Randomized Comparison of Renal Denervation Versus Intensified Pharmacotherapy Including Spironolactone in True-Resistant Hypertension

Six-Month Results From the Prague-15 Study

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

See Editorial Commentary, pp 280–282

Abstract—This prospective, randomized, open-label multicenter trial evaluated the efficacy of catheter-based renal denervation (Symplicity, Medtronic) versus intensified pharmacological treatment including spironolactone (if tolerated) in patients with true-resistant hypertension. This was confirmed by 24-hour ambulatory blood pressure monitoring after excluding secondary hypertension and confirmation of adherence to therapy by measurement of plasma antihypertensive drug levels before enrollment. One-hundred six patients were randomized to renal denervation (n=52), or intensified pharmacological treatment (n=54) with baseline systolic blood pressure of 159±17 and 155±17 mm Hg and average number of drugs 5.1 and 5.4, respectively. A significant reduction in 24-hour average systolic blood pressure after 6 months (−8.6 [95% cofidence interval: −11.8, −5.3] mm Hg; $P<0.001$ in renal denervation versus −8.1 [95% cofidence interval: −12.7, −3.4] mm Hg; $P=0.001$ in pharmacological group) was observed, which was comparable in both groups. Similarly, a significant reduction in systolic office blood pressure (−12.4 [95% cofidence interval: −17.0, −7.8] mm Hg; $P<0.001$ in renal denervation versus −14.3 [95% cofidence interval: −19.7, −8.9] mm Hg; $P<0.001$ in pharmacological group) was present. Between-group differences in change were not significant. The average number of antihypertensive drugs used after 6 months was significantly higher in the pharmacological group (+0.3 drugs; $P<0.001$). A significant increase in serum creatinine and a parallel decrease of creatinine clearance were observed in the pharmacological group; between-group difference were borderline significant. The 6-month results of this study confirmed the safety of renal denervation. In conclusion, renal denervation achieved reduction of blood pressure comparable with intensified pharmacotherapy. **(*Hypertension*. 2015;65:407-413. DOI: 10.1161/HYPERTENSIONAHA.114.04019.)** ● **Online Data Supplement**

Key Words: hypertension resistant to conventional therapy ■ spironolactone ■ sympathetic denervation

The prevalence of patients with resistant hypertension (RH) varies from 5% to 30%.[1] Identification of true-RH, when secondary causes and medication noncompliance are excluded, is becoming more important with the implementation of novel, nondrug therapeutic approaches to RH, such as catheter-based renal-artery denervation (RDN) or baroreflex stimulation. Pilot studies using RDN described the method as feasible, effective, and safe for reducing blood pressure (BP) in the short term.[2–4] The interpretation of the results from the majority of these studies was complicated by the lack of 24-hour ambulatory blood pressure monitoring (24-hour ABPM) data, lack of compliance confirmation, or small follow-up sample sizes.

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, according to the recommendations for RDN.[5] Twenty-four-hour ABPM, 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. To date, only 1 study has compared RDN with intensified pharmacological treatment.[6] However, only 19

Received June 6, 2014; first decision June 17, 2014; revision accepted October 1, 2014.

From the 3rd Department of Medicine, Centre for Hypertension, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic (J.R., O.P., T.Z., R.H., B.Š., Z.Š., J.W.); Cardiocentre, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic (J.R., P.W., P.T., K.Č., F.B.); Department of Anesthesiology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic (P.W.); 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.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.114.04019/-/DC1

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

patients were randomized in this study. This article presents the primary end point (6-month) data from the trial.

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 RH were randomized (in a 1:1 ratio) to either (1) a catheter-based RDN plus optimal antihypertensive treatment group (unchanged after randomization, thus including spironolactone only in rare cases where patients were already using the drug before entering the study) or to (2) an intensified pharmacological treatment group (PHAR), including spironolactone if tolerated and not contraindicated. Other medication changes after randomization were allowed only in clinically significant situations. All patients provided written informed consent. The study was approved by a multicenter Ethics Committee and by all 3 local institutional Ethics Committees. Enrollment in the study was prematurely halted (on ethical grounds) when the Symplicity HTN-3 trial interruption was announced because of failure to meet its primary efficacy end point. Therefore, the study was suspended on January 10, 2014 and an analysis of previously gathered data was performed. On the basis of the results of this analysis, it was decided to permanently terminate study enrollment and to complete the 3-years follow up on the previously enrolled patients as prescribed by the protocol.

The exact study design (Figure S1 in the online-only Data Supplement) and power and sample-size analysis has been previously reported.[7] Only patients with RH were included (with an office systolic BP >140 mm Hg after treatment with ≥3 antihypertensive drugs at optimal doses, including a diuretic). Secondary causes of hypertension (eg, primary aldosteronism, pheochromocytoma, Cushing syndrome, renal parenchymal disease, renovascular hypertension, drug-induced hypertension, or other conditions) were excluded in all subjects before randomization. True-RH was confirmed through 24-hour ABPM (average systolic BP >130 mm Hg) and assessment of treatment compliance (quantitative plasma drugs level measurements) before enrollment.[8,9] Renal anatomy was evaluated during screening using computed tomography or magnetic resonance angiography. The differences in systolic and diastolic BP recorded by 24-hour ABPM between baseline and 6 months postrandomization were the primary end points of the study. In addition, office and 24-hour ABPM BP differences between baseline and 1-, 2-, and 3-year postrandomization were measured, as well as changes in standard clinical and laboratory parameters including renal function and postdenervation renal anatomy, analyzed using computed tomography or magnetic resonance angiography, 1 year after trial commencement. Another secondary end point was the effect of RDN on the medically treated group and the effect of spironolactone in the RDN group, 1 year after randomization. These variables measured after >6 months are not included in this article because the 3-years follow up is still ongoing and will not be completed until the end of 2016.

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), if tolerated, and if no contraindications were evident.

Procedures

The RDN procedure was performed by experienced interventional cardiologists or electrophysiologists using the Symplicity Renal Denervation System (Medtronic Inc, Mountain View, CA). In each of the 3 study centers, only 2 experienced interventionalists performed all procedures and all 6 physicians had previous experience with the system before the study started. Treatment involved ≥4 to 6 applications of low-power (8 W) radiofrequency energy to each renal artery. Each treatment was delivered in a helical fashion within the artery by rotating the catheter during pullback. The distance between ablation sites was ≈5 mm. All patients received intravenous heparin 100 U/kg of body weight at the beginning of the procedure. Procedures were performed under intravenous analgosedation, without endotracheal intubation.

BP Measurements

Office-measured BP values were obtained using validated BP monitors according to European Society of Hypertension and European Society of Cardiology Guidelines for management of arterial hypertension.[1] Twenty-four-hour ABPMs were obtained using an oscillometric device (SpaceLabs 90207/90217; SpaceLabs Medical, Redmond, WA).

