus spironolactone (25 mg daily, as generally recommended),[13] if tolerated, and if no contraindications were present.

Procedural and BP measurement methodology have previously been described in detail.[6] See online-only Data Supplement for details of biochemical, echocardiographic, and pulse wave velocity (PWV) methodology.

Renal Artery Imaging

The diameter of the main renal artery was measured on both sides on pre-RDN and post-RDN computed tomographic angiography that was performed 12 months apart. The degree of atherosclerosis was assessed on a 4-point Likert scale (0=no, 1=mild, 2=moderate, 3=severe) with half-point increments.

Statistical Analysis

The analysis included all randomized participants for whom data were available and was performed using the intention-to-treat and per-protocol principles. Descriptive statistics were used to summarize characteristics of study participants. Continuous variables were summarized using the mean and standard deviation or median and interquartile range. Between-group differences and differences from baseline to the 12-month follow-up assessment were tested with the use of unpaired and paired *t*-tests, respectively. Mean differences are expressed with their 2-sided 95% confidence intervals. All reported subgroup analyses were prespecified. Stata version 13.1 (StataCorp LP, TX) was used to analyze the recorded data.

Results

One hundred and six patients fulfilled all entry criteria and were randomized. Fifty-two patients were randomized to RDN and 54 to the intensified pharmacological treatment, including spironolactone (PHAR). One hundred and one patients (51 randomized to RDN and 50 randomized to PHAR) with available 1-year follow-up were analyzed according to the intention-to-treat principles. The per-protocol cohort comprised 63 patients (44 randomized to RDN and 19 randomized to PHAR).

See Table 1 for the baseline characteristics of study participants and Table 2 for 12-month changes. There were no significant baseline differences between groups in most of the studied parameters. However, body mass index was an exception (P=0.01). This difference remained unchanged after 12 months.

Twenty-Four Hour Ambulatory BP Monitoring

A significant reduction in 24-hour average systolic BP after 12 months was observed, which was comparable in both groups (P=0.54; Figure 1). Similarly, a significant and comparable decrease in the 24-hour average diastolic BP in both groups was observed. Thirty-eight patients did not reach goal 24-hour systolic BP in both groups.

Office Blood Pressure

As with 24-hour ambulatory BP monitoring, significant reductions in systolic (Figure 2) and diastolic office BP were observed with no significant between-group differences in change.

Heart Rate

Borderline office heart rate reduction was recorded in the RDN group (P=0.06), with no between-group differences when compared with PHAR (P=0.79). However, nonsignificant changes in the 24-hour heart rate were present.

Medication

The average number of antihypertensive drugs used after 12 months was comparable in both groups (P=0.69). The number of patients (PHAR group) for whom spironolactone was added and maintained after 12 months was 19. The spironolactone treatment was, for several reasons, not possible in 21 patients. The discontinuation was initiated before the 12-month visit. Ten patients (out of 13) from PHAR group who entered the study already on spironolactone reached 12-month follow-up. See Table S1 for characteristics of antihypertensive treatment and Table S2 for side effects and adverse events.

Biochemistry

Several laboratory changes were recorded. Borderline significance between-group difference in serum creatinine was observed (P=0.04) after 12 months. However, a nonsignificant decrease in RDN (P=0.26) and nonsignificant increase in PHAR (P=0.08) were observed. On the other hand, no significant differences in changes of creatinine clearance were recorded (P=0.53). Borderline increase in direct renin (P=0.04) and aldosterone levels (P=0.06) was observed in PHAR. Increase of direct renin remained significant when compared with the RDN group (P=0.03). No significant changes in plasma metanephrines or other biochemical parameters were recorded. See Table S4 for hormonal analysis.

Procedural Characteristics

The mean number of successful ablations (lasting at least 120 seconds) in the right renal arteries was 5.27±2.33 and 5.48±1.65 in the left. We did not reach the recommended number of ablations (at least 4 per side) in 7 patients; 2 patients out of that number had unilateral ablations for anatomical reasons. The mean value of the impedance drop was 14.63±4.05% on the right side and 13.97±3.37% on the left side. The mean

Table 1. Baseline Characteristics of Studied Subjects

Variable	RDN	PHAR	*P* Value
Number of subjects	52	54	…
Age, y	56±12	59±9	0.20
Male sex, n (%)	40 (77%)	34 (63%)	0.14
Duration of hypertension, y	19±12	15±11	0.11
Type 2 diabetes mellitus patients, n (%)	12 (22%)	9 (17%)	0.63
Coronary heart disease, n (%)	3 (6%)	4 (7%)	1.00
Smokers, n (%)	8 (15%)	8 (15%)	1.00
Statin users, n (%)	22 (44%)	33 (61%)	0.12
Body mass index, kg/m^2	31.2±4.3	33.4±4.7	0.01
Plasma sodium, mmol/L	141±3	141±3	0.76
Plasma potassium, mmol/L	4.1±0.4	4.2±0.4	0.25
Creatinine, μmol/L	87 (78–97)	84 (72–94)	0.96
Creatinine clearance, mL/s per 1.73 m^2	1.5 (1.3–1.9)	1.6 (1.2–2.1)	0.98
Total plasma cholesterol, mmol/L	4.4±1.0	4.7±1.0	0.12
Fasting plasma glucose, mmol/L	5.9 (5.1–7.2)	6.1 (5.1–7.8)	0.79
Office systolic BP, mm Hg	159±19	155±17	0.26
Office diastolic BP, mm Hg	92±14	89±14	0.21
Heart rate, bpm	71±14	72±11	0.78
24-h systolic BP, mm Hg	149±12	147±13	0.54
24-h diastolic BP, mm Hg	86±10	84±10	0.20
24-h heart rate, bpm	69±10	70±10	0.72
Number of drugs used	5.1±1.2	5.4±1.2	0.40

BP indicates blood pressure; PHAR, pharmacological treatment arm; and RDN, renal denervation. Values are shown as means±SD or medians (interquartile range) or absolute numbers and percentages.

tissue temperature after energy delivery was 55.5±10.18°C on the right side and 55.9±6.4°C on the left side.

