Sustained Sympathetic and Blood Pressure Reduction 1 Year After Renal Denervation in Patients With Resistant Hypertension

Dagmara Hering, Petra Marusic, Antony S. Walton, Elisabeth A. Lambert, Henry Krum, Krzysztof Narkiewicz, Gavin W. Lambert, Murray D. Esler, Markus P. Schlaich

Abstract—Renal denervation (RDN) reduces muscle sympathetic nerve activity (MSNA) and blood pressure (BP) in resistant hypertension. Although a persistent BP-lowering effect has been demonstrated, the long-term effect on MSNA remains elusive. We investigated whether RDN influences MSNA over time. Office BP and MSNA were obtained at baseline, 3, 6, and 12 months after RDN in 35 patients with resistant hypertension. Office BP averaged 166±22/88±19 mm Hg, despite the use of an average of 4.8±2.1 antihypertensive drugs. Baseline MSNA was 51±11 bursts/min ≈2- to 3-fold higher than the level observed in healthy controls. Mean office systolic and diastolic BP significantly decreased by –12.6±18.3/–6.5±9.2, –16.1±25.6/–8.6±12.9, and –21.2±29.1/–11.1±12.9 mm Hg (P<0.001 for both systolic BP and diastolic BP) with RDN at 3-, 6-, and 12-month follow-up, respectively. MSNA was reduced by –8±12, –6±12, and –6±11 bursts/min (P<0.01) at 3-, 6-, and 12-month follow-up. The reduction in MSNA was maintained, despite a progressive fall in BP over time. No such changes were observed in 7 control subjects at 6-month follow-up. These findings confirm previous reports on the favorable effects of RDN on elevated BP and demonstrate sustained reduction of central sympathetic outflow ≤1-year follow-up in patients with resistant hypertension and high baseline MSNA. These observations are compatible with the hypothesis of a substantial contribution of afferent renal nerve signaling to increased BP in resistant hypertension and argue against a relevant reinnervation at 1 year after procedure. (Hypertension. 2014;64:00-00.)

Key Words: hypertension resistant to conventional therapy ■ sympathetic nervous system

Uncontrolled blood pressure (BP) remains the leading cause of cardiovascular morbidity and mortality globally.1 Despite the availability of potent antihypertensive drugs, only 53% of patients with documented hypertension achieve target BP levels.2 Although determining the exact prevalence of patients with resistant hypertension (RH) remains complex, data available from United States and Europe have indicated that resistance to pharmacological treatment occurs in 13% of treated patients with elevated BP.3 Furthermore, the prevalence3 and incidence of RH is projected to increase progressively.4 Patients with true RH commonly display evidence of end organ damage5 and are at high risk for cardiovascular events.6 Accordingly, even a mild reduction in BP has been demonstrated to reduce overall cardiovascular morbidity and mortality substantially.7,8 As part of the complex and multifactorial pathophysiology of RH,9 enhanced sympathetic activation is a critical contributor to BP elevation.10–12 In fact, both low-risk subjects with high-normal BP13 and high-risk patients with RH14 have increased muscle sympathetic nerve activity (MSNA). Furthermore, patients with RH are characterized by persistent sympathetic activation as evidenced by increased single- and multiunit MSNA and augmented renal noradrenaline spillover.14–16 In this context, catheter-based sympathetic renal denervation (RDN) provides a rational approach in patient management given that both efferent and afferent renal nerves are pivotal in the initiation and maintenance of elevated BP.17 Indeed, RDN has been associated with substantial and sustained BP reduction, decreased noradrenaline spillover, and postganglionic efferent single- and multiunit MSNA in RH.18–21 Although the majority of currently available results with RDN are promising and the rationale for the use of this approach for other conditions characterized by sympathetic excitation is apparent, not all studies demonstrated a reduction in MSNA after RDN.22 Furthermore, renal nerves have the capacity to regrow, which may affect the long-term effects of the procedure. At this stage, it is unclear whether any reinnervation that may occur is of functional relevance.23 Likewise, the long-term effect of RDN on MSNA has not yet been fully elucidated. Therefore, we investigated whether the continued BP reduction associated with RDN is accompanied by long-term decrease of sympathetic outflow to the periphery in patients with RH.
Methods

