Reduced Effect of Percutaneous Renal Denervation on Blood Pressure in Patients With Isolated Systolic Hypertension

Sebastian Ewen, Christian Ukena, Dominik Linz, Ingrid Kindermann, Bodo Cremers, Ulrich Laufs, Stefan Wagenpfeil, Roland E. Schmieder, Michael Böhm, Felix Mahfoud

Abstract—Renal denervation can reduce blood pressure in certain patients with resistant hypertension. The effect in patients with isolated systolic hypertension (ISH, ≥140/<90 mm Hg) is unknown. This study investigated the effects of renal denervation in 126 patients divided into 63 patients with ISH and 63 patients with combined hypertension (CH, ≥140/≥90 mm Hg) defined as baseline office systolic blood pressure (SBP) ≥140 mm Hg despite treatment with ≥3 antihypertensive agents. Renal denervation significantly reduced office SBP and diastolic blood pressure (DBP) at 3, 6, and 12 months by 17/18/17 and 5/4/4 mm Hg in ISH and by 28/27/30 and 13/16/18 mm Hg in CH, respectively. The reduction in SBP and DBP in ISH was lower compared with patients with CH at all observed time points (P<0.05 for SBP/DBP intergroup comparison). The nonresponder rate (change in office SBP <10 mm Hg) after 6 months was 37% in ISH and 21% in CH (P<0.001). Mean 24-hour ambulatory SBP and DBP after 3, 6, and 12 months were significantly reduced by 10/13/15 and 6/6/9 mm Hg in CH, respectively. In patients with ISH the reduction in systolic ambulatory blood pressure was 4/8/7 mm Hg (P=0.032/P<0.001/P=0.009) and 3/4/2 mm Hg (P=0.08/P<0.001/P=0.130) in diastolic ambulatory blood pressure after 3, 6, and 12 months, respectively. The ambulatory blood pressure reduction was significantly lower after 3 and 12 months in SBP and after 12 months in ambulatory DBP, respectively. In conclusion, renal denervation reduces office and ambulatory blood pressure in patients with ISH. However, this reduction is less pronounced compared with patients with CH. (Hypertension. 2015;65:193-199. DOI: 10.1161/HYPERTENSIONAHA.114.04336.)

Key Words: isolated systolic hypertension ■ pulse pressure ■ renal denervation ■ resistant hypertension ■ sympathetic nervous system

Renal sympathetic activity is contributing to the development and maintenance of arterial hypertension by interacting with renin release, renal blood flow, and tubular sodium reabsorption.¹ Catheter-based renal denervation (RDN) has been shown to reduce sympathetic activity² and thereby office and ambulatory blood pressure (BP) in certain but not all patients with resistant hypertension.³–⁵ Data about the effectiveness of RDN in different types of hypertension are lacking. Interestingly, in the Symplicity HTN-3 study, patients aged <65 years tended to respond better to RDN when compared with patients aged ≥65 years, although the primary efficacy end point of the trial was not met.⁶ The predominant hypertensive subtype in elderly patients is isolated systolic hypertension (ISH),⁷,⁸ defined as office systolic BP (SBP) ≥140 mm Hg and diastolic BP (DBP) <90 mm Hg.⁹ ISH is characterized by an increased aortic stiffness attributable to fatigue of elastin, increased pressure wave reflections, and low pulse pressure amplification¹⁰ and is associated with high risk for future stroke¹¹ and cardiovascular mortality.¹²–¹⁴ Although, RDN has been shown to reduce central pulse pressure, to decrease peripheral pulse pressure and pulse wave velocity,¹⁵ suggesting increased peripheral vascular remodeling, the BP-lowering effect of RDN in patients with ISH is unknown. Therefore, this study aimed to investigate the effect of RDN on office BP and 24-hour ambulatory BP in patients with ISH, fulfilling the criteria of resistant hypertension.⁵

Methods

Studied Patients

The study included a total of 126 patients undergoing bilateral RDN, aged ≥18 years, with resistant hypertension according to the European Society of Hypertension/European Society of Cardiology guidelines (office SBP ≥140 mm Hg despite treatment with ≥3 antihypertensive drugs of different classes, including a diuretic at maximum or highest tolerated dose) and completed (at least) 6-month follow-up.⁶ Sixty-three patients with ISH (office BP ≥140/<90 mm Hg) were compared with 63 patients with combined (systolic/diastolic) hypertension (CH; office BP ≥140/≥90 mm Hg). The analyses were performed as part of a prospective study aimed to document the long-term safety and effectiveness of RDN (NCT01888315). Patients with ISH were retrospectively compared with patients with CH. None of the patients included in the current study was part of the Symplicity HTN-1 or HTN-2 trial. Only patients with stable antihypertensive drug regimen were included in the study and patients with secondary, treatable causes

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of hypertension were excluded. Stable antihypertensive drug regime was defined as no change in antihypertensive medication for ≥24 weeks prior RDN. Patients and physicians were instructed not to change antihypertensive medication during the study period except when medically required. Written informed consent for each investigation was obtained from all participating patients. The study was approved by the local ethic committee in accordance with the Declaration of Helsinki.

