Renal Denervation: An Update

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Abstract

Resistant hypertension is a growing cardiovascular problem worldwide and despite significant pharmacological advances medical management of the pathology remains challenging. In early clinical trials renal denervation, a catheter based therapy that denervates renal afferent and efferent sympathetic nervous system has demonstrated significant blood pressure reduction in patients with resistant hypertension. However, Symplicity HTN-3, the recent randomized controlled trial has challenged the efficacy of the procedure and underscored that there remain key issues to overcome before the procedure can be used as a standard of care in patients with resistant hypertension. This review provides a balanced update on the recent preclinical and clinical studies in the field and, focuses on the important advances required to enhance the forward progression of a technique that has the potential to treat this highly heterogeneous pathology.

Keywords: Percutaneous renal sympathetic denervation, Resistant hypertension, Radio-frequency ablation, Sympathetic nervous system


Introduction

Systemic hypertension (sHTN) remains a major health problem worldwide with an estimated 1 billion people affected by the disease and this figure is projected to reach 1.5 billion by 2025.1,2 Resistant hypertension (rHTN) is defined as failure to attain goal blood pressures (BP’s) despite treatment with optimal doses of three or more antihypertensive medications including a diuretic. Although the exact prevalence of true rHTN is difficult to gauge due to suboptimal therapies, variations in patient compliance and secondary causes of HTN, it is estimated that approximately 10-15% of patients diagnosed with sHTN are resistant to treatment.3,4 It is well documented that antihypertensive therapies markedly reduce the incidence of stroke (35-40%), myocardial infarction (20-25%) and heart failure (>50%)3 yet, control of BP has been challenging and remains inadequate. It is this unmet need that has once again garnered the interest of both physicians and patients in alternative therapeutic strategies such as renal denervation. The procedure was initially described in the 1930’s as radical lumbo-dorsal splanchnicectomy6, 7 and over the last decade renal denervation has been redeveloped and refined as an elegant catheter based interventional approach for the treatment of rHTN.

Renal sympathetic nervous system

Renal sympathetic nerves are located in the adventitia of the renal artery and consist of a dense network of postganglionic efferent nerve fibers that originate at the intermediolateral column of the spinal cord at thoracic and lumbar levels. Several studies have demonstrated that these nerve fibers play a significant role in the development and maintenance of HTN via norepinephrine synthesis and spill over which promotes sodium and water retention plus activates the renin angiotensin aldosterone system (RAAS) via the beta adrenergic receptors resulting in increased BP’s. The latter is also coupled with reduced renal blood flow mediated by the alpha-adrenergic receptors that once again leads to increased sympathetic tone and therefore increased blood pressures. Similarly afferent nerve fibers located in the renal pelvis respond to decreased renal blood flow and activate the central nervous system increasing vasopressin release and systemic vascular resistance compounding the issue.8-11 Thus the efferent and afferent pathways play a significant role in the communication between the CNS and the kidneys in maintaining overall sympathetic tone and blood pressures.

Rationale for renal denervation

The positive impact of renal denervation in reducing blood pressures was initially identified in patients undergoing renal transplantation or nephrectomy where a significant reduction of BP was identified post procedure. These studies demonstrated the presence of sympathetic overactivity in patients with end stage renal disease that could only be corrected by nephrectomy and furthermore, centrally acting sympatholytic agents decreased BP’s in these patients.12-15 There is a strong association of renal sympathetic overactivity and increased norepinephrine spill over in both lean and obese patients with HTN often resulting...
in stimulation of cardiac sympathetic nerves and subsequent development of left ventricular hypertrophy and ventricular arrhythmias. Animal models have demonstrated that renal denervation resulted in decreased sodium and water retention resulting in decreased blood pressures. Finally, rabbit models showed an increase in renal blood flow post renal denervation and rat models demonstrated that wall-to-lumen ratio in renal vasculature was increased in HTN and renal sympathetic denervation reversed this phenomenon demonstrating the significance of sympathetic overactivity in HTN. Thus a catheter-based procedure that avoids the serious complications associated with total sympathectomy was devised to target the sympathetic nerves within the renal vasculature.