Echocardiography

A significant left ventricle mass and left ventricle mass indexed for height$^{2.7}$ reduction were observed in PHAR (P=0.02 for both) with no significant between-group difference in change.

PWV

Borderline reduction of central PWV was observed in PHAR (P=0.07). See Table S3 and S4 for echocardiographic and PWV analysis.

Renal Artery Imaging

Computed tomographic renal angiograms to compare the changes 12 months after RDN were available for 37 patients. The average renal artery diameter did not change (7.5±1.2 mm vs 7.5±1.3 mm; P=0.91). Minimal unilateral progression of atherosclerosis (half point on the Likert scale) could be detected in 9 patients (24% of the analyzed subjects; P=0.003), with no other major structural changes.

Safety

As reported previously,[6,14] no severe complications with clinically significant consequences for the patients were recorded with the RDN procedure. There was 1 ischemic stroke and 1 myocardial infarction (without ST elevations) in the RDN group during the 12-month follow-up, and 1 case of unstable angina was observed in the PHAR group. No deaths occurred during the 12-month follow-up.

Per-Protocol Analysis

As mentioned, 44 patients reached complete RDN (recommended number of ablations, at least 4 per side). In 19 patients from the PHAR group, spironolactone was added and continued within the 12-month period. According to this per-protocol analysis, a significant reduction in 24-hour average systolic BP after 12 months was observed, with marked between-group difference (P=0.04; Figure 1). A significant reduction in systolic office BP was observed, which was comparable in both groups (P=0.64; Figure 2). Furthermore, significant changes of plasma sodium, potassium, creatinine, number of drugs, and PWV were observed. Creatinine clearance remained unchanged. See Table S5 for results of per-protocol analysis.

Discussion

This randomized, prospective study showed that in the settings of true RH, RDN is not superior to intensified pharmacological treatment over a period of 12 months, similarly to that over a 6-month period. According to intention-to-treat principles, BP decline—office, as well as 24 hour—was comparable in both treatment arms, without marked between-group differences.

Table 2. Differences After 12 Months According to Intention-to-Treat Analysis

Variable	Change From Baseline in RDN		Change From Baseline in PHAR		RDN to PHAR Between-Group Difference in Change	
	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value
Number of subjects	51		50		…	
Body mass index, kg/m^2	−0.3 (−0.8, 0.1)	0.11	−0.1 (−0.7,0.5)	0.76	−0.3 (−1, 0.5)	0.48
Plasma sodium, mmol/L	−0.1 (−1.1, 0.8)	0.80	−0.5 (−1.4, 0.3)	0.23	0.4 (−0.9, 1.7)	0.53
Plasma potassium, mmol/L	0.08 (−0.1, 0.3)	0.36	0.04 (−0.1, 0.2)	0.54	0.04 (−0.2, 0.3)	0.74
Creatinine, μmol/L	−1.6 (−4.6, 1.3)	0.26	6.1 (−0.8, 13)	0.08	−7.8 (−15, −0.4)	0.04
Creatinine clearance, mL/s per 1.73 m2	0.04 (−0.2, 0.3)	0.76	−0.08 (−0.3, 0.2)	0.56	0.12 (−0.3, 0.5)	0.53
Total plasma cholesterol, mmol/L	−0.2 (−0.5, 0.1)	0.16	−0.1 (−0.3, 0.2)	0.57	−0.1 (−0.5, 0.2)	0.48
Fasting plasma glucose, mmol/L	−0.3 (−0.9, 0.2)	0.23	−0.1 (−0.7, 0.5)	0.75	−0.2 (−1, 0.6)	0.56
Office systolic BP, mm Hg	−13.4 (−18.9, −7.9)	<0.001	−11.3 (−17.1, −5.5)	<0.001	−2.1 (−9.9, 5.8)	0.61
Office diastolic BP, mm Hg	−8.4 (−11.9, −4.9)	<0.001	−6.2 (−10.5, −1.9)	0.006	−2.2 (−7.7, 3.2)	0.42
Heart rate, bpm	−3 (−6.1, 0.1)	0.06	−2.5 (−5.4, 0.5)	0.09	−0.6 (−4.8, 3.7)	0.79
24-h systolic BP, mm Hg	−6.4 (−10.1, −2.7)	0.001	−8.2 (−13.2, −3.3)	0.002	1.9 (−4.2, 8.0)	0.54
24-h diastolic BP, mm Hg	−5.6 (−7.8, −3.3)	<0.001	−6.0 (−8.8, −3.2)	<0.001	0.4 (−3.1, 4.0)	0.81
24-h heart rate, bpm	−1.1 (−3.4, 1.3)	0.36	−1.6 (−3.6, 0.4)	0.12	0.5 (−2.6, 3.6)	0.74
Number of drugs used	0.1 (−0.06, 0.3)	0.20	0.2 (−0.2, 0.6)	0.33	−0.1 (−0.5, 0.3)	0.69

BP indicates blood pressure; PHAR, pharmacological treatment arm; and RDN, renal denervation.

