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Premise, Promise, and Potential Limitations of Invasive Devices to Treat Hypertension

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Abstract Invasive device-based therapies for drug-resistant hypertension are undergoing active clinical investigation. The two approaches are 1) permanent implantation of a carotid baroreceptor pacemaker and 2) radiofrequency catheter ablation of the renal nerves. Both are designed to reduce the sympathetic nervous system component of drug-resistant hypertension. Several excellent comprehensive articles have reviewed each of these devices separately. In contrast, this brief article aims to provide a conceptual framework for evaluating the premise, promise, and potential limitations of both invasive antihypertensive therapies.

Keywords Hypertension · Carotid baroreceptor pacemaker · Radiofrequency catheter ablation · Antihypertensive therapies · Sympathetic nervous system · Parasympathetic nervous system · Sympathetic overactivity · Norepinephrine · Renal vasoconstriction · Renin · Sodium · Vascular resistance · Blood pressure · Blood flow · Heart rate · Efferent renal nerves · Afferent renal nerves · Kidney disease · Renal disease · Heart failure · Left ventricular dysfunction · Innervation · Denervation · Electrical stimulation

Introduction

Invasive device-based therapy for clinical hypertension has created much new buzz, even before receiving US Food and Drug Administration (FDA) approval. Two different approaches are under active clinical investigation: 1) permanent implantation of a carotid baroreceptor pacemaker [1••, 2–5] and 2) radiofrequency (RF) catheter ablation of the renal nerves [6•, 7••]. The recent publications have captured the attention of invasive cardiologists, vascular surgeons, and entrepreneurs who previously have had less interest in hypertension management. The new research also has rekindled scientific interest in neural mechanisms of hypertension as viable therapeutic targets for hypertension—especially drug-resistant hypertension.

Several excellent comprehensive articles have reviewed each of these devices separately [3, 8–12]. In contrast, this brief article aims to provide a conceptual framework for evaluating the premise, promise, and potential limitations of both invasive antihypertensive therapies. We will focus solely on clinical hypertension, discussing none of the preclinical data, and base our comments on peer-reviewed published data to date [13–15].

For decades, the sympathetic nervous system has been the "stepchild" of clinical hypertension. Sympathetic neural activity is too hard to measure in routine clinical practice. The measurement techniques require specialized training and research infrastructure, which are not widely available. Also, anti-adrenergic drugs are not first- or second-line therapy for uncomplicated hypertension because they have undesirable side-effect profiles and have performed poorly in treatment trials [16–18]. Standard β blockers are far less effective than other classes of antihypertensives in lowering central blood pressure and thus offer little if any stroke protection [19, 20]. They can cause diabetes, depression, and fatigue, and precipitate asthma or heart block in predisposed patients. α Blockers can precipitate heart failure in patients with asymptomatic left ventricular dysfunction [16, 17]. Central sympatholytics cause fatigue, depression, and rebound hypertension.

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However, there now is overwhelming evidence that sympathetic overactivity constitutes a major factor in the pathogenesis and progression of human hypertension. The best evidence comes from radiotracer measurements of regional norepinephrine (NE) spillover [21, 22] and microelectrode measurements of postganglionic sympathetic nerve activity, the proximate neural stimulus to NE release [23, 24]. The former shows that sympathetic outflow is typically increased to the heart and kidneys in patients with primary hypertension. The increased cardiac NE spillover is thought to promote the development of left ventricular hypertrophy [25, 26]. The increased renal NE spillover is thought to promote the development and progression of hypertension by at least three mechanisms: renal vasoconstriction, renin secretion, and reduced sodium renal excretion [8]. The nerve recordings show that patients with primary hypertension typically have a sustained increase in the basal firing rate of sympathetic nerves innervating the skeletal muscle vasculature, one of the main beds determining total systemic vascular resistance and blood pressure (as well as insulin-mediated glucose disposal) [27].

Figure 1 shows the major central and reflex mechanisms thought to drive sympathetic overactivity in human hypertension. These include, among others, resetting of the baroreceptors and activation of renal afferents. The figure also shows the specific mechanisms that are targeted by the device-based therapies and those that are not.

