Novel strategies for treatment of resistant hypertension

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Resistant hypertension, defined as blood pressure (BP) remaining above goal despite the use of 3 or more antihypertensive medications at maximally tolerated doses (one ideally being a diuretic) or BP that requires 4 or more agents to achieve control, occurs in a substantial proportion (>10%) of treated hypertensive patients. Refractory hypertension is a recently described subset of resistant hypertension that cannot be controlled with maximal medical therapy (⩾5 antihypertensive medications of different classes at maximal tolerated doses). Patients with resistant or refractory hypertension are at increased cardiovascular risk and comprise the target population for novel antihypertensive treatments. Device-based interventions, including carotid baroreceptor activation and renal denervation, reduce sympathetic nervous system activity and have effectively reduced BP in early clinical trials of resistant hypertension. Renal denervation interrupts afferent and efferent renal nerve signaling by delivering radiofrequency energy, other forms of energy, or norepinephrine-depleting pharmaceuticals through catheters in the renal arteries. Renal denervation has the advantage of not requiring general anesthesia, surgical intervention, or device implantation and has been evaluated extensively in observational proof-of-principle studies and larger randomized controlled trials. It has been shown to be safe and effective in reducing clinic BP, indices of sympathetic nervous system activity, and a variety of hypertension-related comorbidities. These include impaired glucose metabolism/insulin resistance, end-stage renal disease, obstructive sleep apnea, cardiac hypertrophy, heart failure, and cardiac arrhythmias. This article reviews the strengths, limitations, and future applications of novel device-based treatment, particularly renal denervation, for resistant hypertension and its comorbidities.

Kidney International Supplements (2013) **3,** 357–363;
doi:10.1038/kisup.2013.77

KEYWORDS: blood pressure; denervation; device; hypertension; renal; refractory; resistant; therapy; treatment

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Despite the availability of a large variety of pharmacologic agents that, alone and in combination, are highly effective in lowering blood pressure (BP), >10% of hypertensive patients cannot be controlled with drug treatment and lifestyle modification alone.[1] Resistant hypertension, defined as BP remaining above goal despite the use of three or more antihypertensive medications at maximally tolerated doses (one ideally being a diuretic) or BP that requires four or more agents to achieve control, occurs in approximately 13% of treated hypertensive patients in the United States.[1,2] Further, patients with refractory hypertension, a subset of those with resistant hypertension, have BP that cannot be controlled with maximal medical therapy (⩾5 antihypertensive medications of different classes at maximal tolerated doses).[3] Refractory hypertension accounts for 2–3% of all treated hypertensives and 6% of resistant hypertensives.[3] As patients with resistant hypertension and, in particular, those with refractory hypertension, are at greatly increased cardiovascular disease (CVD) risk, they are in urgent need of novel approaches for BP lowering.

Emerging therapies for resistant hypertension include efforts to modulate epigenetic regulation of genes involved in BP homeostasis, novel pharmacologic agents, and device-based interventions, including baroreceptor activation and renal denervation (RDN) therapy.[4–6] Although several new pharmacologic agents have shown promise in preclinical models, their clinical development has been more difficult and less productive than expected.[6] In contrast, the device-based therapies, particularly RDN, have been shown to be effective in reducing BP of patients with resistant hypertension in early clinical trials. This article will focus on device-based therapies, particularly RDN, in the treatment of resistant hypertension.

DEVICE-BASED THERAPEUTIC INTERVENTIONS

Two distinct device-based approaches have been developed to lower BP by reducing sympathetic nervous system activity in patients with resistant hypertension. Carotid sinus stimulation activates the carotid sinus baroreceptor in order to directly inhibit sympathetic nervous outflow from the brain, whereas RDN disrupts efferent and afferent renal nerve signaling by ablating the nerves in the adventitia of the renal

arteries, thus indirectly reducing total body sympathetic activity.

