Renal Nerve Stimulation–Induced Blood Pressure Changes Predict Ambulatory Blood Pressure Response After Renal Denervation


Abstract—Blood pressure (BP) response to renal denervation (RDN) is highly variable and its effectiveness debated. A procedural end point for RDN may improve consistency of response. The objective of the current analysis was to look for the association between renal nerve stimulation (RNS)–induced BP increase before and after RDN and changes in ambulatory BP monitoring (ABPM) after RDN. Fourteen patients with drug-resistant hypertension referred for RDN were included. RNS was performed under general anesthesia at 4 sites in the right and left renal arteries, both before and immediately after RDN. RNS-induced BP changes were monitored and correlated to changes in ambulatory BP at a follow-up of 3 to 6 months after RDN. RNS resulted in a systolic BP increase of 50±27 mm Hg before RDN and systolic BP increase of 13±16 mm Hg after RDN (P=0.001). Average systolic ABPM was 153±11 mm Hg before RDN and decreased to 137±10 mm Hg at 3- to 6-month follow-up (P=0.003). Changes in RNS-induced BP increase before versus immediately after RDN and changes in ABPM before versus 3 to 6 months after RDN were correlated, both for systolic BP (R=0.77, P=0.001) and diastolic BP (R=0.79, P=0.001). RNS-induced maximum BP increase before RDN had a correlation of R=0.61 (P=0.020) for systolic and R=0.71 (P=0.004) for diastolic ABPM changes. RNS-induced BP changes before versus after RDN were correlated with changes in 24-hour ABPM 3 to 6 months after RDN. RNS should be tested as an acute end point to assess the efficacy of RDN and predict BP response to RDN. (Hypertension. 2016;68:00-00. DOI: 10.1161/HYPERTENSIONAHA.116.07492.)

Key Words: 24-hour ABPM ■ drug-resistant hypertension ■ renal denervation ■ renal nerve stimulation

Renal denervation (RDN) has been reported as a successful treatment of resistant hypertension in multiple trials studying the efficacy of RDN.1–6 The sham-controlled Symplicity Hypertension-3 (HTN-3) trial, however, failed to show significant RDN-induced changes in blood pressure (BP) versus control,7 raising serious doubts about the efficacy of RDN.8–11 Variable effects of RDN on BP have been reported, with a wide spectrum ranging between nonresponse to marked reduction in BP.12 The absence of an ablation procedural end point for RDN is a potential explanation for variable responses, and the successful implementation of a reliably predictable end point could improve procedural success and clinical response.

Recently, we reported on the feasibility of high-frequency electric renal nerve stimulation (RNS) in patients with resistant hypertension and demonstrated that RNS-induced BP increase was significantly blunted after RDN.13 We hypothesized that the difference between RNS-induced BP rise before and after RDN could be used as a procedural end point for RDN and may prove a reliable functional test to predict BP response to RDN. The main goal of the current analysis was to investigate the 24-hour ambulatory BP changes after RDN and the relation to RNS before and after RDN.

Methods

Patients

All patients with treatment-resistant hypertension referred for RDN between May 2014 and February 2015 were screened for inclusion in the RNS study. Patients were eligible if they were on a stable treatment of resistant hypertension in multiple trials studying the efficacy of RDN.1–6 The sham-controlled Symplicity Hypertension-3 (HTN-3) trial, however, failed to show significant RDN-induced changes in blood pressure (BP) versus control,7 raising serious doubts about the efficacy of RDN.8–11 Variable effects of RDN on BP have been reported, with a wide spectrum ranging between nonresponse to marked reduction in BP.12 The absence of an ablation procedural end point for RDN is a potential explanation for variable responses, and the successful implementation of a reliably predictable end point could improve procedural success and clinical response.

Recently, we reported on the feasibility of high-frequency electric renal nerve stimulation (RNS) in patients with resistant hypertension and demonstrated that RNS-induced BP increase was significantly blunted after RDN.13 We hypothesized that the difference between RNS-induced BP rise before and after RDN could be used as a procedural end point for RDN and may prove a reliable functional test to predict BP response to RDN. The main goal of the current analysis was to investigate the 24-hour ambulatory BP changes after RDN and the relation to RNS before and after RDN.

