Interventional Approaches to Reduce Sympathetic Activity in Resistant Hypertension
To Ablate or Stimulate?

Italo Biaggioni

In this issue of Hypertension, Lohmeier et al compare, in a dog model of obesity-hypertension, 2 interventional techniques currently being tested in clinical trials for the treatment of resistant hypertension.1 Sympathetic inhibition is the mechanism by which these interventions are proposed to control hypertension.

That sympathetic activity plays a role in hypertension is not a new concept. From the mid 1930s until late 1950s, surgical sympathectomy was practically the only effective treatment for malignant hypertension, and, although plagued by significant side effects, it improved survival of an otherwise fatal disease. Ganglionic blockers and reserpine were the earliest antihypertensives developed, and central sympatholytics followed shortly thereafter.

Drugs targeting the sympathetic nervous system, however, are no longer considered as first-line antihypertensives. Central sympatholytics are limited by their side effects, and outcome trials have shown that α- and β-blockers are inferior in lowering the incidence of heart failure and strokes, respectively, compared with other drugs.

There is, therefore, a mismatch between the need to target sympathetic activation in hypertension and the limitations of available medical therapies. Novel interventional approaches are trying to fill this void. One of these approaches relates to the work by Lohmeier et al, who showed that chronic carotid sinus stimulation produced a sustained decrease in blood pressure in a dog model of obesity-induced hypertension.2 This work provided further evidence that sympathetic activation plays a role in obesity hypertension and demonstrated that the autonomic nervous system not only plays a role in transient blood pressure regulation but can also contribute to sustained elevations of blood pressure.

Treatment of human hypertension with carotid sinus stimulation was attempted for a short period in the 1960s, but only recently have technological advances resulted in the development of an implantable device for bilateral electric baroreceptor stimulation (Rheos, CVRx Inc). A nonrandomized study in 45 patients demonstrated the feasibility and safety of this approach, and sustained reductions in blood pressures were observed after up to 2 years of follow-up.3 As expected, carotid stimulation decreased sympathetic tone as assessed by muscle sympathetic nerve activity.4 In a double-blind clinical trial, the Rheos device was implanted in 265 patients, but activation of the device was randomly delayed by 6 months in one-third of patients to constitute a control group. Blood pressure was significantly lower in the stimulated group at 6 months, but the predefined primary efficacy end point (proportion of patients reaching a decline in systolic blood pressure of 10 mm Hg) was not reached, in part because almost half of the control group reached this efficacy end point.5 This may reflect a placebo effect or more likely better adherence to medical treatment in patients participating in a clinical trial. A second-generation device using a simplified stimulating electrode (Barostim Neo, CVRx Inc) is currently being tested in Europe.

A second interventional approach is based on the observation that sympathetic activity to the kidneys is increased in hypertension and that renal denervation prevents or alleviates hypertension in a variety of animal models of hypertension. Translating this concept to the treatment of human hypertension became possible with the development of a percutaneous radiofrequency ablation catheter (Simplicity, Ardian). Ablations are performed at 6 sites along each renal artery wall in a spiral distribution. This procedure was effective in reducing blood pressure for up to 1 year of follow-up in a nonrandomized feasibility study in 45 patients with resistant hypertension.6 A substantial (47%) but not complete reduction in renal norepinephrine spillover was confirmed in a subset of patients. A subsequent open-label, randomized, controlled clinical trial in 106 patients confirmed that this procedure significantly reduced blood pressure in resistant hypertension compared with medically treated control subjects, with good safety profile.7 A double-blind study design with a sham denervation control group would have been scientifically preferable. In this regard, we should contrast the lack of improvement in blood pressure in the medical treatment control in this renal denervation study with the decrease in systolic blood pressure of $-17 \pm 29$ mm Hg observed in the patients implanted with the Rheos device in whom stimulation was delayed.8 Regardless, the catheter is already commercially available in Australia, and Medtronic (which purchased Ardian) is about to start a multicenter US trial using a randomized, double-blind, sham intervention control group design.

Renal denervation probably lowers blood pressure by decreasing efferent sympathetic input to the kidneys, increasing
renal plasma flow and decreasing sodium reabsorption leading to natriuresis, and decreasing plasma renin activity. Elimination of renal afferents, whose input increases central sympathetic activation, is also proposed to contribute to the hypotensive effect. There is evidence from animal models supporting this mechanism, but the evidence from clinical trials is limited to case reports showing reductions in muscle sympathetic nerve activity after renal denervation in 1 patient with resistant hypertension\(^9\) and 2 patients with polycystic ovary disease.\(^9\)

In this context, the article by Lohmeier et al\(^{11}\) compared both interventions in a dog model of obesity hypertension. Both interventions decreased plasma renin activity and abolished hypertension. Carotid sinus stimulation but not renal denervation also suppressed systemic sympathetic activity and reduced glomerular hyperfiltration. The authors conclude that carotid stimulation is superior to renal denervation in the treatment of hypertension.

There are limitations in the design of this study and in the generalizability of the results. A side-to-side comparison of parallel groups would have been a preferable study design to the sequential allocation used, in which renal denervation always followed carotid stimulation. More importantly, it is not clear if obesity hypertension in the dog is a good model for resistant hypertension in humans. Renal afferents are not important in this dog model of hypertension, given that renal denervation failed to decrease plasma norepinephrine, but may be important in other forms of hypertension. Whether or not they play a role in resistant hypertension in humans could be answered by expanding on the observations of the effects of renal denervation on systemic sympathetic activity.

We will need to wait for the results of definitive clinical trials with appropriate follow-up to define the long-term efficacy and safety of either technique. Bilateral implantation of carotid stimulators is arguably a more “physiological” approach to sympathoinhibition, but it is surgically more complicated and carries a risk of procedural events.\(^5\) The safety profile could improve with the simplified electrode design of the new device, and unilateral rather than bilateral carotid sinus stimulation may also be possible. Nonetheless, renal nerve ablation is less invasive and more likely to be accepted by patients. Thus far, the safety data of both interventions is reassuring, but longer-term monitoring, for example, using a registry, would be desirable.

It is unlikely that comparative effectiveness studies will be forthcoming. It would be important, therefore, that appropriate hypothesis-driven studies are performed to improve our understanding of the mechanisms of action, beneficial effects, and safety profile of each approach. Recent reports showing that renal denervation improves sleep apnea\(^{10}\) and insulin resistance\(^{11}\) are examples of such studies. Also, it would be reassuring to have more detailed studies on the effect of renal denervation on renal function.

Both techniques are being developed as alternative treatments to reduce sympathetic activation in resistant hypertension. It is noteworthy, however, that less than half of all patients enrolled in any of the published trials were being treated with central sympatholytics or with \(\alpha\)-blockers. Furthermore, less that 20% were treated with aldosterone antagonists. We can question, therefore, if these patients had indeed failed medical treatment. On the other hand, adherence to medical treatment is challenging in resistant hypertension and, given a choice, patients may prefer to have an acute therapeutic intervention to control their hypertension rather than continue on a complicated chronic medication regimen. In this regard, it is likely that the use of these procedures will expand beyond their approved indication once they become available. That there is already great interest in these novel interventional approaches is evidence by the fact that the number of editorials and reviews written about them exceed the number of actual research reports. There are already plans to explore their use to heart failure, polycystic ovary disease, and less severe forms of hypertension. It would be regrettable if this occurs before their long-term safety and efficacy are determined. We hope that instead, these novel approaches stimulate much-needed research about the role of the sympathetic nervous system in hypertension and related comorbidities.

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**Disclosures**

None.

**References**


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