Residual Effect of Renal Denervation in Patients With Truly Resistant Hypertension

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See related article, pp 526–532

The SYMPLICITY investigators reported a 25- to 30-mm Hg decrease in office systolic blood pressure 6 to 12 months after renal sympathetic denervation in patients with resistant hypertension.1,2 In the SYMPLICITY studies,1,2 resistant hypertension was a systolic blood pressure of ≥160 mm Hg (150 mm Hg in patients with diabetes mellitus) on treatment with ≥3 different classes of antihypertensive drugs.1,2 This definition of resistant hypertension complies with current guidelines3 but is weak and urgently needs revision.4 Indeed, patients categorized as being apparently resistant according to this generic definition often cumulate clinical conditions that do not justify renal denervation as the preferred treatment option. These conditions include white-coat hypertension,5 poor adherence,6 suboptimal drug treatment, undiagnosed secondary hypertension,7 and isolated systolic hypertension in the elderly, a highly prevalent and difficult to treat form of hypertension driven by arterial stiffening rather than enhanced sympathetic drive.7 Neither the SYMPLICITY studies nor most nonrandomized observational reports published subsequently8 implemented a systematic strategy for differentiating between truly resistant hypertension and conditions that might benefit from an alternative approach, such as addressing the specific cause of the blood pressure elevation or optimizing lifestyle, drug treatment, or adherence.

Before the rediscovery9 of sympathetic denervation as a way to treat high blood pressure in certain conditions, hypertension specialists supported the adagio that while accounting for all aforementioned factors and using currently available classes of long-acting blood pressure–lowering drugs with few side effects, all forms of hypertension could be properly treated. Catheter-based renal denervation certainly builds on the pioneering research and solid evidence from basic studies, as published by Esler10 and DiBona11 during the past 20 years. However, recent publication of several small uncontrolled studies in high-ranking journals are not helpful in overcoming the current lack of evidence in support of renal denervation as a treatment option in resistant hypertension. Although anecdotal, the recent case report of renal denervation performed in a patient with Munchausen syndrome12 exemplifies how unsubstantiated expectations are replacing sound medical reasoning.

Given the context described above, the pilot study by Fadl Elmula et al13 breaks new grounds and should be an eye opener for those who believe that renal denervation is a miracle treatment, one size fitting all patients. In the report of Fadl Elmula et al, resistant hypertension was an office systolic blood pressure of ≥140 mm Hg in patients on treatment with the maximally tolerated doses of ≥3 antihypertensive drugs, including a diuretic. Specialists referred 18 patients with resistant hypertension to the Oslo center for renal denervation. Of those referred, 12 did not meet the criteria of resistant hypertension for various reasons, including primary aldosteronism (n=1), renal artery abnormality (n=1) and, notably, a normalized ambulatory blood pressure monitoring after witnessed drug intake (n=5). In the 6 patients who finally complied with all eligibility criteria for renal denervation, the conventional and ambulatory blood pressures did not significantly decrease up to 6 months after renal denervation, and the number of blood pressure–lowering drugs to be taken remained unchanged. Only 2 patients showed a consistent blood pressure decrease on conventional and ambulatory measurement, whereas 1 patient had an increase in his ambulatory blood pressure.

The small Norwegian study confirms the results of a larger scale French report,14 which shows that after careful screening, only a minority of patients with so-called resistant hypertension are eligible for renal denervation. Moreover, the Norwegian data are in agreement with the absence of a significant 24-hour ambulatory blood pressure decrease (Table) reported in at least 3 other studies.15–17 In one study,17 individual blood pressure changes between baseline and 6 months (Figure) confirm the high variability of office blood pressure responses and absence of mean change in ambulatory blood pressure. As suggested by Fadl Elmula et al,13 the more convincing results observed in the SYMPLICITY studies1,2 and subsequent observational studies8 may be explained by improved drug compliance after renal denervation, but also placebo and Hawthorne effects and regression to the mean.4