Subjects
The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients. Thirty-five patients (22 men and 13 women) with established RH were enrolled as extensions to the Symplicity protocols (NCT00888433). Three of 35 investigated patients were current smokers. Twenty patients included in the present study participated in the previous study describing changes in MSNA at 3 months after RDN who were followed up to 12 months. Patients underwent a comprehensive medical history, physical examination, and review of medication. Patients were interviewed to determine whether they had taken their complete medication at defined doses. Treating physicians and patients were instructed not to change medications except when medically required. Hypertension was diagnosed based on the 2007 European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension, and secondary forms of hypertension were ruled out. Nine patients were previously diagnosed with obstructive sleep apnea but remained hypertensive, despite adequate treatment efforts, including continuous positive airway pressure treatment in 4 patients, and were therefore included in our study. RH was defined according to the current statement of the American Heart Association. None of the patients had history of chronic kidney disease or previous stroke. All patients were studied at baseline, 3-, 6-, and 12-month follow-up. Seven patients from the initial control arm of the Symplicity Hypertension (HTN)-2 trial had MSNA and BP assessment at baseline and 6 months and were included in this analysis as a nontreated control group. These 7 patients then crossed over to RDN treatment, and their data were included in the entire cohort of 35 patients who were followed up at 3, 6, and 12 months after the procedure.

Study Protocol
Subjects were comprehensively examined in a quiet room and in a comfortable position. Measurements were obtained at baseline (before RDN) and at 3, 6, and 12 months after the procedure. The same measurements were obtained at baseline and 6-month follow-up in 7 patients who were recruited into the Symplicity HTN-2 trial and randomized to the control arm, therefore, not undergoing RDN. On the first visit, BP was measured as described below followed by fasting biochemistry assessments. On the second visit, patients were studied in the supine position and were asked to refrain from smoking and alcoholic beverages for ≥24 and 48 hours, respectively, before the study. Participants were asked to empty their bladder before the study to minimize the possible effects of bladder distension on sympathetic activity assessment.

Serum Biochemistry
Routine blood tests and estimated glomerular filtration rate calculated using the Modified Diet in Renal Disease formula were performed in all patients before study enrollment and repeated at each follow-up time point after the procedure.

Office-Seated and Ambulatory BP
Average sitting office BP was measured after 5 minutes of rest on both arms and was calculated as the average of 3 consecutive measurements within a 2-minute interval at baseline and during each visit at follow-up with a validated device (Omron HEM-907; Omron Healthcare Singapore Pte Ltd). The arm with higher BP readings was used for subsequent measures.

Twenty-four-hour BP and heart rate monitoring (ambulatory BP monitoring [ABPM]) using a validated device (Space labs 90207 or 90217 recorder; Spacelabs Healthcare, Snoqualmie, WA) was performed at baseline, as described previously. ABPM was not achieved in 3 patients at baseline because of previous intolerance with arm discomfort and sleep disturbance. As per guidelines, only ABPM data fulfilling the described standards in regards to the proportions of valid values were used for analysis. At 3-month follow-up, ABPM recordings were only available from 24 patients because the remaining 11 patients were participants of the Symplicity HTN-2 trial, the protocol of which required ABPM to be performed at 6-month but not at 3-month follow-up.

