Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension After Witnessed Intake of Medication Before Qualifying Ambulatory Blood Pressure

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Abstract—It is unknown whether the decline in blood pressure (BP) after renal denervation (RDN) is caused by denervation itself or concomitantly improved drug adherence. We aimed to investigate the BP lowering effect of RDN in true treatment-resistant hypertension by excluding patients with poor drug adherence. Patients with resistant hypertension (n=18) were referred for a thorough clinical and laboratory work-up. Treatment-resistant hypertension was defined as office systolic BP >140 mmHg, despite maximally tolerated doses of ≥3 antihypertensive drugs, including a diuretic. In addition, ambulatory daytime systolic BP >135 mmHg was required after witnessed intake of antihypertensive drugs to qualify. RDN (n=6) was performed with Symplicity Catheter System. The mean office and ambulatory BPs remained unchanged at 1, 3, and 6 months in the 6 patients, whereas there was no known change in antihypertensive medication. Two patients, however, had a fall in both office and ambulatory BPs. Our findings question whether BP falls in response to RDN in patients with true treatment-resistant hypertension. Additional research must aim to verify potential BP lowering effect and identify a priori responders to RDN before this invasive method can routinely be applied to patients with drug-resistant hypertension.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01673516.

Key Words: drug adherence • renal sympathetic denervation • treatment-resistant hypertension

Approximately 10% of patients treated for hypertension remain with uncontrolled high blood pressure (BP), despite prescription of antihypertensive drugs. Renal sympathetic denervation has been introduced as a new treatment of hypertension apparently resistant to drug treatment. However, it has been known for decades that poor drug adherence is a major problem among these patients. It is unknown to what degree the decline in BP after renal denervation (RDN) is caused by denervation itself or concomitantly improved drug adherence. We aimed to investigate for the first time the BP lowering effect of RDN in treatment-resistant hypertension after witnessed intake of medication just before qualifying ambulatory BP.

Methods

Study Design and Patients

Patients referred specifically for RDN from hospitals and specialist practices in the southern part of Norway (n=18) after publication of the Symplicity HTN-2 study were worked up in the nephrology outpatient clinic at Oslo University Hospital, Ullevål in the time period from December 2011 through June 2012. Treatment-resistant hypertension was defined as uncontrolled hypertension (office systolic BP >140 mmHg), despite regular intake of maximally tolerated doses of ≥3 antihypertensive drugs, including a diuretic. In addition, patients had to qualify by having mean ambulatory daytime systolic BP ≥135 mmHg immediately after investigator witnessed intake of their antihypertensive morning drugs. Patients were asked to bring their prescribed medication to the clinical visit with one of the investigators (one of the authors of the article). Medication was documented and administered by the investigator and swallowed by the patient under continuous observation, to secure the intake of prescribed medication in prescribed doses. Patients were then continuously under the observation by the investigator to prohibit throwing up again of the pills until 24-hour ambulatory BP device had been mounted and tested out in a somewhat more lengthy procedure than usually to prolong the period of observation. Patients stayed in the hospital for 2 hours to capture those with potential symptomatic hypotension caused by full intake of medication. Visits with subsequent ambulatory BP measurements were done in the morning, and further observation of patients in the hospital was done during working hours.

Plasma and urine metabolites of drugs were not measured because these tests would not have contributed in the present situation. Such tests could have identified the nondrug compliant patients but not secured their intake of medication.
Before the qualifying ambulatory BP measurements, drug treatment was unchanged for 2 weeks and no other changes in medication were planned for the following 6 months. Patients could be 18 to 80 years of age with normal renal arteries at computed tomography or MRI examination within the past 2 years. Patients with estimated glomerular filtration rate <45 mL/min per 1.73 m² (MDRD formula), urine albumin/creatinine ratio >50 mg/mmol, or type 1 diabetes mellitus could not be included in line with the criteria for a randomized study of BP lowering effects of RDN. We compared ambulatory BPs after witnessed intake of the antihypertensive medication with ambulatory BPs taken by the referring physicians in the patients who had normal ambulatory BPs after witnessed intake of medication.

The study was approved by an institution review board (Oslo University Hospital) and all patients received written information and gave consent for publication of the results. All patients who qualified for the procedure within the 7-month time period were included. All expenses were covered by the hospital (public) and patients were not paid.