Statistical Analysis

Stata version 13.1 (StataCorp LP, TX) was used to analyze the recorded data. The analysis included all randomized participants for whom data were available and was performed using the intention-to-treat principle. Descriptive statistics were used to summarize characteristics of study participants. For continuous variables, the Student *t* test was used for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. The Fisher exact test was used for proportions. Longitudinal data analysis (comparison of baseline and 6-month data), including adjustment for the number of antihypertensives and use of aldosterone antagonists, was performed by generalized estimating equations with an unstructured correlation matrix to adjust for correlations over the assessment time points. $P<0.05$ was considered statistically significant. All reported subgroup analyses were prespecified.

Results

One hundred six patients fulfilled all entry criteria and were randomized. Fifty-two patients were randomized to RDN and 54 to PHAR group. Baseline office BP was 159±19/92±14 mm Hg (while on 5.1±1.2 antihypertensive drugs) in the RDN group and 155±17/89±14 mm Hg (while on 5.4±1.2 antihypertensive drugs) in the PHAR group. Baseline 24-hour average BP was 149±12/86±10 mm Hg in the RDN group and 147±13/84±10 in the PHAR group. See Tables 1–3 for the baseline characteristics of study participants and 6-month results. There were no significant baseline differences between groups in most of the studied parameters, however, body mass index was an exception (31.2 in RDN versus 33.4 in PHAR, $P=0.01$). This difference remained unchanged after 6 months.

Twenty-Four-Hour ABPM

A significant reduction in 24-hour average systolic BP after 6 months (−8.6 mm Hg in RDN; $P<0.001$ versus −8.1 mm Hg in PHAR; $P=0.001$) was observed, which was comparable in both groups. Similarly, a significant decrease in the 24-hour average diastolic BP (−5.7 mm Hg in RDN; $P<0.001$ versus −4.5 mm Hg in PHAR; $P<0.001$) was also observed and was comparable in both groups (Figure 1).

Table 1. Baseline Characteristics of Studied Subjects

Variable	RDN	PHAR	*P* Value
Age, y	56±12	59±9	0.20
Male, n (%)	40 (77%)	34 (63%)	0.14
Duration of hypertension, y	19±12	15±11	0.11
Patients with type 2 diabetes mellitus, 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

Values are shown as means±SD or absolute numbers and percentages. PHAR indicates intensified pharmacological treatment; and RDN, renal-artery denervation.

Table 2. Clinical Characteristics of Studied Subjects

Variable	Baseline				After 6 Months			
	RDN	PHAR	RDN to PHAR Difference Mean (95% CI)	P Value	RDN	PHAR	RDN to PHAR Difference Mean (95% CI)	*P* Value
Number of subjects	52	54	…	…	52	54	…	…
Body mass index, kg/m^2	31.2±4.3	33.4±4.7	−2.2 (−3.9, −0.5)	**0.01**	31.1±4.4	33.6±4.7	−2.3 (−4.0, −0.6)	**0.01**
Plasma sodium, mmol/L	141±3	141±3	0.2 (−0.9, 1.2)	0.76	141±3	139±3	1.3 (−0.3, 2.4)	**0.01**
Plasma potassium, mmol/L	4.1±0.4	4.2±0.4	−0.1 (−0.3, 0.1)	0.25	4.1±0.5	4.2±0.5	−0.1 (−0.3, 0.04)	0.13
Creatinine, µmol/L	87 (78–97)	84 (72–94)	−0.2 (−7.2, 6.8)	0.96	86 (76–92)	88 (73–101)	−5.9 (−14.4, 2.6)	0.17
Creatinine clearance, mL/s per 1.73 m^2	1.5 (1.3–1.9)	1.6 (1.2–2.1)	−0.01 (−0.32, 0.3)	0.98	1.7 (1.2–2.0)	1.5 (1.1–1.8)	0.3 (0.1, 0.6)	**0.02**
Total plasma cholesterol, mmol/L	4.4±1.0	4.7±1.0	−0.3 (−0.7, 0.1)	0.12	4.3±1.1	4.6±1.0	−0.3 (−0.7, 0.1)	0.09
Fasting plasma glucose, mmol/L	5.9 (5.1–7.2)	6.1 (5.1–7.8)	−0.2 (−1.2, 0.9)	0.79	5.9 (5.2–6.8)	5.8 (5.1–7.5)	−0.1 (−0.8, 0.6)	0.81
Office systolic BP, mm Hg	159±19	155±17	3.8 (−2.9, 10.5)	0.26	147±20	141±18	5.8 (−1.4, 13.0)	0.12
Office diastolic BP, mm Hg	92±14	89±14	3.4 (−1.9, 8.8)	0.21	85±12	82±13	3.3 (−1.5, 8.0)	0.18
Heart rate, beats/min	71±14	72±11	−0.6 (−4.6, 3.5)	0.78	68±10	71±11	−2.8 (−6.,8, 1.3)	0.18
24-h systolic BP, mm Hg	149±12	147±13	1.5 (−3.3, 6.4)	0.54	140±13	139±16	1.0 (−4.6, 6.7)	0.36
24-h diastolic BP, mm Hg	86±10	84±10	2.6 (−1.4, 6.5)	0.20	80±10	79±11	1.4 (−2.5, 5.4)	0.48
24-h heart rate, beats/min	69±10	70±10	−0.7 (−4.6, 3.2)	0.72	68±9	68±10	−0.5 (−4.2, 3.1)	0.78
Day systolic BP, mm Hg	152±12	150±13	2.7 (−2.6, 8.0)	0.32	143±13	141±16	1.9 (−3.4, 7.2)	0.48
Day diastolic BP, mm Hg	88±10	85±11	2.8 (−1.4, 7.0)	0.19	83±10	81±12	1.8 (−2.4, 6.0)	0.40
Day heart rate, beats/min	72±12	72±11	0.1 (−3.9, 4.2)	0.95	70±10	70±10	−0.2 (−4.2, 3.9)	0.94
Night systolic BP, mm Hg	141±16	141±17	−0.2 (−6.5, 6.0)	0.94	133±14	133±19	−0.8 (−7.0, 5.5)	0.81
Night diastolic BP, mm Hg	80±11	78±10	2.5 (−1.5, 6.5)	0.23	74±10	74±11	0.9 (−3.2, 4.9)	0.68
Night heart rate, beats/min	63±9	65±10	−1.4 (−5.2, 2.4)	0.46	62±9	63±11	−1.3 (−5.1, 2.4)	0.49
Number of drugs used	5.1±1.2	5.4±1.2	−0.2 (−0.7, 0.3)	0.40	5.0±1.3	5.6±1.3	−0.5 (−1.0, −0.1)	**0.02**

Values are shown as means±SD or medians (interquartile range) or absolute numbers. BP indicates blood pressure; CI, confidence interval; PHAR, intensified pharmacological treatment; and RDN, renal-artery denervation. A *P* value <0.05 was considered statistically significant (in bold).