Carotid baroreflex activation

Two carotid sinus stimulation devices (Rheos and Barostimneo) have been shown to effectively lower BP in some patients.[7,8] The pivotal trial testing baroreflex activation therapy implanted the Rheos system in 265 patients with resistant hypertension and randomized them in a 2:1 manner to device activation at 1 month or 6 months after implantation.[7] Pre-specified study end points were not met, but baroreflex activation therapy did produce significant reductions in systolic BP from baseline that persisted over 12 months (mean systolic BP reduction >30 mm Hg). Higher than expected procedure and device-related complications prompted the development of a second-generation system, the Barostimneo, which has a simpler design with unilateral lead placement and a smaller implantable device. Results from a single-arm, open-label study in 30 patients with resistant hypertension showed a BP reduction of $26/12 \pm 4/3$ mm Hg at 6 months from a baseline of $172/100 \pm 20/14$ mm Hg.[8] Only three minor procedure-related complications were reported, and the Barostimneo was felt to have a safety profile comparable to a pacemaker. However, deployment of these devices requires surgical implantation and is associated with persistent procedural safety concerns.

Renal denervation

Interruption of the efferent and afferent renal nerves, which travel together in the adventitia of the renal arteries, lowers BP by a variety of mechanisms. Reducing efferent renal nerve traffic attenuates the increases in renin release/renin–angiotensin system activation and renal sodium reabsorption and the reductions in the renal blood flow that result from sympathetic nervous system activation. Reducing afferent renal nerve traffic to the brain attenuates central sympathetic outflow to the vasculature and the peripheral organs, including the heart and kidneys. RDN in humans is achieved by delivery of radiofrequency or other forms of energy or norepinephrine-depleting pharmaceuticals through catheters placed in the renal arteries. RDN has the advantage of not requiring general anesthesia or surgical implantation of a device.[9–12]

As a result of the dramatic BP reductions reported in early trials of RDN in patients with resistant hypertension (Table 1), coupled with the ease and safety of the procedure, this approach to treating resistant hypertension and its comorbidities has gained wide acceptance and has been approved for clinical use in many parts of the world.[13] A partial list of completed and ongoing clinical trials of RDN for the treatment of hypertension is included in the Table 2.

Randomized controlled trials (RCTs) in resistant hypertension. Safety and efficacy of RDN were demonstrated in patients with resistant hypertension in an initial observational, proof-of-principle trial (Symplicity HTN-1).[14] Office BP was reduced by an average of 27/17 mm Hg at 1-year post-procedure. The initial cohort was then expanded from 45 to 153 patients and followed for a minimal of 2 years. Office BP reductions persisted 24 months after the procedure (mean reduction of 32/14 mm Hg).[15]

The first RCT of RDN for BP reduction, Symplicity HTN-2, enrolled 106 patients with resistant hypertension (mean baseline BP $178/96 \pm 18/16$ mm Hg on an average of five or more antihypertensive medications) and randomized them 1:1 to RDN or control (continuation of their current medical treatment).[16] At 6-month follow-up, office BP was reduced by an average of $32/12 \pm 23/11$ mm Hg in the treatment group and $1/0 \pm 21/10$ mm Hg in the control group. In contrast, mean 24-h ambulatory BP monitoring (ABPM), obtained in only 20 participants showed a mean BP reduction of only 11/7 mm Hg. The large discrepancy between clinic and ABPM responses raises the possibility that a substantial component of the BP response to RDN is due to a decrease in the office or white-coat effect.[17] This interpretation is consistent with the finding from a large observational study that 37.5% of persons diagnosed with resistant hypertension based on office BP had normal ambulatory BP ('white-coat resistance').[18] Although the clinical importance of treating white-coat–resistant hypertension has been challenged, it is possible that the attenuating effect of RDN on the white-coat component of hypertension may translate into reduced BP variability, an effect that has been has been linked with reductions in CVD events and mortality in RCTs and in the general population.[17,19]

In an effort to minimize the effect of white-coat resistance on outcomes, the ongoing pivotal Symplicity HTN-3 Trial in the United States has used ABPM to screen potential participants.[20] Eligibility criteria include 24-h ABPM systolic BP $\geqslant 135$ mm Hg, as well as office systolic BP $\geqslant 160$ mm Hg on full (and stable) doses of $\geqslant 3$ BP medications. The primary effectiveness end point is the change in office systolic BP from baseline to 6 months; a major secondary end point is the change in average 24-h systolic BP by ABPM. (Symplicity HTN-3 has enrolled the planned 530 participants, so results are expected by the spring of 2014).