Radio frequency based renal denervation

The minimally invasive percutaneous procedure pioneered by Krum et al was utilised in the first in human proof of concept studies conducted in 2009. The procedure is performed under fluoroscopic guidance and involves insertion of the ablation catheter via the femoral approach using a 6F - 8F guide catheter. The ablation catheter is advanced into the renal artery and low radiofrequency energy is applied to ablate the sympathetic nerves within the artery. The ablations are performed from the distal end to proximal end of the artery in a circumferential pattern to achieve complete ablation. The energy applied and time of procedure depends entirely on the type of catheter used since single electrode catheters vary significantly from multi-electrode catheters. The catheters that are presently approved in several countries include Medtronic’s Symplicity catheter, St. Jude’s EnligHTN catheters, the Vessix system from Boston Scientific and the OneShot system from Covidien.

Non-radio frequency centred renal denervation

Techniques such as ultrasound, β radiation (vascular brachytherapy) and pharmaceuticals have also been used to control blood pressures in patients with uncontrolled hypertension. Kona Medical, Inc. utilizes externally delivered, focused ultrasound waves to disrupt sympathetic nerves leading to and fro from the kidney and, they have recently begun the WAVE I clinical trial to demonstrate the safety and efficacy of this procedure. Similarly the Peregrine System™ uses a three needle-based device to deliver alcohol into the perivascular space of the renal artery to achieve renal sympathetic denervation. Animal and early human trials using this technology has shown encouraging results thus far.

Clinical trials

The initial renal denervation trial (Symplicity-HTN1) was performed using the Symplicity catheter in fifty patients with systolic blood pressures between 160-180mmHg despite taking an average of 4.7 anti-hypertensive medications. Renal imaging was performed at screening to identify and rule out anatomic variations or alterations such as atherosclerosis that would exclude patient from the study. Blood pressures were assessed at 1,3,6,9,12 and 36 months and significant reductions in both office and ambulatory blood pressures were observed.

Symplicity-HTN2, a randomised control trial using the same catheter system closely followed the first trial and included 52 patients in the procedural arm and 54 in the control arm. BP assessment was performed at 1,3 and 6 months in 49 and 51 patients in each arm respectively. At 1-month post renal denervation there was a significant decrease in blood pressures in the procedural arm compared to the control group (20/7 mmHg (systolic/diastolic)) vs. (0/0 mmHg). The difference at 3 months between the two groups was 24/8 and 4/2 mmHg respectively and at 6 months there was a decrease of 32+23/12+11 mmHg from 178+18/97+16 mmHg at baseline and 1+21/0+10 mmHg from 178+16/98+17 mmHg at baseline in the renal sympathetic denervation and control groups respectively. While there were no significant adverse events in the study 13% of patients in the procedural arm noted transient bradycardia. The 36 months follow up results of Symplicity HTN-2 showed that the blood pressure reduction was sustained at 3 years post procedure and that there was no safety concerns associated with the technique. Interestingly, a couple of studies following Symplicity HTN-2 demonstrated an improvement in cardiac function and glucose metabolism post renal denervation.

Symplicity-HTN3 which included 535 patients and was performed in over 80 centers, was the very first randomized, sham-controlled, blinded trial designed to assess the benefits of renal denervation in patients with office blood pressures >160mmHg despite treatment with three or more antihypertensive medications. In contrast to the first two Symplicity trials mentioned above, this study failed to demonstrate a significant reduction in office systolic blood pressure in the renal denervation arm (−14.13+23.93 mmHg) compared to the sham procedure arm (−11.74+25.94 mmHg) 6 months post procedure. The difference between the two groups was −2.89 mmHg. This was also evident in ambulatory blood pressures where the treatment group had a reduction of −6.75+15.11 mmHg and the control group had a decrease of −4.79+17.25 mmHg, mounting to an intergroup difference of −1.96 mmHg. Thus the study did not demonstrate a benefit of renal denervation using its two efficacy endpoints, reduction in office or ambulatory systolic blood pressures at 6 months post renal denervation.