Office BP

As with 24-hour ABPM, significant reductions in systolic office BP (−12.4 mm Hg in RDN; *P*<0.001 versus −14.3 mm Hg in PHAR; *P*<0.001) and diastolic BP (−7.4 mm Hg in RDN; *P*<0.001 versus −7.3 mm Hg in PHAR; *P*<0.001) were observed (Figure 2). Between-group differences in change were not significant.

Heart Rate

A significant reduction in heart rate was recorded in RDN (−3.4 beats per minute; *P*=0.02) with no significant between-group differences when compared with PHAR. However, nonsignificant changes in the 24-hour heart rate were present. Differences in the studied parameters are summarized in Table 3.

Medication

The average number of antihypertensive drugs used was significantly higher after 6 months in PHAR (+0.3 drugs; *P*<0.001) group, which reflected the increased number of patients on spironolactone (+20; *P*<0.001). See Tables 4 and S1 for the characteristics of antihypertensive treatment and changes. In the PHAR group, the spironolactone treatment was, for several reasons, not possible in 21 patients (see Table 5 for side effects and adverse events). The discontinuation was initiated before the 6-month visit. An alternative option (eplerenone) was offered when possible, but was refused by all patients because of the financial costs of the drug. After adjustment for the number of drugs and aldosterone antagonist use, the 24-hour systolic BP reduction remained significant in both groups (*P*<0.001) and between-group differences remained nonsignificant (*P*=0.46). Similarly, other differences in BP parameters did not change after this adjustment. Furthermore, adjustment for body mass index did not influence the significance of BP differences.

Predictors of BP Response

Logistic regression analysis showed that the main predictors of successful RDN, defined as ≥10 mm Hg decrease in systolic 24-hour BP, were related to the total number of ablations, day systolic BP and day heart rate. After adjustment, day systolic BP remained the main predictor. Linear regression analysis showed similar results, with day systolic BP and day heart rate as the main predictors after adjustment. See Table S2 for results from the logistic and linear regression analysis and Tables S3 and S4 for the response rates in both groups.

Biochemistry

Several laboratory changes were observed. Significant sodium level decline was observed in the PHAR group, while no significant reduction was observed in the RDN group, and no between-group differences in change were present after 6 months. A significant increase in serum creatinine levels was observed in the PHAR group (+5.3 µmol/L; *P*=0.048).

Table 3. Differences After 6 Months

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
Body mass index, kg/m^2	−0.1 (−0.5, 0.3)	0.64	−0.01 (−0.3, 0.3)	0.94	−0.1 (−0.6, 0.4)	0.75
Plasma sodium, mmol/L	−0.2 (−1.2, 0.7)	0.60	−1.4 (−2.3, −0.5)	**<0.01**	+1.2 (−0.1, 2.5)	0.07
Plasma potassium, mmol/L	0.03 (−0.1, 0.2)	0.71	0.1 (−0.1, 0.2)	0.42	−0.03 (−0.2, 0.2)	0.76
Creatinine, µmol/L	−0.4 (−3.1, 2.3)	0.76	5.3 (0.1, 10.5)	**0.048**	−5.7 (−11.6, 0.2)	0.06
Creatinine clearance, mL/s per 1.73 m^2	0.1 (−0.2, 0.4)	0.46	−0.3 (−0.5, 0.003)	**0.048**	0.4 (−0.01, 0.7)	0.06
Total plasma cholesterol, mmol/L	−0.1 (−0.4, 0.1)	0.35	−0.1 (−0.3, 0.1)	0.33	−0.02 (−0.4, 0.3)	0.89
Fasting plasma glucose, mmol/L	−0.5 (−1.0, 0.02)	0.06	−0.6 (−1.2, 0.1)	0.07	0.1 (−0.9, 0.8)	0.88
Office systolic BP, mm Hg	−12.4 (−17.0, −7.8)	**<0.001**	−14.3 (−19.7, −8.9)	**<0.001**	1.9 (−5.2, 9.0)	0.60
Office diastolic BP, mm Hg	−7.4 (−11.0, −3.9)	**<0.001**	−7.3 (−10,3, −4,2)	**<0.001**	−0.2 (−4.8, 4.5)	0.94
Heart rate, beats/min	−3.4 (−6.3, −0.5)	**0.02**	−1.2 (−3.5, 1.1)	0.29	−2.2 (−5.9, 1.5)	0.25
24-h systolic BP, mm Hg	−8.6 (−11.8, −5.3)	**<0.001**	−8.1 (−12.7, −3.4)	**0.001**	−0.5 (−6.1, 5.2)	0.87
24-h diastolic BP, mm Hg	−5.7 (−7.9, −3.4)	**<0.001**	−4.5 (−6.8, −2.3)	**<0.001**	−1.1 (−4.3, 2.0)	0.48
24-h heart rate, beats/min	−1.4 (−3.5, 0.7)	0.20	−1.6 (−3.7, 0.4)	0.12	0.2 (−2.7, 3.1)	0.90
Day systolic BP, mm Hg	−9.0 (−13.2, −4.7)	**<0.001**	−8.2 (−12.4, −4.0)	**<0.001**	−0.8 (−6.8, 5.2)	0.79
Day diastolic BP, mm Hg	−5.6 (−8.1, −3.1)	**<0.001**	−4.6 (−7.0, −2.1)	**<0.001**	−1.0 (−4.5, 2.5)	0.57
Day heart rate, beats/min	−2.0 (−4.2, 0.1)	0.06	−1.8 (−3.9, 0.4)	0.10	−0.3 (−3.3, 2.7)	0.85
Night systolic BP, mm Hg	−8.1 (−12.7, −3.6)	**<0.001**	−7.6 (−12.1, −3.1)	**0.001**	−0.5 (−6.9, 5.9)	0.87
Night diastolic BP, mm Hg	−6.0 (−8.7, −3.3)	**<0.001**	−4.4 (−7.0, −1.7)	**0.001**	−1.6 (−5.4, 2.1)	0.39
Night heart rate, beats/min	−1.2 (−3.6, 1.2)	0.31	−1.3 (−3.7, 1.1)	0.28	0.1 (−3.3, 3.4)	0.97
Number of drugs used, n	−0.02 (−0.2, 0.1)	0.81	0.3 (0.2, 0.5)	**<0.001**	−0.3 (−0.6, −0.1)	**<0.01**

BP indicates blood pressure; CI, confidence interval; PHAR, intensified pharmacological treatment; and RDN, renal-artery denervation. A *P* value <0.05 was considered statistically significant (in bold).

Between-group difference in change had borderline statistical significance (*P*=0.06). A parallel decrease of creatinine clearance was also observed (−0.3; *P*=0.048), with similar between-group difference in change (*P*=0.06). A significant increase in potassium levels (+0.2; *P*=0.02) was observed, but only in the subgroup where spironolactone was added and continued (see Tables S7 and S8 for the subanalysis of the PHAR group according to spironolactone addition and its continuation).

Procedural Characteristics

The mean number of successful ablations (lasting ≥120 s) in 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 (≥4 per side) in 7 patients, 2 patients out of that number had unilateral ablations for anatomic 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 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.

