Resistant Hypertension: Clinical Considerations and the Potential for Renal Denervation

The current landscape of major clinical trials and treatment strategies.

BY VIKAS KAPIL, MD, MRCP, PHD, AND MELVIN D. LOBO, MD, FRCP, PHD

Resistant hypertension (RHTN) is commonly defined as the presence of uncontrolled blood pressure (BP) (systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg) despite appropriate lifestyle measures and adherence to adequate or maximal tolerated doses of at least three antihypertensive medications from different classes, including a diuretic.[1-3] Neither national nor international guidelines specify what the optimal or adequate doses are, but a pragmatic approach may be to consider prescribing half (or above) the maximal licensed dose for hypertension. By definition, this group also includes patients whose BP is controlled on four or more medications.

The true prevalence of RHTN is not currently well known, and to date, there has been no large, prospective study with forced titration to optimal doses of three classes of medications. Estimates of RHTN have been taken from post hoc analyses of large clinical trials of antihypertensive therapy and suggest prevalence rates of up to 35% in treated hypertensive patients.[4-6] However, analysis of retrospective cohort studies and registries has put the annual incidence rate of developing RHTN in newly diagnosed hypertensive patients at 1.9%,[7] whereas prevalence rates have been estimated to be 8% to 20% for all treated hypertensive patients.[8-10]

RHTN itself can be further subdivided into two important divisions: apparent RHTN and true RHTN. Apparent RHTN can be due to inaccurate clinical BP measurements (ie, using a bladder cuff that is inappropriately small for the circumference of the patient's arm and/or the "white coat effect" that overestimates the true BP when measured in the clinic)[11] and nonadherence to medications, with adherence estimated to drop to 50% within 1 year after initiation.[12] The white coat effect is potentially a large confounder in studies that report the incidence and prevalence of RHTN, as in studies that have used out-of-office BP monitoring by ambulatory BP (ABP) monitoring, approximately one-third of patients with RHTN had controlled BP when measured with ABP criteria.[8] Epidemiological predictors of true RHTN include older age, African American and other minority ethnicities, higher baseline BP, obesity, chronic kidney disease, and diabetes mellitus.[1,9,13] Furthermore, there are multiple secondary causes of hypertension that should be excluded or treated/removed before further therapy is considered for true RHTN (Table 1).

It has been shown that patients with RHTN are at a markedly increased risk of cardiovascular target organ damage and cardiovascular events.[7,14] It is therefore of considerable interest to hypertension specialists that novel approaches to treat RHTN are being developed and evaluated in clinical trials and international registries (see *The Role of Hypertension Specialists in the Context of RSD* sidebar). These include baroreceptor activation therapy,[15,16] iliac arteriovenous fistula forma-

tion,[17] and the focus of this review: selective renal sympathectomy through endovascular renal sympathetic denervation (RSD).

CURRENT TREATMENT STRATEGIES FOR RHTN

All international guidelines recommend that patients with RHTN are given lifestyle advice and are prescribed three different classes of medications, including a diuretic.[2,3,18] However, only the 2011 UK NICE guidelines are prescriptive for mineralocorticoid receptor antagonism (eg, spironolactone) as the preferred fourth-line agent if serum potassium is < 4.5 mmol/L or extra-thaizide-like diuretic if > 4.5 mmol/L.[3] This lack of direction as to preferred fourth-line agents in the other guidelines is due to the paucity of good-quality clinical trials in this difficult therapeutic area.