MSNA Recording and Categorization of MSNA
After 15 minutes of rest, multunit MSNA was recorded from post-ganglionic sympathetic nerves using microneurography (662C-3 Nerve Traffic Analysis System; Bioengineering of Iowa University, Iowa City, IA), as described previously. Given the previously described dependence of MSNA on age and sex in healthy normal subjects, we generated a qualitative categorization of MSNA levels, which allowed us to demonstrate the categorical changes in MSNA after RDN. Therefore, we used previously published data on MSNA levels obtained from healthy subjects in various age groups for men and women to define normal levels of MSNA and by extrapolation introduced for the first time the following 5 age-corrected categories of MSNA for both sexes: normal, mildly elevated, moderately elevated, highly elevated, and extremely elevated MSNA (Table 4).

Catheter-Based RDN
Bilateral RDN was performed using a radiofrequency ablation catheter (Symplicity; Medtronic Ardian Inc, Palo Alto, CA), as described previously. Peri- and Postprocedural Medications
Baseline medication was kept unchanged for ≥6 weeks before RDN and was maintained in 31 patients at follow-up. Antihypertensive medication was reduced in 4 of 35 patients because of achieved BP control after the procedure (in first patient, prazosin was stopped at 3 months; in the second patient, moxonidine and atenolol were ceased at 3 months; in the third patient, spironolactone was stopped at 3 months and metoprolol at 6 months; and in the fourth patient, moxonidine was reduced at 6 months). Similarly, antihypertensive medication from baseline to 6-month follow-up remained unaltered in 7 control patients who did not undergo RDN. Female subjects were postmenopausal and were not receiving hormone replacement therapy.

Data Analysis
Multunit MSNA
During a period of 15 minutes, MSNA bursts were identified, and sympathetic activity was calculated as burst frequency (bursts/min) and as burst incidence (bursts/100 heartbeats). Changes in MSNA recording were performed and analyzed by an experienced investigator without the knowledge of the patient identity and treatment status, as described previously.

Statistical Analysis
Data in the text and tables are presented as the mean±SD and data in figures as meansSEM. Statistical analysis was performed using SigmaStat version 3.5 (Systat Software, Point Richmond, CA). The comparisons between visits in office BP and MSNA from baseline to 3-, 6-, and 12-month follow-up were analyzed using 1-way ANOVA for repeated measurements. Because 3-month follow-up ABPM data could be performed in only 24 patients, for the comparison from baseline to follow-up, we used 6- and 12-month ABPM data for statistical analysis. The comparisons in parameters from baseline to 6-month follow-up in the control subjects were analyzed using a paired t test. A value of P<0.05 was considered significant.

Results
Baseline Characteristics
Baseline clinical characteristics of the 35 treated patients are summarized in Table 1. Four of 9 patients with obstructive sleep apnea were on continuous positive airway pressure therapy at study enrollment, which was unaltered during the study. The
Table 1. Baseline Characteristics of the Entire Treated Patient Cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±11</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>22/13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33±5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>107±16</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.94±0.16</td>
</tr>
<tr>
<td>CAD</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>T2DM</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>OSA</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>4.8±2.1</td>
</tr>
<tr>
<td>ACEI</td>
<td>17 (49%)</td>
</tr>
<tr>
<td>ARB</td>
<td>27 (77%)</td>
</tr>
<tr>
<td>ACEI+ARB</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>28 (80%)</td>
</tr>
<tr>
<td>α-Blockers+vasodilators</td>
<td>11 (29%)</td>
</tr>
<tr>
<td>Diuretics (thiazide type or loop)*</td>
<td>30 (86%)</td>
</tr>
<tr>
<td>Aldosterone antagonists (spironolactone)</td>
<td>15 (43%)</td>
</tr>
<tr>
<td>Centrally acting sympathetic agents</td>
<td>24 (69%)</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>166±22</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>88±19</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>66±14</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>77.7±11.6</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD and percentage (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; OSA, obstructive sleep apnea; SBP, systolic blood pressure; and T2DM, type 2 diabetes mellitus.

*Five patients did not tolerate diuretics.

remaining 5 patients did not tolerate or chose not to use continuous positive airway pressure therapy before baseline assessment. Their treatment also did not change during the study.