Methods

Patients

All patients with treatment-resistant hypertension referred for RDN between May 2014 and February 2015 were screened for inclusion in the RNS study. Patients were eligible if they were on a stable
antihypertensive drug regimen of at least 3 antihypertensive drugs (preferably with a diuretic) for at least 1 month, guided by hyperten-
sion specialists. Office systolic BP (SBP) was >140 or diastolic BP (DBP) >90 mm Hg, and 24-hour SBP was >130 or DBP >80 mm Hg, despite stable treatment, excluding patients with white coat hyper-
tension. Patients were screened for eligibility by a multidisciplinary


team, including cardiologists, hypertension specialists, and a radiolo-
gist. All patients were willing and able to comply with the protocol
and had provided written informed consent. Age range for possible
inclusion was 18 to 80 years, and glomerular filtration rate had to
be >45 mL/min per 1.73 m² according to the Modification of Diet in
Renal Disease formula.14

Exclusion criteria were an unsuitable anatomy for RDN assessed
by computed tomographic angiography (main renal artery lumen di-


ameter ≤3 mm or a total length <20 mm of the main arteries), type I
diabetes mellitus, chronic oxygen use, primary pulmonary hyper-
tension, pregnancy, and a mental or physical inability to participate.
Patients enrolled in another investigational drug or device study were
also excluded. Secondary hypertension was excluded by a rigorous
protocol, excluding hyperaldosteronism, pheochromocytoma, renal
artery stenosis (>50% stenosis in one or both arteries on computed
tomographic angiography), drug or substance abuse–induced hyper-
tension when appropriate, according to the European guidelines for
the management of hypertension.15 The study was approved by the
local medical ethical committee (ABR number 47172) and was con-
ducted according to the declaration of Helsinki. The trial is registered
under ClinicalTrials.gov ID: NCT02496117.

Outcomes

The primary end points of the current study were invasively mea-

sured RNS-induced BP changes before and after RDN, the change in
24-hour ambulatory BP monitoring (ABPM) before RDN versus
3- to 6-month follow-up after RDN, and the correlation between these
variables.1,14 Secondary end points were office BP measurements dur-
ing follow-up and number of antihypertensive drugs. To guard safety
during RNS, we set the maximum SBP during RNS at 180 mm Hg, at
which point RNS was immediately discontinued.

Procedures

RDN was performed under general anesthesia. Throughout the RDN
procedure, no changes were made in use of vasoactive medication,
and no inotropic medication was necessary. The procedure was per-
formed by experienced cardiac electrophysiologists. Two sheaths
were placed in the right femoral artery, one for continuous BP mea-
surement and one for catheter access. 5000 IU of heparin were admin-
istered during the procedure. In addition, patients not previously on
acetylsalicylic acid, we administered 500 mg of acetylsalicylic acid.

We performed angiography with a pigtail catheter to visualize the
aorta and renal arteries. Initially, a conventional quadripolar catheter


with a tip electrode of 2 mm, other electrodes of 1 mm, and in-


electrode spacing of 5 mm (EP-XT; C. R. Bard, Inc, Murray Hill,
NJ) was introduced in the renal artery, under fluoroscopic guidance.
Unipolar stimulation was performed from the tip of the catheter. This
catheter was used only when performing RDN with the single-elec-
trode ablation catheter (Symplicity Flex Renal Denervation Catheter;
Medtronic, Minneapolis, MN). In patients who were ablated with the
multi electrode basket ablation catheter (EnligHTN; St Jude Medical,
Saint Paul, MN), bipolar stimulation was performed by the ablation
catheter itself, with bipolar stimulation from poles 1 to 2 and 3 to 4
proximally and distally in the renal artery. The first renal artery to
undergo RNS was alternated between left and right among consecu-
tive patients. RNS was performed at multiple sites with a minimum of
4 sites in both arteries, ensuring that different quadrants of the
arterial circumference were stimulated in proximal and distal areas of
the renal artery, in which ablations were usually performed. Pacing
frequency was set at 20 Hz, pacing output at 20 mA with a pulse dura-
tion of 2 ms, based on earlier research.15,16–19 Stimulation duration was
60 s or shorter when SBP increased beyond 180 mm Hg. We waited
for the BP to return to baseline values before proceeding to the next
stimulation site.

After RNS in both arteries (total of at least 8 stimulation sites),
we performed a standard RDN procedure. The single-electrode
Medtronic renal ablation catheter was used in 3 patients and the St
Jude multielectrode EnligHTN catheter in 11 patients. In 1 patient,
a combination of both single-electrode and multielectrode RDN caths-
ters was used. In this latter patient, the left renal artery was denervat-
ed with the multielectrode basket catheter. We switched to the flexible
single-electrode catheter because of anatomic variation, prohibiting
the introduction of the multielectrode basket catheter in the right
renal artery. The use of the single-electrode catheter (Symplicity,
Medtronic) has been described previously.11 The multielectrode RDN
catheter contains 4 electrodes separated from each other in a basket
configuration. Up to 4 discrete radiofrequency (RF) ablations were
applied simultaneously, each application lasting ≤120 s with a power
≤8 Watts (W) and a target temperature of 70°C (158°F). Electrodes
that did not reach the target temperature or impedance drop were
switched off. In each renal artery, ≤3 sets corresponding to 12 abla-
tion points were performed, separated both longitudinally and rota-

tionally under fluoroscopic guidance. During RF energy application,
temperature and impedance were monitored. RDN was considered
successful when the maximum number of anatomically possible abla-
tion points was reached, in accordance with standard care.

