Renal Denervation for Resistant Hypertension and Beyond

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Despite the availability of more than 125 approved antihypertensive medications, 36 million (48%) of 75 million people with hypertension, including 16 million treated with antihypertensive medications in the United States, do not achieve guideline blood pressure goals known to reduce cardiovascular morbidity and mortality and progression of kidney disease; 3% to 6% of these 75 million hypertensive individuals are estimated to have resistant hypertension. A major contributing factor for poor blood pressure control, besides inadequate diuretic therapy, is failure of antihypertensive agents to inhibit the sympathetic nervous system effectively. Consequently, alternative device-driven approaches have been developed. Recent technical advances targeting renal sympathetic nerves, that is, renal denervation therapy, are the focus of more invasive therapies to treat resistant hypertension. Encouraging results from the SYMPLICITY HTN-2 trial, regarding efficacy and safety of renal denervation therapy, were countered by disappointing efficacy results of SYMPLICITY HTN-3. Reasons for these divergent results and the future of the field are discussed.

Key Words: Hypertension, Resistant, Denervation, Renal

Introduction

Resistant hypertension is defined as failure to achieve a guideline-driven blood pressure (BP) of less than 140/90 mm Hg in patients who are adherent to maximally tolerated doses of at least 3 antihypertensive drugs, one of which must be a diuretic appropriate for kidney function.[1,2] Individuals with resistant hypertension have a high absolute cardiovascular and renal risk[3] and higher prevalence of target organ damage and BPs that are more difficult to control.[4]

The prevalence of resistant hypertension among US adults continues to increase. Population-based studies published within the last 3 years indicate that the prevalence of resistant hypertension in the United States involves 2.5 to 4.5 million people.[5] This raises a major concern; despite the improvement in BP control rates observed in the past decade, the prevalence of resistant hypertension continues to rise. Reasons for this observation include the association between resistant hypertension and risk factors such as African-American race/ethnicity, obesity, advanced age, diabetes, and CKD.[6] Presence of these risk factors makes hypertension more difficult to control and markedly increases cardiovascular and renal disease.[7]

The prognosis of resistant hypertension is not adequately defined. However, published data indicate that resistant hypertension is associated with poor prognosis. Resistant hypertension typically occurs in patients with high cardiovascular risk, for example, age >55 years, obesity, diabetes, and CKD. Major cohort studies demonstrate an increased risk of stroke, myocardial infarction, heart failure, and CKD, including ESRD, directly linked to the extent of BP elevation.[8,9]

Patients with resistant hypertension are more likely to have associated end-organ damage including left ventricular hypertrophy, microalbuminuria, retinopathy, and thickening of the carotid intima vessels. Indeed, cross-sectional studies of large cohorts of hypertensive patients demonstrate that resistant hypertension is associated with higher comorbidity, more target organ damage, and higher rates of cardiovascular disease than in patients without resistant hypertension.[10,11] The extent to which cardiovascular morbidity and mortality related to resistant hypertension reduced by optimal BP control is controversial.[12] However, major outcome studies support that higher baseline BP and larger decreases in BPs with treatment are associated with marked reduction in hypertension-associated target organ damage.[13]

Despite the availability of numerous effective BP-lowering agents—7 drug classes and over 120 different medications, including fixed dose combinations—36 million (48%) of 75 million adults with hypertension are not at goal.[14] Of those who do not reach their goal BP, a majority have resistant hypertension. Its prevalence among African-Americans continues to rise and also its worldwide prevalence as populations age and become more obese. Data from the National Health and Nutrition Examination Survey from 2003 to 2008 showed that African-Americans accounted for 18.5% of adults with resistant hypertension.[15]

The prevalence of resistant hypertension is falsely elevated in these databases in that only about 45% of patients in specific studies actually take their medications as prescribed. Hence, although the "true" prevalence of resistant hypertension is high, the cardiovascular and renal risk is high if pressure is not controlled regardless of physiologic or psychological mechanism.[16]

A major contributor to the lack of adequate BP control, besides inadequate diuretic therapy, is failure to inhibit the sympathetic nervous system adequately, which plays

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an important role in chronic BP elevation. Adrenergic overdrive in younger patients and altered sympathetic and parasympathetic balance in older individuals trigger elevated BP and its consequences (see Fig 1). Pharmacologic inhibition of the sympathetic nervous system with centrally active α 2-adrenergic receptors medications, such as α-methyldopa and clonidine, effectively lower BP in most patients. However, these therapies elicit intolerable side effects limiting their use.[14] Alternative device therapies are being explored to solve this problem.

