Despite significant improvements in diagnosis and pharmacotherapy, arterial hypertension remains a global health problem. The development of new antihypertensive drugs has not provided a satisfactory benefit. Resistant hypertension (defined as the failure to reach goal blood pressure [BP] in patients adhering to full doses of an appropriate three-drug regimen including a diuretic) is still diagnosed in approximately 13% of patients. This subgroup of patients has an increased risk of cardiovascular and renal events and requires additional therapy options. One of these options may be the renal denervation (RDN) method, which is based on the attenuation of a great contributor to the pathogenesis of arterial hypertension—the sympathetic nervous system.

Both animal experimental models and human studies have proven the role of sympathetic renal nerves in hypertension development and perpetuation. The activation of efferent nerves results in increased renin release, tubular sodium reabsorption, and reduced renal blood flow. The afferent sympathetic fibers originating from the kidneys modulate central sympathetic outflow, thus directly modifying neurogenic hypertension.

Surgical sympathectomy was introduced in the 1930s with good clinical effect. However, splanchnicectomy or posterior thoracolumbar sympathectomy was associated with numerous side effects, such as orthostatic hypotension, tachycardia, and bladder, bowel, and erectile dysfunctions. High perioperative mortality and complication rates led to the abandonment of this method of treatment. On the other hand, the favorable location of both afferent and efferent nerves adjacent to the adventitia of the renal arteries enabled the endovascular approach and selective, minimally invasive RDN.

PERCUTANEOUS RDN
Percutaneous RDN is achieved via the renal artery lumen using the Symplicity renal denervation system (Ardian, acquired by Medtronic, Inc., Minneapolis, MN), which consists of the 5-F Symplicity catheter and Symplicity (RF) generator. Under local anesthesia and using the routine femoral approach, the Symplicity catheter is advanced into the distal part of the renal artery trunk (proximal to the bifurcation) through a 6-F guiding catheter inserted into the renal artery ostium. Low-powered (5–8 W) RF ablations are then applied for up to 2 minutes. Sequential catheter retraction and rotation enables achievement of up to six ablations separated longitudinally and rotationally within the trunk of each renal artery (Figure 1). Catheter tip impedance and temperature are constantly recorded, and energy delivery is performed according to the predefined algorithm. During the procedure, unfractionated heparin is administered to maintain adequate anticoagulation (activated clotting time > 250 seconds), whereas analgesics and sedatives manage the visceral abdominal pain accompanied with the procedure.

RESULTS OF CLINICAL STUDIES
After animal studies were performed confirming the safety and efficacy of RDN, a “proof-of-concept” trial was conducted and published in The Lancet in 2009. In that study, 50 patients with resistant hypertension (defined as systolic BP ≥ 160 mm Hg on three or more antihypertensive drugs [including diuretics]) were recruited. The procedure was performed in 45 adult patients with eligible renal arterial anatomy (trunk of at least 4 mm in diameter and 20 mm in length) and not meeting the following exclusion criteria: an estimated glomerular
filtration rate (eGFR) < 45 mL/min per 1.73 m², type 1 diabetes mellitus, renovascular abnormalities including multiple main renal arteries, previous angioplasty, and hemodynamically significant renal artery stenosis or a known secondary cause of hypertension other than sleep apnea or chronic kidney disease.

RDN resulted in a significant reduction of systolic/diastolic BP after 1, 3, 6, and 12 months (-14/-10, -21/-10, -22/-11, and -27/-17 mm Hg, respectively). In a subgroup of 10 patients, total norepinephrine outflow from the kidneys into the circulation (ie, norepinephrine spill-over), as assessed with the radiotracer dilution method, was impressively reduced by 47% and clearly confirmed a substantial degree of efferent nerve denervation consistent with BP response.

The median duration of the procedure was 38 minutes. Two adverse events were reported (one renal artery dissection and one femoral artery pseudoaneurysm), but they were not directly related to energy application. Follow-up imaging after 1 and 6 months did not show any substantial abnormalities such as renal artery stenosis or aneurysm.