See Tables S5 and S6 for the subanalysis of the RDN group according to the number of ablations per side.

Safety

We recently published that no significant complications were recorded in association with the RDN procedure,[10] see Table 5 for minor side effects and adverse events. None of these led to clinically significant consequences for the patients. One case of renal artery dissection was resolved by immediate stenting. All spasms were fully treated or reduced through intra-arterial administration of nitrates. There was 1 ischemic stroke and 1 myocardial infarction (without ST elevations) in the RDN group during the 6-month follow up; and 1 case of unstable angina was observed in the PHAR group. No deaths occurred during follow-up.

Discussion

This randomized, prospective study showed that in the settings of true-RH, RDN is not superior to intensified PHAR over

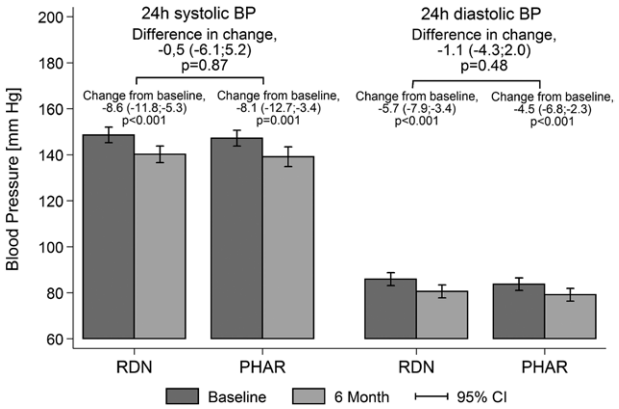


Figure 1. Ambulatory 24-hour average blood pressure (BP) changes. Significant 24-hour average BP changes from baseline to 6 months were observed in both groups. However, between-group differences in change were not significant. CI indicates confidence interval; PHAR, intensified pharmacological treatment; and RDN, renal-artery denervation.

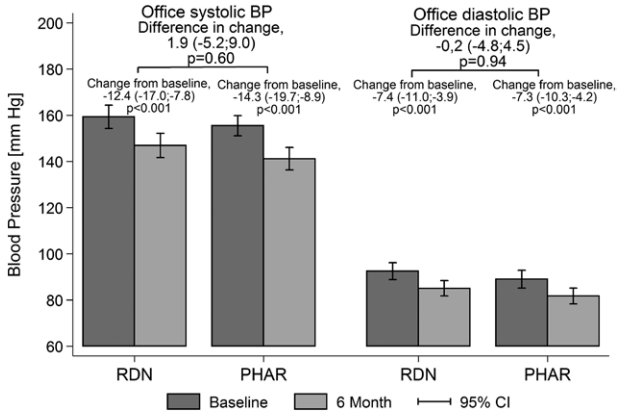


Figure 2. Office blood pressure (BP) changes. Significant office BP changes from baseline to 6 months were observed in both groups. However, between-group differences in change were not significant. CI indicates confidence interval; PHAR, intensified pharmacological treatment; and RDN, renal-artery denervation.

a period of 6 months. Twenty-four-hour ABPM parameters, as well as office BP values were comparably affected in both treatment arms, without marked between-group differences.

The study was designed to assess the efficacy of RDN as a treatment for true-RH. Discrepant results in RDN efficacy have been observed in previous studies.[2,4,6,11,12] Several differences in the methodology of these trials might have contributed to the disparity of results. Currently, the Symplicity HTN-3 study, which was recently published, is considered the most robust RDN study.[13] Despite the fact that our study was smaller and a sham procedure was not part of our protocol, our study has several potential advantages. First, we totally excluded the possibility of secondary hypertension in all study participants before allowing enrollment in the PRAGUE-15 study, and every patient underwent a thorough examination in a hypertension center.[8] Second, compliance with treatment was fully confirmed in all patients, using quantitative

Table 4. Characteristics of Antihypertensive Treatment

	Baseline		After 6 Months	
Variable	RDN	PHAR	RDN	PHAR
Number of patients	52	54	52	54
Number of drugs used, n	5.1±1.2	5.4±1.2	5.0±1.3	5.6±1.3
Calcium channel blockers, n (%)	46 (89%)	48 (89%)	45 (87%)	47 (87%)
β-Blockers, n (%)	34 (66%)	37 (69%)	31 (60%)	39 (72%)
Diuretics, n (%)	52 (100%)	54 (100%)	52 (100%)	54 (100%)
Amiloride, n (%)	11 (21%)	19 (35%)	12 (23%)	19 (35%)
Thiazide diuretic, n (%)	48 (92%)	50 (93%)	46 (89%)	49 (91%)
Furosemide, n (%)	1 (2%)	3 (6%)	2 (4%)	5 (9%)
Aldosterone antagonists, n (%)	14 (27%)	13 (24%)	13 (25%)	33 (61%)
ACE inhibitors/sartans, n (%)	52 (100%)	54 (100%)	52 (100%)	54 (100%)
α-Blockers, n (%)	28 (54%)	25 (46%)	28 (54%)	24 (44%)
Centrally acting drugs, n (%)	28 (54%)	33 (61%)	26 (50%)	33 (61%)

Values are shown as means±SD or absolute numbers or percentages. ACE indicates angiotensin-converting enzyme; PHAR, intensified pharmacological treatment; and RDN, renal-artery denervation.

Table 5. Side Effects/Adverse Events

Renal denervation arm
Spasms after application of radiofrequency energy, 4 patients (8%)
Dissection of renal artery, 1 patient (2%)
Postpunctual 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 (11%)
Worsening of renal function, 1 patient (2%)
Antiandrogen effect of spironolactone, 7 patients (13%)
Refusal to continue treatment with spironolactone because of symptomatic blood pressure reduction, 5 patients (9%)
Refusal to start spironolactone treatment, 2 patients (4%)

measurements of plasma drug levels, before enrollment. To our knowledge, this was not performed in any prior study that tested the effect of RDN on RH; although, there was 1 smaller study that used witnessed intake of medication to systematically measure treatment compliance.[6] Currently, urine or plasma drug levels are considered the most reliable methods for identifying noncompliance.[9,14] On the basis of a previous study, treatment noncompliance is a common cause of inadequate BP control.[8,9] Furthermore, as only pharmacologically treated hypertensive patients enter RDN studies, the issue of compliance is crucial to identify the actual effects of RDN. When assessing additive therapeutic modalities, such as RDN, patient compliance with the basic therapeutic modality, in this case pharmacological treatment, is critical. Otherwise, it is impossible to know if the observed BP changes were associated with RDN or were the result of variations in treatment compliance. Sham procedures can eliminate possible placebo and Hawthorne effects; however, it does not eliminate variations as a result of treatment adherence, which would necessitate using RDN only on untreated hypertensive patients. Compliance together with a thorough examination at a hypertension center before enrollment, ensured selection of true-resistant essential hypertensive patients for the PRAGUE-15 study. This design might explain the relatively low baseline values of office BP, as well as 24-hour ABPM compared with all other Symplicity trials.[2–4,13] However, our BP values are comparable with the study that systematically tested for a secondary cause of hypertension before enrollment and monitored treatment noncompliance using witnessed intake of medication.[6] Additional clinical value came from comparing RDN with intensified pharmacological treatment, which included spironolactone. It has been shown that spironolactone effectively reduces BP in resistant hypertensive patients.[15,16] The effect of spironolactone in those who did not respond to RDN will be evaluated 1 year after randomization.

