Device-based Therapies for Resistant Hypertension: Current Status

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ABSTRACT
Resistant hypertension is a serious consequence of uncontrolled hypertension. This condition can lead to significant target organ damage. Individuals with resistant hypertension are highly vulnerable to excessive morbidity and premature mortality. Hence, it is important to recognise resistant hypertension as a distinct clinical entity. Whereas aggressive medical therapy is indicated to control resistant hypertension, there is a growing interest and considerable ongoing research on the role of mechanical device based approaches to control hypertension. Although the results of device based therapy of resistant hypertension are inconsistent, this alternative approach should be pursued further by newer research protocols and novel methodology.

Keywords: Baroreceptor activation therapy, Resistant hypertension, Renal denervation therapy, Uncontrolled hypertension.

INTRODUCTION
Systemic hypertension is a pervasive public health problem and is the chief contributor for excessive morbidity and premature mortality worldwide. Despite the professional and public educational efforts in the last three decades, hypertension vastly is poor controlled, untreated, undertreated, and undiagnosed in the community. Even under optimal conditions of proper diagnosis and treatment of hypertension, the goal blood pressure levels are generally not achieved in clinical practice. The reasons for poor rates for blood pressure control are complex and no unifying explanation is possible. One factor (and not the only one) for poor control of hypertension is patients’ nonadherence to therapy. Effective therapy exists for hypertension – lifestyle changes and antihypertensive drugs – but patient compliance remains a challenging issue. To provide alternate therapies for hypertension and to circumvent the problem of nonadherence, some device-based therapeutic approaches have been developed. Various device-based therapies are in different phases of clinical development, and no conclusive practical recommendations can be made out. This review provides an encapsulated update on device-based therapy for (resistant) hypertension. It should be clear that the development of device-based therapy has been restricted to “resistant” hypertension, although there is some experience with the technique in patients with other forms of hypertension, metabolic syndrome, congestive heart failure (CHF), and obstructive sleep apnea (OSA). The views expressed in this review are mainly pertinent to “resistant” hypertension.

BACKGROUND RATIONALE FOR DEVICE-BASED THERAPY FOR HYPERTENSION
There is ample and well-accepted clinical and experimental evidence to correlate the pathophysiology of hypertension to the activity of sympathetic nervous system (SNS). The level of blood pressure is dictated partially by the level of SNS activity. Systemic hypertension is of multifactorial etiology, but the supremacy of SNS is unquestionable; inappropriate and heightened SNS activity elevates the blood pressure directly and indirectly. This concept has led to the development of antisympathetic blood pressure-lowering medicines aimed at blocking the SNS activity at the cellular receptor level. Further, understanding of this pathophysiology has allowed for the exploration of (physical) sympathectomy to treat human hypertension in the middle of last century. Nonselective crude surgical lumbar sympathectomy provided significant relief from severe hypertension but unfortunately (as expected) caused a number of bothersome side effects, such as symptomatic postural hypertension. Hence, the procedure did not find a place in the therapy of hypertension and was abandoned. Moreover, when effective antisypathetic blood pressure-lowering medicines became available in the 1950s, surgical sympathectomy vanished from clinical utility. Nevertheless, the surgical
sympathectomy results revealed the importance of SNS overactivity as a major factor in the pathogenesis of hypertension.

In the last decade, technological and safety advances have led to the refined techniques to selectively ablate renal sympathetic activity, so-called renal denervation (RDN) therapy (Table 1).1,2 The field of RDN as a clinical and research tool expanded at a rapid pace, culminating in a number of clinical trials in human hypertension. Similarly, baroreceptor activation therapy (BAT) has also been developed simultaneously as a method of sympathetic deactivation to treat hypertension. Like RDN therapy, clinical trials with BAT for resistant hypertension have yielded excellent initial results. In spite of the enthusiasm for device-based therapy to treat (resistant) hypertension, its role for clinical application remains to be clarified. This article provides a status update on the evolving role of device-based therapies for hypertension.

RENNAL DENERVATION THERAPY IN PATIENTS WITH (RESISTANT) HYPERTENSION

While experimental RDN therapy has been tried for a number of years, it is only in the last decade that we have applied this technique in clinical hypertension. With advances in our knowledge about renal sympathetic fibers and their correlated integration with SNS, and advent of transcatheter techniques, several devices have been developed to cause selective RDN in patients with hypertension. The RDN catheters inserted in the renal arteries deliver enough thermal injury through the renal artery to disrupt the local afferent and efferent nerve fibers. Radiofrequency ablation is the preferred mode of energy to achieve RDN. Minimum number of ablation sites in both renal arteries is required for effective denervation with the interruption of afferent and efferent renal nerve traffic. The SNS activity falls and so does the blood pressure level.