Recognizing this lack of evidence-based medicine, there are several large, randomized, double-blind, head-to-head clinical trials currently recruiting or recently completed. These include the British Hypertension Society's Pathway[2] study that rotates RHTN patients between 12 weeks each of spironolactone, alpha-adrenergic blockade, beta-adrenergic blockade, and placebo; the ReHOT study, which is a direct head-to-head comparator of spironolactone to the centrally acting alpha-adrenergic agonist, clonidine; and a recently completed study showing superior BP-lowering efficacy with a sequential nephron-blocking regime compared to sequential renin-angiotensin-aldosterone (RAAS) axis blockade.[19]

NOVEL PHARMACOLOGICAL TREATMENT STRATEGIES FOR RHTN

Due to the lack of a clear evidence base for established fourth-line pharmacotherapy and the high burden of morbidity and mortality with RHTN, there is clearly a need for novel approaches to treatment.

The burgeoning pipeline of novel medication classes that are at various phases of development, including vasopeptidase inhibitors, aldosterone synthase inhibitors, and novel nitric oxide donors, was recently reviewed by Laurent et al.[20] Vaccines against the RAAS axis have been developed, although the two most recent human vaccine studies did not show long-term beneficial effects above and beyond those achievable with standard RAAS-blocking medications.[21] Medications that are well used in pulmonary hypertension have been retasked to systemic arterial hypertension with mixed success.[22-25]

Combination therapy is recommended by all guidelines, as meta-analyses have demonstrated that adding in another class of medication to monotherapy produces a five-times greater BP reduction than doubling the monotherapeutic medication.[26] Therefore, as most patients with hypertension require at least two medications to

TABLE 1. SECONDARY CAUSES OF HYPERTENSION

Classification	Cause
Cardiovascular	Coarctation of the aorta
	Mid-aortic syndrome
Endocrine	Primary hyperaldosteronism
	Pheochromocytoma
	Acromegaly
	Cushing's syndrome
	Hyperthyroidism
	Hyperparathyroidism
Renal	Renovascular disease
	Polycystic kidney disease
	Glomerulonephritides
	Renin-secreting tumor
	Chronic kidney disease from any cause
	Liddle's syndrome and Gordon's syndrome
Neurological	Stroke (hemorrhagic, ischemic)
	Intracranial mass
	Traumatic brain injury
	Brainstem neurovascular compression
Respiratory	Obstructive sleep apnea
Obstetric	Gestational hypertension
	Pre-eclampsia
Medications and drugs	Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors
	Glucocorticoids
	Oral contraceptive pill
	Calcineurin inhibitors
	Antidepressants (MAOIs, venlafaxine)
	VEGF inhibitors
	Sympathomimetics (including recreational drugs)
	Alcohol
Other	Licorice consumption
	Salt consumption

THE ROLE OF HYPERTENSION SPECIALISTS IN THE CONTEXT OF RSD

Secondary forms of hypertension, such as endocrine hormone excess and renovascular and aortic vascular disease, are more common in patients with RHTN.[1] As such, referral of patients with RHTN to specialist centers is recommended by international guidelines to facilitate identification and treatment of the underlying cause.[2,3,18] This is especially important in the context of RSD, given the irreversibility of the procedure and the lack of long-term safety or efficacy data to date.

Centers with active programs for detecting and managing obstructive sleep apnea and primary hyperaldosteronism are ideal given the high prevalence of these conditions and the fact that they are commonly overlooked as causes of RHTN in nonspecialist settings.[27,28] Hypertension specialists have expertise in the medical management of RHTN and are familiar with off-label/unlicensed use of pharmacotherapies to enable BP lowering.

It is imperative to exclude patients who are not adhering to medication by directly observing tablet taking and urinary analysis of detectable medications. Furthermore, familiarity with ABP monitoring and detection of both white coat and masked hypertension is important in selecting appropriate patients for RSD.

It is also important that, in an era when novel device therapies span multispecialist teams including vascular surgeons for baroreflex activation as well as interventional radiologists/cardiologists for endovascular procedures, a "device agnostic" hypertension specialist who may not actually undertake any of the procedures has overarching responsibility for the patient.