Procedural Aspects

Renal angiograms were performed before the introduction of the radiofrequency catheter via femoral access and anatomic eligibility, and absence of significant vascular pathology was confirmed in all patients. An average of 10.8±3.1 ablation treatments\(^\text{15,19}\) was delivered in each patient without any peri- or postprocedural complications. Angiographic evaluation directly after RDN revealed no compromise of treated arteries. There were no intra- or periprocedural complications. No short-term (at 3-month follow-up) and long-term (≤12 months) adverse events related to the procedure were noted in any of the treated patients.

Effects of RDN

Average office systolic BP (SBP) and diastolic BP (DBP) at baseline and at 3-, 6-, and 12-month follow-up are shown in Table 2. RDN significantly reduced SBP and DBP at 3, 6, and 12 months (\(P<0.001\); Table 2; Figure 1). There were no significant changes in resting office heart rate after RDN (Table 2). The effect of RDN on 24-hour BP profile is summarized in Table 3.

On average, patients with RH had high baseline MSNA expressed as both burst frequency (51±11 bursts/min) and burst incidence (80±16 bursts/100 heartbeats). MSNA was significantly reduced at 3, 6, and 12 months after RDN, indicative of a sustained reduction in central sympathetic outflow after RDN (\(P<0.01\); Table 2; Figure 2A and 2B).

At baseline, 33 (>90%) of 35 patients had MSNA levels that were above those reported for age- and sex-matched healthy subjects.\(^\text{26}\) Our novel categorization of patients into age- and sex-related levels of MSNA (Table 4) revealed that at baseline, 43% (n=15) of the study patients displayed extremely elevated MSNA, 14% (n=5) of patients highly elevated MSNA, 17% (n=6) moderately elevated MSNA, and 17% (n=6) mildly elevated MSNA, whereas only 3 patients had normal levels of MSNA before the RDN procedure (Figure 3).

In contrast, at 3 months after the procedure, 34% of patients (n=12) had MSNA levels that were in the normal range (Figure 3). Over time, more patients were classified in lower MSNA categories after RDN with a total of 57% of patients being in the moderately elevated MSNA category (n=20) at 12-month follow-up (Figure 3). The proportion of patients with extremely elevated MSNA was reduced by one third at 12-month follow-up (Figure 3).

The changes in multiunit MSNA expressed as bursts per minute were not related to the changes in SBP (\(r=0.01\); \(P=0.93\)) or DBP (\(r=0.03\); \(P=0.83\)) at neither 3 months nor 6 months (\(r=0.11\); \(P=0.53\) and \(r=0.14\); \(P=0.45\)) or 12 months (\(r=0.001\); \(P=0.534\)).

Table 2. Effects of Renal Denervation on Office Blood Pressure, HR, and Multiunit MSNA in the Entire Patient Cohort at 3-, 6-, and 12-Month FU

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=35)</th>
<th>3-Mo FU (n=35)</th>
<th>6-Mo FU (n=35)</th>
<th>12-Mo FU (n=35)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>166±22</td>
<td>154±24</td>
<td>150±27</td>
<td>144±24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>88±19</td>
<td>82±17</td>
<td>79±16</td>
<td>77±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>66±14</td>
<td>66±14</td>
<td>65±14</td>
<td>67±13</td>
<td>0.66</td>
</tr>
<tr>
<td>Multunit MSNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursts per min</td>
<td>51±11</td>
<td>43±14*</td>
<td>45±13†</td>
<td>45±15†</td>
<td>0.001</td>
</tr>
<tr>
<td>Bursts per 100 heartbeats</td>
<td>80±16</td>
<td>69±17*</td>
<td>70±16*</td>
<td>69±18*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. \(P\) values were derived from 1-way repeated measures ANOVA from baseline to FU. DBP indicates diastolic blood pressure; FU, follow-up; HR, heart rate; MSNA, muscle sympathetic nerve activity; and SBP, systolic blood pressure.