Symplicity HTN-1 was the first clinical study to evaluate the safety and efficacy of RDN therapy in 50 patients with resistant hypertension (Graph 1).3 The RDN therapy resulted in phenomenal blood pressure reduction in the office at 1 month (−14/−10 mm Hg) and at 6 months (−27/−17 mm Hg). Ambulatory blood pressure monitoring (ABPM) in a small subset of patients, however, showed only a modest BP reduction [−11 mm Hg, systolic (SBP)].4 The subsequent Symplicity HTN-2 was conducted in a larger group (106 patients) with resistant hypertension.5 In 50% of the study population RDN was performed and in the other 50%, medical treatment was continued. In the RDN therapy group blood pressure fell significantly at 1 month (−20/−7 mm Hg) and at 6 months (−32/−12 mm Hg), while the control group showed no change in the BP level. As in Symplicity HTN-1 trial, in this study also, ABPM showed only a modest fall in BP (−11/−7 mm Hg) in a small subgroup of patients.

Along with these trials, other RDN studies showed impressive results in the unblinded, single-arm protocols. The office BP reductions were indeed dramatic (↓SBP 20–30 mm Hg). Thus, the earlier unblinded, non-randomized RDN therapy trials generated much enthusiasm, offering a possible breakthrough in the management of resistant hypertension. However, the enthusiasm quickly waned after the publication of trials with rigorous study designs, such as Symplicity HTN-3.

Symplicity HTN-3 was a randomized, sham-controlled, single-blind study to evaluate the safety and efficacy of RDN in a resistant hypertension. The study utilized a rigorous protocol design to measure the true therapeutic effect as a result of intervention. In contrast to the previous RDN studies, Symplicity HTN-3 was a US-based study in 90 research sites. It included African-Americans in the study as this group is prone to have resistant hypertension. At 6 months, the study met its “safety” objective, which is reassuring. However, the study failed to meet its “efficacy” primary objective (Graph 2).6 Results indicated that there were no differences in the achieved BP levels between the RDN and Sham (medical) groups. The SBP fell by

Table 1: Why RDN for hypertension?

- Adherence to drug treatment
- Adverse effects of drugs
- Non compliance with life style changes
- BP “escape” from control
- Drug interactions
- Cumulative costs
- Patient beliefs
14.1 ± 24 mm Hg in the RDN group and by 11.7 ± 26 mm Hg in the sham group (p = 0.255). Similarly, the ABPM results showed a drop of SBP by 6.75 ± 15.11 mm Hg in the RDN group compared with a drop by 4.79 ± 17.25 mm Hg in the control group (p = 0.979). The results of Symplicity HTN-3 as expected caused a serious setback to the role of RDN to treat resistant hypertension. The very concept of RDN to lower the BP has been brought into debate by the Symplicity HTN-3 results (Table 2). However, Symplicity HTN-3 has left many unanswered questions and created a need to develop newer ways to cause “effective” and “complete” RDN in patients with hypertension (Tables 3 and 4; Graph 3).

Table 2: Why did Symplicity-3 fail?
1. Patient selection
2. Operator failure. Too many Operators
3. Was denervation accomplished? Technical failure
4. Symplicity catheter → faulty?
5. Approach with a new, improved RDN catheter

Table 3: Renal denervation: Issues
1. Who will benefit?
2. Operator factors
3. Technique factors
4. Advanced methods for radiofrequency ablation

Table 4: Revival of RDN-factors
- Selection of patients
- Define "resistant" hypertension
- Renal nerve anatomy and proximity to the blood vessels
- "Quantity" of ablation procedures
- "Quality" of ablation procedures
- Markers/signs of effective denervation
- Chemical/pharmacological denervation

OFFICE/CLINIC BLOOD PRESSURE MEASUREMENTS VS ABPM IN RDN THERAPY TRIALS

Until the Symplicity HTN-3 trial, ABPM was utilized only in small subsets in the previous RDN studies. Although ABPM was only done in small numbers in the previous studies, the results indicated a remarkable discrepancy between the office BP levels and ABP levels. Another RDN study – Enlig HTN-1 – also showed a marked discrepancy between the office BP levels and ABP levels utilizing a different multielectrode catheter. Small studies in special populations with hypertension, such as chronic kidney disease and OSA also exposed the discrepancies between the office BP and ABP levels after RDN therapy. Taken together, these results show an important difference between the office BP levels and ABP levels, raising questions about the enduring efficacy of RDN in clinical practice. The exact reason for the discrepancy is not conclusively known and remains speculative. The RDN therapy appears to eliminate the white coat effect!

NEWER TECHNIQUES AND DEVICES FOR RDN

The Symplicity HTN trials utilized single-electrode catheter for renal nerve ablation. Complete RDN may not be possible with this catheter, which may not create precise energy-driven lesions; operators’ experience and technical skills may be a critical factor in achieving adequate RDN. The newly designed next generation of multiple electrode catheters is aimed to deliver radiofrequency energy to arterial adventia with “precision” and to all the four quadrants, possibly eliminating the operator-dependent factors. The newer techniques (and catheters) will allow for targeted denervation sites circumferentially in both the main renal artery and the branches. Research is also being done to evaluate “chemical” RDN using alcohol or sympatholytic drugs at the catheter tip. Whether drug-eluded catheters
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offer a special benefit beyond a mere electromechanical ablation remains to be determined.

