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Renal Denervation Therapy: The Evolving Treatment of Hypertension and How African Americans Stand to Benefit

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Abstract

Renal Denervation Therapy has shown promise in treating resistant hypertension. Hypertension in African Americans, which occurs more often and at an earlier age compared to whites and Hispanics, has a prevalence of approximately 43.0% and 45.7% for men and women, respectively. After exploring the various pathophysiological mechanisms of hypertension, specifically the pathways affecting the black population, this paper proposes that renal denervation therapy will have a significant impact on the management of resistant hypertension in this cohort of patients. It will be important for future trials to include certain subgroups of the population so as to maximize any benefits that are seen from this therapy and tailor them to each patient appropriately.

Keywords: Hypertension; Resistant hypertension; Renal denervation; African Americans; Symplicity trials

Introduction

Hypertension, defined as blood pressure greater than 140/90 mmHg, affects an estimated 67 million or 1 in 3 Americans with a cost of $47.5 billion annually in direct medical expenses [1,2]. Despite seven out of ten of these hypertensive Americans using antihypertensive medications, less than 50% have controlled blood pressure [1]. Among all adults with hypertension in the United States, it is estimated that 8.9% meet criteria for resistant hypertension, defined as systolic blood pressure greater than 160 mmHg despite the use of three antihypertensive medications of different classes [3]. Risk factors associated with resistant hypertension include older age, increased baseline systolic blood pressure, black race, female sex, obesity, excessive dietary salt ingestion, chronic kidney disease, diabetes, and left ventricular hypertrophy [4]. After controlling for socioeconomic status, black race is the only ethnicity that presents not only a significant risk factor for hypertension but also for treated yet uncontrolled hypertension [5]. Hypertension in African Americans, which occurs more often and at an earlier age compared to whites and Hispanics, has a prevalence of approximately 43.0% and 45.7% for men and women, respectively and was estimated to be the direct cause of death in 9.9 per 100,000 African Americans in 2010 [6,7].

This is significantly greater than the estimated rates of hypertension in the white population of 33.9% and 31.3% for men and women, respectively. Perhaps even more alarming is that blacks are more susceptible to the sequelae of hypertension, including coronary artery disease, heart failure, stroke, myocardial infarction, and renal failure [8]. This paper will explore the various mechanisms of hypertension and propose that renal denervation therapy will have an impact on the management of resistant hypertension in the black population.

Mechanisms of Hypertension

Classic mechanisms of primary or "essential" hypertension include over-activation of the renin-angiotensin-aldosterone system (RAAS), increased sympathetic nervous system reactivity, and heightened peripheral resistance [9,10]. Antihypertensive medications specifically target these mechanistic pathways. ACE inhibitors and angiotensin-receptor blockers inhibit RAAS while beta-blockers primarily decrease sympathetic tone and calcium channel blockers impact peripheral resistance [10]. The high prevalence of hypertension and, more specifically, resistant hypertension in blacks has stirred investigation into specific racial differences of hypertensive pathogenesis including differences in RAAS, salt sensitivity, and sympathetic reactivity.

RAAS depression, salt sensitivity, and sympathetic tone

It has been well-established that the RAAS system, particularly renin activity, is suppressed in black individuals compared to whites [11,12]. Low renin levels are present in normotensive, hypertensive, and pediatric age blacks. The mechanisms underlying the low renin state are likely multi-factorial though salt sensitivity, specifically increased sodium retention, probably plays a major role [13]. The significant difference in salt sensitivity compared to whites was demonstrated in response to a 14-day sodium load (10g/day NaCl), where 37% of young black adults exhibited a sodium-sensitive increase in blood pressure, compared to 18% of young white adults ($p<0.01$) [14].

This salt sensitivity is observed in both normotensive and hypertensive blacks [15]. Moreover, differences in sympathetic reactivity are also more pronounced. Using microneurography of the peroneal nerve in response to a cold pressor test, a significantly greater increase in mean arterial pressure (MAP) and total minute muscle sympathetic nerve activity was observed in the black population compared to whites ($p<0.05$) [16]. Other studies have demonstrated similar findings to various stressors, including isometric hand-grip exercises and video game challenge [17]. In addition, increased renal vascular resistance at any blood pressure, along with increased systemic arterial pressures, correlates with left ventricular size and cardiac mass in the black population, potentially explaining the greater burden of cardiac disease when compared to whites [18]. These findings, along

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with the relatively high prevalence of resistant hypertension, make new therapies, such as renal denervation, an exciting area of exploration.

Renal denervation

A standard femoral artery catheter-based therapy targeting the renal sympathetic system has shown promise in patients with resistant hypertension. The minimally-invasive renal denervation procedure (RDN) employs radiofrequency ablation to the afferent and efferent nerves lying within the adventitia of the renal arteries, thereby disrupting the renal sympathetic outflow to the kidneys [19]. Increased efferent nerve activity has been shown to increase blood pressure via renin release, sodium retention independent of changes in angiotensin II, and vasoconstriction [20]. Signaling via afferent nerves allows the kidney to further stimulate sympathetic outflow from the central nervous system, thereby leading to systemic increases in blood pressure [21]. Multiple clinical trials have evaluated the impact of renal denervation (RDN) in patients with resistant hypertension.