Comparable BP decline with comparable drug change in both groups might raise the question whether RDN might be reserved for patients with intolerance of spironolactone.[15] However, the results of per-protocol analysis with significantly higher reduction of 24-hour systolic BP in patients in whom spironolactone was added and continued within 12 months, in comparison to RDN (BP decline in whole PHAR might thus be underestimated), do not support this idea. A relatively high prevalence of spironolactone side effects, with anti-androgen effect as the most common, was observed (see Table S2) and discussed previously.[6] The development of hyperkalemia and renal function worsening were corrected conservatively with treatment adjustment without the need for hospital admission.

Therefore, these findings might rather indicate a preference of eplerenone instead of spironolactone. Despite the fact that higher doses of eplerenone are needed,[13] the efficacy of this drug was proved with a lower incidence of side effects.[16,17] Furthermore, according to European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension, eplerenone might be considered in RH. Unfortunately, the price and prescription limitations in the Czech Republic (eplerenone is indicated only in heart failure according to the summary of product characteristics)[18] do not allow wider implementation of this potent drug in resistant hypertensive patients. This is in contrast to the United States where eplerenone is indicated in hypertension as well.[19]

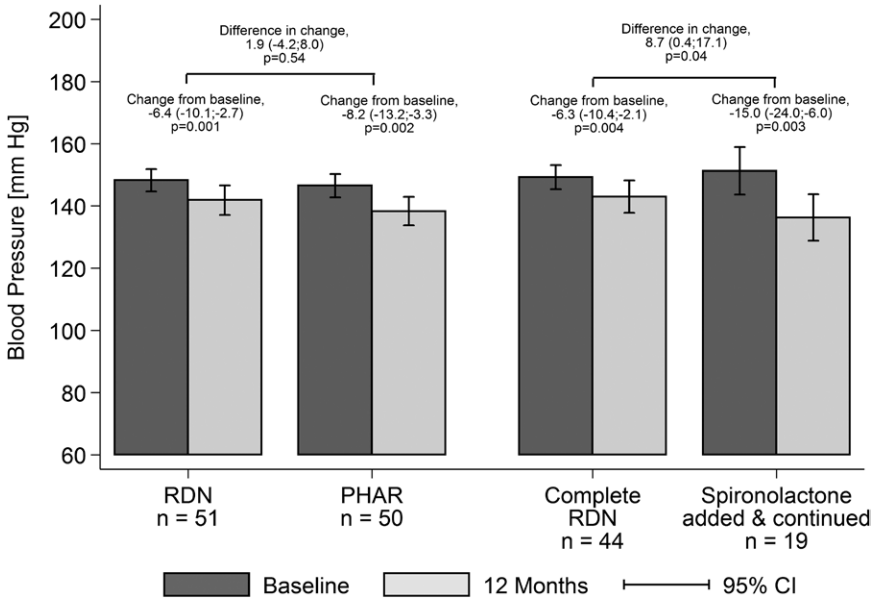

Figure 1. Ambulatory 24-h systolic average blood pressure changes. Significant 24-h systolic blood pressure changes from baseline to 12 months were observed. These changes were more apparent in the subgroup where spironolactone was added and continued. **Left**, Results according to intention-to-treat analysis. **Right**, Results according to per-protocol analysis. CI indicates confidence interval; PHAR, pharmacological treatment arm; and RDN, renal denervation.

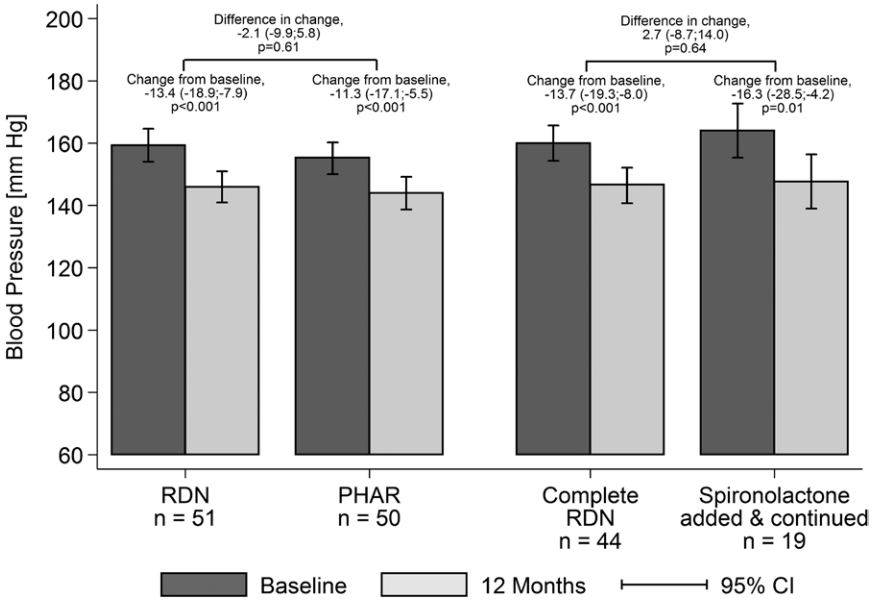

Figure 2. Office systolic blood pressure changes. Significant and comparable office blood pressure changes from baseline to 12 months were observed. **Left**, Results according to intention-to-treat analysis. **Right**, Results according to per-protocol analysis. CI indicates confidence interval; PHAR, pharmacological treatment arm; RDN, renal denervation.

