Renal Hemodynamics and Renal Function After Catheter-Based Renal Sympathetic Denervation in Patients With Resistant Hypertension

Felix Mahfoud, Bodo Cremers, Julia Janker, Britta Link, Oliver Vonend, Christian Ukena, Dominik Linz, Roland Schmieder, Lars Christian Rump, Ingrid Kindermann, Paul Andrew Sobotka, Henry Krum, Bruno Scheller, Markus Schlaich, Ulrich Laufs, Michael Böhm

Abstract—Increased renal resistive index and urinary albumin excretion are markers of hypertensive end-organ damage and renal vasoconstriction involving increased sympathetic activity. Catheter-based sympathetic renal denervation (RD) offers a new approach to reduce renal sympathetic activity and blood pressure in resistant hypertension. The influence of RD on renal hemodynamics, renal function, and urinary albumin excretion has not been studied. One hundred consecutive patients with resistant hypertension were included in the study; 88 underwent interventional RD and 12 served as controls. Systolic, diastolic, and pulse pressure, as well renal resistive index in interlobar arteries, renal function, and urinary albumin excretion, were measured before and at 3 and 6 months of follow-up. RD reduced systolic, diastolic, and pulse pressure at 3 and 6 months by 22.7/26.6 mm Hg, 7.7/9.7 mm Hg, and 15.1/17.5 mm Hg (P for all <0.001), respectively, without significant changes in the control group. SBP reduction after 6 months correlated with SBP baseline values (r=−0.46; P<0.001). There were no renal artery stenoses, dissections, or aneurysms during 6 months of follow-up. Renal resistive index decreased from 0.691±0.01 at baseline to 0.674±0.01 and 0.670±0.01 (P=0.037/0.017) at 3- and 6-month follow-up. Mean cystatin C glomerular filtration rate and renal albumin excretion remained unchanged after RD; however, the number of patients with microalbuminuria or macroalbuminuria decreased. RD reduced blood pressure, renal resistive index, and incidence of albuminuria without adversely affecting glomerular filtration rate or renal artery structure within 6 months and appears to be a safe and effective therapeutic approach to lower blood pressure in patients with resistant hypertension. (Hypertension. 2012;60:00-00.)

Key Words: renal sympathetic denervation ■ therapy resistant hypertension ■ renal resistive index ■ renal function ■ urinary albumin excretion ■ microalbuminuria

Chronic kidney disease is an important cause and consequence of uncontrolled hypertension. Patients with high blood pressure, especially those who are therapy resistant, are at high risk for renal impairment and other cardiovascular complications. There is a linear correlation between blood pressure levels and loss in glomerular filtration rate. Doppler sonographic renal resistive index (RRI) reflects systemic and renal hemodynamics, arterial compliance, and pulse pressure and has been associated with progression of renal impairment, as well as morbidity and mortality in hypertensive patients. Increased sympathetic tone is an important factor related to the progression of renal disease. Activation of the sympathetic nervous system induces renal vasoconstriction and renin release and increases sodium retention. Catheter-based renal denervation (RD) has been introduced into clinical practice to selectively denervate efferent and afferent renal sympathetic fibers. Other than marked and sustained blood pressure reductions, RD has also been shown to reduce renal norepinephrine spillover and muscle sympathetic nerve activity and to improve glucose metabolism in patients with resistant hypertension. Less is known about the influence of RD on renal hemodynamics, urinary albumin (UA) excretion (UAEx), and renal function. In the Symplicity HTN-1 trial with extended follow-up of 24 months, estimated glomerular filtration rate (GFR) (measured by Modification of Diet in Renal Disease) remained stable during the first year of follow-up (n=64), whereas estimated GFR data of 2-year follow-up is only available for 10 patients. In these 10 patients, estimated GFR altered by 16 mL/min per 1.73 m² and was influenced by

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changes in diuretic therapy. In 37 patients from the Symplicity HTN-2 trial, cystatin C GFR is available, showing no significant changes during follow-up of 6 months. This study aimed to assess the changes that occur in RRI, UAE, and renal function after interventional RD in patients with resistant hypertension.

