

## Renal Denervation Therapy for Hypertension

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### Clinical Vignette

An overweight 78-year-old man with hypertension treated with spironolactone (50 mg daily), amlodipine (10 mg daily), lisinopril (40 mg daily), and extended-release metoprolol (200 mg daily), intolerant of multiple antihypertensives including clonidine (dry mouth) and hydralazine (diarrhea), is referred for renal sympathetic denervation (RSDN). He reports dietary and medication compliance. Secondary causes of hypertension have been excluded. Blood pressure (BP) is 184/93 mmHg.

### Background

Hypertension remains a major modifiable risk factor associated with cardiovascular morbidity and mortality.<sup>1</sup> Resistant hypertension is defined as BP $\geq$ 160/100 mmHg, despite maximally tolerated doses of  $\geq$ 3 classes of antihypertensives, including a diuretic, without secondary hypertension (eg, renovascular hypertension, chronic kidney disease, mineralocorticoid excess, or obstructive sleep apnea).<sup>2</sup> Recently, the prevalence of resistant hypertension in patients with atherosclerosis was reported to be 12.7%.<sup>3</sup> It is associated with a high risk for future adverse cardiovascular events.<sup>4</sup>

### The Rationale for Renal Sympathetic Denervation

Sympathetic hyperactivity promotes hypertension (Figure 1). In hypertensive rats demonstrating renal sympathetic hyperactivity, renal efferent denervation delays the onset and lessens the severity of hypertension.<sup>5</sup> Renal afferent denervation through dorsal rhizotomy mitigates hypertension.<sup>6</sup> Following renal transplantation, sympathetic hyperactivity continues until the diseased kidneys are excised; BP improvement typically follows.<sup>7</sup> The BP reduction following renal excision provides evidence that detrimental sympathetic signals originate from diseased kidneys.<sup>8</sup>

### Early Surgical Experience and Contemporary Innovation

Before modern pharmacotherapy, malignant hypertension had a  $\approx$ 100% mortality at 5 years.<sup>9</sup> Radical sympathectomy was used and RSDN was achieved, albeit nonselectively. In an observational study of 1266 patients undergoing sympathectomy in comparison with 467 treated conventionally, improved survival rates and BP control were demonstrated with surgery.<sup>10</sup> With high operative mortality and adverse effects including orthostatic hypotension and sexual dysfunction,

sympathectomy was abandoned as effective antihypertensives emerged.

By specifically interrupting renal sympathetics, catheter-directed RSDN theoretically offers durable BP reduction without detrimental consequences. This strategy is feasible because renal sympathetic efferents and afferents are closely juxtaposed within the renal artery adventitia.

The radiofrequency (RF) ablation RSDN catheter has been the focus of clinical investigation. In principle, RF ablation heats the underlying tissue, destroying adventitial nerves. Nociceptive C fibers are affected, making adequate analgesia imperative. Following renal angiography to exclude anatomic contraindications, bilateral RSDN is performed by first placing a guiding catheter in the renal artery; the RF catheter is then positioned in the renal artery and energy is applied. Multielectrode catheters, simplifying the procedure by making it faster and less painful, have supplanted initial single-tipped electrode catheters. Further technological refinements are ongoing.<sup>11</sup>

### RSDN Clinical Trial Data

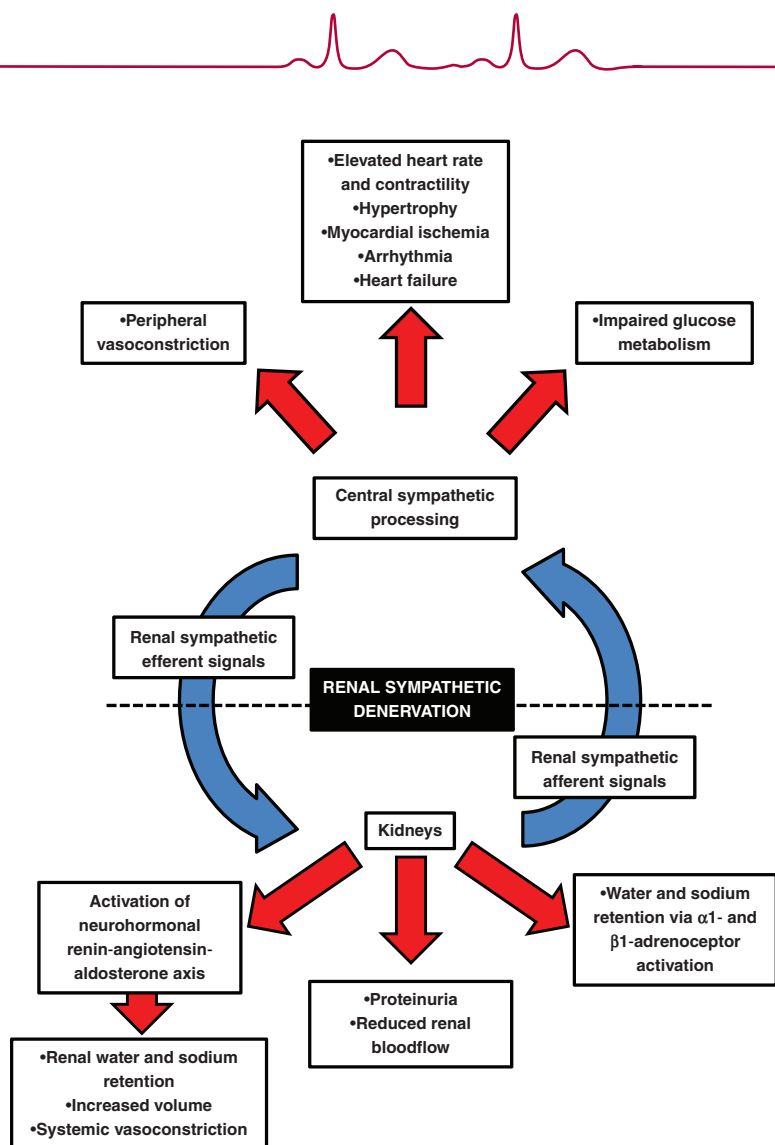
In Symplicity HTN-1, the proof-of-concept study using the Symplicity (Medtronic, Minneapolis, MN) catheter,