There are several potential factors influencing the BP reduction observed in both groups. Despite the fact, that computed tomography or magnetic resonance angiography was used to confirm anatomic eligibility, we did not reach the recommended number of ablations (≥4 per side) in 7 patients

(13.5%). Because the study was performed using intention-to-treat principles, we did not exclude these patients from the analysis. Furthermore, our results indicate that the number of ablations might be a possible predictor of response to RDN. This fact might support the efficacy of the method and might suggest a need to perform even more ablations. However, at the time of study preparation and according to the Symplicity HTN-1 and 2 trials,[3,4] 4 to 6 ablations were recommended, which were achieved in most of the patients. Furthermore, there was no evidence of a correlation between the number of ablations and the response to RDN at that time. A subanalysis of patients, with 4 to 6 ablations, showed that BP changes are more pronounced in this group. Further analyses on large samples would be necessary to confirm these findings and to identify patients who would benefit from RDN.However, these results might suggest that new, multielectrode systems could be more effective in producing a decline in BP.

Similarly, there are several important factors influencing BP reduction in the PHAR group. First, 13 patients in PHAR (14 in RDN) entered the study already taking an aldosterone antagonist. However, we considered it unethical to withdraw this potent drug before randomization. Second, in another 21 patients spironolactone treatment was discontinued during the 6-month follow up because of intolerance or hyperkalemia. Finally, medication changes were necessary in this group more often to maintain treatment safety (to prevent hyperkalemia and worsening of renal function), for example, ACEi/sartan/amiloride dose reductions. Another reason for therapy reduction was symptomatic BP decline. When we evaluated the effect in patients in whom spironolactone was added after enrollment and continued for 6 months, we observed a 12 mm Hg reduction in systolic 24-hour average BP. The rate of intolerance of spironolactone observed in our study (39%) was higher than generally observed (10% to 30%).[17] The psychological effect of expecting (and possibly hoping for) crossover when not reaching the BP goal might be one of the explanations. The subanalysis of the PHAR group indicates that BP decline was mostly driven by patients in whom spironolactone was added and continued.

Apart from BP changes, a significant reduction in heart rate was observed in RDN. This might be a consequence of a lowered whole-body sympathetic activity mediated by a reduction of renal afferent nerve activity. Heart rate changes, independent of BP changes, after RDN were reported previously.[18]

Several other laboratory changes were recorded in the PHAR group, mostly associated with spironolactone treatment. Significant decrease in plasma sodium was present. Slight, but significant, plasma potassium level increase was recorded in the subgroup of PHAR where spironolactone was added and continued. We observed a significant increase in serum creatinine level and a parallel decrease of creatinine clearance in the PHAR group, which might have also been the result of spironolactone treatment. Between-group differences in change were borderline, but not significant. Furthermore, spironolactone treatment led to significant worsening of renal function (without the need of dialysis), which persisted after its discontinuation, only in 1 patient with diabetic nephropathy. All the observed spironolactone side effects were well known and have been previously described; as expected this medication required careful and regular monitoring.[15,16] However, further follow-up would be necessary to evaluate long-term safety relative to renal function, especially in RDN.

There are several possible limitations to our study. Potential disadvantages of not performing a sham procedure have already been discussed. However, we consider an invasive pseudoprocedure including sedation, with all its possible side effects, to be problematic. Another possible limitation was the relatively small number of participants. However, it was expected that careful screening of participants would significantly reduce the number of eligible patients for RDN.[8,19] That was the reason why the initial study design was for only 120 patients. Post hoc power analysis showed that it is possible to identify between-group differences of 6.9 mm Hg (when P=0.05; power=0.08) for systolic 24-hour BP and 5.5 mm Hg for diastolic 24-hour BP with the current number of enrolled patients. The number of patients enrolled to our study was comparable with the number enrolled in Symplicity HTN-2.

Perspectives

This study shows that over a period of 6 months, RDN is safe, with no serious side effects. However, in the settings of true-RH with confirmed compliance, it is not superior to intensified pharmacological treatment including the use of spironolactone. Further studies on a larger sample of subjects with true-RH would be appropriate before the final role of denervation is established. Currently, renal denervation is not a routine therapeutic approach in patients with severe hypertension and should be reserved for use only in hypertension centers, and only after a thorough examination.

Sources of Funding

This work was supported by a research project from the Ministry of Education of Czech Republic (NT14155-3/2013) and by Charles University research project UNCE (No. 204010) and PRVOUK (No. P35/LF1/5).

Disclosures

None.

References

1. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219.
2. 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;376:1903–1909.
3. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension*. 2011;57:911–917.
4. Esler MD, Krum H, Schlaich M, Schmieder RE, Bohm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. *Circulation*. 2012;126:2976–2982.
5. Widimský P, Filipovský J, Widimský Jr J, Branny M, Monhart V, Táborský M. Expert consensus statement of the Czech Society of Cardiology and the Czech Society of Hypertension on catheter-based sympathetic renal denervation procedures (RDN) in the Czech Republic. *Cor et Vasa*. 2012;54:e108–e112.
6. Fadl Elmula FE, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, Gjønnæss E, Hjørnholm U, Kjaer VN, Rostrup M, Os I, Stenehjem A, Høieggen A. Adjusted drug treatment is superior to renal

sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension*. 2014;63:991–999.
7. Toušek P, Widimský Jr J, Rosa J, Čurila K, Branny M, Nykl I, Táborský M, Václavík J, Widimský P. Catheter-based renal denervation versus intensified medical treatment in patients with resistant hypertension: Rationale and design of a multicenter randomized study - PRAGUE-15. *Cor et Vasa*. 2014;56:e228–e234.
8. Rosa J, Zelinka T, Petrák O, Štrauch B, Šomlóová Z, Indra T, Holaj R, Čurila K, Toušek P, Šenitko M, Widimský P, Widimský Jr J. Importance of thorough investigation of resistant hypertension before renal denervation: should compliance to treatment be evaluated systematically? *J Hum Hypertens*. 2014; 28:684–688.
9. Štrauch B, Petrák O, Zelinka T, Rosa J, Šomlóová Z, Indra T, Chytil L, Marešová V, Kurcová I, Holaj R, Wichterle D, Widimský J Jr. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens*. 2013;31:2455–2461.
10. Čurila K, Rosa J, Toušek P, Widimský Jr J, Widimský P. Technical and safety aspects of renal denervation. *Cor et Vasa*. 2014;56:e228–e234.
11. Persu A, Azizi M, Burnier M, Staessen JA. Residual effect of renal denervation in patients with truly resistant hypertension. *Hypertension*. 2013;62:450–452.
12. Persu A, Jin Y, Azizi M, et al. . Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens*. 2014;28:150–156.
13. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393–1401.
14. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens*. 2013;31:766–774.
15. de Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension*. 2010;55:147–152.
16. Václavík J, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, Václavík T, Husár R, Kociánová E, Táborsky M. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. *Hypertension*. 2011;57:1069–1075.
17. Calhoun DA, White WB. Effectiveness of the selective aldosterone blocker, eplerenone, in patients with resistant hypertension. *J Am Soc Hypertens*. 2008;2:462–468.
18. Ukena C, Mahfoud F, Spies A, Kindermann I, Linz D, Cremers B, Laufs U, Neuberger HR, Böhm M. Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. *Int J Cardiol*. 2013;167:2846–2851.
19. Persu A, Jin Y, Baelen M, et al. Eligibility for renal denervation: experience at 11 European expert centers. *Hypertension*. 2014;63:1319–1325.