Carotid Sinus Pacemaker

The Premise

Baroreceptors are pressure-sensitive nerve endings located in the adventitia of the carotid sinuses and aortic arch [23, 28]. With each cardiac cycle, they fire during each systole and are silent during each diastole. The baroreceptors buffer acute increases in blood pressure as with emotional or physical stress. When blood pressure rises suddenly, increased baroreceptor firing sends inhibitory signals to the nucleus tractus solitarius (Fig. 1). This triggers a reflex increase in vagal efferent activity—slowing sinus rate—and a reflex decrease in sympathetic efferent activity to multiple vascular beds—decreasing vascular resistance and thus blood pressure.

The baroreceptors are thought to play a permissive role in chronic hypertension [23, 28]. They reset to defend a higher level of blood pressure, and the reflex gain can be attenuated. This attenuation is due in part to stiffening of the vessel walls in which pressure-sensitive nerve endings are embedded: a given increase in blood pressure causes less mechanical deformation of their receptive fields.

The proof-of-concept studies for carotid baroreceptor pacing dates back to the 1950s when this approach was used to treat angina and hypertension [29, 30]. Despite some short-term success, the approach was abandoned due to technical limitations—electrode contact with the carotid sinus nerve deteriorated over time due to seepage of tissue juice—and the advent of β blockers [29, 30]. Over 50 years later, the premise behind the Rheos system (CVRx, Minneapolis, MN) is a technological advance allowing durable electrode contact.

The Rheos Baroreflex Hypertension System consists of an internal programmable pulse generator and electrode leads for bilateral carotid nerve stimulation [31]. Following neck incision under general anesthesia, electrodes are placed around both carotid bifurcations. The stimulation protocol in the operating room involves changing the placement of the electrodes until optimal blood pressure response to acute electrical stimulation is found. The pacemaker itself is placed in a subcutaneous pocket and then turned off until the patient returns for a follow-up visit 1 month after the surgery.

The Promise

The appropriate initial target patient population is drug-resistant hypertension, which is said to represent as many as 1 in 5 hypertensive patients [32]. Even if a substantial portion of such patients have pseudoresistance, the actual target population in the United States alone could be 2 to 7 million Americans.

What is clear from the published data so far is that in chronically implanted patients with drug-resistant hypertension, acute activation of the baroreceptor pacemaker for 10 min evokes voltage-dependent decreases in blood pressure, with parallel decreases in heart rate and muscle sympathetic nerve activity [1••, 2–5]. These parameters return to baseline levels when the stimulation is turned off. For example, one study of 12 patients showed peak drops in blood pressure of 32/15 mm Hg (from baseline blood pressure 193/94 mm Hg), heart rate of 5 bpm, and sympathetic nerve activity of 9% in 12 patients [1••].

What is yet to be determined is whether long-term carotid baroreflex stimulation is effective antihypertensive therapy. To date, there are two multicenter trials of Rheos for drug-resistant hypertension—one in Europe (DEBuT-HT trial [Device Based Therapy in Hypertension Extension Trial]; clinicaltrials.gov identifier NCT0 0710294) and the other in the United States (Rheos Pivotal trial; clinical trials.gov identifier NCT00442286). The European DEBuT-HT trial is a single-arm, open-label trial with end points of safety and blood pressure at 1 year post surgery with an enrollment goal of 50 patients. Forty-five patients have been enrolled with a