\(\text{*}P<0.001\) for baseline vs set time points at FU.

\(\text{†}P<0.01\) (\(P=0.005\) for baseline vs 6-month FU; \(P=0.001\) for baseline vs 12-month FU).
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(r=-0.01; P=0.94 and r=-0.06; P=0.70) after the RDN procedure. Baseline resting MSNA was related neither to SBP decrease (r=0.31; P=0.08) or DBP (r=0.18; P=0.30) at 3 months nor to SBP and DBP at 6 months (r=-0.06; P=0.73 and r=-0.01; P=0.94) or 12 months (r=-0.06; P=0.71 and r=-0.19; P=0.26) after the procedure, respectively.

There were no changes in body mass index from baseline (32.4±4.9 kg/m²) to 3-month (32.9±4.7 kg/m²), 6-month (32.9±4.4 kg/m²), and 12-month (33.1±4.7 kg/m²) follow-up (P=0.16). No significant alterations in kidney function as assessed by estimated glomerular filtration rate based on serum creatinine from baseline (77.7±11.6 mL/min per 1.73 m²) to 3-month (74.7±12.7 mL/min per 1.73 m²), 6-month (76.1±13.5 mL/min per 1.73 m²), and 12-month (75.9±12.7 mL/min per 1.73 m²) follow-up (P=0.38) were observed. No disturbances in plasma sodium from baseline (139.8±1.8 mmol/L) to 3-month (139.0±2.2 mmol/L), 6-month (139.4±2.4 mmol/L), and 12-month (139.2±2.1 mmol/L) follow-up (P=0.10) and plasma potassium from baseline (3.9±0.3 mmol/L) to 3-month (4.0±0.4 mmol/L), 6-month (4.0±0.4 mmol/L), and 12-month (4.0±0.3 mmol/L) follow-up (P=0.33) were noted after the procedure.

No significant changes in office and 24-hour BP, heart rate, and MSNA from baseline to 6-month follow-up were observed in 7 patients who served as a control group (Table 5).

Discussion

The present findings provide the first evidence for a long-term effect of RDN on MSNA in patients with RH. The major findings of this study are that catheter-based RDN results in a significant reduction in MSNA that is sustained out to 12-month follow-up and accompanied by a substantial and sustained reduction in BP in patients with RH. After RDN, the proportion of patients with normal levels of MSNA, that is, levels commonly observed in healthy age-matched subjects, rose from 9% at baseline to ≈30% at 3-, 6-, and 12-month follow-up.

Table 3. Ambulatory Blood Pressure and HR Monitoring Before and After Renal Denervation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=32)</th>
<th>6-Mo FU (n=32)</th>
<th>12-Mo FU (n=32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>147±21</td>
<td>142±21</td>
<td>139±19*</td>
<td>0.04</td>
</tr>
<tr>
<td>Daytime</td>
<td>154±22</td>
<td>147±22</td>
<td>145±19</td>
<td>0.013</td>
</tr>
<tr>
<td>Nighttime</td>
<td>136±27</td>
<td>135±23</td>
<td>129±23</td>
<td>0.08</td>
</tr>
<tr>
<td>Maximum daytime</td>
<td>187±24</td>
<td>180±25</td>
<td>179±24</td>
<td>0.07</td>
</tr>
<tr>
<td>Maximum nighttime</td>
<td>160±29</td>
<td>160±26</td>
<td>154±25</td>
<td>0.16</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>81±15</td>
<td>78±15</td>
<td>76±13†</td>
<td>0.03</td>
</tr>
<tr>
<td>Daytime</td>
<td>85±16</td>
<td>82±15</td>
<td>80±14†</td>
<td>0.03</td>
</tr>
<tr>
<td>Nighttime</td>
<td>72±14</td>
<td>71±14</td>
<td>68±14</td>
<td>0.18</td>
</tr>
<tr>
<td>Maximum daytime</td>
<td>110±18</td>
<td>105±18</td>
<td>104±14</td>
<td>0.12</td>
</tr>
<tr>
<td>Maximum nighttime</td>
<td>88±16</td>
<td>88±18</td>
<td>86±18</td>
<td>0.79</td>
</tr>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>67±13</td>
<td>69±15</td>
<td>70±13</td>
<td>0.17</td>
</tr>
<tr>
<td>Daytime</td>
<td>70±15</td>
<td>72±16</td>
<td>71±14</td>
<td>0.26</td>
</tr>
<tr>
<td>Nighttime</td>
<td>61±11</td>
<td>63±13</td>
<td>64±11</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values expressed as mean±SD. Data are shown as a 1-way repeated measures ANOVA when compared with baseline. DBP indicates diastolic blood pressure; FU, follow-up; HR, heart rate; and SBP, systolic blood pressure.