BARORECEPTOR ACTIVATION THERAPY

Modulation (activation) of baroreceptors has been shown to cause a decrease in the SNS activity via central mechanisms (Fig. 1). Afferent reflexes originating from the carotid body inhibit the cardiovascular efferents from the brain, resulting in a sympathetic deactivation which leads to a fall in the systemic vascular resistance and in the heart rate. In essence, carotid body stimulations lower the peripheral sympathetic tone by inhibiting the SNS pathways in the brain. This neural mechanism has been invoked to lower the blood pressure in experimental and clinical hypertension, further confirming the role of SNS in the pathogenesis of hypertension. Long-term observations with BAT are not yet available, but the short-term results are encouraging.10,11

The Rheos BAT system is an implantable device to treat hypertension and possibly CHF. The first human study done with the Rheos system was a proof-of-concept efficacy and safety study; at 3 months BAT device placed patients showed an office BP reduction of 21/12 mm Hg and ABP was reduced by 6/4 mm Hg. At 2 years follow-up, the office BP was reduced by 33/22 mm Hg and ABP was reduced by 24/13 mm Hg (Graph 4).12 These results were significant. In general, BAT was well tolerated and safe except one instance of postoperative stroke and one instance requiring repositioning of the device. The Rheos pivotal trial13 was a larger, placebo-controlled, and properly randomized trial; 265 patients participated in this trial. Although the blood pressure fell significantly when the device was turned “on,” there was no difference when the device was turned “off.” Long-term follow-up (48 months) showed sustained BP reduction and safety (Graph 5).

Graph 1: The baroreflex as a therapeutic target

Graph 4: Sustained reduction in 24-hour ABPM with BAT application

Graph 5: New 5-year long-term SBP data in resistant HTN
The second-generation Rheos device is considerably smaller than its predecessor and the procedure (surgical) is much simpler. In the Barostim neo trial using the new and improved BAT device for resistant hypertension, investigators showed a remarkable drop in BP (26/12 mm Hg) at 6 months. The ABPM results also showed significant reductions in the BP. No major procedure- or device-related complications were observed. Further validation of BAT results will need a sham-controlled trial like Symlicity HTN-3. Studies are in progress to further elucidate the role of BAT in the long-term management of (resistant) hypertension and to test the concept potential in the management of CHF.

MEDIAN NERVE MODULATION

Median nerve modulation concept has been revived by the technological development of a small coin which gently stimulates the median nerve. The Ecoin is implanted under the forearm skin to activate the median nerve. The relatively low-powered electrical stimulus, thus generated, communicates with the multiple pathways in the brain that control the blood pressure. The procedure takes only 20 minutes to perform in the office setting. The dormant science of median nerve modulation has been successfully revived by the technological development of Ecoin and median nerve mapping.

A recent multicenter double-blinded, and sham-controlled study in resistant hypertensives showed that median nerve modulation with Ecoin showed a significant improvement in the office and ABP levels. At 6 months, patients’ office BP and ambulatory BP fell significantly (Graph 6). No major procedure-related adverse effects were noted. The results of this promising pilot study warrant larger controlled trials to determine the applicability of median nerve modulation in the clinical management of (resistant) hypertension.

CENTRAL ARTERIOVENOUS COUPLER THERAPY FOR RESISTANT HYPERTENSION

Hypertrophy of the arteries makes the blood vessels stiff and less compliant, leading to an increase in vascular resistance (and, thus, in the BP). A more advanced technique, the Rox coupler creates a small arteriovenous fistula (AVF) between the iliac artery and vein with a controlled shunt flow creating a low-resistance vascular bed and the system vascular resistance table. In a preliminary Rox coupler AVF study, the office and ABP levels were lower at 6 months. A larger study (40 active patients and 40 controls) showed that at 6 months the AVF group showed a significant reduction in the office BP as well as in the ABP levels. The novel technique was shown to be effective, but a third of AVF patients developed ipsilateral venous stenosis, which resolved after stenting or venoplasty. This unique promising procedure awaits further testing and additional research studies.

CONCLUSION

Resistant hypertension is a complex clinical problem with multiple pathophysiological mechanisms. Resistant hypertension can cause significant target organ damage, premature mortality, and excessive morbidity. At present, chronic management of resistant hypertension is unsatisfactory. Side effects from drug therapy and poor adherence are the chief reasons why blood pressure control is difficult in the community setting.

Device-based therapies for hypertension have been developed on the basis of pathophysiological mechanisms, which raise the blood pressure. Interrupting these mechanisms by mechanical means has been shown to lower the blood pressure in experimental hypertension and in clinical studies. So far, most experience with devices to treat hypertension has been gained with RDN and BAT for resistant hypertension. While the initial results from RDN were “sensational,” randomized trials with strict criteria showed that RDN was not superior to medical treatment. Hence, the development of RDN therapy has taken a big setback. Currently, RDN therapy for hypertension is being reassessed with newer refined techniques to achieve “effective” RDN. The methods of accomplishing RDN more optimally are also being evaluated; similarly, techniques to improve BAT are underway. While the enthusiasm for device-based therapies is somewhat tempered at present, the approach is being revived through innovations in device technology, technical modifications, and proper selection of patients. The ongoing research studies will define possible role of device-based therapy to treat hypertension in select populations.
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