Procedures
RDN was performed using Symplicity Catheter System (Ardian, Mountain View, CA) by experienced invasive cardiologist/radiologist (P.H.), as described by others with product manager from the manufacturer (Medtronic) present following all steps in the procedure for all patients. Pain was treated with appropriate analgesics. All procedures took between 40 and 50 minutes and were considered successful by both interventionalist and product manager. Patients were hospitalized overnight and followed with office BP measurements at 1, 3, and 6 months and ambulatory BP measurements at 3 and 6 months after the procedure. All patients and all BP measurements were handled by the same experienced physician (F.E.M.F.E.) using the same calibrated and validated devices. Office BPs were taken by Microlife WatchBP O3 (Microlife Health Management Ltd, United Kingdom) and ambulatory BPs were taken by Spacelabs 90217 (Spacelabs Inc, Redmond, WA). Ambulatory BP was measured every 30 minutes during daytime (15 hours) including the first few hours when the patients were observed in the hospital area.

Statistical Analysis
Office and ambulatory BP data are shown as mean and individual values. Formal calculation of $P$ values was not considered necessary.

Results

Patients
Twelve patients were excluded because of reasons described in the flow diagram in Figure 1. Five patients were excluded because they had normal ambulatory BP after witnessed intake of their BP medication just before the qualifying measurement. Three of them were considered to have poor drug adherence inasmuch as they had high ambulatory BPs taken by the referring physicians. Two of them did not have previous ambulatory BPs and we could not discriminate between poor drug compliance and white coat hypertension. None of these 5 patients had symptomatic hypotension during the ambulatory BP measurement period.

The characteristics of the RDN patients (n=6) are further compared with the patients who were excluded from RDN (n=12) in Table 1, and the 2 groups were fairly comparable on demographic characteristics, disease history, and number of antihypertensive drugs.

Table 1. Characteristics of Referred Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noneligible for RDN (n=12)</th>
<th>Eligible for RDN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55 (39–68)</td>
<td>53 (45–67)</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.4 (21.3–34.0)</td>
<td>30.5 (28.4–35.3)</td>
</tr>
<tr>
<td>eGFR&lt;60 mL/min per 1.73 m²</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral arteriosclerosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>5 (3–7)</td>
<td>5 (3–8)</td>
</tr>
</tbody>
</table>

Values of age, body mass index, and No. of antihypertensive drugs represent mean (range); others represent total number of patients. eGFR indicates estimated glomerular filtration rate calculated by the MDRD equation; and RDN, renal denervation.
patient No. 3, and with 11 and 18 mm Hg at 3 and 6 months, respectively, for patient No. 4. Ambulatory daytime systolic BPs decreased with 21 and 13 mm Hg at 3 and 6 months, respectively, for patient No. 3, and with 21 and 27 mm Hg at 3 and 6 months, respectively, for patient No. 4. Patient No. 5 had a rise in ambulatory systolic BP at 6 months and underwent additional MRI examination of the renal arteries which had not changed compared with pretreatment.

Assessment of Responder Rate

Although decreases in BPs in the consecutive patient Nos. 3 and 4 were not large enough to influence the mean office and ambulatory BP readings, the consistent fall in all BP measurements in these 2 patients indicated that they had a true decrease in BP.

Discussion

We investigated 6 patients who had severe hypertension resistant to drug treatment being verified by our witnessed intake of antihypertensive medication immediately before qualifying ambulatory BP measurements. They underwent renal sympathetic denervation using the Symplicity Catheter System. During 6 months of follow-up the group as a whole remained with unchanged office and ambulatory BPs; however, 2 of the 6 patients had consistent lowering of both office and ambulatory BPs and were by us considered to have real decreases in BPs.

The outcome of the Symplicity HTN-2 study has previously been published. A total of 106 patients were randomized to renal sympathetic denervation or control, and office BPs were reduced by 32/12 mm Hg in the intervention group at 6 months and remained unchanged in the control group.