*R<0.05 for set time points vs baseline.

†P<0.01 for set time points vs baseline.

Figure 1. Mean fall in office systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3-, 6-, and 12-month (M) follow-up (FU) after renal denervation in 35 patients who completed each visit time point. Data are expressed as mean±SEM.

Figure 2. Mean fall in muscle sympathetic nerve activity (MSNA) expressed as burst frequency (A) and burst incidence (B) at 3-, 6-, and 12-month (M) follow-up (FU) after renal denervation in 35 patients who completed each visit time point. Data are expressed as mean±SEM.
follow-up. This indicates that sympathetic activation is normal-
ized in a considerable number of patients with RH and
elevated baseline MSNA. Similarly, the proportion of patients
with extremely high MSNA was reduced from 43% at base-
to 29% at 12 months after RDN. An overall reduction in
MSNA was observed across the entire study cohort. However,
the reduction of multiunit MSNA bore no direct relationship
with the concomitant changes in BP.

Although the contribution of augmented sympathetic acti-
vation to the complex pathophysiology of human hyperten-
sion is well established, persistent sympathetic drive is often
left unopposed. Indeed, our previous findings demonstrated
that sympathetic activation is not directly related to the BP
decrease after RDN both at short-term (3 months)\(^{14}\) and at long-term follow-up (12
months). The reduction in BP associated with RDN was also
unrelated to baseline resting MSNA levels.

The absence of a direct relationship between MSNA and BP
changes is perhaps not surprising given the limited number of
patients included, the high level of baseline MSNA across the
entire cohort at baseline, the multitude of pathophysiologic
mechanisms other than neural control likely to be affected by
RDN, and the potential influence of background medication.
However, when the total study cohort was divided into 2
groups according to their baseline level of MSNA, there
seemed to be a trend toward more pronounced reduction in
BP in response to RDN in those patients with higher levels
of MSNA at baseline (average 60±6 bursts/min and 88±12
bursts/100 heartbeats) when compared with the patients with
lower MSNA levels (average 41±6 bursts/min and 72±17
bursts/100 heartbeats) for both SBP (\(-18±29\ \text{v} \ -14±23\ \text{mm Hg}\)) and DBP (\(-9±15\ \text{v} \ -8±12\ \text{mm Hg}\)) at 6-month
follow-up and for SBP (\(-24±33\ \text{v} \ -18±27\ \text{mm Hg}\)) and
DBP (\(-14±13\ \text{v} \ -10±17\ \text{mm Hg}\)) at 12 months after the
procedure, respectively. However, none of these differences
reached levels of statistical significance.

Although the magnitude of the RDN-induced office BP
reduction continues to increase over time (Figure 1), our data
indicate that the reduction of MSNA observed at 3 months
after the procedure was sustained at 6- and 12-month follow-
up. Similar to the recent findings,\(^ {27}\) we observed significant,
however, less pronounced reduction in 24-hour BP profile.