Chronic kidney disease (CKD). RDN is potentially useful for BP management in the CKD population, where sympathetic nervous system activation contributes to the pathogenesis of hypertension and medical treatment is often unsuccessful in controlling BP. Clinical data on this issue are limited, however, because most ongoing trials of RDN have excluded patients with CKD. A pioneering study of RDN in 15 patients with resistant hypertension and moderate-to-severe CKD (mean estimated glomerular filtration rate 31 ml/min per 1.73 m^2) demonstrated impressive reductions in office BP ($-32/-15$ and $-33/-19$ mm Hg at 6 and 12 months of follow-up, respectively), as well as significant decreases in night-time BP and the morning BP power surge on ABPM.[21] No significant reductions in estimated glomerular filtration rate were seen on follow-up, attesting to the safety of the intervention. Additional benefits of the RDN procedure included a trend toward increased plasma

Table 1 | Selected clinical trials of renal denervation in humans

Study (reference)	Year	*N*	Study population	Results/comments
Symplicity HTN-1[9,10]	2009	153	RHTN	Post-procedure office BPs were reduced by 23/11 and 32/14 mm Hg at 12 (*n*=64) and 24 months (*n*=8), respectively. Procedure was complication free in 149 out of 153 patients; complications included 1 renal artery dissection and 3 femoral pseudoaneurysms.
Symplicity HTN-2[11]	2010	106	RHTN	Randomized controlled trial of denervation (*n*=52) vs. control (*n*=54) with 6-month cross-over (*n*=35). One-year post-procedure, mean fall in office systolic BP was 28 mm Hg; 95% CI 21–35 mm Hg (*n*=49). One renal artery dissection occurred during guide catheter insertion. Mean systolic BP by 24 h ABPM (*n*=20) was significantly reduced by 11 ± 15 mm Hg 6 months post-procedure.
Brandt *et al.*[a]	2012	110	RHTN	Central aortic BP reduced from 167/92 to 141/85 mm Hg at 6 months; PWV reduced from 11.6 ± 3.2 to 9.6 ± 3.1 m/s at 6 months.
Mahfoud *et al.*[b]	2012	100	RHTN	Consecutive patients, 88 underwent renal denervation and 12 acted as controls. Mean 6-month reduction in BP 26.6/9.7 ± 2.5/1.5 mm Hg; no change in GFR by cystatin C or urine albumin-to-creatinine ratio between treatment and control.
Mahfoud *et al.*[18]	2011	50	RHTN	Prospectively assigned 37 to renal denervation and 13 to control. Mean office BP reduced by 32/12 mm Hg from a baseline of 178/96 ± 3/2 mm Hg. Fasting glucose significantly reduced from 118 ± 3.4 to 108 ± 3.8 mg/dl 3 months post-procedure.
Pokushalov *et al.*[22]	2012	27	RHTN+symptomatic atrial fibrillation	Randomized controlled trial of PVI with (*n*=13) or without (*n*=14) renal denervation. Office BP with 25/10 ± 5/2 mm Hg reduction 1-year post-denervation. Atrial fibrillation recurrence was significantly reduced in the PVI with renal denervation group.
Hering *et al.*[16]	2012	15	RHTN+CKD (moderate-to-severe, stages III–IV)	Mean eGFR 31 ml/min per 1.73 m^2; office BP reduction of 33/19 mm Hg at 1 year (*n*=5); no significant difference in mean BPs by 24-h ABPM (*n*=8); no significant change in eGFR despite radio contrast exposure in 9 of the 15 patients.
Schlaich *et al.*[17]	2013	12	RHTN+ESRD	Denervation unable to be performed due to atrophic renal arteries in 3 out of 12 patients. Office systolic BP reduced from 166 ± 16 to 138 ± 17 mm Hg at 1 year. Renal norepinephrine spillover and muscle sympathetic nerve activity was significantly reduced 12 months post-procedure (*n*=2).
Brinkmann *et al.*[29]	2012	12	RHTN	Office BP were not significantly different 6 months post-procedure (157/85 ± 7/4 vs. 157/85 ± 6/4 mm Hg). Only 3 patients had BP reductions; however, 3 out of 11 were controlled before denervation.
Witkowski *et al.*[20]	2011	10	RHTN+obstructive sleep apnea	Office BP reduced by 34/13 mm Hg and AHI reduced from 16.3 to 4.5 events per hour 6 months post-procedure. Plasma glucose decreased 2 h after a glucose load 6 months post-procedure (median 7 vs. 6.4 mmol/l).
Schlaich *et al.*[19]	2011	2	RHTN+PCOS+obesity	Whole body norepinephrine spillover was reduced by 5–8% immediately following denervation. Insulin sensitivity improved 12 weeks following denervation.