In addition to BP, changes in other parameters were recorded. Borderline differences in plasma creatinine and direct renin and plasma aldosterone levels in the PHAR group might be explained by spironolactone addition. On the contrary, we did not record significant renal function improvement in RDN (as indicated in chronic kidney disease).[20] With the anticipated reduction of sympathetic renal nerve activity, one would expect plasma normetanephrine or renin–angiotensin–aldosterone system changes, as were already described 3 months after RDN.[21] However, no similar humoral changes were observed 12 months after RDN. There is evidence of left ventricle mass reduction 6 months after RDN.[22] However, no changes either in echocardiographic parameters or in large artery properties were observed in the RDN group. These findings are in line with another 12-month RDN study.[23] A trend to decrease left ventricle mass was observed only in PHAR. A nonsignificant trend to improve large artery properties was observed in PHAR (more apparent in the subgroup where spironolactone was actually added). These changes might be attenuated by the fact that only 19 patients were able to continue spironolactone treatment within 12 months. The fact that no additional changes in RDN (except for BP reduction) were observed, together with the current results of the per-protocol cohort and knowledge of the results of sham procedure studies,[5,9] questions the real long-term efficacy of RDN.

Similarly, the results of later animal studies cast doubts upon the lasting effect of catheter-based RDN when reinnervation was proved even after 5.5 months.[24] The total number of ablations[25] or even treatment locations[26] are discussed to improve the efficacy. However, evidence of the long-lasting effect of RDN, as well as evidence of better efficacy of multielectrode systems, is lacking.[27,28]

A diversity of BP decline in RDN studies indicates other possible issues that might contribute to the effect of RDN: patients' selection, BP level required for eligibility, choice of the primary endpoint, and the technique of BP measurement.[29–31] These results raise the question whether the correct population of hypertensive patients for RDN was chosen—RH patients. In the present state of knowledge, initiatives aimed at diagnosing and improving poor drug adherence and optimization of drug treatment may prove much more cost-effective, both at the individual and public health policy level.[4,32,33] Future RDN studies might possibly rather be focused on never-treated hypertensive patients with lower risk factor profile and evidence of sympathetic overactivity.[31,34]

There are indications that RDN might be a cost-effective intervention for patients with RH.[35] Because this study was not focused on this issue and there is a lack of data on the cost-effectiveness of mineralocorticoid antagonists in hypertension, further studies are needed to compare the cost-effectiveness of these methods.

Acute renal changes visualized by optical coherence tomography and not apparent on renal angiography have been proved.[36] However, long-lasting data on renal artery angiograms are still lacking. The fact that the diameter of renal arteries remained unchanged in our study may advocate the safety of RDN. Minimal progression of atherosclerosis is the natural course of the disease.

There are several possible limitations of this study, which were also discussed in detail in the manuscript presenting the 6-month data:[6] the recommended number of ablations was not reached in all the patients (at least 4 per side, according to guidelines at the time of study preparation),[37] the absence of a sham procedure, the relatively small number of participants (especially for subgroup analysis), and the subgroup of patients already on spironolactone being permitted to enter the study. The latter issue might cause bias, especially in further evaluation after crossover. The fact that compliance to treatment was checked only at baseline might also affect the results. Despite the fact that the Hawthorne effect is usually expected, the adherence might decrease with time; thus, real BP decline might be underestimated. However, this might affect both groups. The use of different kits for specialized hormonal analysis in local laboratories might affect the descriptive values, which are not displayed. However, this was not the primary end point, and changes during follow-up might not be influenced. Results of this study cannot necessarily be extrapolated to other RDN systems, especially multielectrode.

Perspectives

This study shows that, over a period of 12 months, RDN is safe, with no serious side effects. However, within the setting of true RH with confirmed compliance, it is not superior to intensified pharmacological treatment. Spironolactone addition itself, when tolerated and maintained within 12 months, seems to be more effective in BP reduction, when compared with complete RDN. Other studies with RDN aimed at an improvement of the technical aspects or population selection are needed for a final evaluation of RDN.

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Disclosures

None.

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Novelty and Significance

What Is New?

- In the settings of true resistant hypertension with confirmed compliance, spironolactone addition (if tolerated and continued) seems to be more effective in blood pressure reduction than renal denervation within 12 months.
- No relevant changes occurred on renal computed tomographic angiograms within 12 months.

What Is Relevant?

- Renal denervation does not represent a routine therapeutic approach in true resistant hypertension.

Summary

Renal denervation is safe and leads to a significant blood pressure reduction (office, as well as 24-h ambulatory blood pressure monitoring) over a 12-month period in the settings of true resistant hypertension. However, spironolactone addition, if tolerated and not contraindicated, seems to be more effective.

Online supplement

The role of adding spironolactone and renal denervation in true resistant hypertension.

One-year outcomes of randomized PRAGUE-15 study.

Ján Rosa[1,2], Petr Widimský[2], Petr Waldauf[3], Lukáš Lambert[4], Tomáš Zelinka[1], Miloš Táborský[5], Marian Branny[6], Petr Toušek[2], Ondřej Petrák[1], Karol Čurila[2], František Bednář[2], Robert Holaj[1], Branislav Štrauch[1], Jan Václavík[5], Igor Nykl[6], Zuzana Krátká[1], Eva Kociánová[5], Otakar Jiravský[6], Gabriela Rappová[6], Tomáš Indra[1], Jiří Widimský Jr[1].