The exact mechanisms through which RDN may reduce
central sympathetic outflow as assessed by MSNA remain
unclear but are likely to involve alterations in afferent sig-
alling from the kidneys to integrative structures in the brain
stem, which in turn suppresses central sympathetic outflow to
the muscle vascular bed and possibly to other organs, such as
the heart. Although the 47% reduction in renal noradrenaline
spillover after radiofrequency ablation is clearly attributable
to silencing efferent renal sympathetic nerves,\(^ {15}\) indirect addi-
tional effects via reduced afferent signaling from the kidneys
seem likely. Given the close relationship between multunit

### Table 4. Novel Categories of Abnormal Resting MSNA Expressed as Bursts Per Minute in Men and in Women According to Age Based on Normal Healthy Subjects, as Previously Demonstrated

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20–29</td>
<td>30–39</td>
</tr>
<tr>
<td>Men</td>
<td>22*</td>
<td>26*</td>
</tr>
<tr>
<td></td>
<td>37–43</td>
<td>41–47</td>
</tr>
<tr>
<td></td>
<td>≥44</td>
<td>≥48</td>
</tr>
<tr>
<td>Women</td>
<td>14*</td>
<td>23*</td>
</tr>
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<td></td>
<td>29–38</td>
<td>38–44</td>
</tr>
<tr>
<td></td>
<td>≥39</td>
<td>≥45</td>
</tr>
</tbody>
</table>

MSNA indicates muscle sympathetic nerve activity.

\(^{*}\text{Previously demonstrated MSNA values for healthy male and female subjects described by Narkiewicz et al.}^{26}\)
RDN as demonstrated by beneficial effects on left ventricular vascular outcomes.

The small number of control patients is a potential limitation.

In view of continued and sustained BP reduction out to 36 months after RDN procedure,13 it is perhaps unlikely, albeit not impossible, that renal reinnervation can occur and may modulate central integrative pathways to affect BP reductions achieved with RDN. However, further studies are warranted to determine whether reduced sympathetic activity is sustained for a period longer than a year and potentially contributes to attenuation of disease progression and improvement in cardiovascular outcomes.

Regression of hypertensive organ damage associated with RDN as demonstrated by beneficial effects on left ventricular hypertrophy, diastolic function, and vascular remodeling in patients with RH29–31 is also likely to have a favorable systemic effect over time, potentially contributing to improved BP control. A possible inhibitory effect on the renin–angiotensin system32 after renal nerve ablation could also play a role in the long-term effect of RDN on MSNA and BP responses in patients with RH. Here, we describe the effect of RDN on MSNA out to 12 months after the procedure and demonstrate that RDN results in a significant and sustained reduction in central sympathetic outflow and BP in this patient cohort. This study identifies the renal nerves as an attractive therapeutic target in the scenario of RH.

**Sources of Funding**

This study was funded, in part, by grants from the National Health and Medical Research Council of Australia and the Victorian Government’s Operational Infrastructure Support Program and by Medtronic. The funding organizations played no role in the design and conduct of the study, collection, management, analysis or interpretation of the data, or preparation, review, or approval of the article.

**Disclosures**

Drs. Schlaich, Esler, and Lambert are supported by career fellowships from the National Health and Medical Research Council. Drs. Walton, Krum, Lambert, Esler, and Schlaich are investigators in studies sponsored by Medtronic. The laboratories of Drs. Schlaich, Lambert, and Esler currently receive research funding from Medtronic, Abbott Pharmaceuticals, Servier Australia, and Allergan. Dr. Lambert has acted as a consultant for Medtronic and has received honoraria or travel support for presentations from Pfizer, Wyeth Pharmaceuticals, Servier, and Medtronic. Dr. Esler serves on scientific advisory boards of Abbott (formerly Solvay) Pharmaceuticals and Medtronic. Dr. Schlaich serves on scientific advisory boards for Abbott (formerly Solvay) Pharmaceuticals, BI, Novartis Pharmaceuticals, and Medtronic and has received honoraria and travel support from Abbott, BI, Servier, Novartis, and Medtronic. Dr. Hering is a clinical research fellow from Medical University of Gdansk, Poland, and was awarded a research fellowship from Polish Foundation for Science (KOLUMB 2010-1). Dr. Narkiewicz has received grants, lecture, and consultancy fees from Medtronic.

