Interventional Therapies for Resistant Hypertension: A Brief Update

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Abstract

Resistant hypertension remains a clinical challenge with few management options beyond maximisation of medications. Catheter-based renal artery denervation (RDN) was proposed in 2009 as a possible therapy for resistant hypertension and early feasibility trials caused excitement among cardiologists and antihypertensive specialists, showing remarkable and sustained blood pressure reductions. In 2014, enthusiasm for RDN dampened following the SYMPPLICITY 3 trial results, which showed no statistically significant difference in blood pressure between the intervention and control arms. However, hope remains for the improved management of resistant hypertension; procedural understanding, technological advancements and alternative targets – such as baroreceptor activation therapy and arteriovenous shunts – may aid the identification of those patients for whom specific interventional therapies will be effective.

Keywords

Resistant hypertension, interventional therapy, renal artery denervation, baroreceptor activation therapy, arteriovenous shunting

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Resistant hypertension remains a serious clinical burden despite significant advances in cardiology and healthcare. Hypertension is a chronic condition without any available cure, with significant associated morbidity and mortality, and necessitates lifelong use of medications. It is multifactorial in origin, associated with genetics, lifestyle factors and the metabolic syndrome. Resistant hypertension is defined as “blood pressure that remains above target (usually 140/90) despite the use of three classes of antihypertensives, one being a diuretic, or requiring four medications to control blood pressure.”¹ Refractory hypertension is the term to describe the 10% of these patients that remain uncontrolled despite maximal medication use (four or more drugs) while attending a hypertensive specialist.

The incidence and prevalence of resistant hypertension remains unclear as there are no direct studies to evaluate this. Extrapolation of data from large scale antihypertensive trials suggests a prevalence of 10–20%.^{2,3} It is likely that this is increasing on analysis of medication prescriptions and in the setting of obesity and an ageing population. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)⁴ showed 27% of participants were on three or more medications and only 49% were controlled on one or two medications.

Diagnosis of resistant hypertension can be difficult to confirm. Variables such as secondary causes of hypertension must be excluded, alongside other possibilities including white coat hypertension, nonadherence to treatment, diet and lifestyle measures and medication use that may be contributing, such as steroids, oestrogen, etc. Resistant hypertension remains a serious clinical unmet need as this patient population is exposed to a three-to-five-fold higher risk of cardiovascular events⁵ including ischaemic heart disease, congestive heart failure, stroke, chronic renal failure and peripheral vascular disease. The role for invasive management strategies, alongside medications, is a growing

area of interest as a possible solution for this patient profile. Current invasive strategies that have been tried include:

1. Catheter-based renal artery denervation (RDN)
2. Baroreceptor activation therapy
3. Arteriovenous shunts

Renal Artery Denervation Background and Pathophysiology

In the early 1900s the importance of sympathetic hyperactivity and comprised primarily of sympathectomy in hypertension was recognised. Various procedures were trialled including subdiaphragmatic bilateral resection of the splanchnic nerves with superior lumbar sympathectomy and often included adrenalectomy or renal decapsulation. Sustained improvements in blood pressure were seen but treatment was limited by serious side effects including surgical complications, hypotension and autonomic dysfunction. With the discovery of thiazide diuretics these procedures became redundant in the late 1950s.^{6,7} In recent years observational evidence from kidney transplantation suggested that diseased kidney removal reduces blood pressure further.⁸

The pathophysiology of hypertension explains the interest in RDN. Essential hypertension is a complex multifactorial condition with interplay between the central and peripheral nervous systems, heart, vasculature and kidneys. The kidneys have norepinephrine releasing sympathetic efferent and afferent nerves running in the adventitia of the renal artery. Efferent renal nerve stimulation causes upregulation of renin secretion, increases sodium absorption in the distal tubule and vasoconstriction, all contributing to increased water retention and hypertension. Stimulation of sensory afferent renal nerves leads to increased sympathetic activity via signals to the central nervous system, causing vasoconstriction and increased cardiac output.

Norepinephrine spillover was investigated to assess the theory of increased renal sympathetic activity contributing to hypertension. Renal venous concentration of norepinephrine was significantly higher in people with hypertension in comparison to controls and was reduced following renal nerve removal.^{9,10} Muscle sympathetic nervous activity can also be utilised to test the activity of the sympathetic nervous system being elevated in people with hypertension.

Experimental work in animals suggested that RDN has a plausible role in hypertension, as rats with bilateral renal sympathetic denervation showed delayed onset of hypertension with attenuated severity.¹¹ The concept of catheter-based RDN was introduced in 2009. It was a reinvention of an old concept with further understanding of the pathophysiology, alongside clinical observation in renal transplantation and animal models, suggesting that it may have a very real and exciting role in the treatment of hypertension.