Renal Sympathetic Denervation Procedure

The RDN procedure was performed bilaterally via femoral access with a dedicated radiofrequency catheter (Symplicity Flex Catheter System, Ardian/Medtronic, Inc, CA) inserted percutaneously as described elsewhere. All RDN procedures were performed by experienced operators between August 2010 and April 2013.

Follow-Up and Assessment of BP

All patients underwent 3-, 6-, and 12-month follow-up including a full history and physical examination, blood chemistry, and office and ambulatory BP measurements. Office BP was measured in the morning 1 hour after medication intake in a sitting position after resting for ≥5 minutes at each arm. The arm with the higher BP was used for all subsequent readings. Averages of the triplicate measures were calculated and used for analysis. At 6-month follow-up, patients were classified, based on their office BP, into a responder group (SBP reduction ≥10 mm Hg) and a nonresponder group (SBP reduction <10 mm Hg). Twenty-four-hour ambulatory BP monitoring (Mobil-O-Graph, Medispec Deutschland GmbH, Krefeld, Germany) was performed before RDN to exclude pseudo-resistance in all patients. Averages of the triplicate measures were calculated and used for analysis. At 6-month follow-up, patients were classified, based on their office BP, into a responder group (SBP reduction ≥10 mm Hg) and a nonresponder group (SBP reduction <10 mm Hg). Twenty-four-hour ambulatory BP monitoring (Mobil-O-Graph, Medispec Deutschland GmbH, Krefeld, Germany) was performed before RDN to exclude pseudo-resistance in all patients. Readings were taken every 15 minutes during daytime (7:00 AM to 10:00 PM) and every 30 minutes at nighttime (10:00 PM to 7:00 AM). Patients were assessed while adhering to their usual activity and nocturnal sleep routine. Only patients with >70% valid BP measurements of either awake or asleep were included. Mean SBP and DBP were calculated as overall 24-hour average.

Statistical Analysis

Data are presented as mean±SD unless otherwise specified. Statistical comparisons between groups were performed using the Pearson χ² test for categorical variables and paired and unpaired t test or Wilcoxon rank-sum test for continuous variables where appropriate. Linear mixed-effects models were used to assess changes within groups during follow-up time. Multivariable unconditional logistic regression analysis was performed for risk analyses with response (reduction of office SBP ≥10 mm Hg at 6 months) as outcome variable. Significance tests were 2-tailed with P<0.05 considered significant. All statistical analyses were calculated using the SPSS statistical software (version 20.0, SPSS, Inc, Chicago, IL).

Results

Baseline patients’ characteristics in both groups are depicted in Table 1. Patients mean age was 66.7±8.4 years, 55% were men, with a mean body mass index of 29.5±4.6 kg/m². Office BP, ambulatory BP, and heart rate were significantly higher in the CH group compared with the ISH group. All 126 RDN procedures were performed without any serious adverse events by experienced operators who had performed ≥15 RDN procedures (Table 2). On average 11.4±2.3 radiofrequency ablations have been performed circumferentially along both renal arteries with special emphasis on the distal segment. However, ablation attempts (prematurely interrupted, <120 seconds) were not counted. One serious adverse event (syncope) was documented at 6-month follow-up.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All Patients (n=126)</th>
<th>CH (n=63)</th>
<th>ISH (n=63)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.7±8.4</td>
<td>65.4±8.7</td>
<td>67.9±7.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Male (%)</td>
<td>69 (55%)</td>
<td>36 (57%)</td>
<td>33 (52%)</td>
<td>0.353</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.5±4.6</td>
<td>29.3±4.5</td>
<td>29.7±4.6</td>
<td>0.579</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>175±21</td>
<td>182±22</td>
<td>169±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>90±17</td>
<td>103±13</td>
<td>77±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ambulatory 24-h SBP, mm Hg</td>
<td>153±16</td>
<td>156±16</td>
<td>150±17</td>
<td>0.028</td>
</tr>
<tr>
<td>Ambulatory 24-h DBP, mm Hg</td>
<td>82±13</td>
<td>90±11</td>
<td>75±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office heart rate, bpm</td>
<td>65±12</td>
<td>68±14</td>
<td>62±9</td>
<td>0.006</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>31 (25%)</td>
<td>13 (19%)</td>
<td>18 (29%)</td>
<td>0.305</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>63 (50%)</td>
<td>28 (44%)</td>
<td>35 (56%)</td>
<td>0.215</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (%)</td>
<td>50 (40%)</td>
<td>20 (32%)</td>
<td>30 (48%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cystatin c, GFR, mL/min per 1.73 m²</td>
<td>68.5±15.3</td>
<td>69.7±16.6</td>
<td>66.2±14.6</td>
<td>0.104</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>5.1±1.1</td>
<td>5.1±1.0</td>
<td>5.1±1.2</td>
<td>0.872</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CH, combined (systolic/diastolic) hypertension; DBP, diastolic blood pressure; GFR, glomerular filtration rate; ISH, isolated systolic hypertension; and SBP, systolic blood pressure.
(recovered without sequelae) deemed unrelated to the procedure. Hemodynamically significant renal artery stenoses after RDN were excluded via duplex ultrasound in all patients at 6- and 12-month follow-up.