Novelty and Significance

What Is New?

- In the settings of true-resistant hypertension with confirmed compliance, renal denervation is not superior to intensified pharmacological treatment.

What Is Relevant?

- Renal denervation should be reserved only for true-resistant hypertension patients with excluded secondary hypertension and confirmed compliance to treatment.
- Renal denervation does not represent routine therapeutic approach in patients with severe hypertension and should be applied only in hypertension centers after thorough examination.

Summary

Renal denervation leads to a significant blood pressure reduction (office, as well as 24-hour ambulatory blood pressure monitoring) over a 6 months period in the settings of true-resistant hypertension. However, this decline is comparable with intensified pharmacological treatment, including spironolactone.

Online supplement

A RANDOMIZED COMPARISON OF RENAL DENERVATION VERSUS INTENSIFIED PHARMACOTHERAPY INCLUDING SPIRONOLACTONE IN TRUE-RESISTANT HYPERTENSION. 6-MONTHS RESULTS FROM THE PRAGUE-15 STUDY.

Ján ROSA[1,2], Petr WIDIMSKÝ[2], Petr TOUŠEK[2], Ondřej PETRÁK[1], Karol ČURILA[2], Petr WALDAUF[3], František BEDNÁŘ[2], Tomáš ZELINKA[1], Robert HOLAJ[1], Branislav ŠTRAUCH[1], Zuzana ŠOMLÓOVÁ[1], Miloš TÁBORSKÝ[4], Jan VÁCLAVÍK[4], Eva KOCIÁNOVÁ[4], Marian BRANNY[5], Igor NYKL[5], Otakar JIRAVSKÝ[5], Jiří WIDIMSKÝ Jr.[1]

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

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

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

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

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

Short title: Renal denervation versus intensified pharmacotherapy.

Corresponding author: Ján Rosa, 3rd Department of Medicine, Centre for Hypertension, General University Hospital, U Nemocnice 2, 128 08 Prague, Czech Republic, tel.:+420224962945, fax:+420224963245, email: jan.rosa@lf1.cuni.cz

Table S1. Characteristics of antihypertensive treatment changes after 6 months.

Variable	RDN	PHAR	P Value
Number of patients	52	54	-
Number of drugs used n	5.0±1.3	5.6±1.3	**0.02**
Patients with unchanged number of drugs n (%)	33 (64%)	36 (67%)	0.84
Patients with increased number of drugs n (%)	3 (6%)	15 (28%)	**<0.01**
Patients with increased doses of drugs n (%)	5 (10%)	11 (20%)	0.18
Patients with decreased number of drugs n (%)	5 (10%)	5 (9%)	1
Patients with decreased doses of drugs n (%)	7 (14%)	9 (17%)	0.79

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

Table S2. Analysis of RDN response.

Logistic regression.

Variable	Odds ratio (95% CI)	P Value	Adjusted odds ratio (95% CI)	P Value
Day heart rate [bpm]	1.07 (1.01, 1.13)	**0.03**	1.08 (1.00, 1.16)	0.07
Number of total ablations	1.22 (1.01, 1.47)	**0.04**	1.20 (0.97, 1.49)	0.10
Day systolic BP [mmHg]	1.08 (1.02, 1.14)	**0.01**	1.11 (1.03, 1.20)	**0.01**

Linear regression.

Variable	Coefficient (95% CI)	R squared	P Value	Adjusted Coefficient (95% CI)	R squared	P Value
Day heart rate [bpm]	0.39 (0.12, 0.66)	0.15	**<0.01**	0.35 (0.08, 0.63)		**0.01**
Number of total ablations	0.42 (0.5, 1.34)	0.02	0.37	0.01 (0.82, 0.83)	0.32	0.99
Day systolic BP [mmHg]	0.39 (0.14, 0.64)	0.15	**0.03**	0.40 (0.16, 0.65)		**<0.01**

RDN - renal denervation; BP - blood pressure.

Table S3. Target BP acquirement after 6 months.

Variable	RDN	PHAR	P Value
Number of patients n	52	54	-
<140 mmHg office systolic BP	23 (44%)	29 (54%)	0.34
<90 mmHg office diastolic BP	34 (65%)	42 (78%)	0.20
<130 mmHg 24h systolic BP	9 (17%)	15 (28%)	0.24
<80 mmHg 24h diastolic BP	21 (40%)	28 (52%)	0.25

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

Table S4. Systolic and diastolic BP response based on ≥5 mmHg and ≥10 mmHg reduction from baseline at 6 months.

Variable	RDN	PHAR	P Value
Number of patients n	52	54	-
≥5 mmHg office systolic BP reduction	35 (67%)	39 (72%)	0.67
≥10 mmHg office systolic BP reduction	31 (60%)	31 (57%)	0.85
≥5 mmHg office diastolic BP reduction	26 (50%)	25 (46%)	0.85
≥10 mmHg office diastolic BP reduction	23 (44%)	19 (35%)	0.43
≥5 mmHg 24h systolic BP reduction	27 (52%)	32 (59%)	0.55
≥10 mmHg 24h systolic BP reduction	18 (35%)	22 (41%)	0.55
≥5 mmHg 24h diastolic BP reduction	22 (42%)	22 (41%)	1.00
≥10 mmHg 24h diastolic BP reduction	12 (23%)	14 (26%)	0.82

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

Table S5. Clinical characteristics of studied subjects in RDN according to number of ablations per side.