Importantly, the results of RNS were only monitored and did not
influence the number of RF applications or the RDN procedure. After
RDN, we repeated the RNS procedure, fluoroscopically placing the
pacing electrodes at the site at which the maximum BP response to
RNS was observed before RDN. We chose to check the site of maxi-
mum BP response to ensure that the difference between patients who
still showed an increase in BP after RDN and patients who no longer
showed an increase in BP in response to RNS would become clear.
The Bard EP system (Labsystem Pro, Bard) was used to record and
monitor BP changes throughout the procedure. Additionally, we doc-
umented all RNS-related BP changes on a study work list.

Patients were followed and monitored as an outpatient by a vascular
internist, who was informed that RDN was successfully performed,
but was unaware of the results of the RNS. In all patients, a validated
24-hour ABPM with 30 minutes BP measuring intervals was obtained
(Spacelabs, Snoqualmie, WA) at 3 or 6 months after the procedure to
assess the effect of RDN.20 Office BP measurements were executed
either by repeated automated oscillometry measurements (intrinsi-
cally blinded) or by sphygmomanometry during outpatient contacts.
BP measurements by sphygmomanometry were performed by tech-
nicians not involved in the analysis of the study and were regarded
blinded. Antihypertensive drug therapy was left unchanged, unless
symptomatic hypotension or out of range hypertension (>180 mm Hg
SBP) warranting immediate control were present.

Statistical Analysis

Categorical variables were summarized by frequencies and percent-
eges. Continuous variables (ie, ABPM, office SBP, office DBP) are
reported as mean and standard deviation or median and interquartile
range where appropriate. Variables were tested for normality of distri-
bution. A paired t test was used to compare continuous variables, and
Wilcoxon signed-rank test was applied to compare the difference in
number of antihypertensive drugs. Pearson’s correlation was used to
assess the relation of RNS-induced BP changes assessed by office BP
and 24-hour BP measurements. To compare the different correlations,
a Fisher’s R to Z transformation was used. Statistical analysis was
performed using IBM SPSS statistics version 20 (IBM Inc, Armonk,
NY). A P value of ≤0.05 was considered statistically significant.

Results

Demographics

Fourteen patients were included in the RNS study. Patients
underwent their RDN procedure between May 2014 and
February 2015. The demographic and clinical characteristics
at baseline are shown in Table 1. The anatomy of the renal
vasculature is represented by the Okada classification.
In all 14 patients, denervation of the renal arteries was performed. The median number of ablations was 8 in both arteries. The number of RF ablations ranged from 4 to 16 in the right renal artery and from 4 to 12 in the left renal artery. Six out of the 14 patients had accessory renal arteries. Details of renal vasculature based on the Okada classification are summarized in Table 1. The accessory arteries were deemed too small for additional denervation. Depending on the RDN system used, RF energy was delivered based on tip temperature or impedance drop. EnligHTN multielectrode RDN system (St Jude Medical) simultaneously delivers RF energy at 4 electrodes of the basket catheter in a temperature-controlled mode with a target 70°C (158°F). In patients denervated with the Symplicity RDN system, RF energy delivery is fully automated, and the system displays changes in impedance during RF energy application. An impedance drop of >10% was considered successful. If target ablation point did not reach adequate impedance drop or target temperature, the RF application was automatically turned off. Delivered RF energy ranged from 2.0 to 6.6 W and was not allowed to exceed 8.0 W.

Of the cumulative 105 sites that were successfully stimulated, an increase in SBP of >10 mm Hg in response to RNS was elicited at 78 sites (74.3%). Procedural data on the RNS sites are summarized in Table 2. Of note, in 1 patient, no RNS was performed in the right renal artery because of technical failure of the stimulator (Micropace). No significant differences between the left and right renal arteries were observed. BP indicates blood pressure; RF, radio frequency; RNS, renal nerve stimulation; and SBP, systolic blood pressure.

Procedural Data
In all 14 patients, denervation of the renal arteries was performed. The median number of ablations was 8 in both arteries. The number of RF ablations ranged from 4 to 16 in the right renal artery and from 4 to 12 in the left renal artery. Six out of the 14 patients had accessory renal arteries. Details of renal vasculature based on the Okada classification are summarized in Table 1. The accessory arteries were deemed too small for additional denervation. Depending on the RDN system used, RF energy was delivered based on tip temperature or impedance drop. EnligHTN multielectrode RDN system (St Jude Medical) simultaneously delivers RF energy at 4 electrodes of the basket catheter in a temperature-controlled mode with a target 70°C (158°F). In patients denervated with the Symplicity RDN system, RF energy delivery is fully automated, and the system displays changes in impedance during RF energy application. An impedance drop of >10% was considered successful. If target ablation point did not reach adequate impedance drop or target temperature, the RF application was automatically turned off. Delivered RF energy ranged from 2.0 to 6.6 W and was not allowed to exceed 8.0 W.