Methods
The local ethic committee approved the study. Patients were treated between January 2010 and February 2011 with subsequent follow-up to 6 months. Systolic, diastolic, and mean arterial blood pressures, as well as RRI, renal function, and UAE, were measured before and 3 and 6 months after treatment. All of the patients gave written informed consent. Eligible patients were ≥18 years of age and had an office systolic blood pressure (SBP) ≥160 mm Hg (≥150 mm Hg for type 2 diabetic patients), despite being treated with ≥3 antihypertensive drugs at maximum or maximum tolerated doses (including 1 diuretic), with no changes in medication for a minimum of 2 weeks before enrollment. Patients were included if they were not pregnant and had a glomerular filtration rate ≥45 mL/min per 1.73 m² (using the Modification of Diet in Renal Disease formula or cystatin C). Patients with renal artery anatomy ineligible for treatment (hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery or a history of previous renal artery intervention, including balloon angioplasty or stenting) were excluded from the study. One hundred patients were enrolled, of whom 88 were prospectively assigned to treatment group following protocols of ongoing therapeutic RD trials, and 12 patients were assigned to continued medical therapy for 6 months. The rather small control group was implemented to monitor the changes of repeated measurements. All of the patients from the control group underwent RD after completion of 6-month follow-up. Nineteen patients were included in the Symplicity HTN-1 or HTN-2 trial. In all of the other patients, the measurements were performed as an extension to the Symplicity protocol (www.clinicaltrials.gov identifiers NCT00664638 and NCT00888433), using the same inclusion and exclusion criteria. All of the patients underwent a complete history and physical examination, assessment of vital signs, and review of medication. Patients were interviewed whether they had taken their complete medication at defined doses. Treating physicians and patients were instructed not to change medications except when medically required. Blood samples were taken under standardized conditions. Blood chemistry, including cystatin C and serum electrolytes, was obtained using standard techniques and measured at baseline and at each follow-up visit, performed at 3 and 6 months. The presence of albuminuria was evaluated in each patient by measuring the UAE and creatinine excretion on 3 first morning samples. UAE was graded into the following groups: no albuminuria (UA: <20 mg/L; UA creatinine ratio [UACR]: <2.5 mg/mmol [males], <3.5 mg/mmol [females]), microalbuminuria (MUA: UA: 20–200 mg/L; UACR: 2.5–25.0 mg/mmol [males], 3.5–35.0 mg/mmol [females]), and macroalbuminuria (UA: >200 mg/L; UACR: >25 mg/mmol [males], >35 mg/mmol [females]). Office blood pressure readings were taken in a seated position after 5 minutes of rest according to the standard Joint National Committee VII guidelines. Averages of the triplicate measures were calculated and used for analysis. Patients undergoing RD were graded according their baseline SBP into 3 groups: <160 mm Hg (n=13), 160 to 175 mm Hg (n=33), and >175 mm Hg (n=42).

Catheter-Based RD
In patients randomized to the intervention group, renal angiograms were performed via femoral access to confirm anatomic eligibility. The treatment catheter (Symplicity and Flex, Aridian/Medtronic Inc, Mountain View, CA) was introduced into each renal artery using a guiding catheter (internal mammary artery or renal double curve), and ablations were performed in both renal arteries using a standardized treatment protocol and algorithm. Up to 8 ablations for 2 minutes each were performed in both renal arteries. Catheter tip impedance and temperature were constantly monitored, and radio frequency energy delivery was regulated according to a predetermined algorithm with a maximum of 8 watts. Treatments were delivered from the first distal main renal artery bifurcation to the ostium proximally and were spaced longitudinally and rotationally under fluoroscopic guidance. Visceral pain at the time of energy delivery was managed with intravenous analgetics and sedatives. Heparin was given to achieve an activated clotting time during the procedure of >250 seconds.

Renal Duplex Ultrasound
Ultrasonic examinations of the kidneys and color duplex sonography of the intrarenal arteries were performed using a Logiq S6 ultrasound machine (GE Healthcare, Milwaukee, WI) after intake of medication. The patients were instructed to fast for ≥8 to 12 hours before the ultrasound. In each kidney, intrarenal Doppler spectra were obtained at 6 representative locations of the interlobar arteries along the border of medullary pyramids, 2 in the cranial, 2 in the middle, and 2 in the caudal third of the kidney. Peak systolic velocity (maximum velocity [V_max] in centimeters per second) and end diastolic velocity (minimum velocity [V_min] in centimeters per second) were obtained for the calculation of the dimensionless resistance index values, as follows: RRI = (1 − [V_min/V_max]). Mean RRI was calculated by using ≥6 measurements from each kidney. Velocities in the renal arteries were measured in the origin and in the proximal, middle, and distal segments of each renal artery.

