Device-Directed Therapy for Resistant Hypertension

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KEYWORDS

• Resistant hypertension • Renal denervation • Baroreceptor activation therapy
• Median nerve stimulation

KEY POINTS

- Hypertension is a chronic medical condition with increasing risk for renal, cerebrovascular, and cardiovascular disease if left untreated.
- Of patients with diagnosis of hypertension, 20% to 30% have uncontrolled blood pressures despite appropriate medical management.
- Innovative techniques such as renal denervation therapy, baroreceptor activation therapy, and median nerve stimulation therapies are potential solutions for the management of resistant hypertension.

Hypertension, the most prevalent chronic disease worldwide, is a major risk factor for vision loss, renal disease, cardiovascular and cerebrovascular illnesses. Approximately 70 million Americans, that is one out of every three adults, are diagnosed with hypertension. With only about half of this population having their condition under control, the economic burden was projected to be $46 billion in 2011.[1] With such a significant impact on society, there have been tremendous efforts and continued progress toward tackling this issue in the last century. Historically, surgical approaches such as sympathectomies and nerve stimulation[2,3] have provided encouraging results for lowering blood pressure. However, due to the high incidence of procedural and long-term complications, as well as the irreversible nature of such surgical operations, the focus on managing hypertension has since transitioned to pharmacologic agents, including sympatholytic agents, calcium channel blockers, diuretics, and ACE inhibitors/angiotensin receptor blockers.

Despite the availability of various drug classes, a large number of patients fail to achieve goal blood pressures. Resistant hypertension is defined as blood pressure that is persistently above goal (<140/90 mmHg for most patients) despite the use of maximally tolerated doses of three different antihypertensive medications, one being a diuretic. The prevalence of resistant hypertension is estimated to be approximately 20% to 30% among the population with a known diagnosis of hypertension.[4] With the aging population, increasing rates of obesity, and sedentary lifestyle, the incidence of resistant hypertension is expected to increase. There are several reasons why individuals develop resistant hypertension. First, patients can falsely be categorized with resistant hypertension secondary to issues with medication adherence in the setting of

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polypharmacy and barriers to accessing health care. Per Tomaszewski and colleagues,[5] up to 25% to 65% of the population is nonadherent to their antihypertensive therapy. Second, despite the appropriate management of hypertension, patients remain on medications such as nonsteroidal antiinflammatory drugs, amphetamines, and nasal decongestants that are known to contribute to elevated blood pressures. Additionally, chronic medical conditions such as heart failure and kidney disease may present with persistently elevated blood pressures unless these conditions are properly managed. Finally, chronic pain and stress, along with undiagnosed secondary hypertension from conditions such as obstructive sleep apnea, renal artery stenosis, pheochromocytoma, hypothyroidism or hyperthyroidism, and many more could potentially interfere with proper hypertension management while on maximum pharmacotherapy.[6] There is strong evidence to suggest that lowering blood pressure can reduce the risk of certain illnesses such as cardiovascular disease or stroke.[7] Therefore, the role of device-directed interventions such as renal denervation therapy, baroreceptor activation therapy (BAT), and median nerve stimulators are crucial and, perhaps in certain cases, necessary in the setting of resistant hypertension. There are ongoing research efforts to improve these innovative devices, with a keen focus on therapeutic efficacy and safety to best manage resistant hypertension. The following is a review of these innovative interventions.

RENAL DENERVATION

The kidneys have several mechanisms to regulate blood pressure, with several pharmaceutical options available to influence this regulation. Medications such as ACE inhibitors/angiotensin receptor blockers that disrupt the angiotensin-renin pathway and diuretics that prevent water reabsorption are already used extensively. However, evidence demonstrating an interplay between renal sympathetic activity and hypertension has brought about device-directed therapies for blood pressure control, including renal denervation therapy. This treatment modality consists consists of advancing a catheter to the renal arteries, which are in close proximity to the renal nerves. Energy, mostly in the form of radiofrequency, is released from the catheter with goals to achieve denervation, thus inhibiting the sympathetic pathway and lowering blood pressure.[8,9]

This promising approach to disrupting sympathetic input through the renal nerves led to the Symplicity Hypertension (HTN) trials. Symplicity HTN-1 was a prospective, single-arm study that monitored blood pressure readings for 45 subjects who had met the criteria for resistant hypertension and undergone renal denervation. The study aimed to monitor in-office blood pressure readings at incremental months up to a year following the procedure. The significant outcome from the study was the immediate reduction of in-office blood pressure readings (systolic blood pressure [SBP] −14 and diastolic blood pressure [DBP] −10 mmHg) after the first month and its sustained effect after 12 months (SBP −27 and DBP −17 mmHg). These were encouraging results and heralded advancing therapies for resistant hypertension. However, due to the small sample size and statistically insignificant reduction of ambulatory blood pressure in a relatively small subset (n = 9, SBP −11 mmHg), more research on a larger sample size was necessary to validate the success of renal denervation.[8–10]

The subsequent study, the Symplicity HTN-2 trial, included a larger sample size of 106 subjects who again met the criteria for resistant hypertension. Additionally, this trial was the first randomized trial to compare the therapeutic benefits of renal denervation (52 subjects) versus standard antihypertensive medications (54 subjects). The Symplicity HTN-2 trial demonstrated superior therapeutic outcomes at the six month in-office blood pressure readings for the group that underwent renal denervation therapy (SBP −32 and DBP −12 mmHg) compared with the group that was on traditional antihypertensive medications (SBP −0 and DBP −1 mmHg). Despite these promising results, including improvement of in-office blood pressure readings, as well as minimizing adverse events from the procedures, these two trials failed to show improvement of 24-hour ambulatory blood pressure.[9–11] The EnligHTN-1 was another trial that evaluated the efficacy and safety of renal denervation therapy delivered via advanced multielectrode system. The study consisted of 46 subjects with resistant hypertension with goals to monitor in-office blood pressure readings up to 6 months after implementation. The trial demonstrated good results with immediate (1-month SBP −28 and DBP −10 mmHg) and sustained (6-month SBP −26 and DBP −10 mmHg) in-office blood pressure reductions. However, similar to the Symplicity HTN trials, EnligHTN-1 failed to show any significant changes in 24-hour ambulatory blood pressure readings (6-months SBP −10 and DBP −6 mmHg).[12] The cause remains unclear for the difference between in-office and 24-hour ambulatory blood pressure readings. In an extensive review conducted by investigators Li and colleagues,[9] factors including the white coat effect, medication adherence, and inclusion of subjects