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**Figure 1.** Systemic effects of sympathetic nervous system hyperactivity.

initially in 45 patients with resistant hypertension, defined as systolic BP  $\geq 160$  mmHg on  $\geq 3$  antihypertensives at maximally tolerated doses, significant BP reductions were noted and appeared durable up to 36 months of follow-up.<sup>12,13</sup> Treatment response, defined as a fall in systolic BP  $\geq 10$  mmHg, appeared to increase over time as well. Total body and renal norepinephrine production were reduced. No significant renal artery stenoses were noted on follow-up. Adverse events included 1 renal artery dissection induced by the guiding catheter before RF ablation and 3 femoral artery pseudoaneurysms. Although encouraging, this small study lacked controls and relied upon office rather than ambulatory BP.

The Symplicity HTN-2 trial, an expanded efficacy study, randomly assigned 106 patients with similar inclusion criteria for resistant hypertension (including  $\geq 150$  mmHg for diabetic patients) to RSDN or medical therapy to assess office BP at 6 months.<sup>14</sup> Crossover from the medical arm was then permitted. At 6 months, BP decreased significantly in the RSDN group only. A total of 84% of RSDN patients showed a decrease in systolic BP  $\geq 10$  mmHg. The effect was durable at 12 months; at this time, the crossover patients demonstrated a similar BP decrement.<sup>15</sup> Adverse events were infrequent, comprising 1 femoral artery pseudoaneurysm, 1 case of postprocedural hypotension requiring

a reduced antihypertensive dose, and 7 cases of intraprocedural bradycardia necessitating atropine. Two-year data demonstrated continued durability.<sup>16</sup>

The Symplicity HTN-2 study had important limitations. Ambulatory systolic BP was reduced by 11 mmHg versus the 32 mmHg reduction in office BP, perhaps as a result of unrecognized white coat hypertension. Secondary hypertension was not systematically excluded. Potential placebo effects and measurement bias, owing to the lack of sham controls, remained possibilities. Symplicity HTN-3, a randomized, single-blinded trial of 500 patients incorporating a sham procedural arm, more rigorous screening, and ambulatory BP monitoring, has recently completed enrollment.<sup>17</sup>

Beyond severe resistant hypertension, the next frontier for the evaluation of RSDN will likely be moderate resistant hypertension. Pilot studies have already been published showing the safety and relative efficacy in this population.<sup>18–21</sup> The Symplicity HTN-4 trial, focusing on moderate treatment-resistant hypertension, has recently been announced (refer potential patients to sites listed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)).<sup>22</sup>

Other catheter-based systems are being investigated in resistant hypertension. The first-in-man study using the EnligHTN catheter (St. Jude Medical, St. Paul, MN) configured with 4 RF electrodes was recently published with encouraging data.<sup>23</sup> The use of RSDN to treat heart failure,<sup>24</sup> ventricular and atrial arrhythmias,<sup>25,26</sup> glucose intolerance,<sup>27</sup> and obstructive sleep apnea<sup>28</sup> is being evaluated. Pulmonary artery denervation as an adjunctive treatment for pulmonary hypertension is also intriguing.<sup>29</sup>

### RSDN in Clinical Practice

RSDN has been approved and is being used in Europe and Australia; it is still investigational in the United States. Although its use in treating moderate treatment-resistant hypertension and even mild hypertension has been reported,<sup>18,19</sup> a European Society of