Statistical Analysis
Baseline data were compared between RD and control group using either an independent samples t test for means or a χ² test for proportions. Changes in office blood pressures, RRI, cystatin C, and UACR were analyzed from baseline to 3 and 6 months by 2-factor ANOVA with repeated measures. Duncan test was used to compute post hoc comparisons of significant values. A 2-tailed P value of <0.05 was regarded as statistically significant. Simple associations were assessed with Pearson tests for 2 independent proportions. Multivariate regression analysis was used to determine predictors of blood pressure reduction. Correlations were assessed by using a Pearson correlation coefficient. Data are presented as mean±SEM. All of the statistical analyses were performed with SPSS statistical software (version 17.0, SPSS Inc, Chicago, IL).

Results
Patient characteristics are depicted in Table 1. Patients were middle aged (61.7±1.0 years), mostly male (61%), with a mean body mass index of 30.1±0.7 kg/m² and a long history of hypertension (11.4±5.1 years). Type 2 diabetes mellitus was diagnosed in 35 patients (35%; mean hemoglobin A1c 6.6±0.2%). Diagnosis was confirmed as recommended by the American Diabetes Association. Patients were treated with 5.7±0.2 antihypertensive drugs on average, with 97% (97%) receiving an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or both; 77 (77%) receiving β-blockers; 68 (68%) receiving calcium-channel blockers; and 48 (48%) receiving centrally acting sympatholytic agents. All of the patients received diuretics, with 33 (33%) taking aldosterone antagonists. Despite antihypertensive treatment, baseline SBP, diastolic blood pressure, and pulse pressure were 175±2, 96±2, and 80±2 mm Hg, respectively, with a heart rate of 71.8±1.5 bpm.

RD reduced SBP, diastolic blood pressure, and pulse pressure at 3 and 6 months by 22.7/26.6, 7.7/9.7, and 15.1/17.5 mm Hg (P for all <0.001; Table 2), respectively. There were no significant changes in the control group (Table 2). Fifteen patients (17%) who underwent RD had an office
SBP reduction of <10 mm Hg after 6 months (defined as nonresponse). Patients and physicians were instructed not to change antihypertensive medication during the study period. However, antihypertensive drug regimen was reduced after 3-month follow-up in 18 patients (18%) because of confirmed blood pressure levels below respective target blood pressure or the development of symptoms and confirmed low blood pressure. Antihypertensive treatment was increased in 7 patients (7%) who remained above target blood pressure after 3 months of follow-up. Control patients had a small nonsignificant change in SBP/diastolic blood pressure of 3 mm Hg at 3 months (P = 0.301/0.403) and -4/-3 mm Hg at 6 months (P = 0.479/0.506), respectively. There was a correlation between SBP at baseline and the SBP reduction 6 months after RD (r = -0.46; P < 0.001), with the highest blood pressure reduction in patients with baseline SBP > 175 mm Hg.

Table 2. Change in Blood Pressure, Renal Function, and Resistive Indices

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3 mo</th>
<th>6 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>−22.7 ± 2.3 (−13%)</td>
<td>&lt; 0.001</td>
<td>−26.6 ± 2.5 (−15%)</td>
<td>&lt; 0.001</td>
<td>−7.2 ± 7.6 (−4%)</td>
<td>0.301</td>
<td>−4.4 ± 6.2 (−2%)</td>
<td>0.479</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DBP, mm Hg</td>
<td>−7.7 ± 1.3 (−8%)</td>
<td>&lt; 0.001</td>
<td>−9.7 ± 1.5 (−10%)</td>
<td>&lt; 0.001</td>
<td>−4.1 ± 4.7 (−4%)</td>
<td>0.403</td>
<td>−3.0 ± 4.3 (−3%)</td>
<td>0.506</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PP, mm Hg</td>
<td>−15.1 ± 2.1 (−19%)</td>
<td>&lt; 0.001</td>
<td>−17.5 ± 2.0 (−22%)</td>
<td>&lt; 0.001</td>
<td>−3.9 ± 4.7 (4%)</td>
<td>0.430</td>
<td>−1.6 ± 5.2 (−2%)</td>
<td>0.766</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystatin C GFR, mL/min</td>
<td>−4.2 ± 2.8 (−5%)</td>
<td>0.107</td>
<td>−4.0 ± 2.8 (−5%)</td>
<td>0.161</td>
<td>−9.4 ± 12.5 (−10%)</td>
<td>0.458</td>
<td>−15.1 ± 11.1 (−15%)</td>
<td>0.208</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RRI</td>
<td>−0.017 ± 0.003 (−2%)</td>
<td>0.037</td>
<td>−0.021 ± 0.004 (−3%)</td>
<td>0.017</td>
<td>+0.029 ± 0.016 (4%)</td>
<td>0.114</td>
<td>−0.002 ± 0.022 (0%)</td>
<td>0.943</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UACR, mg/mmol</td>
<td>−0.49 ± 0.51 (−31%)</td>
<td>0.335</td>
<td>−0.25 ± 0.35 (−16%)</td>
<td>0.471</td>
<td>−0.48 ± 0.56 (−32%)</td>
<td>0.407</td>
<td>+0.17 ± 0.29 (11%)</td>
<td>0.573</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SEM and relative changes (%) compared with baseline values or No. (n). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure (in millimeters of mercury); RRI, renal resistive index; UACR, urinary albumin creatinine ratio.