Symplicity (1 and 2) and EnligHTN-1 trials

The open-label, non-randomized Symplicity HTN-1 trial treated 153 patients with resistant hypertension with RDN [22]. The original cohort of the Symplicity HTN-1 trial included only 4% non-white patients [22]. MAP was reduced by -22/-10 at 6 months [22]. At 3 years, patients continued to experience significant reductions in MAP of -32/-14 ($p<0.01$). Remarkably, 50% of patients achieved target systolic blood pressure less than 140 mmHg [23].

The phase 2 Symplicity HTN-2 trial included 106 patients randomized one-to-one to either immediate RDN or control [24]. In this trial, 98% of patients randomized to RDN and 97.1% of control were white [24]. Anti-hypertensive medications were continued in all patients and the study's primary endpoint at 6-month post-randomization demonstrated a reduction in MAP by -32/-12 with RDN compared to +1/0 in control ($p<0.0001$). Following these results, patients in the control group were allowed to cross over to RDN at 6 months. At 30 months post-randomization, pooled results of the original RDN and cross-over RDN patients demonstrated a prolonged reduction in MAP by -34/-13. Systolic blood pressure was decreased by greater than 10mmHg in 84% of patients and by greater than 20mmHg in 70% of patients [25].

The safety profile of RDN in the Symplicity trials has demonstrated no serious adverse events in association with delivery of radiofrequency to the renal artery. Patients treated with RDN demonstrate preserved glomerular filtration rate, creatinine, and cystatin c levels. One patient in both SymplicityHTN-1 and Symplicity HTN-2 experienced a renal artery dissection as a result of catheter manipulation before radiofrequency ablation though notably, both cases were stented with no further complications or delay in hospital course [23,25].

In comparison to the Symplicity trials which used a single-electrode radiofrequency system, the 2013enligHTN-1 trial investigated a multi-electrode radiofrequency system for RDN in 46 patients with resistant hypertension [26]. In this trial, 98% of patients were white [26]. Again, blood pressure was significantly decreased with RDN by -28/-10 ($p<0.0001$) and the effects were sustained at 1-yearfollow-up with 80% of RDN patients achieving at least a 10mmHg drop in systolic blood pressure. No renal artery dissections were observed in this small cohort of patients and it was postulated that a multi-electrode system may reduce catheter manipulation, the risk of renal artery injury, and procedure time [27].

Future directions

Given the sustained success in blood pressure reduction and favorable safety profile, further investigations into RDN are currently being conducted and analyzed. Symplicity HTN-3 is a clinical trial of 535 patients with uncontrolled hypertension randomized to RDN or control with standardized ambulatory blood pressure measurements and blinding of participants [28]. Initial results of that trial, which are only recently becoming available, have failed to achieve the primary efficacy endpoint, which was the change in office systolic blood pressure at six months, but was able to meet the safety endpoint, which was the incidence of major adverse events that occurred one month after treatment until six months [29]. Due to these results, it will be even more important to analyze the data closely to see if certain subgroups benefit. Expanding investigation into patients with multiple medical conditions, Symplicity HF is an on-going, open-label pilot study evaluating RDN in 40 patients with both heart failure and renal impairment [30]. Finally, the Global Symplicity trial is a phase 4 study of more than 5000 patients worldwide evaluating the real-world impact and safety of RDN for blood pressure reduction [31].

RDN has the theoretical potential to significantly impact renin and aldosterone levels and inhibit negative feedback to the sympathetic and central nervous systems which are ultimately responsible for blood pressure control. However, while animal studies and limited case studies have led to hypotheses regarding mechanisms of RDN's antihypertensive effects, further large-scale human investigation is necessary. A proof-of principle, safety study of 45 patients treated with RDN demonstrated a 47% decrease in norepinephrine spillover 1 month after bilateral denervation [32]. An additional study demonstrated reduction in renin release as well as increased renal blood flow with RDN [33]. Expansion of these efforts to understand denervation's mechanistic effects as well as electrolyte and hormonal changes could potentially aid in the identification of target subgroups for RDN treatment [34].

With the continued success of clinical trials and the use of different catheters and techniques to further reduce adverse events, RDN may one day become a frequently utilized and cost-effective tool for the treatment of hypertension. The cost of the RDN procedure is estimated to be an upfront value of $12,500 which is a considerable investment. However, a recent study using a decision analytic model to predict long-term cost-effectiveness of the Symplicity HTN-2 data found that the cost-saving benefits are reaped over a lifetime as RDN decreased cardiovascular mortality by 30% and all-cause mortality by 15% compared with standard medical therapy over 10 years [35]. In addition, lifetime and 10-year risks of adverse events associated with hypertension, including stroke, MI, coronary artery disease, heart failure, and end-stage renal failure are all significantly decreased with RDN. Median survival is increased from 17.07 to 18.37 years and quality-adjusted life expectancy from 12.07 to 13.17 quality-adjusted life-years.

Conclusion

The success of renal denervation therapy in recent trials and its potential application for resistant hypertension makes understanding all of its risks and benefits a high priority. As new and more rigorous studies come out and the evolution of medicine leads to further individualization of therapy, it will be important for future trials to include and analyze data for individuals of diverse races and populations so as to maximize any benefits that are seen and tailor them to each patient appropriately.

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Conflicts of Interest/Disclosures

None.

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