Variable	Baseline				After 6 months			
	Pts with ≥4 ablations per side	Pts with <4 ablations per side	Pts with ≥4 to <4 ablations per side difference mean (95% CI)	P Value	Pts with ≥4 ablations per side	Pts with <4 ablations per side	Pts with ≥4 to <4 ablations per side difference mean (95% CI)	P Value
Number of subjects	45	7	-	-	45	7	-	-
Plasma sodium [mmol/l]	141±3	141±3	0.04 (-2.0, 2.1)	0.97	141±3	140±3	0.7 (-1.2, 2.5)	0.48
Plasma potassium [mmol/l]	4.0±0.4	4.3±0.4	-0.3 (-0.5, 0.1)	0.11	4.1±0.5	4.0±0.5	0.1 (-0.2, 0.4)	0.50
Creatinine [µmol/l]	87 (78-97)	82 (72-88)	5.2 (-6.6, 17.0)	0.39	87 (81-92)	80 (72-90)	5.5 (-6.6, 17.6)	0.38
Creatinine clearance [ml/s/1.73m2]	1.5 (1.3-1.9)	1.5 (1.2-2.1)	0.1 (-0.4, 0.5)	0.84	1.7 (1.3-2.3)	1.3 (1.1-1.6)	0.6 (0.2, 0.9)	**0.001**
Office systolic BP [mmHg]	161±19	153±19	7.1 (-5.8, 20.0)	0.28	147±20	149±15	-2.2 (-13.50, 9.0)	0.39
Office diastolic BP [mmHg]	94±14	85±11	8.7 (0.7, 16.6)	**0.03**	85±12	86±14	-1.5 (-10.7, 7.8)	0.76
Heart rate [bpm]	72±11	71±10	1.1 (-6.1, 8.3)	0.77	68±10	72±15	-4.5 (-13.9, 4.9)	0.35
24h systolic BP [mmHg]	150±12	143±11	7.0 (-0.7, 14.8)	0.07	141±14	138±12	2.9 (-5.4, 11.1)	0.49
24h diastolic BP [mmHg]	87±10	80±9	6.7 (0.4, 12.9)	**0.04**	81±10	77±10	4.6 (-2.2, 11.5)	0.19
24h heart rate [bpm]	69±10	69±12	0.4 (-7.5, 8.3)	0.93	68±10	66±8	2.2 (-3.3, 7.7)	0.44
Number of drugs used	5.1±1.3	5.0±0.7	0.1 (-0.5, 0.7)	0.70	5.1±1.3	4.9±0.6	0.2 (-0.5, 0.7)	0.73

RDN - renal denervation arm; BP - blood pressure; pts - patients.

Values are shown as means±SD or medians (interquartile range) or absolute numbers.

Table S6. Differences after 6 months in RDN according to number of ablations per side.

Variable	Change from baseline in pts with ≥4 ablations per side		Change from baseline in pts with <4 ablations per side		Between-group difference in change	
	mean (95% CI)	P Value	mean (95% CI)	P Value	mean (95% CI)	P Value
Number of subjects	45	-	7	-	-	-
Plasma sodium [mmol/l]	-0.1 (-1.3, 1.0)	0.82	-0.8 (-2.3, 0.8)	0.35	0.6 (-1.3, 2.6)	0.54
Plasma potassium [mmol/l]	0.1 (-0.1, 0.3)	0.33	-0.3 (-0.6, 0.02)	0.07	0.4 (0.02, 0.7)	**0.04**
Creatinine [µmol/l]	-0.4 (-3.2, 2.4)	0.80	-0.7 (-8.9, 7.6)	0.87	0.3 (-8.4, 8.9)	0.95
Creatinine clearance [ml/s/1.73m^2]	0.2 (-0.1, 0.5)	0.23	-0.3 (-0.7, 0.1)	0.14	0.5 (-0.02, 1.0)	0.06
Office systolic BP [mmHg]	-14.0 (-18.5, -9.5)	**<0.001**	-4.7 (-19.2, 9.8)	0.53	-9.3 (-24.5, 5.9)	0.23
Office diastolic BP [mmHg]	-9.2 (-12.6, -5.6)	**<0.001**	0.9 (-9.7, 11.4)	0.87	-10.1 (-21.2, 1.0)	0.08
Heart rate [bpm]	-4.4 (-7.5, -1.3)	**<0.01**	1.2 (-5.9, 8.4)	0.74	-5.6 (-13.4, 2.2)	0.16
24h systolic BP [mmHg]	-9.2 (-13.0, -5.3)	**<0.001**	-5.0 (-8.0, -2.0)	**0.001**	-4.2 (-9.0, 0.7)	0.09
24h diastolic BP [mmHg]	-6.0 (-8.3, -3.7)	**<0.001**	-3.7 (-6.4, -0.9)	**<0.01**	-2.3 (-5.9, 1.2)	0.26
24h heart rate [bpm]	-1.1 (-3.6, 1.4)	0.40	-2.9 (-6.3, 0.5)	0.10	1.8 (-2.4, 6.1)	0.40
Number of drugs used n	-0.02 (-0.2, 0.15)	0.80	-0.1 (-0.3, 0.1)	0.42	0.1 (-0.2, 0.2)	0.89

RDN - renal denervation arm; BP - blood pressure; pts - patients.

Table S7. Clinical characteristics of studied subjects in PHAR according to spironolactone addition.

Variable	Baseline				After 6 months			
	Spironolactone added and continued	Spironolactone added but discontinued	Spironolactone continued to spironolactone discontinued mean (95% CI)	P Value	Spironolactone added and continued	Spironolactone added but discontinued	Spironolactone continued to spironolactone discontinued mean (95% CI)	P Value
Number of subjects	20	21	-	-	20	21	-	-
Plasma sodium [mmol/l]	141±2	140±3	1.2 (-0.3, 2.6)	0.11	139±3	140±3	-1.3 (-2.9, 0.4)	0.14
Plasma potassium [mmol/l]	4.1±0.4	4.1±0.3	-0.04 (-0.3, 0.2)	0.79	4.3±0.4	4.0±0.3	0.3 (0.1, 0.5)	**0.01**
Creatinine [µmol/l]	84 (71-92)	83 (68-87)	-1.7 (-13.7, 10.2)	0.78	86 (71-94)	84 (71-95)	1.9 (-11.0, 14.7)	0.28
Creatinine clearance [ml/s/1.73m2]	1.6 (1.2-1.9)	1.8 (1.3-2.2)	-0.3 (-0.9, 0.2)	0.22	1.6 (1.0-1.8)	1.6 (1.3-2.3)	-0.3 (-0.7, 0.1)	0.13
Office systolic BP [mmHg]	166±19	147±12	19.2 (9.5, 28.9)	**<0.001**	145±21	139±11	6.6 (-3.5, 16.7)	0.20
Office diastolic BP [mmHg]	96±18	83±9	13.3 (4.5, 22.1)	**<0.01**	86±15	80±10	5.9 (-1.9, 13.8)	0.14
Heart rate [bpm]	75±10	69±10	5.1 (-1.2, 11.5)	0.11	72±10	70±13	2.1 (-5.0, 9.1)	0.56
24h systolic BP [mmHg]	150±16	147±10	3.4 (-4.7, 11.5)	0.41	138±14	143±16	-4.9 (-14.0, 4.3)	0.30
24h diastolic BP [mmHg]	84±12	82±10	1.7 (-4.9, 8.4)	0.61	79±13	79±10	-0.4 (-7.5, 6.7)	0.92
24h heart rate [bpm]	70±10	69±10	0.4 (-5.6, 6.4)	0.90	70±10	67±9	2.2 (-4.3, 7.8)	0.67
Number of drugs used	5.5±1.1	4.9±1.2	0.6 (-0.02, 1.3)	0.06	6.3±1.1	4.9±1.2	1.4 (0.8, 2.1)	**<0.001**

PHAR - pharmacological treatment arm; BP - blood pressure; pts - patients.