Abbreviations: ABPM, ambulatory blood pressure monitoring; AHI, apnea–hypopnea index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; eGFR, estimated GFR; PCOS, polycystic ovarian syndrome; PVI, pulmonary vein isolation; PWV, pulse wave velocity; RHTN, resistant hypertension.
[a]Data from Brandt *et al. J Am Coll Cardiol* 2012;60(19):1956–1965.
[b]Data from Mahfoud *et al. Hypertension* 2012;60(2):419–424.

hemoglobin concentration, decreases in brain natriuretic peptide, urinary albumin and protein and glycated hemoglobin levels, and a significant reduction in arterial stiffness. Although exploratory, these promising findings suggest a potential role for RDN to slow the progression of CKD and its CVD complications and point out the need for larger RCTs in this patient population.

Enhanced afferent neural signaling from the failing native kidneys with resultant increased efferent sympathetic outflow from the brain are key mediators of resistant hypertension in patients with end-stage renal disease. A safety and proof-of-concept study of RDN carried out in 12 patients with end-stage renal disease and uncontrolled BP showed significant reductions in office systolic BP in nine of the participants that were sustained for up to 2 years of follow-up.[22] RDN could not be performed in the other three because of renal artery atrophy. Although exploratory, findings of this study offer promise that RDN may be a suitable alternative to bilateral nephrectomy in patients with end-stage renal disease and refractory hypertension.

Effects of RDN on hypertension-related comorbidities. Exploratory hypothesis-generating studies have revealed potential benefits beyond BP lowering of RDN for treatment of a variety of conditions in which the sympathetic nervous system is activated, including impaired glucose metabolism/insulin resistance, obstructive sleep apnea (OSA), cardiac hypertrophy, heart failure, and cardiac arrhythmias.

Impaired glucose metabolism/insulin resistance. The effect of RDN on glucose metabolism was examined as an extension to the Symplicity HTN-2 protocol in 37 patients with resistant hypertension.[23] At 3 months after RDN, significant reductions in fasting glucose, insulin and C-peptide levels, and improvements in oral glucose tolerance and in insulin sensitivity indexed by homeostasis model assessment-insulin resistance were observed, in concert with impressive BP lowering. None of these parameters changed in a control group of 13 patients with resistant hypertension who were randomized to continued medical therapy. These findings suggest that RDN may provide benefit beyond BP reduction

Table 2 | Overview of clinical trials enrolling hypertensive patients for endovascular renal nerve ablation

Product name	Product design	Clinical trial name	HTN type studied	Clinical trial ID	Sponsor
Radiofrequency ablation					
Symplicity RFA catheter	Single-electrode RFA catheter	SYMPLICITY HTN-1	Resistant	NCT00664638	Medtronic
Symplicity RFA catheter	Single-electrode RFA catheter	SYMPLICITY HTN-2	Resistant	NCT00888433	Medtronic
Symplicity RFA catheter	Single-electrode RFA catheter	SYMPLICITY HTN-3	Resistant	NCT01418261	Medtronic
Symplicity RFA catheter	Single-electrode RFA catheter	Effect of renal denervation on biological variables	Resistant	NCT01427049	Medtronic
Symplicity RFA catheter	Single-electrode RFA catheter	Renal nerve ablation in CKD patients	Resistant, with stages 3–5 CKD	NCT01442883	Medtronic
Symplicity RFA catheter	Single-electrode RFA catheter	PRAGUE-15	Uncontrolled	NCT01560312	Medtronic
Symplicity RFA catheter	Single-electrode RFA catheter	Renal denervation in patients with RH and OSA	Uncontrolled, with OSA	NCT01366625	Medtronic
EnligHTN RFA catheter	Multielectrode RFA catheter	ARSENAL	Resistant	NCT01438229	St Jude
Vessix V2 RFA catheter	Balloon-mounted RFA catheter	REDUCE-HTN	Resistant	NCT01541865	Vessix Vascular
OneShot RFA catheter	Irrigated, balloon-mounted RFA catheter	RAPID	Resistant	NCT01520506	Maya Medical
ThermoCool cryoablative catheter	Irrigated RFA catheter	SWAN HT	Uncontrolled	NCT01417221	Biosense Webster
ThermoCool cryoablative catheter	Irrigated RFA catheter	SAVE	Uncontrolled	NCT01628198	Biosense Webster
ThermoCool cryoablative catheter	Irrigated RFA catheter	RELIEF	Uncontrolled	NCT01628172	Biosense Webster
Chilli II cryoablative catheter	Irrigated RFA catheter	SAVE	Uncontrolled	NCT01628198	Boston Scientific
Ultrasonic ablation					
PARADISE ultrasonic catheter	Ultrasonic balloon catheter	REALISE	Resistant	NCT01529372	ReCor Medical
TIVUS ultrasonic catheter	Ultrasonic autoregulating balloon catheter	In development	—	—	Cardiosonic
Kona medical ultrasonic system	Low-intensity external ultrasonic	In development	—	—	Kona Medical
Tissue-directed pharmacological ablation					
Bullfrog microinfusion catheter	Microneedle-equipped balloon catheter	In development	—	—	Mercator MedSystems

