Review Article

Device Therapies for Resistant Hypertension

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ABSTRACT

Purpose: Resistant hypertension (RH) is a major and growing public health problem. While noncompliance to antihypertensive medication is a major concern in RH patients, it is estimated that even with adequate multidrug regimens, approximately 10% of patients diagnosed with hypertension fulfill the criteria of true RH. Patients with sustained blood pressure (BP) elevation display high risk for development of target organ damage and associated cardiovascular morbidity and mortality. While optimized pharmacologic therapy, including the use of mineralocorticoid receptor antagonists to guideline-based antihypertensive drug therapy, is effective for improving BP control in this patient cohort, a sizable proportion of RH patients' BP remains uncontrolled, and alternative therapeutic strategies are warranted.

Methods: In the past few years, device-based approaches have been studied extensively. Among these, robust clinical experience in patients with RH exists for renal denervation, baroreflex activation therapy, central arteriovenous anastomosis, and, to a lesser extent, deep brain stimulation. Carotid body modulation is the most recent approach under clinical investigation. The common aim of these approaches is direct targeting of relevant pathophysiologic mechanisms involved in BP control, most commonly activation of the sympathetic nervous system.

Findings: This review article briefly summarizes relevant clinical and experimental evidence and highlights the potential utility, as well as limitations, of each approach.

Implications: Several device-based approaches show promise in the treatment of RH and have been associated with improved BP control, while generally finding an acceptable side effect profile. Ongoing research is addressing relevant issues relating to patient selection and technical and procedural aspects, and will help to define the future role of device-based approaches for RH in the next few years. (*Clin Ther.* 2016;38:2152–2158)

Key words: resistant hypertension, sympathetic, denervation, devices, baroreflex.

INTRODUCTION

While the pathogenesis of essential hypertension is complex and multifactorial, the mechanisms implicated in drug-resistant hypertension, commonly defined as blood pressure (BP) above target levels despite prescription of at least three antihypertensive drugs at maximally tolerated doses, including a diuretic, are not entirely understood. Ample evidence indicates that neurohumoral activation is integral in the initiation and maintenance of elevated BP and its adverse consequences.[1] Even high-normal BP is associated with autonomic neural imbalance resulting in sympathetic activation and arterial stiffness preceding established hypertension.[2] Increased muscle sympathetic nerve activity is evident in low-risk subjects with high-normal BP[3,4] and essential hypertension,[5,6] and remains markedly elevated in patients with RH,[7–9] irrespective of the concomitant antihypertensive drug combination. Other conditions frequently

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characterized by high sympathetic activation, such as diabetes, chronic kidney disease, and obstructive sleep apnea, are frequent comorbidities and may perpetuate disease progression and cardiovascular complications. While development of antihypertensive drugs focusing primarily on inhibition of the renin–angiotensin–aldosterone system is ongoing,[10] device-based approaches have been an important clinical research focus during the last decade. Recently tested interventional approaches frequently target the sympathetic nervous system at various levels, including sympathetic nerves innervating the kidneys (renal denervation [RDN]), neural mechanism involved in baroreflex control (baroreflex activation therapy [BAT]), carotid body–mediated neural signaling (carotid body modulation), and central sympathetic drive by stimulation of the periventricular and periaqueductal gray area by (deep brain stimulation). While not directly inhibiting sympathetic tone, creation of a central arteriovenous anastomosis is another device-based approach aimed at reducing BP by altering mechanical vascular properties.

RENAL DENERVATION

Among recent developments in the management of drug-resistant hypertension that oppose sympathetic activation, RDN has generated substantial interest, with a series of investigations in patients with resistant or uncontrolled hypertension and associated comorbidities during the past few years. Various experimental models of hypertension and human studies found that disruption of renal sympathetic nerves has considerable pathophysiologic consequences, ultimately resulting in lower BP.[11] Data from the initial clinical trials applying catheter-based RDN found a substantial BP reduction and attenuation of target organ damage in patients with RH.[8,12–19]

While relatively small in size, with a total of 45 RH patients (baseline mean BP of 177/101 mm Hg) undergoing RDN in an initial nonblinded proof-of-concept study (Symplicity HTN-1),[12,14] the tolerability of the procedure could be reported, along with clear evidence of efficacy with a reduction in office BP of −22/−11 mm Hg and −27/−17 mm Hg at 6 and 12 months after the procedure, respectively. Initial concerns about the durability of the BP reduction were addressed by subsequent longer-term follow-up out to 36 months post-procedure, finding a sustained office BP reduction of −32/−14 mm Hg.[14] Importantly, a sub-group of participants underwent state of the art norepinephrine spillover assessment to document the degree of RDN that was achieved with the first-generation, single-electrode device and revealed a 47% reduction in renal norepinephrine spillover. Clearly, partial RDN was achieved, however, this was far from being complete.