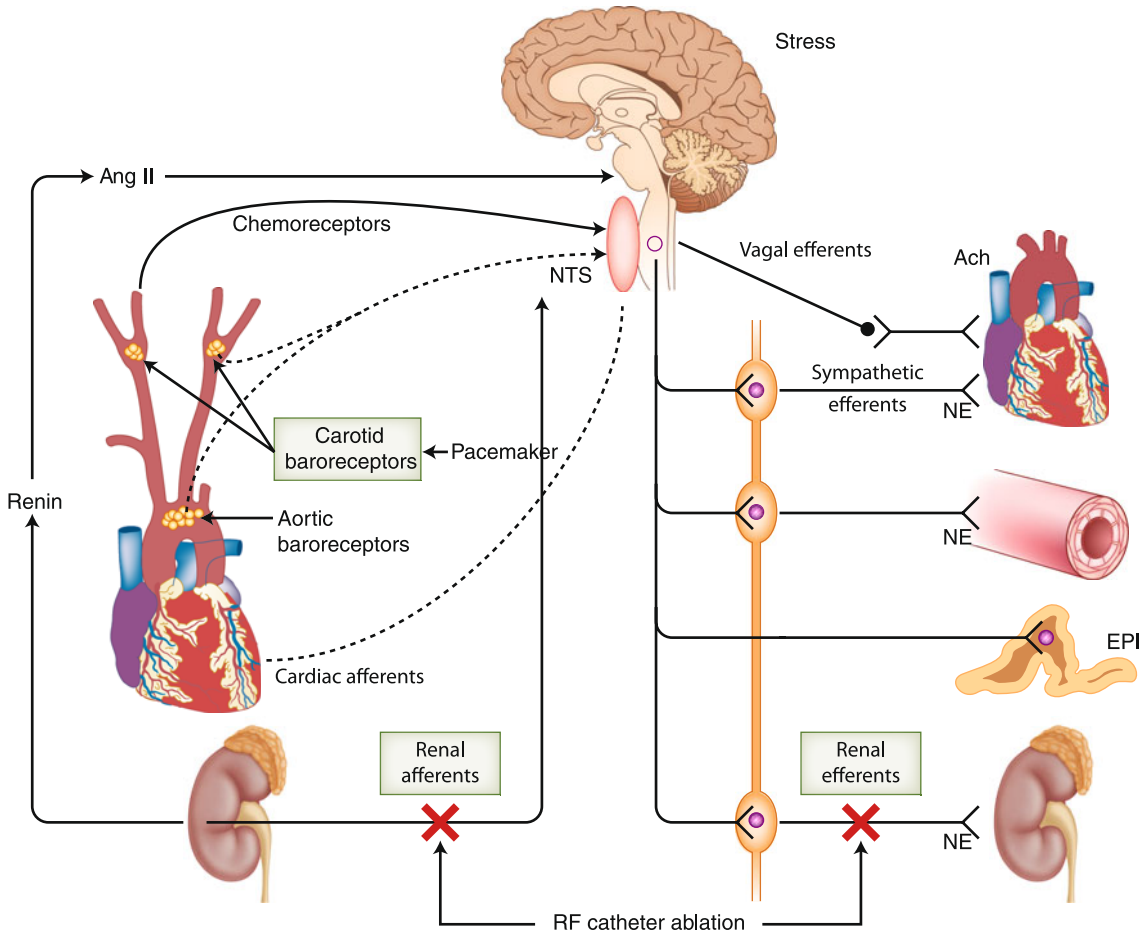

Fig. 1 Central and reflex mechanisms involved in the neural control of blood pressure. *Bold boxes* and *"X" marks* show target areas for invasive therapeutic devices for the treatment of hypertension, including carotid baroreceptor pacemakers and radiofrequency (RF) catheter ablation of the renal afferent and efferent nerves. *Dotted arrows* represent inhibitory neural influences and *solid arrows* represent excitatory neural influences on sympathetic outflow. *Ach* acetylcholine, *Ang II* angiotensin II, *EPI* epinephrine; *NE* norepinephrine, *NTS* nucleus tractus solitaries. (*Modified from* Victor and Shafiq [28])

baseline blood pressure of 179/105 mm Hg. The recently published results show that office blood pressures dropped by 21/12 mm Hg at 3 months (n=37), 30/20 mm Hg at 1 year (n=26), and 33/22 mm Hg at 2 years (n=17). In a subset of patients, ambulatory blood pressures dropped 6/4 mm Hg at 3 months, 13/8 mm Hg at 1 year, and 24/13 mm Hg at 2 years [33••]

The US Pivotal trial was designed as a randomized, controlled, double-blind trial with end points of safety and blood pressure reduction at 1 year and an enrollment goal of 300 patients: 322 patients were enrolled. One month following pacemaker implantation, patients were randomized to an active intervention arm in which the pacemaker was turned on for the full 12 months or a comparison arm in which the pacemaker was off for the first 6 months and turned on for the final 6 months. An interim analysis by the Data Safety Monitoring Board found that the 6-month efficacy and 30-day safety endpoints were unlikely to be met [34].

Potential Limitations

Potential limitations of a carotid baroreceptor pacemaker for hypertension involve 1) challenges of clinical trial methodology, 2) surgical skill, and 3) conceptual issues. Because the first two issues are common to both devices, they will be discussed later in the paper.