Clinical Trials for Renal Artery Denervation

SYMPPLICITY-1¹² was the first in-human feasibility and safety study for RDN, published in *The Lancet* in 2009. Primary endpoints included safety and blood pressure reduction. There were 153 patients, all deemed treatment resistant, taking more than three antihypertensives with an average office blood pressure of 175/98. The Symplicity™ Renal Denervation catheter (Medtronic) was used with a single electrode tip requiring between four and eight ablations of 2 minutes in a circumferential fashion along the renal artery. This showed sustained 4-, 12- and 36-month reductions in office blood pressure measurements with few procedural complications,¹³ thus confirming safety.

SYMPPLICITY-2¹⁴ was a multicentre, randomised, controlled, clinical trial, following the promising success of the first trial, published in *The Lancet* in 2010. Investigators used the same catheter as the previous trial and followed similar methodology with addition of a control arm. There were 106 patients with resistant hypertension, on an average of five antihypertensives, randomised in a 1:1 fashion to RDN or medication, with crossover allowed at 6 months. Results showed a significant and sustained reduction in office blood pressure measurements at 6 months with a mean reduction of 33/11 mmHg in those treated with RDN and few procedural complications.¹⁵ Of note, only 20 RDN patients had 24-hour ambulatory blood pressure monitoring (ABPM) in whom blood pressure reductions were less pronounced, with a mean difference of 11/7 mmHg from controls.

EnLight™ was a non-randomised, unblinded, clinical trial,¹⁶ evaluating the St Jude Medical catheter device for RDN, similar to SYMPPLICITY-1, being the first in-human use of the device. The trial had 46 patients with resistant hypertension, using three or more antihypertensives for a sustained period, office systolic blood pressure >160 mmHg, alongside confirmatory 24-hour ABPM. Primary efficacy endpoints mirrored that of SYMPPLICITY-1, showing sustained office blood pressure reductions at 1, 3, 6 and 18 months, with a good safety profile. ABPM showed an average reduction of 10/5 mmHg at 6 months, below the average 26/10 mmHg reduction of office recordings.¹⁷

SYMPPLICITY-3¹⁸ was a prospective multicentre, randomised, double-blinded trial, with 535 patients evaluated, assigned in a 2:1 fashion to undergo RDN with the Symplicity Medtronic catheter or renal angiography alone, a sham procedure. Primary efficacy endpoints looked at office blood pressure measurements at 6 months, and secondary endpoints included ambulatory recordings. Primary

safety endpoints looked at major adverse events. This trial showed no statistically significant difference in baseline blood pressures, both office and ambulatory, in both groups at 6 months, which was contradictory to the previous trials. There was no significant safety difference thus confirming procedure safety.

Post-hoc Analysis of Negative Trials

Multiple analyses have been undertaken to explain this trial being negative in the setting of two prior strongly positive trials. The earlier trials were unblinded and primarily feasibility and safety trials, creating a bias. In SYMPPLICITY-3, there was more extensive screening of the population prior to trial entry for secondary causes, and definite diagnosis of resistant hypertension requiring a 24-hour ambulatory monitor. Patient characteristics showed a higher demographic of African-Americans than earlier trials, a higher proportion of obese patients and usage of aldosterone antagonists. Operator experience may have played a role, given the wider scale of the trial. Also the addition of the placebo intervention may have contributed to a Hawthorne effect where patients in both arms are aware they are being closely observed and modify their behaviour in response to this scrutiny.

Post-trial analysis published in the *European Heart Journal*¹⁹ revealed that 39 % of patients underwent medication changes during the trial, despite strict criteria in place to reduce this, as patients were supposed to be on maximally tolerated doses before entering the trial. From a procedural aspect, there was significant variability in the number of ablation attempts per patient, between one and 26. Partial denervation may result from too few ablations with significant sustained blood pressure reductions noted when >14 ablations are done. Additionally it appears necessary to ablate in all four quadrants of the renal artery, as in-depth analysis reveals that this contributes to greater blood pressure reductions. These issues may give guidance and provide hope to future trials. However it remains a sobering outcome for the previously exciting development of RDN.

Current Renal Denervation Technologies

There are a number of different catheters designed and in development for RDN. The ideal catheter should be safe, easily delivered to the renal artery, effective in a reproducible fashion with minimal operator variability, cause little local trauma to the tissue and facilitate as short a procedure time as possible. There is significant design variability in the attempt to address these all needs. Anatomic variations are also an issue for successful RDN, as anatomy must be favourable for the procedure. Typically, the renal artery must be ≥4 mm in diameter, ≥20 mm in length, with absence of significant atherosclerosis, previous angioplasty, fibromuscular dysplasia or accessory arteries. Femoral access is required, along with a baseline renal angiogram.