**Office BP**

In the CH group, office SBP and DBP at 3-, 6-, and 12-month follow-up were significantly reduced by 28/27/30±25/21/24 mm Hg (P<0.001 for all) and by 13/16/18±13/12/15 mm Hg (P<0.001 for all), respectively. In patients with ISH at 3-, 6-, and 12-month follow-up a significant reduction in SBP by 17/18/21±24/25/26 mm Hg (P<0.001 for all) and DBP by 5/4/4±9/11/10 mm Hg (P<0.001 after 3 months, P=0.004 after 6 months, and P=0.003 after 12 months) was observed. The change in SBP and DBP was significantly higher in CH compared with that in ISH at all follow-up time points (Figure 1A and 1B). Even after adjusting for baseline office SBP and possible effect modification because of linear regression the difference between SBP reduction in patients with ISH and CH at 3-, 6-, and 12-month follow-up remained significant (P=0.022 at 3-month follow-up, P=0.032 at 6-month follow-up, and P=0.01 at 12-month follow-up).

Fifty patients (79%) in the CH group and 40 patients (63%) in the ISH group had a SBP reduction ≥10 mm Hg 6 months after treatment, subsequently defined as responders (P<0.001 for intergroup comparison). Odds ratios for response at 6 months according to sex, age ≥65 years, type 2 diabetes mellitus, number of antihypertensive drugs above or equal to mean at baseline, treatment with aldosterone antagonists, treatment with central sympatholitics, office SBP above or equal to mean at baseline, ambulatory SBP above or equal to mean at baseline, and office pulse pressure (PP) above or equal to mean at baseline were shown in Table 3. Variables with P<0.1 were included in a multivariable analysis. After adjusting for covariates such as age, sex, and diabetes mellitus, office SBP above or equal to mean at baseline was identified as a correlate of response at 6-month follow-up (odds ratio, 4.081; 95% confidence interval, 1.55–10.79; P=0.005).

Five patients (8%) in the CH group and 7 patients (11%) in the ISH group were lost to follow-up after 12 months. One patient migrated, 6 patients continued follow-up closer to their living place, and in the 5 other patients the reasons were unknown.

**Pulse Pressure**

PP was significantly reduced in the CH group from 79±21 mm Hg at baseline by 14±16 mm Hg (P<0.001) after 3 months, by 12±19 mm Hg (P<0.001) after 6 months, and by 12±17 mm Hg (P<0.001) after 12 months, respectively. In the ISH group a significant reduction was observed from 92±18 mm Hg at baseline by 12±16 mm Hg (P<0.001) at 3-month follow-up, by 13±18 mm Hg (P<0.001) at 6-month follow-up, and by 12±18 mm Hg (P<0.001) at 12-month follow-up, respectively. Baseline PP was significantly lower in CH compared with patients with ISH (P<0.001). However, there were no significant differences between the absolute changes in PP reduction between both groups during the study period.