Conceptually, the key question is whether sustained electrical stimulation of the carotid sinus nerves can cause sustained reductions in blood pressure or whether there will be partial blood pressure escape. To test for escape or adaptation, it first would be necessary to show that electrode contact with the nerve does not deteriorate over time. If so, the next key issue is potential compensation from many other blood pressure control mechanisms, especially from aortic baroreceptors that are not being paced. With carotid baroreceptor pacing, the fall in blood pressure should be sensed by the aortic baroreceptors, evoking reflex increases in sympathetic activity that would

be expected to at least partially offset the desired blood pressure reduction. Moreover, previous research suggested that in normotensive humans the aortic baroreceptors are dominant in the baroreflex control of sympathetic activity, vascular resistance, and blood pressure, whereas the carotid baroreceptors are dominant in the vagal control of heart rate [35]. The acute stimulation studies with Rheos in hypertensive individuals may call the earlier conclusion into question.

A large body of research has shown that baroreflex control of vagal activity (heart rate) is attenuated with even mild hypertension [36], whereas baroreflex control of sympathetic activity (vascular resistance and blood pressure) is preserved until much later in the hypertensive process—until stage 2 hypertension associated with left ventricular hypertrophy [37, 38]. Thus, in some patients with advanced hypertension in the Rheos trials, the carotid pacemaker may be driving an attenuated reflex.

Radiofrequency Ablation of the Renal Nerves

The Premise

The kidney is richly innervated by sympathetic nerve terminals. The renal sympathetic nerves have long been considered one of the most important regional sympathetic outflows in long-term blood pressure regulation [39]. Renal sympathetic nerves cause renal vasoconstriction and hypertrophy via α_1 receptors, stimulate renin release via β_1 receptors, and enhance renal sodium and water reabsorption via α_1 receptors [39].

The kidney is also a sensory organ, innervated by a rich supply of sensory afferents that signal the brain of changes in the chemical composition of the urine and mechanical changes in the renal pelvis [14, 40, 41]. Some of these afferents have inhibitory effects on sympathetic outflow [14, 40] but most seem to evoke sympathetic excitation [41]. Chemosensitive renal afferents can be activated by ischemic metabolites such as adenosine and uremic metabolites such as urea; they have been implicated in triggering reflex sympathetic activation and thus contributing to the pathogenesis and progression of hypertension in chronic kidney disease, renovascular hypertension, and cyclosporine A–induced hypertension [42, 43]. The renal nerves also have been implicated in the progression of hypertensive chronic kidney disease [44, 45].

The proof-of-concept studies for this invasive antihypertensive therapy began as early as the 1930s, when complete surgical sympathectomy was used to reduce blood pressure in patients with hypertension [46]. These methods were abandoned because they were associated with high perioperative morbidity and mortality. In contrast, the RF catheter allows selective, nonsurgical ablation of the renal sympathetic nerves.

The catheter (Symplicity; Ardian, Palo Alto, CA) is used for hopefully complete and permanent ablation of both renal nerves, both efferents and afferents [47]. The procedure is performed under conscious sedation because patients will experience transient renal colic with the ablation (renal afferent nerve activation). The catheter is inserted into the femoral artery and then advanced to each renal artery under the guidance of renal angiography. The premise is that the renal nerves, which are located on the adventitial surface of the renal arteries, are destroyed by application of an RF current via the intraluminal catheter. An advantage of this approach is that this is a one-time procedure, and there is no implanted hardware.

The Promise

Once again, the appropriate initial target patient population is drug-resistant hypertension. The ongoing safety and proof-of-principle cohort study is being performed at five medical centers in Australia and Europe (clinicaltrials.gov identifiers NCT00483808 and NCT00664638). The study is designed as an uncontrolled, open-label, single-group assignment study to assess the safety and feasibility of the interventional treatment in patients with 1) blood pressure of 160 mm Hg or higher, 2) treatment with three or more antihypertensives, 3) no known secondary cause of hypertension, and 4) glomerular filtration rate of 45 mL/min/1.73 m^2 or more. To date, 50 patients have been enrolled, and recruitment is ongoing.