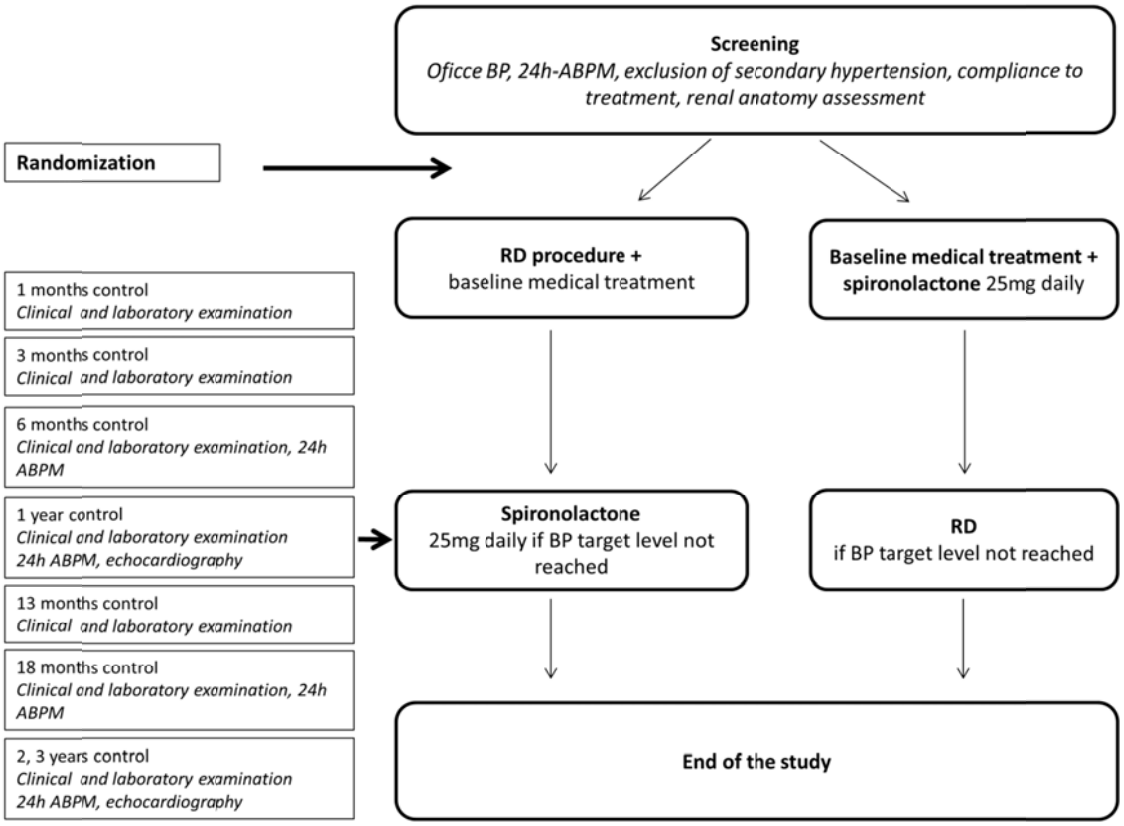
Values are shown as means±SD or medians (interquartile range) or absolute numbers.

Table S8. Differences after 6 months in PHAR relative to addition of spironolactone.

Variable	Change from baseline when spironolactone added and continued		Change from baseline when spironolactone added but discontinued		Between-group difference in change	
	mean (95% CI)	P Value	mean (95% CI)	P Value	mean (95% CI)	P Value
Number of subjects	20	-	21	-	-	-
Plasma sodium [mmol/l]	-2.6 (-3.7, -1.4)	**<0.001**	-0.1 (-1.2, 1.0)	0.85	-2.5 (-4.0, -0.9)	**<0.01**
Plasma potassium [mmol/l]	0.2 (0.03, 0.5)	**0.02**	-0.1 (-0.3, 0.1)	0.29	0.3 (0.1, 0.6)	**0.02**
Creatinine [µmol/l]	3.0 (-4.3, 10.3)	0.42	-0.6 (-6.6, 5.4)	0.85	3.6 (-5.9, 13.0)	0.46
Creatinine clearance [ml/s/1.73m^2]	-0.2 (-0.5, 0.2)	0.37	-0.2 (-0.6, 0.2)	0.32	0.05 (-0.5, 0.6)	0.86
Office systolic BP [mmHg]	-20.9 (-29.7, -12.0)	**<0.001**	-8.3 (-15.4, -1.2)	**0.02**	-12.6 (-23.9, 1.3)	**0.03**
Office diastolic BP [mmHg]	-10.4 (-16.4, 4.3)	**0.001**	-3.0 (-6.7, 0.69)	0.11	-7.4 (-14.4, -0.3)	**0.04**
Heart rate [bpm]	-2.8 (-6.6, 1.1)	0.16	0.3 (-3.1, 3.7)	0.88	-3.0 (-8.2, 2.1)	0.24
24h systolic BP [mmHg]	-11.7 (-18.8, -4.6)	**0.001**	-3.5 (-11.8, 4.8)	0.41	-8.2 (-19.2, 2.7)	0.14
24h diastolic BP [mmHg]	-5.2 (-9.2, -1.1)	**0.01**	-3.1 (-7.2, 1.1)	0.15	-2.1 (-7.9, 3.7)	0.48
24h heart rate [bpm]	-0.8 (-5.1, 2.7)	0.42	-2.6 (-6.2, 1.1)	0.17	1.8 (-3.9, 6.7)	0.72
Number of drugs used n	0.8 (0.4, 1.2)	**<0.001**	0.0 (-0.1, 0.1)	1.00	0.8 (0.4, 1.2)	**<0.001**

PHAR - pharmacological treatment arm; BP - blood pressure.

Figure S1



Design of the Prague-15 Study

Randomized Comparison of Renal Denervation Versus Intensified Pharmacotherapy Including Spironolactone in True-Resistant Hypertension: Six-Month Results From the Prague-15 Study

Ján Rosa, Petr Widimský, Petr Tousek, Ondrej Petrák, Karol Curila, Petr Waldauf, Frantisek Bednár, Tomás Zelinka, Robert Holaj, Branislav Strauch, Zuzana Somlóová, Milos Táborský, Jan Václavík, Eva Kociánová, Marian Branny, Igor Nykl, Otakar Jiravský and Jirí Widimský, Jr

Hypertension. 2015;65:407-413; originally published online November 24, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.04019
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563