What would have been the blood pressure outcome of the numerous small studies looking for the benefits of renal denervation, should the thorough screening procedure of Fadl
Elmula et al\(^{13}\) have been applied? Whether the evidence from many additional small observational studies looking for benefits of renal denervation on office blood pressure in different patient subsets will be strong enough to guide clinical practice is doubtful. As suggested by the Norwegian researchers, research efforts should focus on randomized controlled clinical trials assessing the efficacy and safety of renal denervation in selected patients, as well as on independent registries searching for the determinants of blood pressure responses, as assessed by ambulatory monitoring. In the meantime, renal

### Table. 24-Hour Ambulatory Blood Pressure Before and 6 Months After Renal Denervation

<table>
<thead>
<tr>
<th>Studies</th>
<th>Inclusion Criteria</th>
<th>No. of Patients</th>
<th>24-h Blood Pressure at Baseline</th>
<th>24-h Blood Pressure at 6 mo(^*)</th>
<th>(\Delta) Systolic/Diastolic BP, 0–6 mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPPLICITY HTN-1(^{1})</td>
<td>aRHTN or drug intolerance</td>
<td>12</td>
<td>nr</td>
<td>nr</td>
<td>10–11†/nr</td>
<td>nr</td>
</tr>
<tr>
<td>SYMPPLICITY HTN-2 (patients randomized to renal denervation)(^{2})</td>
<td>aRHTN</td>
<td>20</td>
<td>nr</td>
<td>nr</td>
<td>11/7</td>
<td>0.006/0.014</td>
</tr>
<tr>
<td>Witkowski et al 2011(^{15})</td>
<td>aRHTN</td>
<td>10</td>
<td>140/82</td>
<td>134/nr</td>
<td>6/nr</td>
<td>ns</td>
</tr>
<tr>
<td>Hering et al 2012(^{16})</td>
<td>OSA</td>
<td></td>
<td>159/85</td>
<td>154/79</td>
<td>5/6</td>
<td>0.24/0.08‡</td>
</tr>
<tr>
<td>Hering et al 2012(^{16})</td>
<td>aRHTN stage 3–5 CKD</td>
<td>15 (8 at 6 mo)</td>
<td>159/85</td>
<td>154/79</td>
<td>5/6</td>
<td>0.24/0.08‡</td>
</tr>
<tr>
<td>Zuern et al 2012(^{17})</td>
<td>aRHTN</td>
<td>11</td>
<td>149/82</td>
<td>142/79</td>
<td>7/3</td>
<td>0.086/0.167</td>
</tr>
<tr>
<td>Fald Elmula et al 2013(^{13})</td>
<td>RHTN</td>
<td>6</td>
<td>152/95</td>
<td>148/92</td>
<td>4/3</td>
<td>ns</td>
</tr>
</tbody>
</table>

\(a\)RHTN indicates apparently resistant hypertension; BP, blood pressure (mm Hg); \(\Delta\)BP (0–6 mo), blood pressure difference between baseline and 6 mo; CKD, chronic kidney disease; nr, not reported; ns, not significant; OSA, obstructive sleep apnea; and RHTN, truly resistant hypertension after witnessed intake of drugs.

\(^*\)\(>3\) mo for Symplicity HTN-1.

\(^{†}\)11 in 9 responders; 10 in 3 nonresponders.

\(^{‡}\)Provided only for 3 mo.

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**Figure.** Office blood pressure (BP) and ambulatory blood pressure (ABPM) at baseline and 6 months after renal denervation (RDN) in a cohort of 11 consecutive patients with drug-resistant hypertension. (Figure as originally published in Zuern CS, Rizas KD, Eick C, Stoleriu C, Bunk L, Barthel P, Balletshofer B, Gawaz M, Bauer A. Effects of renal sympathetic denervation on 24-hour blood pressure variability. Front Physiol. 2012;3:1–8. doi: 10.3389/fphys.2012.00134.)
denervation should remain the ultima ratio, that is the last option to be offered to patients with resistant hypertension, after all efforts to normalize blood pressure in expert centers have failed.4

Disclosures
M. Azizi has received adviser fees from Cordis and Boston Scientific. M. Burnier has received lecturer fees from Medtronic. The other authors report no conflicts.

References