Table 2. Eligibility Work-Up Program

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y/sex</th>
<th>Clinical SBP/DBP, mmHg</th>
<th>Daytime ABPM, mmHg</th>
<th>Eligible</th>
<th>Causes of Noneligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/w</td>
<td>152/82</td>
<td>*</td>
<td>No</td>
<td>Renal artery abnormality</td>
</tr>
<tr>
<td>2</td>
<td>68/m</td>
<td>234/117</td>
<td>*</td>
<td>No</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>3</td>
<td>47/m</td>
<td>150/105</td>
<td>149/99</td>
<td>Yes</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>4</td>
<td>49/m</td>
<td>150/90</td>
<td>145/94</td>
<td>Yes</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>5</td>
<td>56/m</td>
<td>160/90</td>
<td>126/71</td>
<td>No</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>6</td>
<td>52/m</td>
<td>150/118</td>
<td>113/86</td>
<td>No</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>7</td>
<td>49/m</td>
<td>151/89</td>
<td>132/86</td>
<td>No</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>8</td>
<td>63/m</td>
<td>160/93</td>
<td>141/82</td>
<td>No</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>9</td>
<td>49/m</td>
<td>142/88</td>
<td>134/85</td>
<td>No</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>10</td>
<td>45/m</td>
<td>155/105</td>
<td>159/100</td>
<td>Yes</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>11</td>
<td>64/m</td>
<td>163/97</td>
<td>165/98</td>
<td>Yes</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>12</td>
<td>47/m</td>
<td>167/90</td>
<td>147/88</td>
<td>Yes</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>13</td>
<td>53/m</td>
<td>200/100</td>
<td>158/80</td>
<td>No</td>
<td>Chronic autoimmune disease</td>
</tr>
<tr>
<td>14</td>
<td>60/m</td>
<td>170/90</td>
<td>140/83</td>
<td>No</td>
<td>Unstable coronary disease</td>
</tr>
<tr>
<td>15</td>
<td>62/w</td>
<td>143/75</td>
<td>115/67</td>
<td>No</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>16</td>
<td>67/m</td>
<td>162/94</td>
<td>149/90</td>
<td>Yes</td>
<td>Normal ABPM</td>
</tr>
<tr>
<td>17</td>
<td>39/m</td>
<td>216/133</td>
<td>170/120</td>
<td>No</td>
<td>Overt proteinuria</td>
</tr>
<tr>
<td>18</td>
<td>65/m</td>
<td>165/80</td>
<td>*</td>
<td>No</td>
<td>Overt proteinuria</td>
</tr>
</tbody>
</table>

ABPM indicates ambulatory blood pressure; DBP, diastolic blood pressure; m, men; SBP, systolic blood pressure; and w, women.

*ABPM was not done because patient was considered noneligible at screening visit.
†Without tumor, normalized BP with treatment with aldosterone antagonist.
However, the Symplicity HTN-2 study put little emphasis on ambulatory BP measurements opening for at least some whitecoat effect could mask the true benefit of RDN. Furthermore, and probably more important in this context is that drug adherence was not thoroughly investigated in the Symplicity HTN-2 study.2 Recently, in a study of 84 patients taking on average 5 antihypertensive drugs, it was proven by blood measurements of the substances that no drug was detectable in the blood in 34.5% of the patients, and 65.5% of the patients fulfilled the criteria of nonadherence.5 It might well be that patients with poor drug adherence who undergo RDN get so much positive attention at follow-up that their drug adherence gradually improve and explain the BP lowering effects. This phenomenon is not covered by the randomized design of Symplicity HTN-2 study and gives the rationale why the ongoing Symplicity HTN-3 study in the United States includes sham operation.6 It is certainly in deep contrast to the widespread offering of RDN in the clinical routine work of apparent treatment-resistant hypertensive patients in certain places in Europe, in particularly in Germany where there are ≈200 active centers and where there are ≈5000 patients who have undergone the procedure.7

Table 3. Characteristics of the Patients With True Treatment-Resistant Hypertension

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/sex</th>
<th>BMI, kg/m²</th>
<th>Antihypertensive Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46/men</td>
<td>30.2</td>
<td>Nifedipine, furosemide, hydrochlorothiazide, amiloride, and candesartan</td>
</tr>
<tr>
<td>2</td>
<td>48/men</td>
<td>29.3</td>
<td>Candesartan, furosemide, nifedipine, moxonidine, and metoprolol</td>
</tr>
<tr>
<td>3</td>
<td>44/men</td>
<td>32.9</td>
<td>Metoprolol, doxazosin, spironolactone, hydrochlorothiazide, amlodipine, and valsartan</td>
</tr>
<tr>
<td>4</td>
<td>64/men</td>
<td>28.4</td>
<td>Diltiazem, losartan, hydrochlorothiazide, amiloride, and doxazosin</td>
</tr>
<tr>
<td>5</td>
<td>46/men</td>
<td>35.3</td>
<td>Metoprolol, nifedipine, valsartan, moxonidine, doxazosin, hydrochlorothiazide, furosemide, and amiloride</td>
</tr>
<tr>
<td>6</td>
<td>67/men</td>
<td>27.7</td>
<td>Nifedipine, valsartan, and hydrochlorothiazide</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