[1]3rd Department of Medicine, Center for Hypertension, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic

[2]Cardiocentre, University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic

[3]Department of Anesthesiology, University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic

[4]Department of Radiology, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic

[5]Department of Internal Medicine I, University Hospital Olomouc, Czech Republic

[6]Cardiocentre, Nemocnice Podlesí, Třinec, Czech Republic

Short title: Renal denervation versus intensified pharmacotherapy including spironolactone.

Corresponding author: Ján Rosa, 3rd Department of Medicine, Center for Hypertension, General University Hospital, U Nemocnice 2, 128 08 Prague, Czech Republic, Tel.:+420 224962945, fax:+420 224963245, e-mail: jan.rosa@lf1.cuni.cz

METHODS

Biochemistry

Biochemical parameters were analyzed in local institutional laboratories. Direct renin and aldosterone measurements were performed using commercially available kits by radioimmunoanalysis (RIA; Immunotech, Beckman Coulter Company, Prague, Czech Republic) or immunoradiometric assay (CISBio Bioassays, Codolet, France). Plasma-fractioned metanephrines (normetanephrine and metanephrine) were quantified by liquid chromatography with electrochemical detection (HPLC-ED, Agilent 1100; Agilent Technologies), by enzyme-linked immunosorbent assay (IBL International, Hamburg, Germany) or by RIA (Immunotech, Beckman Coulter Company, Prague, Czech Republic). All other biochemical parameters were analyzed using multianalyzers (Modular, Roche Diagnostics, Basel, Switzerland; Roche Cobas 8000, Roche Diagnostics Mannheim, Germany).

Echocardiography

Left ventricle (LV) and left atrium parameters were assessed according to the recommendations of the American Society of Echocardiography.[1] Relative wall thickness was calculated as 2 × (posterior wall thickness/LV end-diastolic dimension). LV mass (LVM) was estimated using the formula by Lang *et al.*[1]

The LVM was normalized to the height $^{2.7}$ index. All echocardiographic measurements were obtained by 1-2 investigators in each center.

Pulse wave velocity (PWV).

PWV assessment was performed by the Sphygmocor applanation tonometer (AtCor Medical, Australia). Aortic PWV was assessed by the time difference between pulse wave upstrokes, consecutively measured at the right common carotid artery and right femoral artery, then aligned by the ECG-based trigger. The 'intersecting tangent algorithm' was used to locate the foot of the pulse waves. To determine the distance between the measured sites, a subtraction method was used (sternal notch to femoral site minus sternal notch to carotid site). Similarly, peripheral femoral-ankle PWV (pPWV) was assessed by the time difference between pulse wave upstrokes measured at the right femoral artery and right tibial anterior or posterior artery.

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Table S1. Characteristics of antihypertensive treatment.

Variable	Baseline		After 12 months	
	RDN	PHAR	RDN	PHAR
Number of patients	52	54	51	50
Number of drugs used n	5.1±1.2	5.4±1.2	5.2±1.3	5.6±1.4
Calcium channel blockers n (%)	46 (89%)	48 (89%)	46 (91%)	43 (86%)
β blockers n (%)	34 (66%)	37 (69%)	34 (67%)	37 (74%)
Diuretics n (%)	52 (100%)	54 (100%)	51 (100%)	50 (100%)
- amiloride n (%)	11 (21%)	19 (35%)	16 (31%)	19 (38%)
- thiazide diuretic n (%)	48 (92%)	50 (93%)	48 (94%)	47 (94%)
- furosemide n (%)	1 (2%)	3 (6%)	2 (4%)	4 (8%)
- aldosterone antagonists n (%)	14 (27%)	13 (24%)	12 (24%)	29 (58%)
ACE inhibitors / sartans n (%)	52 (100%)	54 (100%)	51 (100%)	50 (100%)
α blockers n (%)	28 (54%)	25 (46%)	27 (53%)	22 (44%)
Centrally acting drugs n (%)	28 (54%)	33 (61%)	28 (55%)	27 (54%)

RDN - renal denervation arm; PHAR - conservative treatment arm.
Values are shown as means±SD or absolute numbers or percentages.

Table S2. Side effects / adverse events.

Renal denervation arm
- spasms after application of radiofrequency energy, 4 patients (8 %)
- dissection of renal artery, 1 patient (2 %)
- post-punctual pseudoaneurysm, 2 patients (4 %)
- arterio-venous fistula, 1 patient (2 %)
- laryngospasm after analgosedation, 1 patient (2 %)
- asymptomatic bradycardia after procedure, 2 patients (4 %)
- phlebitis associated with peripheral line, 1 patient (2 %)
Pharmacological treatment arm
- hyperkalemia, 6 patients (12 %)
- worsening of renal function, 1 patient (2 %)
- anti-androgen effect of spironolactione, 7 patients (14 %)
- refusal to continue treatment with spironolactone because of symptomatic blood pressure reduction, 5 patients (10 %)
- refusal to start spironolactone treatment, 2 patients (4 %)

Table S3. Baseline characteristics of studied subjects. Echocardiographic and large artery properties' parameters.