After demonstrating the safety and initial efficacy of the procedure, the first randomized trial, Symplicity HTN-2, was designed. In that trial, similar inclusion/exclusion criteria were established, except when diuretic treatment was necessary. One hundred six patients aged 48 ± 12 years with a mean office BP of 178/98 mm Hg on 5.3 antihypertensive medications were randomly assigned to RDN (52 patients) or to a control group (54 patients). More than 70% of patients have been pharmacologically treated for at least 5 years. It is of note that no sham operation was performed in the control group.

The 6-month follow-up data were obtained from 49 RDN patients and 51 control patients. A significant reduction of the office BP at each follow-up interval was achieved, with a -32/-12 mm Hg reduction after 6 months as compared to no changes in the control group. At least 10 mm Hg of BP reduction was achieved in 84% of patients; no reduction was observed only in 10% of the treated group. In 20 patients, 24-hour BP recordings were available—the reduction in BP after 6 months was -11/-7 mm Hg with minor changes (-3/-7 mm Hg) in the control group. Similarly, the BP in home self-measurements decreased in patients by -20/-12 mm Hg in comparison to a mild increase of 2/0 mm Hg in the control group.6

In May 2011, the longer-term follow-up data of the extended group of 153 patients (including the initial cohort of 45 patients from proof-of-concept study) who were treated with RDN in a nonrandomized manner were reported as Symplicity HTN-1 trial results.7 The mean age of patients was 57 ± 11 years, and baseline office BP was 176/98 mm Hg despite treatment with a mean of five antihypertensive medications. Postprocedural office BPs were reduced by -20/-10, -24/-11, -25/-11, -23/-11, -26/-14, and -32/-14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively. Therefore, the findings of this study confirmed the durability of the therapeutic effect of RDN, with sustained BP reduction up to 2 years after the procedure. However, a 24-month reduction has only been observed in a few patients who accomplished entire follow-up. The lack of any attenuation of BP reduction during the follow-up period suggests no nerve regrowth or functional recovery, as well as no development of counterregulatory BP-elevating mechanisms; that is of considerable clinical and pathophysiological relevance.
The largest randomized trial, Symplicity HTN-3, with similar eligibility criteria but including a sham treatment, has just started the recruitment phase and is going to include 530 patients with uncontrolled hypertension at sites in the United States.8

SAFETY OF THE PROCEDURE

The acute procedural complications reported in both Symplicity trials (HTN-1 and HTN-2, 205 procedures) included three groin pseudoaneurysms (treated with manual compression) and one renal artery dissection that was managed with stent implantation without further sequelae. It is noteworthy that all groin complications occurred in patients who were treated with the first-generation Symplicity catheter, which requires an 8-F introducer sheath. Brachycardia during application was reported in 22 patients (10.7%) and was sufficiently managed with atropine. Long-term side effects included transient dizziness (six patients), pitting edema (three patients), and bilateral flank pain (four patients).

In the 81 patients with 6-month noninvasive imaging data, no irregularities or new stenoses at any treatment site were found. One patient had progression of a pre-existing renal artery stenosis in the proximal segment of the renal artery. This stenosis was successfully stented; however, the location of the stenosis was quite distant from the sites of RF energy delivery, suggesting no relationship to the RDN. Two patients died within the follow-up period due to cardiovascular events. Neither death was considered by the study investigator or Data Safety Monitoring Board to be attributed to the device or the procedure.

The Impact of RDN on Kidney Function

The mean of eGFR in Symplicity HTN-2 was 77 ± 19 mL/min/1.73 m² and was 83 ± 20 mL/min/1.73 m² in HTN-1. No significant changes in kidney function parameters after 6 months were observed, as presented in Table 1. However, in the first 10 patients within a 2-year follow-up period, an eGFR reduction by 16 mL/min/1.73 m² was noted. This observation requires further attention in subsequent patients at a longer follow-up period.