Abbreviations: ARSENAL, Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients trial; CKD, chronic kidney disease; HTN, hypertension; OSA, obstructive sleep apnea; PARADISE, ReCor Percutaneous Renal Denervation System catheter; PRAGUE-15, Renal Denervation in Refractory Hypertension trial; RAPID, Rapid Renal Sympathetic Denervation for Resistant Hypertension trial; REDUCE-HTN, Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter; RELIEF, Renal Sympathetic Denervation for the Management of Chronic Hypertension trial; REALISE, Renal Denervation by Ultrasound Transcatheter Emission trial; RFA, radiofrequency ablation; RH, resistant hypertension; SAVE, Impact of Renal Sympathetic Denervation on Chronic Hypertension study; SWAN HT, Renal Sympathetic Modification in Patients with Essential Hypertension study; SYMPLICITY HTN-1, SYMPLICITY I: One-Year Results Following Sympathetic Renal Denervation in Refractory Hypertension trial; SYMPLICITY HTN-2, Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension trial; SYMPLICITY HTN-3, Renal Denervation in Patients with Uncontrolled Hypertension trial; TIVUS, therapeutic intravascular ultrasound.
Adapted from *JACC Cardiovasc Interv*. Bunte MC, Infante de Oliveira E, Shishehbor MH. Endovascular treatment of resistant and uncontrolled hypertension: Therapies on the horizon. *JACC Cardiovasc Interv* 2013; **6**:1–9, with permission from Elsevier.

in patients with resistant hypertension and insulin resistance who are at high CVD risk.

Polycystic ovary syndrome, characterized by ovarian dysfunction, infertility, androgen excess, obesity, the metabolic syndrome, insulin resistance, and hypertension, is associated with sympathetic nervous system activation that is related to the clinical severity of the syndrome. An exploratory study of the effects of RDN in two women with polycystic ovary syndrome and resistant hypertension revealed improvement in BP, metabolic parameters, and ovarian function (regularization of menses).[24] Sympathetic nerve activity, assessed by microneurography, and whole body norepinephrine spillover, was elevated (2.5–3x) at baseline and was reduced by RDN. Insulin sensitivity, assessed by euglycemic hyperinsulinemic clamp, also improved. Glomerular hyperfiltration and microalbuminuria were

present at baseline and responded favorably to RDN. This hypothesis-generating case study suggests that increased sympathetic nerve activity has a pivotal role in the pathogenesis of polycystic ovary syndrome and that modulation of sympathetic activity by RDN may be useful in its treatment.