Drug adherence is a major problem in the treatment of hypertension and it is extensive among patients with apparent resistance to drug treatment.3,4 This is increasing the likelihood that a major part of the BP reduction seen in Symplicity HTN-2 (and uncontrolled studies) can be explained by some or many of the patients starting to take their drugs again in increasing amounts during the course of follow-up for 6 months. It is well known that participating in a study and coming to regular controls is improving the prognosis and it is assumed that this benefit is at least partly explained by better BP control because of improved drug adherence. It adds to the finding that we had to work-up 18 specialist referrals before we found the 6 patients who could participate. The others could not be included partly because their qualifying ambulatory BPs normalized after our witnessed intake of their BP medication. The fact that only a minority of patients are eligible for RDN has been already shown on a much larger scale.8

Our patients had baseline office systolic BP from 150 to 167 mmHg. This is below most patients included in Simplicity. However, our study is quite different from Symplicity-2 because we secured elevated ambulatory daytime systolic BP before RDN. We, therefore, feel that it is difficult to directly compare BP values, but rather look at the principles inasmuch as we for the first time introduced this new aspect with witnessed intake of BP medication to secure the diagnosis of true treatment-resistant hypertension before RDN.
When this is said we had 2 patients who had sustained fall in both office and ambulatory BPs. We believe these 2 patients had true decreases in their BPs; they may have been responders to the renal sympathetic denervation, although we cannot completely rule out the possibility of improved drug adherence also in these 2 patients. They may theoretically have started taking antihypertensive drugs that they were not disclosing at the outset. In light of previous data, this enforces our belief that the method is indicated, in some patients, but that much more research is needed to assess the precise responder rate and at least importantly, identify clinical relevant predictors of who will respond. Symplicity HTN-3 is ongoing in the United States and in the Oslo RDN Randomized Study (Figure 7) we are currently in the process of randomizing patients with true treatment-resistant hypertension in a similar protocol (ie, RDN with the Symplicity Catheter System versus drug treatment which is intensified and guided by noninvasive hemodynamic assessments measured by impedance cardiography). In light of the poor responder rate in the first series of 6 patients with true treatment-resistant hypertension, we will perform an interim analysis and recalculate statistical power.

The effect of RDN on heart rate is also interesting. We believe that also here studies must ensure true treatment-resistant hypertension, which we are doing in our ongoing Oslo RDN Randomized Study (Figure 7). In fact, we like many other centers who are currently doing RDN in prospective protocol-defined studies with regulatory approval are paying special attention to heart rate variability to detect possible a priori responders to RDN.

We have previously investigated the reproducibility of 24-hour BP in patients with newly diagnosed hypertension and reproducibility is reasonably high. Our data in untreated patients cannot automatically be applied to the present population of patients who undergo work-up for apparent treatment-resistant hypertension. However, when seeing our main findings with almost unchanged office and ambulatory BPs for 3 to 6 months after RDN, we believe that we excluded spurious hypertension and poor drug compliance with rather high precision, despite only 1 qualifying measurement of ambulatory BP before RDN.

Regarding plasma and urine metabolites of drugs, these tests were not done as they would not have helped us in the present situation. They could have clarified further details regarding patients who potentially did not take their drugs; however, this has previously been done by others and it was not the aim of the present study.

Regarding white coat hypertension versus low drug compliance, this was neither an aim of our study to elucidate in detail but both groups may have been represented among the patients with normal ambulatory BP after witnessed drug intake.

One may wonder about the physician and patients reactions to the normal ambulatory BPs. However, in light of our long-standing interest in hypertension research including investigating the white coat phenomenon, home BP, and ambulatory BP and the well-known problem with poor drug adherence in patients with apparent treatment-resistant hypertension, we have not made additional scientific observation related to this phenomenon. This also relates to the patients’ reactions inasmuch as these findings were not new to us, but as a curiosity we may mention that one of the patients was referred from another university hospital and had to make airline travel across the country for us to detect normal ambulatory BP after the witnessed drug intake.