Of the cumulative 105 sites that were successfully stimulated, an increase in SBP of >10 mm Hg in response to RNS was elicited at 78 sites (74.3%). Procedural data on the RNS sites are summarized in Table 2. Of note, in 1 patient, no RNS was performed in the right renal artery because of technical failure of the stimulator (Micropace). No significant differences between the left and right renal arteries were observed. BP indicates blood pressure; RF, radio frequency; RNS, renal nerve stimulation; and SBP, systolic blood pressure.

Procedural Data
In all 14 patients, denervation of the renal arteries was performed. The median number of ablations was 8 in both arteries. The number of RF ablations ranged from 4 to 16 in the right renal artery and from 4 to 12 in the left renal artery. Six out of the 14 patients had accessory renal arteries. Details of renal vasculature based on the Okada classification are summarized in Table 1. The accessory arteries were deemed too small for additional denervation. Depending on the RDN system used, RF energy was delivered based on tip temperature or impedance drop. EnligHTN multielectrode RDN system (St Jude Medical) simultaneously delivers RF energy at 4 electrodes of the basket catheter in a temperature-controlled mode with a target 70°C (158°F). In patients denervated with the Symplicity RDN system, RF energy delivery is fully automated, and the system displays changes in impedance during RF energy application. An impedance drop of >10% was considered successful. If target ablation point did not reach adequate impedance drop or target temperature, the RF application was automatically turned off. Delivered RF energy ranged from 2.0 to 6.6 W and was not allowed to exceed 8.0 W.

Of the cumulative 105 sites that were successfully stimulated, an increase in SBP of >10 mm Hg in response to RNS was elicited at 78 sites (74.3%). Procedural data on the RNS sites are summarized in Table 2. Of note, in 1 patient, no RNS was performed in the right renal artery because of technical failure of the stimulator (Micropace). No significant differences between the left and right renal arteries were observed. BP indicates blood pressure; RF, radio frequency; RNS, renal nerve stimulation; and SBP, systolic blood pressure.

### Table 1. Baseline Characteristics (n=14 Patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (3–6 mo)</th>
<th>Follow Up (n=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66 (39–76)</td>
<td>7/14</td>
<td>0.716</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>166±23</td>
<td>149±19</td>
<td>0.003</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>98±14</td>
<td>90±15</td>
<td>0.017</td>
</tr>
<tr>
<td>24-h systolic ABPM, mm Hg</td>
<td>153±11</td>
<td>137±10</td>
<td>0.003</td>
</tr>
<tr>
<td>24-h diastolic ABPM, mm Hg</td>
<td>88±8</td>
<td>80±9</td>
<td>0.018</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>10/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.2±2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>84±16</td>
<td>86±17</td>
<td>0.570</td>
</tr>
<tr>
<td>GFR (MDRD, mL/min per 1.73 m²)</td>
<td>76±16</td>
<td>75±18</td>
<td>0.682</td>
</tr>
<tr>
<td>Smoking</td>
<td>1/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>2/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus type II</td>
<td>1/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±8</td>
<td>66±7</td>
<td>0.716</td>
</tr>
<tr>
<td>No of antihypertensive drugs</td>
<td>4 (3–6)</td>
<td>4 (2–6)</td>
<td>0.206</td>
</tr>
<tr>
<td>Diuretic</td>
<td>9/14</td>
<td>8/14</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>13/14</td>
<td>13/14</td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>1/14</td>
<td>1/14</td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>9/14</td>
<td>10/14</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>12/14</td>
<td>10/14</td>
<td></td>
</tr>
<tr>
<td>α1 blocker</td>
<td>6/14</td>
<td>4/14</td>
<td></td>
</tr>
<tr>
<td>Renin inhibitor</td>
<td>1/14</td>
<td>1/14</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>6/14</td>
<td>5/14</td>
<td></td>
</tr>
<tr>
<td>CAS</td>
<td>2/14</td>
<td>1/14</td>
<td></td>
</tr>
<tr>
<td>Okada classification right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>9/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>1/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>3/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>1/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>0/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okada classification left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>11/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>1/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>2/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>0/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>0/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accessory artery</td>
<td>6/14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values between parenthesis indicate range, and other values represent standard deviation. α1 blocker indicates α1 receptor blocker; ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; β-blocker, beta receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAS, centrally acting sympatholytic; CCB, calcium channel blocker; GFR, glomerular filtration rate; and MDRD, modification of diet in renal diseases.