Whilst this study emphasizes the importance of well-designed blinded trials with sham controls and, the placebo plus Hawthorne effect in the earlier studies cannot be overlooked, there are few potential explanations for the disparity of outcomes in these trials. Most important would be the difference in study populations, whereas, in Symplicity HTN-3 a quarter of patients were African Americans (AA) this was not the case in either of the earlier two studies. This is especially important considering that AA's have genetic polymorphisms in the beta-1 adrenergic receptor gene, have low renin levels and therefore are shown to respond differently to treatments. Secondly, the 8 clinical visits between screening and 6 month follow-up are higher than usually seen in these patients and this could mean higher than normal adherence to medication. Lastly the study was done in 88 centers by 111 operators, 31% of whom had performed only one procedure before the trial, potentially complicating assessment of procedural success. This is important since there is paucity of methodologies currently available to assess procedural success of renal denervation per se. Therefore while the significance of Symplicity-HTN3 is remarkable and it does question the conceptual and technical aspects of renal denervation, it emphasizes the need to regroup and assess selection criteria for the procedure and stresses the need for a well-rounded approach including appropriateness of catheter utilized in order to provide individualized therapy for these patients with varying requirements.

EnligHTN I trial was the first in human prospective, non-randomized, multi-centre trial performed in 46 patients to assess the safety and efficacy of St. Jude’s multi-electrode catheter system. These results demonstrated a significant reduction of office blood pressures by -28/-10, -27/-10, and -26/-10 mmHg (systolic/diastolic) at 1, 3, 6 months post renal
denervation. There was also a reduction of 10/-5, -10/-5 mmHg in ambulatory blood pressures in these patients that correlated well with changes in office blood pressures. The study also identified a significant decrease in resting heart rate from 71 b.p.m at baseline to 66 b.p.m 6 months post intervention.33 The 12 months data by the same group shows that the reduction in ambulatory blood pressures in this period was maintained albeit at a lower level (-7/-4 mmHg), and, that office blood pressure reduction was maintained at the same level (-7/-11 mmHg) even at 12 months post procedure.34 These studies therefore have continued to demonstrate the safety of the procedure and possibly delineate the utility and advantage of multi-electrode catheter systems in the field of renal denervation.35 That being said, the potential of this catheter would largely depend on the results of a randomised, blinded and sham controlled trial designed to assess efficacy of this system.

Limitations of renal denervation

Over the last decade the safety of renal denervation has been well demonstrated however, there are other areas that need to be further investigated. First, there is paucity of techniques currently available to assess procedural success. Sympathetic nerve distribution varies vastly within the renal artery and recent studies have demonstrated that location and number of ablations predicts procedural success and translates to better response to renal denervation.36, 37 Norepinephrine spillover, muscle sympathetic nerve activity and heart rate variability are techniques that have been well documented for this purpose. Recent studies have suggested that cardiac baroreflex sensitivity and higher serum levels of sFLT-1, ICAM-1, and VCAM-1 could potentially be used as predictors of response to renal denervation. A system that measures nerve impulses before and after denervation would undeniably enhance the efficacy of the procedure. Second, identification of patient population that truly have rHTN and therefore would better respond to treatment is imperative although, this has been challenging to date. Several reports suggest the presence of responders and poor or non-responders and therefore the ability to identify these groups using specific biomarkers would enhance the efficacy of the procedure. Third, the importance of identifying patients who are truly compliant to medications through the entire course of the trial has been emphasised by Symplicity HTN-5 and needs to be addressed to find an apt niche for the procedure. Therefore, well powered studies targeted at identifying the optimal catheter type (single vs. multielectrode; Arch vs. Flex) and number of ablations required for procedural success would help provide an individualised therapeutic option which could lead to better outcomes in these patients with rHTN.

Conclusion

Catheter based renal denervation has come a long way since its first use by Esler et al over seven years ago and although during this period we have not reached an unanimous consensus about the efficacy of the procedure or its long term effects on renal vasculature, our understanding of the procedure has advanced significantly. Recent trials and their initial post-hoc analyses have just begun to highlight the need for a holistic approach by primary care physicians, hypertension specialists and interventionists to treat this disease with multifactorial pathophysiology. Therefore, it is not yet time to give up on the technology but, on the contrary, it is time to regroup, assess and design the next trials that would give us a better grasp on the efficacy of the procedure and consequently improve therapies in these patients.

Declarations of Interest

The authors have no conflicts of interest to disclose.

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