In order to provide more robust evidence, Symplicity HTN-2 was designed as a prospective randomized controlled clinical trial.[13,20] Participants fulfilling criteria for RH were randomly assigned to receive RDN in addition to continued pharmacologic treatment (n = 52) or to continuation of their established conventional pharmacologic treatment alone (n = 54). The BP-lowering effect observed in the RDN group at 6 months post-procedure was almost superimposable to that seen in Symplicity HTN-1, with a mean (SD) BP reduction of −32 (23)/12 (11) mm Hg.[13] Again, sustained BP effects could be found with a follow-up report at 12 months, showing a mean (SD) BP reduction of −28 (25)/10 (11) mm Hg.[20] Somewhat unusual for a control group, BP changes were very minimal and nonsignificant (1 [21]/0 [10] mm Hg). Tolerability aspects were again favorable, with an unchanged mean estimated glomerular filtration at 6 months follow-up in both groups.

Despite these initial promising and consistent results, the efficacy of RDN was questioned after publication of the Symplicity HTN-3 trial, a large US pivotal trial that failed to meet its primary efficacy end point of a significant difference in ambulatory BP between active RDN treatment and a sham-control procedure.[21] While this study had an excellent design, shortcomings in the execution of the study, including limited operator experience, preferential ablation of the proximal renal artery, and the likely failure of achieving renal nerve ablation, are now considered major contributors to these findings.[22,23] Indeed, a bilateral circumferential ablation pattern considered crucial for sufficient RDN was achieved in only 6% of treated patients.[24] Although not tested directly, insufficient RDN is also likely to account, at least in part, for the lack of BP response to the procedure, which has been reported in 15% to 30% of treated patients. In contrast, the recent rigorously designed DENERHTN (Renal Denervation in Hypertension) study, supervised by an interventionalist with substantial experience in RDN, found that ablation of renal nerves is associated with significant BP reduction.[25] In this study, patients with RH confirmed by ambulatory BP receiving a 4-week standardized triple antihypertensive treatment

(indapamide 1.5 mg, ramipril 10 mg or, if not tolerated, irbesartan 300 mg, and amlodipine 10 mg or 5 mg in the presence of ankle edema) were randomly assigned in a 1:1 ratio to the RDN or control group. After randomization, patients in both arms received stepped-care antihypertensive drug treatment (ie, spironolactone 25 mg, bisoprolol 10 mg, prazosin 5 mg, and rilmenidine 1 mg daily) during monthly reviews for 5 months if home BP was ≥135/85 mm Hg. The DENERHTN study found a reduction in mean ambulatory daytime systolic BP (SBP) of −15.8 mm Hg in the RDN arm and −9.9 mm Hg in the control arm from baseline to 6 months.[25] The lack of a sham control in the DENERHTN study was compensated for by various study measures (ie, assessment of drug adherence, independent and blinded evaluation of ambulatory BP, consistent monthly team visits, and home BP assessment). The DENERHTN study results clearly support the notion that RDN is a useful add-on therapy to standard pharmacologic treatment and results in clinically meaningful additional lowering of BP.

Another study[26] applying a sham-controlled study design not dissimilar to that used in Symplicity HTN-3 found that in the per-protocol analysis, those who underwent RDN experienced a significantly more pronounced reduction in mean (SD) 24-hour and daytime SBP at 6-month follow-up compared with patients treated with a sham procedure (−8.3 [8.9] mm Hg vs −3.5 [9.5] mm Hg; $P = 0.04$).[26]