Variable	RDN	PHAR	P Value
Number of subjects	52	54	-
LVED [mm]	51±5	52±6	0.47
IVSd [mm]	11±2	12±2	0.53
PWd [mm]	11±2	11±2	0.38
RWT	0.43±0.1	0.44±0.1	0.78
LV mass [g]	216±57	240±73	0.10
LV mass index [$g.m^{-2,7}$]	48±11	54±13	0.07
LV ejection fraction	0.64±0.07	0.63±0.07	0.36
Left atrium [mm]	43±5	44±4	0.56
LAVi [$ml.m^{-2}$]	33±10	32±8	0.73
E/e'	10±3	10±3	0.70
PWV [$m.s^{-1}$]	9.6±2	10.3±3	0.69
pPWV [$m.s^{-1}$]	10±2	10.2±2	0.76

RDN - renal denervation arm; PHAR - pharmacological treatment arm; LV - left ventricle; LVED - LV end-diastolic dimension; IVSd - diastolic interventricular septum; PWd - posterior wall in diastole; RWT - relative wall thickness; LAVi - left atrium volume indexed; PWV - pulse wave velocity; pPWV - peripheral PWV. Values are shown as means±SD.

Table S4. Differences after 12 months according to intention-to-treat analysis. Results of hormonal, echocardiograpic and large artery properties' analysis.

Variable	Change from baseline in RDN		Change from baseline in PHAR		RDN to PHAR between-group difference in change	
	mean (95% CI)	P Value	mean (95% CI)	P Value	mean (95% CI)	P Value
Number of subjects	51		50		-	
Direct renin [pg/ml]	-9 (-38, 20)	0.54	45 (2, 88)	**0.04**	-54 (-103, -5)	**0.03**
Aldosterone [ng/l]	28 (-10, 67)	0.14	93 (-6, 194)	0.06	-66 (-166, 35)	0.20
Metanephrine [nmol/l]	-0.02 (-0.07, 0.02)	0.33	0.02 (-0.02, 0.06)	0.32	-0.04 (-0.1, 0.02)	0.16
Normetanephrine [nmol/l]	-0.01 (-0.09, 0.06)	0.72	-0.001 (-0.1, 0.1)	0.98	-0.01 (-0.1, 0.1)	0.84
LVED [mm]	-0.6 (-1.8, 0.6)	0.31	-1.4 (-3, 0.2)	0.08	0.8 (-1.2, 2.8)	0.42
IVSd [mm]	-0.4 (-0.8, 0.03)	0.07	-0.04 (-0.5, 0.5)	0.89	-0.37 (-1, 0.3)	0.27
PWd [mm]	-0.04 (-0.4, 0.3)	0.83	-0.2 (-0.7, 0.3)	0.43	0.15 (-0.5, 0.8)	0.64
RWT	0.01 (-0.02, 0.03)	0.63	0.003 (-0.03, 0.04)	0.86	0.002 (-0.04, 0.04)	0.91
LV mass [g]	-8 (-26, 11)	0.39	-18 (-33, -3)	**0.02**	10 (-13, 33)	0.38
LV mass index [$g.m^{-2,7}$]	-1.6 (-5.7, 2.4)	0.41	-4 (-7.1, -0.8)	**0.02**	2.3 (-2.7, 7.4)	0.36
LV ejection fraction	0.01 (-0.01, 0.03)	0.44	0.02 (-0.01, 0.05)	0.19	-0.01 (-0.04, 0.03)	0.61
Left atrium [mm]	0.8 (-0.9, 2.5)	0.38	0.5 (-1.1, 2)	0.57	0.3 (-2, 2.7)	0.79
LAVi [$ml.m^{-2}$]	-0.3 (-5.9, 5.4)	0.92	1 (-4, 6)	0.67	-1.3 (-8.5, 5.9)	0.71
E/e'	-0.1 (-2.0, 1.7)	0.89	-0.8 (-2.2, 0.7)	0.30	0.6 (-1.6, 2.9)	0.58
PWV [$m.s^{-1}$]	-0.03 (-0.8, 0.7)	0.94	-1 (-1.7, 0.08)	0.07	0.8 (-0.4, 1.9)	0.18
pPWV [$m.s^{-1}$]	-0.1 (-1.0, 0.7)	0.74	-0.5 (-1.3, 0.3)	0.19	0.4 (-0.8, 1.5)	0.51

RDN - renal denervation arm; PHAR - pharmacological treatment arm; LV - left ventricle; LVED - LV end-diastolic dimension; IVSd - diastolic interventricular septum; PWd - posterior wall in diastole; RWT - relative wall thickness; LAVi - left atrium volume indexed; PWV - pulse wave velocity; pPWV - peripheral PWV.

Table S5. Differences after 12 months according to per-protocol analysis.