**Ambulatory BP Measurements**

Twenty-four–hour SBP and DBP in the CH group was significantly reduced from 156±90±16/11 by 10/6±17/8 mm Hg after 3 months, by 13±6/8/7 mm Hg after 6 months, and by 15/9±18/11 mm Hg after 12 months (P<0.001 for all, respectively. In patients with ISH, 24-hour SBP and DBP decreased from 150±75±8/5 by 4/3±2/8/5 mm Hg (P=0.032/P=0.08) at 3-month follow-up, by 8/4±4/8/7 mm Hg (P<0.001/P<0.001) at 6-month follow-up, and by 7/2±8/5 mm Hg (P=0.009/P=0.130) at 12-month follow-up, respectively. Changes in 24-hour SBP after 3 and 12 months (Figure 2A) as well as DBP after 12 months (Figure 2B) were significantly different between patients with ISH and CH. In 17 patients after 3 months, 17 patients after 6 months, and 29 patients after 12 months the ambulatory BP
monitoring was excluded from the analyses because of <70% valid BP measurements during a 24-hour time period.

**Changes in Renal Function**

Kidney function measured by cystatin c glomerular filtration rate remained unchanged during follow-up in both groups. Cystatin c glomerular filtration rate in the CH group (n=57; 91%) at baseline and 3, 6, and 12 months was 70±17 mL/min per 1.73 m², 68±24 mL/min per 1.73 m² (P value compared with baseline=0.342), 67±18 mL/min per 1.73 m² (P value compared with baseline=0.132), and 67±24 mL/min per 1.73 m² (P value compared with baseline=0.212), respectively. In the ISH (n=54; 86%) group cystatin c glomerular filtration rate at baseline (66±15 mL/min per 1.73 m²) was lower compared with patients with CH (P=0.104). No significant changes in cystatin c glomerular filtration rate were documented during follow-up in patients with ISH (65±17 mL/min per 1.73 m², P=0.782 at the 3-month follow-up; 64±19 mL/min per 1.73 m², P=0.173 at the 6-month follow-up; and 66±17 mL/min per 1.73 m², P=0.632 at the 12-month follow-up).

**Medication**

Patients and physicians were instructed not to change the antihypertensive drug regimen during the study period. However, antihypertensive medication was reduced in 25 (20%) patients (14 [22%] patients with CH, 11 [18%] patients with ISH) and increased in 23 [18%] patients (12 [19%] patients with CH, 11 [18%] patients with ISH) during the study period of 12 months, respectively (Table 4). Even after censoring for postprocedural medication changes, no significant differences were found.

**Discussion**

To the best of our knowledge, this is the first study assessing the effects of RDN on SBP, DBP, and PP in patients with resistant hypertension and ISH. Our results show that RDN lowers office and 24-hour BP in patients with high SBP and normal DBP, although of different magnitude when compared with patients with high SBP and high DBP.

RDN has been shown to decrease office and ambulatory BP in certain patients with resistant hypertension.3,6,19,20
However, less is known about the BP-lowering effects of RDN in different types of hypertension. There is evidence indicating that the sympathetic nervous system activity is less pronounced in older when compared with younger hypertensive patients.\(^{21,22}\) Furthermore, the recently published Symplicity HTN-3 study suggested that patients aged <65 years tended to respond better to RDN when compared with patients aged >65 years, although the primary efficacy end point of the trial was not met.\(^6\) The predominant hypertensive phenotype in elderly patients is ISH, which represents a late manifestation of increased elastic artery stiffness.\(^7,8\) ISH is characterized by an increased PP and is associated with atherosclerosis,\(^9\) a higher risk for future stroke and coronary events,\(^24\) and represents a predictor of mortality.\(^25\) Herein, office BP was significantly reduced in patients with ISH at 3, 6, and 12 months after RDN. However, office SBP and DBP decreased significantly lower in patients with ISH compared with patients with CH, whereas the BP effects of RDN in patients with CH were in line with the findings reported in the Symplicity HTN-1 and HTN-2 trials,\(^3,5\) the EnligHTN-I trial (using a multi-electrode RDN device),\(^4\) and further observational studies.\(^20,26\) The differences in baseline BP might partially explain the different magnitude of BP reductions between the groups as baseline office SBP has been identified as a predictor of response.\(^3,5,19,27\) However, even after adjusting for baseline office SBP the difference remained statistically significant.

The nonresponse rate after 6 months (SBP reduction <10 mmHg) was comparable with previous published studies.\(^3,5,26\) Patients with ISH had a significant higher nonresponse rate compared with patients with CH. ISH may represent a group of patients with long-standing severe hypertension with increased vascular resistance because of maladaptive hypertensive changes of arteriolar hypertrophy. In this particular hypertensive subtype arterial wall reremodeling by RDN to lower BP could be more difficult to achieve compared with patients with CH. Interestingly, PP after RDN was significantly reduced in both groups. These findings are supported by studies showing improvements in arterial stiffness and central hemodynamics after RDN,\(^15,20\) which might have prognostic implications in patients with resistant hypertension at high cardiovascular risk.\(^20\) However, because of the different magnitude of SBP and DBP reductions in both groups, the observed absolute PP reductions were not significantly different at 3-, 6-, and 12-month follow-up.