### Table 2. Procedural Data (n=14 Patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Left Renal Artery (n=54 Sites)</th>
<th>Right Renal Artery (n=51 Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of sites with SBP increase &gt;10 mm Hg</td>
<td>41 (76%)</td>
<td>37 (73%)</td>
</tr>
<tr>
<td>No of sites with no BP response to RNS</td>
<td>13 (24%)</td>
<td>14 (27%)</td>
</tr>
<tr>
<td>Site of maximum SBP response to RNS</td>
<td>N=14 arteries</td>
<td>N=13 arteries</td>
</tr>
<tr>
<td>Distal lower quadrant</td>
<td>7/14 (50.0%)</td>
<td>6/13 (46.2%)</td>
</tr>
<tr>
<td>Distal upper quadrant</td>
<td>0/14 (0.0%)</td>
<td>0/13 (0.0%)</td>
</tr>
<tr>
<td>Proximal lower quadrant</td>
<td>4/14 (28.6%)</td>
<td>4/13 (30.8%)</td>
</tr>
<tr>
<td>Proximal upper quadrant</td>
<td>2/14 (14.3%)</td>
<td>2/13 (15.4%)</td>
</tr>
<tr>
<td>Mid renal roof</td>
<td>0/14 (0.0%)</td>
<td>1/13 (7.7%)</td>
</tr>
<tr>
<td>Mid renal bottom</td>
<td>1/14 (7.1%)</td>
<td>0/13 (0.0%)</td>
</tr>
<tr>
<td>No of RF ablation points</td>
<td>8 (4–12)</td>
<td>8 (4–16)</td>
</tr>
</tbody>
</table>

Table 2 summarizes the procedural data of the patients. In one patient, no RNS was performed in the right renal artery because of technical failure of the stimulator (Micropace). No significant differences between the left and right renal arteries were observed. BP indicates blood pressure; RF, radio frequency; RNS, renal nerve stimulation; and SBP, systolic blood pressure.
The difference in DBP increase before versus after RDN clinical outcome based on office SBP (R before versus after RDN was significantly correlated with the data during the procedure. The difference in SBP increase BP rise after RDN considered alone. ABPM BP changes after RDN and residual RNS-induced response to 9 mm Hg increase in BP. We observed a preference for the site of maximum response to be in the upper quadrants, both distally and proximally (227 versus 527 locations; P = 0.001). No clear differences were observed between the right and left renal arteries. There were no complications.

In agreement with our previous work, the mean increase in SBP in response to RNS at the site of maximum response significantly decreased from 50±27 mm Hg before RDN to 13±16 mm Hg after RDN (P = 0.001). See Figure 1 for a visual depiction of the data.

At a median follow-up of 4.5 months (3–6 months), office SBP decreased from 166±23 mm Hg at baseline to 149±19 mm Hg (P = 0.003). DBP decreased from 98±14 to 90±15 mm Hg during follow-up. At the same time point, 24-hour SBP decreased from 153±11 mm Hg at baseline to 137±10 mm Hg (P = 0.003). Antihypertensive drugs were increased in 2 patients and decreased because of symptomatic hypotension in 5 patients. However, the median number of antihypertensive drugs remained unchanged.

Changes in ABPM SBP documented at median follow-up of 4.5 months after RDN were correlated with RNS-induced SBP rise before RDN at the site of maximum response (R = 0.610; P = 0.020). This correlation further increased after subtracting the RNS-induced BP rise measured immediately after RDN (ΔSBP at site of maximal response=RNS-induced BP increase before RDN-RNS-induced BP increase after RDN) at the same site (R = 0.769; P = 0.001). These findings hold true for DBP as well (see Figure 2). Changes in 24-hour ambulatory DBP were strongly correlated with RNS-induced DBP rise before RDN at the site of maximum response (R = 0.734; P = 0.003). In contrast, no significant correlation was observed between ABPM BP changes after RDN and residual RNS-induced BP rise after RDN considered alone.

Changes in office BP were correlated with the acute BP data during the procedure. The difference in SBP increase before versus after RDN was significantly correlated with the clinical outcome based on office SBP (R = 0.724; P = 0.003). The difference in DBP increase before versus after RDN was significantly correlated with office DBP outcome during follow-up (R = 0.539; P = 0.047). See Figure 3 for depiction of the data. However, initial RNS-induced BP increase before RDN was not correlated with the DBP outcome. The increase in BP after RDN was not correlated with office BP data during follow-up.