Obstructive sleep apnea. OSA is highly prevalent in resistant hypertension and is associated with sympathetic nervous system activation and metabolic abnormalities. A study in 10 patients with resistant hypertension and OSA ($n = 8$) or the mixed sleep apnea syndrome (obstructive and central) ($n = 2$), assessed the effects of RDN on BP, severity of sleep apnea and metabolic indices.[25] At 6 months of follow-up, significant decreases in office BP (median: −34/−13 mm Hg), improvement in glycemic indices (2-h postprandial glucose and hemoglobin A1c), and a tendency for reduction in severity of sleep apnea (decrease in median apnea–hypopnea index from 16.3 to 4.5 events per hour) were observed. The apnea–hypopnea index improved significantly in all patients who had OSA without a central component, even in those with severe disease who were receiving continuous positive airway pressure treatment. These effects occurred in the absence of significant weight loss. Although the mechanisms responsible were not examined in this proof-of-concept study, the findings suggest that RDN may be a useful strategy for patients with OSA and resistant hypertension.

Cardiac hypertrophy and function. Left ventricular hypertrophy occurs commonly in resistant hypertension and is associated with elevated sympathetic activity, diastolic dysfunction, and increased CVD morbidity and mortality. The effects of RDN on left ventricular hypertrophy and cardiac function (systolic and diastolic) were assessed by echocardiography in 46 patients with resistant hypertension who met inclusion criteria for Symplicity HTN-2 compared with 18 controls.[26] At 6 months of follow-up, there were significant reductions in BP (−27.8/−8.8 mm Hg), mean interventricular septal thickness (14.1 ± 1.9 mm to 12.5 ± 1.4 mm), and left ventricular mass index (53.9 ± 15.6 g/m$^{2.7}$ to 44.7 ± 14.9 g/m$^{2.7}$). The mitral valve lateral E/E' decreased from 9.9 ± 4.0 to 7.4 ± 2.7, indicating reduction of left ventricular filling pressures. Isovolumic relaxation time shortened (baseline 109.1 ± 21.7 ms vs. 85.6 ± 24.4 ms at 6 months), whereas ejection fraction increased significantly (baseline 63.1 ± 8.1% vs. 70.1 ± 11.5% at 6 months). No significant changes were seen in control patients. These provocative preliminary findings of reduced left ventricular mass and improved diastolic function with RDN in patients with resistant hypertension suggest a potential outcome benefit for the procedure that should be evaluated in future trials.

Cardiac arrhythmias. Recent evidence suggests that RDN stabilizes abnormal electrical activity in the heart. In a trial that randomized 27 patients with resistant hypertension and refractory atrial fibrillation to pulmonary vein isolation accompanied by RDN versus pulmonary vein isolation alone, recurrent atrial fibrillation was reduced in the RDN group (9 out of 13 patients event-free 1-year post-RDN compared with 4 out of 14 patients in the pulmonary vein isolation alone group).[27] Further, the patients who underwent RDN responded with reductions in systolic BP comparable to those seen in the Symplicity HTN trials at 1-year post-RDN. In another small study in two patients with cardiomyopathy and ventricular arrhythmias that were refractory to usual treatments, RDN reduced the arrhythmias without destabilizing hemodynamic function.[28] Additional clinical trial evidence is needed to confirm the benefits of RDN in treating hypertensive patients with cardiac arrhythmias.

Quality of life (QoL). Health-related QoL has been shown to be markedly diminished in patients with resistant hypertension. A recent hypothesis-generating study examined QoL before and 3 months after RDN using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and Beck Depression Inventory-II (BDI-II) in 62 patients with resistant hypertension who were participants in ongoing clinical trials.[29] Before RDN, the resistant hypertensive patients scored significantly worse in many QoL measures than controls who were normotensive or hypertensive with controlled BP. After RDN, the SF-36 score improved because of increases in the vitality, social function, role emotion, and mental health domains and the BDI-II scores showed decreases in symptoms of sadness, tiredness, and reduced libido. Improvements in QoL were not associated with the magnitude of BP reduction. If confirmed in randomized trials with longer follow-up, these findings provide evidence for an additional benefit of RDN beyond BP lowering.

Cost effectiveness. The cost effectiveness of RDN, which certainly varies from health system to health system, is of major interest to patients and health-care providers. A study that utilized a state-transition (Markov) model to project the impact of RDN and associated BP reductions on CVD and renal outcomes in order to assess cost effectiveness calculated an incremental cost-effectiveness ratio for a cost saving of $31,460 per quality-adjusted life year.[30] Although this model suggests that RDN is a cost-effective strategy for treating resistant hypertension, it assumes that RDN, by lowering BP, will lower CVD morbidity and mortality. However, there are no morbidity and mortality data available for RDN treatment of resistant hypertension.