Ambulatory 24-hour BP correlates more closely with measures of hypertensive target organ damage than office BP measurement\(^10\) and is less or not at all subject to a white coat effect.\(^14\) In general, antihypertensive treatment causes less pronounced reductions in ambulatory BP monitoring when compared with reductions in office BP.\(^23\) This discrepancy seems to be somewhat more pronounced in the RDN studies compared with double-blind hypertension trials using pharmacological approaches. The ambulatory BP reduction in the CH group is in line with previous published studies, investigating the effect of RDN on 24-hour BP.\(^19\) The BP lowering in 24-hour BP was numerically higher in CH compared with patients with ISH although only not being statistically significant at all time points after adjusting for differences in baseline BP.

### Limitations

Our study may have some limitations. Based on the mean change in SBP and the large SD after 6 months the statistical power was theoretically not sufficient enough to evaluate whether the BP reduction after RDN in patients with CH is superior to patients with ISH. However, the study provides important information for patient selection and future trial designs. Furthermore, baseline office SBP was different between the groups, which might have influenced...
the SBP reduction during the study period. Because of the lack of a control group and a sham procedure, a potential Hawthorne effect contributing to the outcome cannot be fully excluded. The observed BP reduction may have partially been influenced by an improved adherence to drug therapy. The adherence to antihypertensive therapy was not specifically investigated in this study but should not be different between the groups. Patients were strictly advised to take their medication as prescribed at each follow-up visit. In total, 48 (38%) changes in the number of antihypertensive drugs or doses were reported. After censoring for postprocedural medication changes, no significant differences of the results were found, making a relevant influence unlikely. These changes are in line with previous RDN trails.

Perspective

RDN can reduce office BP, 24-hour BP, and PP in patients with ISH and CH. Potentially because of the different underlying pathophysiology the office and ambulatory BP reductions after RDN were pronounced in patients with CH.

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Disclosures

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References

Ewen et al Reduced Effectiveness of RDN in Patients With ISH


What Is New?
- This study investigated the effects of renal denervation on blood pressure in patients with isolated systolic hypertension.

What Is Relevant?
- Isolated systolic hypertension is the predominant hypertensive phenotype in elderly patients and is associated with atherosclerosis, a particularly higher risk for future stroke and coronary events, and is mainly associated with an increased vascular stiffness and pulse wave reflection.

Summary
The study shows that renal denervation reduces office and ambulatory blood pressure in patients with isolated systolic hypertension despite the different underlying pathophysiology. However, this reduction is less pronounced compared with patients with combined hypertension.
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Activation of D4 Dopamine Receptor Decreases Angiotensin II Type 1 Receptor Expression in Rat Renal Proximal Tubule Cells

Ken Chen, Kun Deng, Xiaoyan Wang, Zhen Wang, Shuo Zheng, Hongmei Ren, Duofen He, Yu Han, Laureano D. Asico, Pedro A. Jose, Chunyu Zeng

肾去神经术（摘要）

经皮肾去交感神经术对单纯收缩期高血压患者降压效应减小

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肾去交感神经术能够降低某些难治性高血压患者的血压，但是对单纯收缩期高血压（ISH）患者的疗效尚未明确。本研究入选126例患者，63例为ISH（收缩压≥140 mmHg，舒张压<90 mmHg），63例为混合型高血压（CH，收缩压≥140 mmHg，舒张压>90 mmHg），定义为已经使用3种或以上的降压药物之后，基线诊室血压依然≥140 mmHg。肾去交感神经术治疗后3、6、12个月时随访发现，ISH组患者收缩压（SBP）分别下降17、18、17 mmHg，舒张压（DBP）分别下降5、4、4 mmHg；CH组患者SBP分别下降28、27、30 mmHg，DBP分别下降13、16、18 mmHg。在各个时间点，ISH组患者血压的下降值都小于CH组（P<0.05）。术后3、6、12个月时随访24小时动态血压，CH组SBP及DBP分别下降40、37、35 mmHg和9、6、5 mmHg，而ISH组分别下降6、4、7 mmHg（P=0.032，P<0.001，P=0.009）和3、4、2 mmHg（P=0.08，P<0.001，P=0.130）。动态血压检测中，SBP在第3、12个月，DBP在第12个月时的降低明显更小。结论：肾去交感神经术治疗能够降低ISH患者的诊室血压及动态血压，但是其降压程度弱于CH患者的效果。

(Hypertension. 2013;63:193-199.)