To this end, UK, European, and international august bodies have provided consensus documents[29-31] outlining an evidence-based approach to RSD patient selection that recommends a multidisciplinary approach, which includes a hypertension specialist.

control their BP,[32] there has been interest in a fixed-dose combination of two or three medications to improve adherence and control.[33] However, recent meta-analyses have failed to demonstrate significant BP lowering with fixed-dose combinations above and beyond the individual components, despite improved adherence.[34]

CATHETER-BASED RSD FOR RHTN

Several different physiological mechanisms are involved in BP regulation, as first suggested by Page,[35] and the role of the sympathetic nervous system (SNS) (in particular, renal afferent and efferent sympathetic

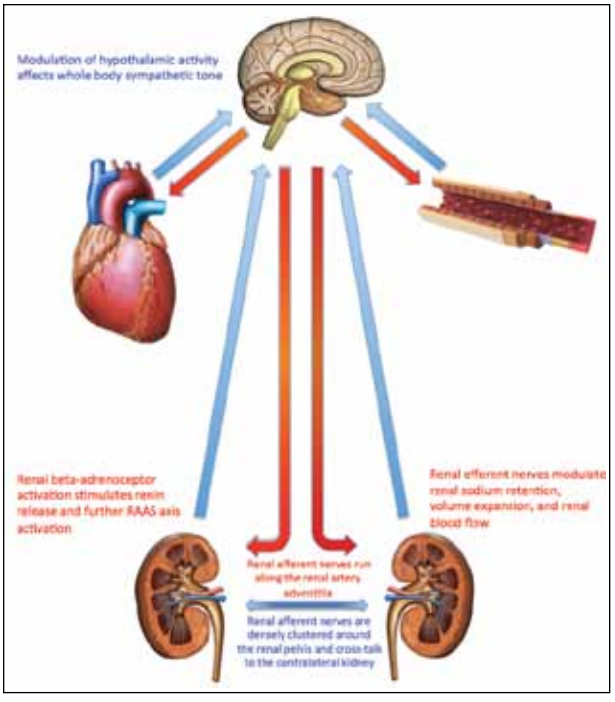

Figure 1. A schematic of the renal sympathetic connections and physiological role in modulating BP. The kidneys have their own efferent and afferent connection to the sympathetic control centers in the central nervous system. Efferent fibers (red) leave the hypothalamus and innervate the kidneys via the pre-/paraverterbral ganglia at T10-L2 and run along the adventitia of the renal arteries.[36] The renal afferent nerves (blue) are densely clustered in the renal pelvis, running in the adventitia alongside the efferent nerves to the ipsilateral dorsal root ganglia, from where they ascend to the autonomic centers in the brain and also cross-innervate to the contralateral kidney.[37] Renal efferent activity mediates renal sodium retention and volume expansion[38] and reduces renal blood flow.[39] Perhaps as importantly for long-term BP control, renal efferent beta–adrenergic sympathetic activation stimulates the release of renin from the renal juxtaglomerular apparatus, stimulating the neurohumoral RAAS axis and further elevating BP through salt/water retention and vasoconstriction.[40] Renal afferent activity regulates whole body sympathetic tone by moderating hypothalamic activity, which can further promulgate renal efferent activity in a positive feedback loop.[41]

nerves) has been extensively reviewed elsewhere[42-46] and is represented in Figure 1.

It is clear that abrogation of renal SNS signalling is effective in preventing the development of hypertension and attenuating pre-existing hypertension in many animal models of hypertension.[47-53] Laboratory-based techniques to achieve RSD, such as renal artery ligation and

reanastomosis, are clearly unsuitable for human use, but recently, targeted RSD using radiofrequency (RF) ablation of the renal arteries through an endoluminal approach has been made possible.[54,55]

The first device to reach clinical studies was the Symplicity RF ablation catheter (designed by Ardian, Inc., and subsequently bought by Medtronic, Inc., Minneapolis, MN).[54] The system involves a percutaneous, flexible catheter that is inserted via a femoral approach, which is attached to a proprietary, low-energy, RF generator and is advanced into the distal lumen of both renal arteries. Energy delivery is performed for 2 minutes at a time, delivered at the tip, which heats local tissue (up to 4 mm deep from the endothelium, which includes the distance to the renal sympathetic nerves in the adventitia[36]) to 70º to 90º C at each application.