**Discussion**

In this study, we have demonstrated that high-frequency RNS before and after RDN is feasible and safe in patients. In addition, it is suggested that the use of RNS may facilitate prediction of the completeness of RDN and subsequent BP changes after the procedure. The current work describes for the first time the significant association between RNS-induced BP responses during RDN and the clinical ABPM response to RDN at 3 to 6 months after RDN. This reflects the potential of using RNS as a functional test to evaluate the efficacy of renal nerve ablation and predict the clinical outcome of the RDN procedure.

Since the publication of the Symplicity HTN-3 trial, a study that failed to demonstrate BP reduction above and beyond a sham procedure, RDN has been the topic of renewed and ongoing debate. Some have questioned the efficacy of RDN and others sought reasons for the negative findings. It has been argued that the poor efficacy of RDN in Symplicity HTN-3 may be partly explained by suboptimal renal nerve ablation. In contrast, in the recent Renal Denervation for Hypertension (DENERHTN) trial, RDN was performed by a limited number of experienced operators, and drug adjustment was fully standardized, with a moderate but significant overall benefit of RDN on daytime ABPM. A recent meta-analysis by Fadi Elmula et al including all published randomized controlled trials testing RDN against stable or intensified medical treatment showed little if any benefit of RDN. The troubling implication is that the BP benefit directly assignable to RDN may have been substantially overestimated in Symplicity HTN-1 and -2 and other nonrandomized unblinded studies using office BP as primary end point.

RDN is supported by a solid rationale, including reports from the years 1940 to 1960. During those times, radical surgery was performed for renal denervation, successfully lowering BP; however, also in these patients, a percentage appeared to be nonresponders. High-frequency electric stimulation of the sympathetic renal afferent pathways is the most likely cause of the rise in BP induced by RNS. This is because the gradual rise in BP 10 to 20 s after starting RNS is consistent with an increase in adrenergic response through stellate ganglion stimulation in canine studies as reported previously. Experimental studies indicate that the afferent nerves play an important role in the sudden increase in BP in response to RNS. The afferent nerves are involved in the increase of central sympathetic tone. Peripheral RDN has a peripheral sympatholytic effect and alters the level of activation excitation of central noradrenergic pathways, but does not alter sodium or water intake or excretion, plasma renin activity, or creatinine clearance, suggesting that efferent renal nerve function does not play an important role in the maintenance of this form of hypertension. Selective lesioning of the renal afferent nerves attenuates the development of hypertension, thus providing direct evidence that the renal response to 9 mm Hg increase in BP. We observed a preference for the site of maximum response to be in the upper quadrants, both distally and proximally (227 versus 527 locations; P = 0.001). No clear differences were observed between the right and left renal arteries. There were no complications.

In agreement with our previous work, the mean increase in SBP in response to RNS at the site of maximum response significantly decreased from 50±27 mm Hg before RDN to 13±16 mm Hg after RDN (P = 0.001). See Figure 1 for a visual depiction of the data.

At a median follow-up of 4.5 months (3–6 months), office SBP decreased from 166±23 mm Hg at baseline to 149±19 mm Hg (P = 0.003). DBP decreased from 98±14 to 90±15 mm Hg during follow-up. At the same time point, 24-hour SBP decreased from 153±11 mm Hg at baseline to 137±10 mm Hg (P = 0.003). Antihypertensive drugs were increased in 2 patients and decreased because of symptomatic hypotension in 5 patients. However, the median number of antihypertensive drugs remained unchanged.

Changes in ABPM SBP documented at median follow-up of 4.5 months after RDN were correlated with RNS-induced SBP rise before RDN at the site of maximum response (R = 0.610; P = 0.020). This correlation further increased after subtracting the RNS-induced BP rise measured immediately after RDN (ΔSBP at site of maximal response=RNS-induced BP increase before RDN-RNS-induced BP increase after RDN) at the same site (R = 0.769; P = 0.001). These findings hold true for DBP as well (see Figure 2). Changes in 24-hour ambulatory DBP were strongly correlated with RNS-induced DBP rise before RDN at the site of maximum response (R = 0.734; P = 0.003). In contrast, no significant correlation was observed between ABPM BP changes after RDN and residual RNS-induced BP rise after RDN considered alone.

Changes in office BP were correlated with the acute BP data during the procedure. The difference in SBP increase before versus after RDN was significantly correlated with the clinical outcome based on office SBP (R = 0.724; P = 0.003). The difference in DBP increase before versus after RDN was significantly correlated with office DBP outcome during follow-up (R = 0.539; P = 0.047). See Figure 3 for depiction of the data. However, initial RNS-induced BP increase before RDN was not correlated with the DBP outcome. The increase in BP after RDN was not correlated with office BP data during follow-up.