*P = 3 mo vs baseline.
†P = 6 mo vs baseline.
Disease formula\textsuperscript{14} or cystatin C) was an inclusion criterion. There were no significant changes in cystatin C GFR after RD (−4.2 mL/min after 3 months, \(P=0.107\) and −4.0 mL/min after 6 months, \(P=0.161\)). Control patients also showed no significant change of renal function with a cystatin C GFR reduction of −9.4 mL/min (\(P=0.458\)) and −15.1 mL/min (\(P=0.208\)). No patient showed doubling of serum creatinine, class IV chronic kidney disease, or required dialysis. Average UACR did not change significantly after RD at 3 and 6 months (0.49 ± 0.51, \(P=0.335\); 0.25 ± 0.35, \(P=0.471\)). Measurement of UAE at baseline revealed 58 patients (66%) with normal UAE, 19 patients (21%) with MAU, and 11 patients (13%) with macroalbuminuria. After 3 and 6 months, the number of patients with normal UAE increased by 5% and 12%, respectively, whereas the number of patients with MAU and macroalbuminuria decreased by 10% and 23%, respectively (\(P<0.001\) for 3 and 6 months; Figure 2).

The procedure was performed without any complication in 97%. Two patients developed a pseudoaneurysm at the femoral access site, which was treated by compression only. In 1 patient contrast medium allergic reaction occurred. No electrolyte disturbances or orthostatic dysregulation were reported. Postprocedural renal duplex ultrasound was performed without detecting abnormalities (eg, significant renal artery stenosis or aneurysm) of the renal arteries through the study period.

**Discussion**

The results of this study indicate that renal sympathetic denervation reduces the RRI and the rate of albuminuria without effects on GFR, as measured by cystatin C, or damage to renal arteries, while significantly reducing blood pressure in patients with resistant hypertension. Measurement of the RRI by duplex ultrasound at the level of interlobar arteries has been proven to be repeatable and reproducible\textsuperscript{18} and reflects downstream impedance and measures renal arterial stiffness.\textsuperscript{19} RRI have been associated with the severity and duration of hypertension and worsening of renal function.\textsuperscript{20} An increase in RRI is related to macrovascular atherosclerotic damage in hypertension, serving as a prognostic marker for hypertensive end-organ damage.\textsuperscript{5,21} Treatment with angiotensin-converting enzyme inhibitors but not calcium channel blockers has been shown to reduce RRI,\textsuperscript{22,23} possibly because of their differential actions on intrarenal pressure and hemodynamics. The changes in RRI after RD found herein are comparable to reductions reported by other studies, investigating the effect of angiotensin-converting enzyme inhibitor treatment on renal hemodynamics.\textsuperscript{22,23} Because angiotensin-converting enzyme inhibitors have proven to effectively delay the progression of renal damage, regard-
less of their blood pressure–lowering effects,24 RD might, therefore, improve renal perfusion through a reduction of intraparenchymal resistance and positively influence renal function. However, the relevance of the observed decrease in RRI after RD and its potential beneficial effects on renal function and cardiovascular morbidity has to be studied in more detail. Interestingly, reduction in RRI after RD did not correlate to reduction in SBP, which might indicate a blood pressure–independent effect, potentially related to decreased sympathetic tone, inducing vasodilatation, and decreased renin release. To assess whether RRI can serve as a predictor of nonresponse before performing RD, subgroup analyses of patients with different RRI values were performed. Even in the subgroups of patients with RRI values >0.70, >0.75, and >0.80, RD effectively reduced SBP. The blood pressure reductions after RD found herein are in accordance with previously published studies,9,10,13,25 ranging between −25 to −32 mm Hg systolic and −10 to 12 mm Hg diastolic after 6 months. Blood pressure–lowering effects after RD significantly correlated with baseline SBP, with the highest reductions in patients with a baseline SBP >175 mm Hg.