Ablations are performed in a distal-to-proximal manner longitudinally with helical rotations to ensure separation between applications. Typically, four to six ablations are performed for each artery to cover the full circumference, with native blood flow cooling the intima to reduce endothelial injury. Application of energy affects sensory C-fibers that run together with the renal sympathetic efferent and afferent nerves, and so adequate analgesia with or without conscious sedation is required for the procedure. Procedural efficacy (confirmed by histology) and anatomical safety (lack of severe vascular or renal injury 6 months postablation) were confirmed in juvenile swine[55] before the proof-of-concept human studies, and these results have, to some extent, been corroborated in the published human studies to date.[54,56-58]

Symplicity HTN-1, the nonrandomized, first proof-of-concept study, recruited 45 RHTN patients with entry office BP of 177/101 mm Hg on a mean of 4.7 antihypertensive medications and demonstrated BP-lowering of 27/17 mm Hg at 12 months, with one renal artery dissection and one groin pseudoaneurysm in total.[54] Registry data, including 18 patients from Symplicity HTN-1, in an expanded cohort recruited to the same criteria as the original study, demonstrated a sustained office BP of approximately 30/15 mm Hg after 24 months of follow-up, with a similarly low rate of serious complications.[57,59]

Symplicity HTN-2 was a randomized trial of RSD plus established treatment versus established treatment only. The 106 participants were randomized, and 100 had analyzable data at the primary endpoint of 6 months. In patients randomized to RSD, entry office BP was 178/97 mm Hg, and they were on a mean of 5.2 antihypertensive medications. Six-month BP-lowering was 32/12 mm Hg compared to 1/0 mm Hg in the controls.[58] This cohort has been further studied, with data reported to 1 year postintervention demonstrating BP-lowering durability of 28/10 mm Hg.[56] Importantly, among patients initially assigned to established medical treatment alone, crossover to RSD produced a similar magnitude of BP-lowering as those who were randomized to RSD for initial therapy.[56]

Although patients recruited to the Symplicity HTN-1 and -2 trials recruited RHTN patients with severely elevated office BPs (approximately 180/100 mm Hg) despite a mean of approximately five medications, it has recently been demonstrated in a cohort of more moderate RHTN patients (office BP, 151/83 mm Hg on a mean of 5.1 antihypertensive medications) that the BP-lowering efficacy of RSD was still statistically significant and appreciable at 6 months (change in office BP, 13/7 mm Hg).[60]

In the Symplicity HTN trial results to date, the procedure showed no compromise in renal function or electrolyte homeostasis and a low rate of procedure-related vascular complications.[54,56-58] Furthermore, efficacy and renal safety has been recently explored in 15 patients with RHTN and moderate-severe chronic kidney disease (stages 3–4) who would have been excluded from the Symplicity HTN-1 and -2 trials. This study revealed robust BP-lowering (change in office BP, 33/19 mm Hg) and preservation of renal function to 1-year follow-up after RSD,[61] which provides limited but further encouraging data regarding renal safety.

Recognizing that RHTN represents a potential market of approximately $2 billion annually in the United States,[62] industry involvement and the development of similar interventional technologies for RHTN have recently gathered pace. There are now several RF ablation catheters at various stages of clinical development, with a recent meta-analyses of 12 studies using five different systems, revealing substantial reduction in office BP up to 1 year postprocedure.[63] Advancements in newer RF ablation catheters include integrated cooling systems, multielectrode catheters to reduce operative time, and balloon-tipped catheters to improve vessel-electrode apposition and energy transfer. Furthermore, other, non-RF-based technologies are being developed to deliver effective RSD, and the current information known on these devices is summarized in Table 2.