**References**


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=7)</th>
<th>6-Mo FU (n=7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mmHg</td>
<td>178±11</td>
<td>174±8</td>
<td>0.38</td>
</tr>
<tr>
<td>Daytime SBP, mmHg*</td>
<td>159±23</td>
<td>158±17</td>
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<tr>
<td>Nighttime SBP, mmHg*</td>
<td>146±35</td>
<td>145±27</td>
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<tr>
<td>Office DBP, mmHg</td>
<td>94±13</td>
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<tr>
<td>Daytime DBP, mmHg*</td>
<td>94±18</td>
<td>93±11</td>
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<tr>
<td>Nighttime DBP, mmHg*</td>
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<td>82±13</td>
<td>0.64</td>
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<tr>
<td>Office HR, bpm</td>
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<td>62±17</td>
<td>0.92</td>
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<tr>
<td>Daytime HR, bpm*</td>
<td>64±20</td>
<td>62±15</td>
<td>0.65</td>
</tr>
<tr>
<td>Nighttime HR, bpm*</td>
<td>58±14</td>
<td>60±10</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Values expressed as mean±SD. ABPM indicates ambulatory blood pressure monitoring; DBP, diastolic blood pressure; FU, follow-up; HR, heart rate; MSNA, muscle sympathetic nerve activity; RDN, renal denervation; and SBP, systolic blood pressure.

*ABPM was available from 5 of 7 control patients with resistant hypertension at baseline and 6-month FU without having undergone RDN.

**Limitations**

The small number of control patients is a potential limitation. However, in line with findings from Symplicity HTN-2,28 BP and MSNA remained unaltered over time in patients with RH who did not undergo RDN.14

Strengths of our study include the precise evaluation of the long-term effect of RDN on MSNA and BP responses in high-risk patients with RH who are characterized by augmented resting sympathetic outflow, despite the use of multidrug regimens. This is the first clinical report on the effects of RDN on MSNA in a relatively large cohort of patients with RH out to 12 months after the procedure, thereby providing new insights into the BP-lowering mechanisms of RDN and perhaps adequate selection of patients for this treatment. In view of the recently published findings of the effect of RDN in 10 patients with less severe BP and MSNA levels (average MSNA 34 bursts/min) before RDN,28 the results of our study may guide clinical practice. In addition, although antihypertensive medication was reduced in some patients, the beneficial effect of RDN on BP and MSNA seems to be maintained out to 12 months after the procedure.

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**References**


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**Novelty and Significance**

**What Is New?**

- First clinical experience of the effect of renal denervation (RDN) on longer term changes of muscle sympathetic nerve activity (MSNA) in humans.
- RDN is associated with both a sustained reduction in MSNA and blood pressure (BP).

**What Is Relevant?**

- Although RDN provides sustained reduction of both MSNA and BP ≤12 months, no direct relationship between baseline MSNA or its change after RDN and the baseline level of BP or its change in response to RDN could be identified.

**Summary**

Our findings provide evidence for a sustained reduction in both MSNA and BP in response to RDN in patients with resistant hypertension. These changes are likely to reduce overall cardiovascular risk in this high-risk population.
Sustained Sympathetic and Blood Pressure Reduction 1 Year After Renal Denervation in Patients With Resistant Hypertension

Dagmara Hering, Petra Marusic, Antony S. Walton, Elisabeth A. Lambert, Henry Krum, Krzysztof Narkiewicz, Gavin W. Lambert, Murray D. Esler and Markus P. Schlaich

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