Variable	Change from baseline in complete RDN		Change from baseline in spironolactone addition		RDN to spironolactone between-group difference in change	
	mean (95% CI)	P Value	mean (95% CI)	P Value	mean (95% CI)	P Value
Number of subjects	44		19		-	
Body mass index [kg.m^{-2}]	-0.3 (-0.8, 0.2)	0.19	0.2 (-0.5, 0.9)	0.62	-0.5 (-1.3, 0.4)	0.3
Plasma sodium [mmol/l]	-0.1 (-1.1, 1)	0.93	-1.5 (-2.8, -0.3)	**0.02**	1.5 (-0.3, 3.3)	0.10
Plasma potassium [mmol/l]	0.1 (-0.1, 0.3)	0.24	0.2 (0.0002, 0.5)	**0.049**	-0.1 (-0.4, 0.2)	0.43
Creatinine [µmol/l]	-2.6 (-5.5, 0.2)	0.07	5.8 (0.2, 11.4)	**0.04**	-8.4 (-14, -2.9)	**0.004**
Creatinine clearance [ml/s/1.73m^2]	0.06 (-0.3, 0.4)	0.7	-0.003 (-0.3, 0.3)	0.99	0.06 (-0.4, 0.6)	0.80
Total plasma cholesterol [mmol/l]	-0.2 (-0.5, 0.1)	0.21	-0.2 (-0.5, 0.2)	0.27	0.004 (-0.5, 0.5)	0.99
Fasting plasma glucose [mmol/l]	-0.5 (-1, 0.1)	0.12	0.3 (-0.6, 1.2)	0.53	-0.7 (-1.8, 0.3)	0.16
Direct renin [pg/ml]	-0.8 (-26, 25)	0.95	66 (-7, 138)	0.07	-67 (-124, -9)	**0.03**
Aldosterone [ng/l]	35 (-7, 77)	0.1	182 (-44, 410)	0.1	-148 (-298, 2)	0.05
Metanephrine [nmol/l]	-0.03 (-0.08, 0.02)	0.25	0.03 (-0.05, 0.1)	0.45	-0.06 (-0.14, 0.03)	0.18
Normetanephrine [nmol/l]	-0.007 (-0.1, 0.1)	0.87	-0.007 (-0.2, 0.2)	0.93	-0.0001 (-0.2, 0.2)	0.99
Office systolic BP [mmHg]	-13.7 (-19.3, -8)	**<0.001**	-16.3 (-28.5, -4.2)	**0.01**	2.7 (-8.7, 14)	0.64
Office diastolic BP [mmHg]	-9 (-12.7, -5.4)	**<0.001**	-11.4 (-19.7, -3.1)	**0.009**	2.4 (-5.2, 9.9)	0.53
Heart rate [bpm]	-3.6 (-7.1, 0.02)	**0.048**	-3.4 (-8.8, 2.1)	0.20	-0.2 (-6.6, 6.2)	0.9
24h systolic BP [mmHg]	-6.3 (-10.4, -2.1)	**0.004**	-15 (-24, -6)	**0.003**	8.7 (0.4, 17.1)	**0.04**
24h diastolic BP [mmHg]	-5.4 (-7.9, -2.9)	**<0.001**	-8.6 (-14.3, -2.8)	**0.006**	3.1 (-2.1, 8.3)	0.24
24h heart rate [bpm]	-0.4 (-2.8, 1.9)	0.71	-1.8 (-5.4, 1.8)	0.30	1.4 (-2.9, 5.6)	0.52
Number of drugs used	0.2 (-0.01, 0.4)	0.05	0.7 (-0.2, 1.2)	**0.01**	-0.5 (-0.9, -0.07)	**0.02**
LVED [mm]	-0.7 (-2.0, 0.5)	0.23	-0.6 (-3, 2)	0.64	-0.1 (-2.6, 2.3)	0.91
IVSd [mm]	-0.4 (-0.9, 0.05)	0.08	-0.5 (-1.3, 0.3)	0.20	0.06 (-0.8, 0.9)	0.89
PWd [mm]	-0.04 (-0.5, 0.4)	0.84	-0.1 (-0.9, 0.7)	0.76	0.08 (-0.7, 0.9)	0.85
RWT	0.007 (-0.01, 0.03)	0.52	0.003 (-0.05, 0.05)	0.91	0.005 (-0.04, 0.05)	0.84

LV mass [g]	-12 (-32, 8)	0.24	-11 (-37, 15)	0.39	-1 (-34, 32)	0.95
LV mass index [$g.m^{-2,7}$]	-2.6 (-7, 1.8)	0.24	-1.9 (-7.2, 3.3)	0.45	-0.6 (-7.6, 6.4)	0.86
LV ejection fraction	0.005 (-0.02, 0.03)	0.72	-0.008 (-0.04, 0.03)	0.63	0.01 (-0.03, 0.06)	0.58
Left atrium [mm]	0.6 (-1.3, 2.5)	0.54	1.8 (-0.9, 4.5)	0.17	-1.2 (-4.7, 2.2)	0.49
LAVi [$ml.m^{-2}$]	-0.2 (-8.2, 7.7)	0.95	3 (-2.6, 8.6)	0.24	-3.2 (-12.3, 5.8)	0.46
E/e'	-0.2 (-2.4, 2)	0.82	0.7 (-2.9, 4.3)	0.67	-0.9 (-4.8, 3)	0.63
PWV [$m.s^{-1}$]	-0.1 (-1, 0.7)	0.71	-1.5 (-2.8, 0,1)	**0.04**	1.3 (-0.1, 2.8)	0.06
pPWV [$m.s^{-1}$]	-0.03 (-1, 0.9)	0.95	-0.8 (-1.8, 0.4)	0.18	0.7 (-0.7, 2.2)	0.31

RDN - renal denervation arm; BP - blood pressure; LV - left ventricle; LVED - LV end-diastolic dimension; IVSd - diastolic interventricular septum; PWd - posterior wall in diastole; RWT - relative wall thickness; LAVi - left atrium volume indexed; PWV - pulse wave velocity; pPWV - peripheral PWV.

Table S6. Characteristics of antihypertensive treatment changes after 12 months.

Variable	RDN	PHAR	P Value
Number of patients	51	50	-
Number of drugs used n	5.2±1.3	5.6±1.4	0.18
Patients with unchanged number of drugs n (%)	38 (75 %)	32 (64 %)	0.36
Patients with increased number of drugs n (%)	9 (18 %)	12 (24 %)	0.47
Patients with increased doses of drugs n (%)	7 (14 %)	21 (42 %)	**0.02**
Patients with decreased number of drugs n (%)	4 (8 %)	6 (12 %)	0.84
Patients with decreased doses of drugs n (%)	11 (22 %)	5 (10 %)	0.32

RDN - renal denervation arm; PHAR - conservative treatment arm.
Values are shown as means±SD or absolute numbers and percentages.