CONCLUSION

The landscape for the treatment of hypertension has been irrevocably altered by the publication of seminal studies demonstrating the BP-lowering effects of device-based therapies targeting the renal SNS. It is likely that both the magnitude of BP-lowering, and perhaps the responder rate, in patients with RHTN following RSD exceed expected BP-lowering rates for additional antihypertensive medications in similar populations already on at least three antihypertensives from the few investigations that have studied this population.[3,19] However, available RSD devices are numerous and ever increasing

TABLE 2. RSD TECHNOLOGIES AVAILABLE AND IN DEVELOPMENT

Technology	Device Name (Manufacturer)	Key Characteristics
Radiofrequency	Symplicity Flex (Medtronic, Inc.)	Single-electrode catheter
	Spyral (Medtronic, Inc.)	Spiral-electrode catheter
	EnligHTN (St. Jude Medical, Inc., St. Paul, MN)	Multielectrode catheter
	OneShot (Covidien, Mansfield, MA)	Irrigated, spiral-electrode catheter
	Vessix V2 (Boston Scientific Corporation, Natick, MA)	Variable size, multielectrode catheter with bipolar energy delivery
	ThermoCool (Biosense Webster, Inc., Diamond Bar, CA)	Irrigated, multielectrode catheter
	Iberis (Terumo Interventional Systems, Somerset, NJ)	Single-electrode, radial artery access system
	Verve Medical System (Verve Medical, Inc., Santa Barbara, CA)	Multielectrode, retroureteric access system
Ultrasound	Paradise (ReCor Medical, Menlo Park, CA)	Nonfocused, endovascular ultrasound energy system
	TIVUS (CardioSonic, Tel Aviv, Israel)	Nonfocused, endovascular, high-intensity ultrasound system with safety lock if blood temperature rises
	Kona System (Kona Medical, Campbell CA)	Externally applied, low-intensity ultrasound energy system
	Sound 360 (Sound Innovations, Inc., Stony Brook, NY)	Endovascular ultrasound energy system
Cryoablation	Not yet named (Friedrich-Schiller University, Jena, Germany)	Standard cryoablation catheter, as used in atrial fibrillation ablations
Brachytherapy	CyberHeart (CyberHeart, Inc., Sunnyvale, CA)	Catheter-based, beta-radiation brachytherapy
Pharmacological	Not yet named (University of Athens Medical School, Athens, Greece)	0.1-mg vincristine delivered from six-holed proprietary balloon catheter
	Bullfrog (Mercator MedSystems, Inc., San Leandro, CA)	Guanethidine microinjection into the adventitia
	Peregrine (Ablative Solutions, Kalamazoo, MI)	Ethanol microinjection into the adventitia
	ApexNano system (ApexNano Therapeutics, Inc., Herzliya, Israel)	Magnetic nanoparticles impregnated with Botox

(Table 2), and without direct head-to-head comparisons, device selection will be uninformed.

There have been major criticisms of RSD studies to date that broadly fall into the following categories: trial design, patient selection, lack of ABP data, renal safety, durability of BP-lowering, and endpoints (Table 3). Furthermore, it has been suggested that adoption of RSD strategies may have exceeded the current evidence base, particularly in groups at lower total cardiovascular risk than have been included in published peer-reviewed publications.[64] This may be partly due to the strict inclusion criteria in the studies to date and perhaps due to physician and patient preference for non-pharmacological panacea for hypertension, but this group will likely have a more adverse risk:benefit profile related to interventional treatments for BP due to low overall cardiovascular risk at baseline. There is currently no published evidence to support initial device-based therapy for hypertension despite its recent suggestion.[65]