**Discussion**

In this study, we have demonstrated that high-frequency RNS before and after RDN is feasible and safe in patients. In addition, it is suggested that the use of RNS may facilitate prediction of the completeness of RDN and subsequent BP changes after the procedure. The current work describes for the first time the significant association between RNS-induced BP responses during RDN and the clinical ABPM response to RDN at 3 to 6 months after RDN. This reflects the potential of using RNS as a functional test to evaluate the efficacy of renal nerve ablation and predict the clinical outcome of the RDN procedure.

Since the publication of the Symplicity HTN-3 trial, a study that failed to demonstrate BP reduction above and beyond a sham procedure, RDN has been the topic of renewed and ongoing debate. Some have questioned the efficacy of RDN and others sought reasons for the negative findings. It has been argued that the poor efficacy of RDN in Symplicity HTN-3 may be partly explained by suboptimal renal nerve ablation. In contrast, in the recent Renal Denervation for Hypertension (DENERHTN) trial, RDN was performed by a limited number of experienced operators, and drug adjustment was fully standardized, with a moderate but significant overall benefit of RDN on daytime ABPM. A recent meta-analysis by Fadi Elmula et al including all published randomized controlled trials testing RDN against stable or intensified medical treatment showed little if any benefit of RDN. The troubling implication is that the BP benefit directly assignable to RDN may have been substantially overestimated in Symplicity HTN-1 and -2 and other nonrandomized unblinded studies using office BP as primary end point.

RDN is supported by a solid rationale, including reports from the years 1940 to 1960. During those times, radical surgery was performed for renal denervation, successfully lowering BP; however, also in these patients, a percentage appeared to be nonresponders. High-frequency electric stimulation of the sympathetic renal afferent pathways is the most likely cause of the rise in BP induced by RNS. This is because the gradual rise in BP 10 to 20 s after starting RNS is consistent with an increase in adrenergic response through stellate ganglion stimulation in canine studies as reported previously. Experimental studies indicate that the afferent nerves play an important role in the sudden increase in BP in response to RNS. The afferent nerves are involved in the increase of central sympathetic tone. Peripheral RDN has a peripheral sympatholytic effect and alters the level of activation excitation of central noradrenergic pathways, but does not alter sodium or water intake or excretion, plasma renin activity, or creatinine clearance, suggesting that efferent renal nerve function does not play an important role in the maintenance of this form of hypertension. Selective lesioning of the renal afferent nerves attenuates the development of hypertension, thus providing direct evidence that the renal
afferent nerves, at least in part, participate in the pathogenesis of renovascular hypertension. Therefore, RNS influences this BP-regulating mechanism by increasing the central sympathetic tone through an afferent mechanism. The efferent nerve fibers would take more time to increase BP, and renal artery vasoconstriction alone cannot explain a transient increase in BP in the femoral artery where BP was measured. We think that the increase in central sympathetic tone accounts for an increase in systemic vascular resistance. One might argue that pain sensation invokes the increase in BP, but we did not observe an increase in the level of consciousness which would be expected when pain sensation increased greatly. All of the procedures were performed supervised by a cardiac anesthesiologist, ensuring that pain was prevented. This study demonstrates a relationship between the increase in BP before versus after an RDN procedure and the decrease in 24-hour ambulatory BP. It is unlikely that this can be an effect of the ablation of pain fibers surrounding the renal arteries. RNS enables the operator to determine the location of the renal nervous fibers, in which both afferent and efferent fibers are located. Both are to be targeted during an RDN procedure to diminish hypertension. Differences in BP increase are attributed to the differences in distribution of sympathetic nerve fibers in the tunica adventitia of the renal artery. The between-patient differences herein account for differences in response to high-frequency electric stimulation.

Failure to improve BP after RDN may reflect a poor contribution of the renal nerve denervation system to the pathophysiology of hypertension in a particular patient or alternatively failure to ablate a sufficient proportion of sympathetic fibers. Unfortunately, to date, RDN has been performed unguided, mostly using unipolar electrodes, in the absence of a straightforward method, allowing quantification of the renal sympathetic traffic before RDN and assessment of the completeness of renal nerve ablation after RDN. We hypothesized that periprocedural high-frequency RNS could be an attractive candidate to address both issues. One heavily criticized RDN study in the treatment of AF has used this modality in the setting of catheter ablation in patients with atrial fibrillation and hypertension. Although acute RNS-induced BP rise before RDN may reflect the contribution of renal sympathetic nervous system, the difference between RNS-induced BP rise before and after RDN may be a reliable indicator of the efficacy of the RDN procedure. The patient who did not show an increase in BP exceeding 10 mm Hg in response to RNS at any point was a nonresponder with office BP unchanged. This could theoretically be predicted by RNS because no sympathetic overdrive was observed before RDN. More importantly, patients who do show an impressive increase in BP before RDN and still do after RDN might require more extensive ablation. However, this has not been addressed in this explorative study.