Table S7. Target BP acquirement after 12 months.

Variable	RDN	PHAR	P Value
Number of patients n	51	50	-
<140 mmHg office systolic BP	22 (43%)	22 (44%)	1.00
<90 mmHg office diastolic BP	37 (73%)	41 (82%)	0.66
<130 mmHg 24h systolic BP	13 (25%)	12 (24%)	0.82
<80 mmHg 24h diastolic BP	21 (41%)	29 (58%)	0.18

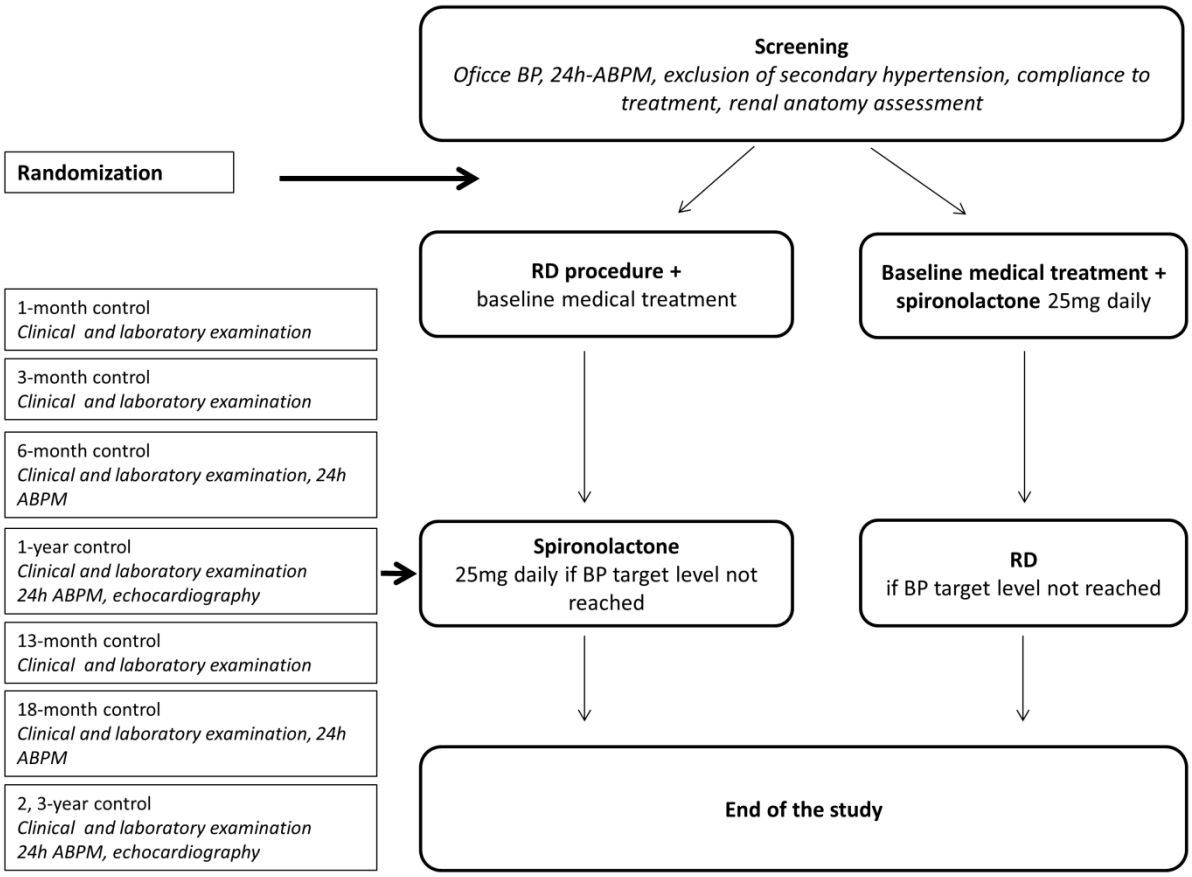
RDN - renal denervation arm; PHAR - conservative treatment arm; BP - blood pressure.

Table S8. Systolic and diastolic BP response based on ≥5 mmHg and ≥10 mmHg reduction from baseline at 12 months.

Variable	RDN	PHAR	P Value
Number of patients n	51	50	-
≥5 mmHg office systolic BP reduction	32 (63%)	30 (60%)	0.56
≥10 mmHg office systolic BP reduction	29 (57%)	25 (50%)	0.34
≥5 mmHg office diastolic BP reduction	31 (61%)	27 (54%)	0.34
≥10 mmHg office diastolic BP reduction	18 (35%)	16 (32%)	0.68
≥5 mmHg 24h systolic BP reduction	27 (53%)	30 (60%)	0.85
≥10 mmHg 24h systolic BP reduction	19 (37%)	23 (46%)	0.56
≥5 mmHg 24h diastolic BP reduction	25 (49%)	26 (52%)	1.00
≥10 mmHg 24h diastolic BP reduction	12 (24%)	15 (30%)	0.66

RDN - renal denervation arm; PHAR - conservative treatment arm; BP - blood pressure.

Figure S1



Design of the Prague-15 Study

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Role of Adding Spironolactone and Renal Denervation in True Resistant Hypertension: One-Year Outcomes of Randomized PRAGUE-15 Study

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