Very recently however, another sham-controlled, double-blinded randomized, single-center trial assessed the efficacy of RDN on ambulatory BP control.[27] In this study, patients with RH and daytime SBP of ≥145 mm Hg after 1 month of therapy on stable medication were randomly assigned to the RDN group or sham-controlled group. While the procedure was performed by an experienced operator using the same unipolar catheter as in the Symplicity HTN-3 and DENERHTN studies, it found similar mean (SD) reductions in daytime SBP at 3 and 6 months follow-up in the RDN (−6.2 [18.8] mm Hg and −6.1 [18.9] mm Hg) and in the sham-controlled (−6.0 [13.5] mm Hg and −4.3 [15.1] mm Hg) group. Whether the circumferential ablation pattern required to reach sufficient RDN has actually been achieved was not addressed in the paper.[27]

In view of the conflicting results of these clinical randomized trials, recent data from autopsy studies[28,29] aimed at gaining a better understanding of renal nerve anatomy and their localization relative to the renal artery lumen are of high relevance. Findings from these sophisticated anatomic studies found that human renal nerves are not universally and equally distributed along the renal arteries, possibly explaining some of the variability in BP response rates to RDN and failure of the procedure to lower BP in some patients. Ablating more distal parts of the main renal artery, where sympathetic nerves are in closer proximity to the arterial lumen, combined with treatment of renal artery branches purposely spared in the initial studies, has now been found to be substantially more efficient in achieving a reduction in renal noradrenaline content as an indicator of adequate RDN.[30] Currently ongoing sham-controlled studies have been designed to address these issues and aim at more complete denervation with more extensive ablation using multi-electrode catheters, thereby increasing the likelihood of proper circumferential ablation. Combined with direct assessment of RDN efficacy using noradrenaline spillover methodology, these studies will provide definite answers to the most relevant open questions and help define the future role of RDN in resistant hypertension and beyond.

BAROREFLEX ACTIVATION THERAPY

Prolonged electric stimulation of the carotid baroreceptors through its modulatory influence on afferent signaling is another attractive target for the treatment of uncontrolled hypertension. Baroreflex sensitivity is commonly disturbed in hypertension and fails to maintain BP at appropriate levels through its rapid negative feedback loop, in which an elevated BP reflexively causes heart rate to decrease and BP to fall. In an initial proof-of-concept study, BAT has been found to exert substantial BP-lowering effects using the CVRx Rheos System (CVRx, Minneapolis, MN) (DEBuT-HT [Device Based Therapy in Hypertension Trial) consisting of implantable electrodes connected to a subcutaneously placed stimulator.[31,32] Implantation of the first-generation device was associated with serious procedure-related adverse events and the short-term battery life limited its utility. Next-generation devices could largely overcome these issues and implantation of the Barostim neo (CVRx) was associated with a significant BP reduction at 3 and 6 months follow-up, even in patients previously treated with RDN, with less device-related side effects compared with earlier models.[33] A recent study in 28 patients[34] revealed further evidence of the beneficial

effects achieved by BAT in patients who remained hypertensive despite RDN performed 5 months prior. Interestingly, BAT therapy was recently found to control BP in a 34-year-old male with hypertensive crisis after aortic dissection due to RH that was unresponsive to sympatholytic agents.[35] While the BAT device is usually activated 2 to 4 weeks after surgical implantation to allow the site to heal, immediate activation of BAT in this specific scenario produced a rapid, significant, and sustained reduction in BP. Although a device that requires surgical placement of electrodes may be impractical in an emergency situation, the concept of electrical stimulation of the baroreceptors as a means of achieving prompt and sustained BP reduction is intriguing, and highlights the potential of this approach. Further refinement of the technology and longer-term follow-up of treated patients will help to define the clinical utility of BAT as an alternative therapy in RH.

Carotid Body Modulation

The well-recognized association between augmented chemoreflex sensitivity and sympathetic activation as an important contributor to the pathophysiology of hypertension led to the initiation of studies investigating the feasibility of a therapeutic intervention aimed at selectively targeting peripheral arterial chemoreceptors located in the carotid body.[36] A first-in-man study of surgical carotid body removal in patients with RH was completed recently and found significant BP-lowering effects in most treated patients (Narkiewicz K, personal communication, 2016). Final results of this pilot study will be available shortly. Clearly, surgical removal of the carotid body is unlikely to attract widespread acceptance by patients or treating physicians, even in patients at high cardiovascular risk. In contrast, a catheter-based interventional approach, which is feasible either directly via arterial access through the carotid artery or preferably via a transjugular access, appears justifiable if an acceptable safety profile and a clear signal for BP-lowering efficacy can be found. Safety profile and proof-of-concept studies are currently ongoing with first-generation devices and will soon shed light on the potential clinical utility of targeting yet another important regulatory component of neural cardiovascular control.