![Figure 6. Individual daytime ambulatory systolic blood pressures at baseline and at 6 months after renal denervation (RDN).](http://hyper.ahajournals.org/)
Our hypothesis that BP decrease observed in previous cohorts is partly explained by increased drug adherence remains currently a speculation and may even be counter-intuitive and at odds with observations of patients stopping their drugs after RDN. Further, the BP response of poorly adherent patients to RDN is unknown until more specifically investigated.

**Limitations**

In light of 84% of patients in Symplicity-2 identified as responders with a decrease in systolic BP of ≥10 mm Hg, the likelihood of our negative finding with much more thorough methods of identifying true treatment-resistant hypertensive patients being by chance rather low. Further, the possibility of chance finding must be balanced against the seriousness of the whole issue (i.e., RDN not being done in many countries and particularly in Germany on very loose ground, in fact possibly on misleading ground). We think that our results may contribute to guiding further research in this area in the way that RDN in the future will be done in people with true treatment-resistant hypertension, properly identified, and it will be possible to identify the true responder rate in future larger and ongoing studies.

Our number of patients (n=6) may thus be considered as a limitation. However, they were thoroughly diagnosed before they were included and two thirds of the specialist referrals were excluded from RDN for various reasons with normal ambulatory BP being the most common reason. We posit that these patients in this particular setting contribute with higher precision on true BP-lowering effects than the ≥200 patients undergoing renal sympathetic denervation in Symplicity-1 and -2 studies. The Oslo Group has 40 years of experience in investigating the pathophysiological role of sympathetic nervous system in hypertension, performing randomized clinical trials in patients with hypertension and diagnosing spurious hypertension, and we feel that the power of commercial marketing has by far overtaken the ethical considerations and principles of evidence-based medicine in the context of getting RDN done in Germany and some other places in Europe. Renal sympathetic denervation in hypertensive patients is also hampered by multiple other insufficiencies, but we limit our conclusion to question whether there is a BP lowering effect of this new invasive procedure.

**Perspectives**

We did the first ever study of renal sympathetic denervation in patients with true treatment-resistant hypertension after witnessed intake of BP medication and both office and ambulatory BP remained unchanged >6 months. Much more research has to be done in patients with true and verified treatment-resistant hypertension to find out whether this new method truly lowers BP. It is very unlikely that all patients with true treatment-resistant hypertension will respond with fall in BP, and potential predictors of BP lowering response must be clarified before this invasive method is applied in routine treatment of all people with apparent treatment-resistant hypertension.

**Sources of Funding**

The study was entirely funded by Oslo University Hospital and the public health system in South-Eastern Norway Health Authority. The renal denervation procedure was in all patients overseen by a product manager from Medtronic, the manufacturer of the Symplicity Catheter System.

**Disclosures**

Dr Fadl Elmula has received lecture honoraria from Medtronic. Dr Kjeldsen has received lecture honoraria from AZ, Bayer, Medtronic, MSD and Takeda, honoraria for consulting from Bayer, Medtronic, Takeda and Seromed, and research support from AZ and Pronova. Dr Høieggen has received lecture honoraria from Amgen, AZ, Novartis and St. Jude. The other authors report no conflicts.

**References**

Novelty and Significance

What Is New?

- Renal sympathetic denervation has become widespread for the treatment of apparent treatment-resistant hypertension in Europe and particularly in Germany where there are >200 active centers and 5000 patients who have undergone the procedure.
- We investigated for the first time the blood pressure (BP) lowering effects of renal denervation (RDN) in patients with true treatment-resistant hypertension.

What Is Relevant?

- In patients who qualified by having elevated ambulatory systolic BP (>135 mm Hg) after witnessed intake of their BP lowering medication (n=6) both mean office and ambulatory BPs remained unchanged up to 6 months after RDN.
- Two patients had a decline in office and ambulatory BP and they could potentially be responders.

Summary

When we, for the first time, investigated the BP lowering effect of RDN in patients with elevated ambulatory BP documented immediately after witnessed intake of the antihypertensive drugs, we could detect no change in neither office nor ambulatory BPs for 6 months.

RDN for treatment-resistant hypertension is still an experimental procedure. Much more research must be performed to find the responder rate and predictors of who will benefit from this invasive procedure.

We feel that the power of commercial marketing has by far overtaken the ethical considerations and principles of evidence-based medicine in the context of getting RDN done in Germany and some other places in Europe, and the routine use of RDN for apparent treatment-resistant hypertension must pause at least temporarily.
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