Recent technical advances targeting the renal sympathetic nerves, that is, renal denervation therapy (RDN) and increased sympathetic activity of the carotid sinuses, that is, baroreflex activation therapy, have renewed interest in invasive therapy for resistant hypertension. Both procedures demonstrate sound pathophysiological footing in experimental and clinical studies. The following will address the scientific background, early clinical data, the efficacy, and safety of RDN in patients with resistant hypertension.

Renal Denervation Therapy

Role of Renal Nerves in the Development and Progression of Hypertension

The afferent and efferent renal sympathetic nerves are intimately linked with the pathophysiology of hypertension in animal and human experimental models.[17] In response to stimuli, such as renal ischemia, parenchymal injury, and hypoxia, renal afferent nerves are activated. These nerves send signals to the posterior hypothalamus and directly influence central sympathetic outflow, which innervates the heart, peripheral vasculature, and kidney itself. Stimulation of these nerves increases cardiac contractility and heart rate. Sympathetic outflow also controls intravascular circulating blood volume through alterations in the tone of splanchnic storage vessels and plays a role in regulation of salt and water reabsorption through efferent renal innervation.[18]

CLINICAL SUMMARY

- Consistent adherence to medication is key for hypertension treatment.
- Extensive denervation of renal arteries is key to lowering blood pressure.
- Improvement of catheters and techniques will be provide better outcomes.

Efferent renal sympathetic nerves supply the juxtaglomerular apparatus, renal tubules, and renal blood vessels.[19] These noradrenergic nerves demonstrate a graded response to stimulation, starting with an initial increase in renin secretion rate (β-1 adrenoreceptors), followed by an increase in proximal tubular sodium reabsorption (β-1), and with continued stimulation, a direct α-1 adrenergic-mediated increase in renal vascular resistance.[20,21] Increases in efferent activity in hypertensive patients are demonstrated by an increased rate of "norepinephrine spillover," which uses a radiotracer dilution method to quantify the amount of excess norepinephrine after neuronal uptake that is measured in circulation. The effects of efferent stimulation cause a rightward shift of the pressure-natriuresis curve and ultimately lead to progression and sustenance of hypertension.[22]

Increased sympathetic drive is particularly implicated in hypertension secondary to obesity and renal insufficiency.[23] Certain studies demonstrate heightened sympathetic activity in African-Americans, independent of other comorbidities.[24,25] In addition, studies suggest an important difference in the sympathetic activation between sexes within this population. In African-American women with hypertension, increased sympathetic nerve discharge is associated with obesity. However, this association is not observed among African-American men who demonstrate heightened chronic sympathetic nerve activation, regardless of body mass index. Thus, reduction of excessive central sympathetic activity by removal of afferent signals to the hypothalamus, and removal of renal nerves affecting the response to these signals, is a therapeutically attractive target for the treatment of patients with resistant hypertension.

It should also be noted that although there are experimental techniques for measuring sympathetic tone, such as norepinephrine spillover rates and medial sural nerve firing, they are impractical for routine clinical use. Hence, there is no easy way to determine if one has been properly denervated.

Surgical Denervation Studies in Humans

Surgical sympathectomy of humans began in the early 20th century. Such operations classically involved a splanchnicectomy[26] and/or removal of lumbar and thoracic sympathetic ganglia.[26-28] Generally, extensive procedures were performed on younger symptomatic patients. Focused and limited operations were reserved for the elderly population.[27] There is clear evidence of marked improvement in BP recordings in patients with severe hypertension treated in this fashion.[26-30] Despite the favorable effect on BP control, these operations are associated with myriad of adverse effects related to the effects of the sympathectomy. Patients had severely limiting postprocedure hypotension. Some patients reported vasospasm of the hands and intercostal neuralgia.[27,28] Most men who underwent lumbar sympathectomy were rendered impotent.[28] Other long-term effects predictably included bowel and bladder dysfunction.[30] There was also a substantial reported mortality of approximately 7% associated with this major operation.[27] With the advent of antihypertensive medications, this technique was abandoned in the 1970s.[31]

Another historical approach includes blocking of the sympathetic system with pharmacotherapy. Ganglion blockers were used but fell out of favor because of their adverse effects. Currently, antiadrenergic drugs are used to treat hypertension but largely as second- and third-line antihypertensive agents because of undesirable side effects and lack of efficacy compared with other medications.