However, whether RSD should be reserved for the adherent and truly resistant patients with severe hypertension, in whom all other efforts to reduce BP have failed, as has been suggested recently,[66] is still to be debated, as very few lifestyle interventions or pharmacological therapies have either been tested or have proven long-term BP-lowering effects coupled to reductions in cardiovascular morbidity and mortality in RHTN. Furthermore, as commented upon in recent guidance from the European Society of Cardiology, there exists a group of uncontrolled hypertensive patients who are medication intolerant and therefore not meeting the criteria of true RHTN. It has been suggested that in such patients, RSD may be suitable when considered on an individualized basis.[29]

TABLE 3. CRITICISMS OF CLINICAL RSD STUDIES TO DATE

Criticism	Problem	Solution
Trial design	Nonblinded design, lack of sham control	Double-blind RSD vs sham procedure with best medical therapy[67]
Patient selection	No per-protocol exclusion of secondary causes of hypertension	Mandatory per-protocol exclusion of secondary causes of hypertension
	No per-protocol exclusion of nonadherence to medication or lifestyle changes	Use of urine analysis of medications and directly observed therapy before qualifying BP measurement; optimal 24-h urinary sodium excretion
	Heterogeneity of patient suitability rates between RSD centers[68,69]	Referral to hypertension specialist centers
ABP	Overestimation of effect on office BP due to inclusion of potentially pseudoresistant hypertensive patients,[54,58,70] less-impressive results in patients deemed resistant on ABP measurement as well[71]	Use of ABP as entry and outcome criteria[60,72]
Renovascular safety	Reporting of only > 60% stenosis,[59] no histological safety data from humans	Radiographic assessment of renal vascular anatomy postprocedure
	Potential diffuse renal artery vasospasm, local tissue edema and thrombus[73]	Potential need for concurrent, periprocedural antiplatelet therapy,[73] further use of optical coherence tomography[73]
Predictors of response	Only baseline, office systolic BP reliably predicts response across studies,[54,58,70] inability to distinguish between procedural failure or nonresponse	Inclusion of detailed autonomic function testing into all clinical studies and registries[54,74]
Durability of response and endpoints	6-month office BP as primary endpoint[54,58,70]	Major adverse events as primary endpoints
	No data > 2 years postprocedure published	Studies and registries extended to several years

It is imperative that we conduct well-designed, investigator-led, randomized, sham-controlled, double-blinded studies with per-protocol exclusion of secondary forms of hypertension; apparent and pseudo-RHTN; and nonadherent patients (assessed via urine toxicological analyses or direct observation of tablet-taking [or both]). These studies should include extended follow-up periods with hard major adverse cardiovascular event and mortality endpoints to allow a conclusion to this quandary.

Although RSD has been studied in severe RHTN as a spectrum of disease that is well recognized to demonstrate elevated central sympathetic tone, it has been evaluated in other systemic conditions that exhibit similar sympathetic overdrive. Pilot studies have revealed pleiotropic effects of RSD with improvements in obstructive sleep apnea metrics,[75] glycemic control in RHTN patients,[75,76] systolic[77] and diastolic[78] heart failure, and atrial fibrillation.[79]

Despite the challenges ahead in filling in the crucial knowledge gaps previously identified, we should be optimistic about the opportunities that these new therapies provide in testing physiological principles as well as finally being able to offer patients, who are burdened by numerous medications and very high cardiovascular risk, alternative options to pharmacotherapy for hypertension. ■

Vikas Kapil, MD, MRCP, PhD, is with William Harvey Research Institute, Centre for Clinical Pharmacology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London; and Barts Health NHS Trust in London, United Kingdom. He has disclosed that he has received funding from the British Heart Foundation. Dr. Kapil may be reached at v.kapil@qmul.ac.uk.

Melvin D. Lobo, MD, FRCP, PhD, is with William Harvey Research Institute, Centre for Clinical Pharmacology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London; and Barts Health NHS Trust in London, United Kingdom. He has disclosed that he has received educational grant funding from Medtronic, Inc., and is on the medical advisory board of St. Jude Medical, Inc.

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