Cardiology consensus statement recommends that patients conform with the inclusion and exclusion criteria of the clinical trials after undergoing intensive screening (Figure 2).<sup>30</sup> Monitoring thereafter is advised, because renal artery stenosis has been reported following RSDN, and sympathetic reinnervation is a possibility.<sup>31</sup>

### Conclusion

For patients with resistant hypertension unable to be controlled with medications, RSDN represents an

intriguing and potentially cost-effective approach, obviating the current limitations associated with medical therapy.<sup>32</sup> Although available data suggest that RSDN is associated with durable BP reduction in select patients, long-term safety and efficacy data, including its effect on clinically relevant end points, are still required. Until then, in parts of the world where it is available, this innovative technology should be used with caution and in patients with severe resistant hypertension only.

### Clinical Vignette Conclusion

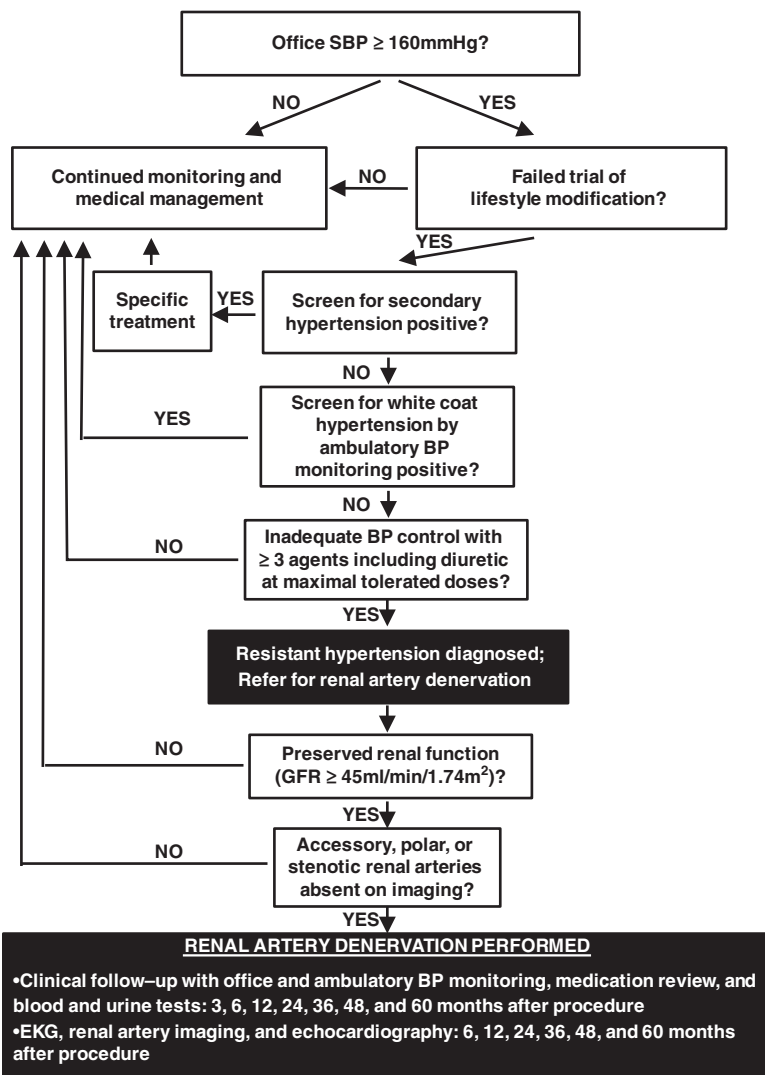
Renal angiography demonstrated no anatomic contraindications and RSDN was performed at a center in Europe without complications. After 1 month, BP was 162/87 mmHg on his original regimen. At 6 months, his BP was 158/80 mmHg, and a renal artery duplex ultrasound study did not show renal artery stenosis. He was advised to follow up in 6 months and was reminded that, despite successful RSDN, continued compliance with his medical regimen would be essential.

### Disclosures


Dr Bhatt discloses the following relationships: Advisory Board: Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Get With The Guidelines Steering Committee; Honoraria: American College of Cardiology (Editor, Clinical Trials, Cardiosource), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), WebMD (CME steering committees); Other: Senior Associate Editor, Journal of Invasive Cardiology; Data Monitoring Committees: Duke Clinical Research Institute; Harvard Clinical Research Institute; Mayo Clinic; Population Health Research Institute; Research Grants: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic (for his role as co-principal investigator of Symplicity HTN-3 and on the steering committee of Symplicity HTN-4), Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda. Dr Thukkani reports no conflicts.

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**Figure 2.** The evaluation of patients with resistant hypertension based on recent guidelines.<sup>30</sup> BP indicates blood pressure; EKG, electrocardiogram; GFR, glomerular filtration rate; and SBP, systolic blood pressure. Copyright © 2013, Oxford University Press. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

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