LIMITATIONS, CONCERNS, AND FUTURE DIRECTIONS

Procedure-related complications of RDN

Procedure-related complications of RDN, most commonly femoral artery pseudoaneurysms, are rare and differ little from those of other interventional procedures involving femoral arterial access. Documented renal artery injury from radiofrequency energy and renal artery dissection requiring stenting are even less common.[14–16] However, a recent examination of renal arteries immediately following RDN with both the EnligHTN and Symplicity(R) catheters using optical coherence tomography revealed evidence of injury.[31] Mean renal artery diameter was significantly decreased by a mechanism that involved vasospasm, thrombus formation, and endothelial edema at the ablation site. The long-term

consequences of these acute injury responses are not well understood and merit further investigation.

Challenges

A variety of challenges stand in the way of widespread acceptance of RDN as a therapy for resistant hypertension.[32,33] Despite a generally high BP response rate, a substantial proportion of patients fail to experience a reduction in BP following the procedure. The proportion of non-responders in the Symplicity HTN Trials has generally been ~15%, whereas some smaller studies have quoted a higher number. For example, in one small study of 12 patients with resistant hypertension, RDN resulted in no BP reduction in 7 of the 12 participants and no change in resting muscle sympathetic nerve activity or other indices of sympathetic activity in the study population or a whole.[34] Importantly, there is no reliable clinical predictor of BP response to RDN, and is not clear whether failed BP responses are due to incomplete RDN or to the pathophysiologic features of the individual patient's hypertension. The gold standard for assessment of successful RDN, measurement of norepinephrine spillover into the renal vein, is useful only for research purposes and not feasible in routine clinical practice. Although innovative preclinical approaches, for example, comparison of BP responses, serum catecholamine concentrations, and sympathetic indices of heart rate variability following renal nerve stimulation before and after RDN are being developed, these methods have yet to be standardized and adapted for routine clinical use.[35]

Additional unanswered questions include the duration of the antihypertensive and sympatholytic responses to RDN. It is known from transplantation studies that efferent renal nerves do regenerate, but whether these are functional and have a role in BP regulation remains unknown. Further, the full magnitude of the BP-lowering effect of RDN is not yet appreciated, because most patients with resistant hypertension who have undergone the procedure have been continued on their pre-treatment drug therapy. Accordingly, the potential benefit of RDN in terms of reducing pill burden and increasing adherence to medical antihypertensive therapy remains undetermined. Most importantly, RCTs with hard clinical end points with blinding, as in Symplicity HTN-3, and with sufficiently long follow-up to assess the possibility of functional reinnervation of the kidneys are needed to fully evaluate the role of RDN in hypertension treatment and the prevention of CVD.

Future directions

As a result of these concerns and the limitations of existing data, it is prudent to follow the recommendations of the European Society of Hypertension for use of RDN.[36,37] RDN should be restricted to patients with true treatment resistant hypertension who are evaluated and followed by hypertension specialists. RDN should be performed by well-trained interventionists working in collaboration with hypertension specialty clinics. Pending results of ongoing clinical trials, clinical uses of RDN will likely extend to other forms of hypertension and comorbidities.

DISCLOSURE

EJ has received grant support from the National Institutes of Health: NIH/NHLBI T32 HL007457 (EJ, SO); NIH R01 HL075614 (EJ); and serves as sub-investigator for a clinical trial with Medtronic. SO has received research support from Duke University (sponsor: AstraZeneca AB), Daiichi Sankyo, Medtronic, Merck, National Institutes of Health/National Heart, Lung, and Blood Institute (NHLBI), Novartis AG, Takeda Global Research and Development, UAB Comprehensive Cardiovascular Center, and Vivus, and has served as PI or Co-PI for clinical trials with Duke University, Merck, Novartis, and Takeda Global Research and Development. SO received honoraria in her capacity as Faculty Presenter for the American Society of Hypertension sponsored by Daiichi Sankyo, and served as advisor for Bayer, Daiichi Sankyo, Novartis, Pfizer, and Takeda. Publication costs for this article were supported by the Turkish Society of Hypertension and Renal Diseases, a nonprofit national organization in Turkey.

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