OTHER POTENTIAL INDICATIONS FOR RDN

Activation of the sympathetic nervous systems contributes to insulin resistance9 and is associated with central obesity,10 and an increased risk of diabetes melitus11 and metabolic syndrome.12 Early results indicate that the glucose metabolism can be favorably influenced by RDN.13 In a study of 50 patients (37 of whom underwent RDN), significant BP reduction was accompanied by substantial glucose and insulin concentration decrease and distinct improvement in insulin sensitivity.

In our center, we evaluated the effects of this procedure on BP and sleep apnea severity in 10 patients with resistant hypertension and sleep apnea. At 6 months, a decrease in the apnea-hypopnea index in polysomnography was noted. Interestingly, significant decreases were also observed on plasma glucose concentration 2 hours after glucose administration and in hemoglobin A1c level.14

RDN could also probably be beneficial in patients with congestive heart failure characterized by increased sympathetic activity. In previous studies, muscle sympa-

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**TABLE 1. CHANGES IN BP AND KIDNEY FUNCTION PARAMETERS 6 MONTHS AFTER RENAL DENERVATIONa**

<table>
<thead>
<tr>
<th>Trial (No. of Subjects)</th>
<th>Clinical Efficacy</th>
<th>Kidney Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic BP (mm Hg)</td>
<td>Diastolic BP (mm Hg)</td>
</tr>
<tr>
<td>Symplicity HTN-1 patients (86)</td>
<td>-25</td>
<td>-11</td>
</tr>
<tr>
<td>Symplicity HTN-2 patients (49)</td>
<td>-32</td>
<td>-12</td>
</tr>
<tr>
<td>Symplicity HTN-2 controls (51)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

aData from Symplicity HTN-1 and HTN-2 trials (modified).
bAssessed in 37 patients and 40 controls.
cAssessed in 38 patients and 37 controls.
Abbreviations: ND, not done.
Both the HTN-1 and HTN-2 studies proved safety and long-term efficacy of RDN using radiofrequency percutaneous ablation.

Sympathetic nerve activity assessed on microneurography was related to heart failure severity. A preliminary case report demonstrated substantial reduction of muscle sympathetic nerve activity in a patient with resistant hypertension. Both the HTN-1 and HTN-2 studies indicated a potential benefit from RDN in individual patients with heart failure and concomitant life-threatening ventricular arrhythmia resistant to conventional pharmacotherapy.

Other Devices for RDN

A recent study demonstrated the potential feasibility of a standard RF ablation catheter (7-F Mariner catheter, Medtronic, Inc.) in an RDN procedure. Twelve patients (mean age, 62 ± 14 years) with drug-resistant hypertension underwent RDN using low-powered RF applications in a similar fashion as with the Symplicity catheter. The mean reduction of 24-hour ambulatory BP was −11/−7 mm Hg at 1 month and −24/−14 mm Hg at 3 months, with unchanged medication and no vascular complications in the short-term follow-up. The preliminary results indicated that the use of a standard RF ablation catheter may be also feasible and safe for sympathetic RDN, but obviously, larger trials with longer follow-up periods should be conducted.

The other potential method of treatment is pharmacological local RDN. The Bullfrog microinfusion catheter (Mercator MedSystems, Inc., San Leandro, CA) is composed of a catheter tipped with a balloon-sheathed microneedle. After advancement of the catheter into the renal artery, the balloon is inflated with saline, securing the system for injection and sliding the microneedle through the vessel wall. Then, guanethidine (the drug causing localized sympathectomy) is delivered through the vessel wall into the adventitia. This method allows for direct, highly controllable, and concentrated treatment, minimizing the toxicity of systemic drug administration, the minimal experimental studies in porcine models showed successful drug delivery, no negative effect on vascular architecture, and a significant reduction in renal norepinephrine content.

CONCLUSION

RDN is an alternative option for patients with resistant hypertension. Both the HTN-1 and HTN-2 studies proved safety and long-term efficacy of RDN using radiofrequency percutaneous ablation. Other future clinical applications include diabetes, obstructive sleep apnea and heart failure. New devices for RDN are pending.

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