Notably, RNS-induced BP changes were better correlated with ambulatory than with office BP, enforcing our belief that true responders to RDN are those defined according to ambulatory BP, which should be used as primary criterion both for patient selection and evaluation of efficacy. The fact that
office BP measurements have not been performed as standardized as the 24-hour ABPM may have played a part as well, leading to overestimation of the effect of white coat hypertension during office measurements.

Our results are in line with the pioneering experimental study of unilateral RDN in dogs by Chinushi et al.16 However, to the best of our knowledge, we are the first to describe this electric stimulation–guided renal nerve mapping technique along with clinical outcome in patients with resistant hypertension.

The presence of an accessory artery might be another explanation why patients fail to respond to regular RDN. Previous reports showed significantly lower BP reduction in patients with accessory arteries that could not be denervated because of small size (<3–4 mm in diameter).34 Because the sympathetic plexus is complex, when the accessory renal artery originates far from the main renal artery, an extra plexus may accompany the accessory artery. The remaining nerve tissue may lead to a possible sympathetic response via this pathway.35

Admittedly, our study has limitations. First, the sample size is small. Second, our study is unblinded and purely observational, and the results may have been obscured by various patient- and physician-related biases. However, the impact of white coat effect was limited by the use of 24-hour ambulatory BP, and other potential confounders, such as changes in drug adherence, have been closely monitored. Finally, although we tried to perform RNS in several quadrants proximally and distally in the renal artery, we cannot exclude that some renal nerves were not stimulated, possibly decreasing the association between RNS and clinical response to RDN. In experimental studies, norepinephrine spillover has been measured to assess efficacy of RDN. A suggestion for future research would be to correlate our findings with norepinephrine spillover or other ways to estimate sympathetic overdrive.

In conclusion, this study demonstrates that the difference between acute RNS-induced BP rise before and after RDN is a significant predictor of BP outcome after RDN, probably because it conveys information on 2 major determinants of BP response to RDN: the importance of renal sympathetic activity at baseline and the completeness of renal nerve ablation after RDN. Future research should aim to demonstrate whether RNS-guided ablation—performed with the goal to decrease as much as possible RNS-induced BP response—allows the procedure to achieve more important and consistent BP decreases than conventional RDN.

**Perspectives**

**Competency in Medical Knowledge**

This study demonstrates that the difference between acute RNS-induced BP rise before and after RDN is a significant predictor of BP outcome after RDN, probably because it conveys information on 2 major determinants of BP response to RDN: the importance of renal sympathetic activity at baseline and the completeness of renal nerve ablation after RDN.

**Competency in Procedural Skills**

RNS may be used as a functional test to identify sympathetic nerve fibers which can be subsequently ablated during an RDN procedure.
Translational Outlook

Future research should aim to demonstrate whether RNS-guided ablation—performed with the goal to decrease as much as possible RNS-induced BP response—allows the procedure to achieve more important and consistent BP decreases than conventional RDN. This would change the procedural approach radically.

Sources of Funding

St Jude Medical (Saint Paul, MN) has provided funds for the EnligHTN system used to deliver electric stimulation and RF energy for ablation. St Jude Medical was not involved in the design of the study, patient recruitment, or data collection/analysis. St Jude Medical provided critical comments.

Disclosures

The authors received research support from St Jude Medical Inc. J.S. Steinberg received research support and consulting fees from Medtronic and Biosense Webster.

References


Novelty and significance

What Is New?

• This study demonstrates for the first time in patients with hypertension that the difference between acute renal nerve stimulation (RNS)–induced blood pressure (BP) rise before and after renal denervation (RDN) is a significant predictor of BP outcome after RDN, probably because it conveys information on 2 major determinants of BP response to RDN: the importance of renal denervation activity at baseline and the completeness of renal nerve ablation after RDN.

What Is Relevant?

• If response RNS proves to be a procedural endpoint, this technique could be used to improve outcome of RDN procedures. The rationale for RDN is strong, however conflicting data on efficacy cause ongoing debate. RNS enables the operator to functionally localize the nervous plexus and fibers, and functionally measure the proportion of elimination of these fibers. Potentially, RNS-guided ablation, allows the procedure to achieve more important and consistent BP decreases than conventional RDN.

Summary

RNS data predict BP data during follow-up. This makes RNS a promising technique to improve RDN procedures. We think that RNS both detects the initial sympathetic overdrive in hypertensive patients and that RNS can be used to determine whether functional sympathetic nerve tissue has been ablated. Further research will show if RNS-guided RDN procedures result in a more extensive BP reduction.
Renal Nerve Stimulation–Induced Blood Pressure Changes Predict Ambulatory Blood Pressure Response After Renal Denervation


Hypertension. published online July 18, 2016; Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2016/07/18/HYPERTENSIONAHA.116.07492

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at: http://hyper.ahajournals.org//subscriptions/