Increased sympathetic tone has been related to worsening renal function6 and contributes to the high incidence of cardiovascular events in patients with renal failure.26 Recently, a significant inverse correlation between sympathetic tone (using microneurography) and estimated GFR ($r = −0.59; P < 0.001$) in hypertensive patients with chronic kidney disease has been reported.27 Consistently, treatment with central sympatholytic agents, such as moxonidine, decreased the progression of renal disease and reduced albuminuria, even independent of blood pressure reduction.28,29 MAU is a sign of vascular inflammation and is associated with high cardiovascular risk.1,30 There is conclusive evidence from randomized trials that a reduction in MAU parallels decreased risk of myocardial infarction, stroke, cardiovascular death, and all-cause death, respectively.31 Among the resistant hypertensives analyzed herein, RD offers the possibility to reduce both high blood pressure and rate of MAU. Whether this effect is related to blood pressure reduction, decreased sympathetic tone, or both deserves further investigation.

Recently, concerns have been raised that RD might negatively influence renal function.32 The present study demonstrates that RD does not impair renal function in patients with resistant hypertension at very high risk for renal insufficiency. It is noteworthy to mention that preserved renal function (GFR $>45 \text{ mL/min}$) was an inclusion criterion. Further studies are warranted to determine whether attenuation of sympathetic drive by RD will positively influence renal function in patients with more advanced stages of renal disease.

Our study might have some limitations. In cannot be fully excluded that vasodilatation attributed to impaired autoregulation after RD could account for at least some of the changes. However, there were no significant changes in GFR, making a relevant hyperfiltration unlikely. Longer observation periods are necessary to detect changes in renal function. Office blood pressure was used as primary outcome. In the Simplicity trials,9,33 office BP was significantly more reduced compared with 24-hour BP. This divergence between office BP and 24-hour BP reductions is typically observed with conventional antihypertensive treatment. However, studies investigating the effect of RD on ABPM are mandatory. After 3-month follow-up, drug treatment was reduced in 18 patients because of symptomatic hypotension with SBP $<120$ mm Hg and increased in 7 of the nonresponders. Even after censoring for postprocedural medication changes, no significant differences of the results were found, making a relevant influence unlikely. The control group consisted of 12 patients with resistant hypertension on stable antihypertensive medication. Because of the relative small number of patients, minor differences between the treatment group and the control group might not have reached statistical significance. The purpose of the control group was to investigate the influence of repeated measurements and regression to the mean on primary outcome.

### Perspectives

RD offers a novel approach to reduce blood pressure, RRI, and rate of (micro)albuminuria in high-risk hypertensives with preserved renal function, without effects on glomerular filtration rate as measured by cystatin C or renal vasculature within 6 months. These findings support the pathophysiologic concept of the importance of increased sympathetic tone in hypertension and associated renal disease. Future trials and long-term follow-up studies are needed to investigate whether RD will, in turn, positively affect long-term cardiovascular and renal outcomes of patients with resistant hypertension.

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### Disclosures

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### References

Catheter-based sympathetic RD offers a new approach to reduce renal sympathetic activity and blood pressure in resistant hypertension. The influence of RD on renal hemodynamics, renal function, and UAE has not been studied.

**What Is Relevant?**

- RD reduced SBP, diastolic blood pressure, and pulse pressure at 3 and 6 months by 22.7/26.6, 7.7/9.7, and 15.1/17.5 mm Hg, respectively, without significant changes in the control group. There were no renal artery stenosis, dissections, or aneurysms on short-term follow-up of 6 months. RRI significantly decreased from baseline to 3- and 6-month follow-up. Mean cystatin C GFR and UAE remained unchanged after RD, however, the number of patients with microalbuminuria or macroalbuminuria decreased.

**Summary**

In patients with resistant hypertension, RD reduced blood pressure, RRI, and incidence of albuminuria without adversely affecting GFR or renal artery structure within 6 months.
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