What has been published in the peer-review literature so far is the initial results of this phase 1 study [6•] and a multicenter, prospective, randomized trial [7••]. After bilateral RF renal nerve ablation, renal NE spillover fell by 47.5%. Office blood pressure fell (from a baseline of 177/101 mm Hg) by 24/10 mm Hg in 39 patients at 3 months of follow-up and by 29/16 mm Hg in the first nine patients followed for 12 months [6•]. However, measured reductions in blood pressure by 24-hour ambulatory monitoring were much smaller: -11 mm Hg (vs −27 mm Hg for office blood pressure in the same 12 patients at 1 month). In the absence of a control group, the precise effect size remains unclear.

In the multicenter Symplicity HTN-2 trial, office blood pressure fell by 32/12 mm Hg from a baseline of 178/96 mm Hg in 49 patients six months following renal denervation, but not in the control group [7••]. Home-based blood pressure measurements and 24-hour blood pressure monitoring confirmed these findings.

Potential Limitations

As with the carotid sinus nerve pacemaker, potential limitations of RF renal nerve ablation for resistant hyper-

tension involve 1) challenges of clinical trial methodology, 2) operator skill, and 3) conceptual issues.

Besides patient safety issues of early and late procedural complications, which are being actively investigated, the main unresolved conceptual concerns are the completeness of renal denervation and possible reinnervation over time. Efficient protocols for quantifying renal denervation and long-term follow-up studies are needed. An RF catheter placed at the level of the renal nerves almost certainly will not destroy all urogenital afferents, which arise densely throughout the renal pelvis as well as the genitofemoral regions; the afferent inputs may exert highly redundant effects on sympathetic outflow.

Continuing with the concept of redundancy, the renal efferents are by no means the only regional sympathetic nerves involved in blood pressure regulation. Major roles have been implicated for the muscle and splanchnic sympathetic nerves [48], which obviously will not be ablated by the procedure. A key question is whether renal afferent denervation causes global decreases in sympathetic nerve activity to multiple vascular beds. The advent of the RF catheter should shed important new light on this topic.

Limitations Common to Both Devices

As mentioned earlier, clinical trial methodology and operator skill complicate the evaluation of both invasive techniques. Standard clinical trial methodology is designed for evaluating drug therapy and is an imperfect fit for evaluating device-based therapy of any kind. Antihypertensive drug trials typically randomize tens of thousands of patients with stage 1 to 2 hypertension to new therapy versus an active comparator arm and are powered to detect a greater benefit of the new therapy on hard outcomes over 5 years. By contrast, the initial device-based trials have a sample size of only 50 to 300 patients mainly because of the much stricter inclusion criteria, starting with drug-resistant hypertension. Due to sample size, the primary outcome is restricted to blood pressure reduction rather than hard outcomes. The ability to detect and measure a treatment effect on blood pressure reduction is complicated by background noise from the inherent variability of blood pressure and changing multidrug blood pressure regimens. Ambulatory blood pressure monitoring will help with the former but not the latter issue.

With the carotid sinus pacemaker, “sham” pacing is a reasonable short-term control, but for ethical reasons, patients cannot be randomized to sham RF renal nerve ablation. In the absence of comparator arms, the expected Hawthorne effect and regression to the mean will lead to overestimation of treatment effects (of both trials).

Operator skill is another uncontrolled variable in these multicenter trials of relatively small numbers of study patients. This will become an even larger issue in the clinical practice setting if FDA approval is obtained. Objective, highly standardized, intermediate end points need to be developed and measured repeatedly to establish in each patient the extent to which the intervention was delivered as intended, both initially and over time. Both devices would be expected to have a larger treatment effect when there is a large sympathetic component to the hypertension, which may or may not be the case in individual patients with drug-resistant hypertension. Finally, the total numbers of patients with truly drug-resistant hypertension will need to be re-evaluated with the increasing use of excellent cost-effective fourth- and fifth-line generic drugs for difficult hypertension, such as vasodilating β blockers and aldosterone antagonists [32].

Conclusions

Device-based therapy is a fascinating new area of clinical research in hypertension. Any firm conclusions at this point would be premature pending publication of final outcome data from the current multicenter trials. Much more research is needed to identify subsets of patients who stand to benefit the most—not only for hypertension but potentially also for treatment of heart failure and chronic kidney disease. Formal long-term cost-effectiveness simulations will be key in the era of health care reform.

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