Deep Brain Stimulation

Deep brain stimulation (DBS) modulates pathologic activity within the central sympathetic nervous system and has gained significant recognition in the treatment of Parkinson's disease in clinical practice. In addition to therapeutic effects in a wide range of neurologic disorders (ie, chronic pain syndrome resistant to analgesics, major depressive disorder, dystonia, epilepsy, and schizophrenia), DBS of the ventrolateral peri-aqueductal gray and peri-ventricular gray matter has been found in case reports to effectively lower ambulatory BP by around 13/10 mm Hg in patients with RH.[37,38] While the effect of DBS on sympathetic activity in RH is unknown, DBS of specific midbrain nuclei and ventrolateral peri-aqueductal gray has been found to acutely improve vasomotor baroreflex sensitivity and reduce muscle sympathetic nerve activity and BP in patients with chronic neuropathic pain and Parkinson's disease. Although DBS confers a 1% stroke risk, it may serve as a last resort for treating severe forms of uncontrolled hypertension in patients who remain unresponsive to less-invasive device-based interventional strategies. Whether the BP-lowering effect achieved with DBS is sustained during the longer term warrants further investigation, as does the potential contribution of procedure-induced pain relief to the BP-lowering effects.

Central Arteriovenous Anastomosis

The ROX coupler system (ROX Medical, San Clemente, CA) allows interventional creation of a 4-mm anastomosis between the iliac artery and vein. The arteriovenous shunt diverges a defined proportion of arterial blood flow into the venous circulation, resulting in beneficial hemodynamic alterations, including a decrease in vascular resistance, an increase in arterial compliance, and, ultimately, a systemic BP-lowering effect. The feasibility and efficacy of this intervention has been reported in a multicenter, prospective, randomized controlled trial.[39] Eligible patients with daytime BP of $\geq$135/85 mm Hg despite treatment with at least three or more antihypertensive drugs, including a diuretic, were randomly assigned in a 1:1 ratio to either interventional creation of anastomosis in addition to concomitant medication (n = 44) or to BP-lowering mediation alone (n = 39). There was a significant reduction in mean (SD) office BP (−26.9 [23.9] mm Hg) and 24-hour daytime BP (−13.5 [18.8] mm Hg) at 6 months follow-up (the primary efficacy end point) in the anastomosis group, whereas only minor changes were observed in the control group (−3.7 [21.2] mm Hg in office SBP, 0.5 [15.8] mm Hg

in daytime SBP). Recent evidence suggests that the antihypertensive effects are predominantly mediated by a profound reduction in systemic vascular resistance.[40] However, the safety profile analysis raised some concerns, with a number of reported adverse events in the intervention group (eg, anemia, transient bradycardia, deep venous thrombosis, intimal dissection of the iliac artery, and lower limb pain), and, most importantly, post-procedural occurrence of late venous stenosis requiring venoplasty or stenting in 12 of 42 patients (29%) treated with the ROX coupler device. In view of these findings, arteriovenous anastomosis may be a valuable tool to modify arterial properties, particularly for a subset of RH patients who are not eligible for RDN (ie, inappropriate renal anatomy) or carotid body modulation (ie, invisible or high-positioned carotid body). While a substantial reduction in ambulatory BP achieved with the coupler device might translate to improved patient outcomes, further studies determining the long-term tolerability and BP efficacy are warranted.

CONCLUSIONS

In view of the increasing hypertension burden, attention should focus on appropriate lifestyle modification and improving patient compliance with medication. The underlying neurogenic component of hypertension has prompted the introduction of interventional therapeutic strategies aimed at modulating autonomic neural mechanisms to improve BP control. Conflicting results regarding the clinical effectiveness of RDN can be partly explained by inadequate patient selection, technical and procedural shortcomings owing in part to incomplete understanding, and knowledge of human renal nerve anatomy and distribution. Randomized double-blind sham-controlled clinical trials using multi-electrode catheter or ultrasound are currently underway and will address numerous limitations encountered in previous trials. At this stage and until more robust evidence is available about the long-term tolerability and efficacy of various interventions, these procedures should be restricted to controlled clinical trials carried out in experienced centers.

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