Radiofrequency Ablation Catheters

SYMPPLICITY – Medtronic

The largest trial to date, SYMPPLICITY-3, was carried out by Medtronic with the sole use of their device, the Symplicity flex catheter. This is a radiofrequency-based catheter, compatible with 6 Fr and 8 Fr introducer sheaths via the femoral artery, passed over-the-wire, with a single unipolar electrode at the tip to create spot lesions using radiofrequency ablation. The device has a handle to flex and rotate the tip of the catheter in the renal artery. It generates a temperature of 75 degrees. At least four ablations per artery are recommended, 2 minutes per ablation, preferably in a circumferential helical fashion with at least 5 mm between lesions. Good wall contact is crucial. Medtronic

has a further device in progress, Symplicity Spyral™, which has a spiral shape with four unipolar electrodes activated simultaneously, allowing a more rapid and easier procedure with better spot lesion location ensuring adequate ablation. This reduces potential operator error.

EnligHTN™ St Jude Medical

St Jude Medical designed the first EnligHTN multi-electrode radiofrequency RDN system. This is passed via an 8 Fr sheath with a 8 Fr guiding catheter used to engage the renal artery. It has a nitinol basket design available in two sizes, 16 mm and 18 mm, allowing 4-point contact per catheter placement, activating each individual electrode in 90 second segments. This aims to increase procedural success with a more predictable ablation pattern and less catheter manipulation. Individual electrodes can be turned on and off. The generator reaches 75 degrees for transmural ablation. Two rounds of ablation are recommended, a total of eight ablation lesions per artery.

Vessix™ Boston Scientific

Boston Scientific's Vessix RDN system is a balloon-based system with an over-the-wire technique. This requires an 7 Fr introducer sheath, passing a guidewire to the renal artery, facilitating delivery of the Vessix noncompliant balloon, available in 4–7 mm diameter balloons. The balloon is inflated to 3 atm, and contrast administered to ensure apposition to the wall and occlusion of the artery. Once inflated the device activates 4, 6, or 8 bipolar electrodes (depending on balloon size), delivering temperatures of 68 degrees to the vessel wall via a temperature controlled algorithm, over 30 seconds. In most cases one cycle is sufficient, longer arteries may require two cycles. The single-arm, multicentre, Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter (REDUCE-HTN) trial in 2013 of 150 patients confirmed safety and sustained blood pressure reductions.^{20,21}

OneShot Covidien

Covidien acquired the OneShot RDN system from Maya Medical in 2012, which consists of an irrigated noncompliant radiofrequency balloon catheter with a unipolar spiral electrode. The catheter is advanced over an 0.014 inch wire via a 7 Fr or 8 Fr sheath, inflated to 1 atm and has eight tiny irrigation holes allowing cooling of the vessel at the time of ablation. This mitigates overheating, vessel damage and thrombus formation. Balloons are available in 5–7 mm and the spiral shape allows a single 2-minute treatment per artery. Their first in-human trial was the Renal Hypertension Ablation system (RHAS) trial.²² This consisted of eight patients and showed no procedural complications with a sustained drop in blood pressure at 6 months. This was followed up by the Rapid Renal Sympathetic Denervation for Resistant Hypertension (RAPID) trial,²³ enrolling 50 patients and meeting primary safety endpoints and sustained blood pressure reductions at 6 and 12 months. In January 2014 Covidien ceased development of their RDN system, with cessation of the RAPID II trial, due to the slower than expected growth in the market.

Ultrasound-based Catheters

Paradise® ReCor Medical

ReCor Medical introduced the Paradise system, a new concept in the field of RDN being the first ultrasound-based catheter, instead of radiofrequency ablation. This design consists of a circumferential balloon catheter, available in 6 mm or 8 mm, delivered to the renal artery over-the-wire via a 6 Fr guiding catheter. The balloon has a cylindrical piezoelectric ultrasound transducer, which emits circumferential high

frequency sound waves over 30 seconds, generating heat to induce nerve injury. It is recommended to target three different spots per artery. The balloon allows cooled fluid to circulate during ultrasound transmission, thus reducing endothelial damage and protecting from overheating. The REDUCE trial was the first in-human trial of 15 patients, proving device safety with reduction in office-based blood pressure readings at 6 months. The follow-on REALISE²⁴ and ACHIEVE trials were small, non-randomised trials with similar results.

Chemical-based Catheters

Peregrine System™ Infusion Catheter, Ablative Solutions

A new area of interest is in the field of chemical RDN with ethanol. Concerns with radiofrequency ablation regarding the possibility of incomplete and inconsistent RDN contributing to negative trials results has been raised. Circumferential burns and adequate depth can be difficult to obtain and few people have renal arteries >4–5 cm to allow adequate burns per artery. The Peregrine infusion catheter was developed by Ablative solutions to deliver micro doses of the known neurolytic ethanol to the adventitia by placing three 0.008-inch needles through the media and injecting 0.3–0.6 ml of ethanol. This was shown in animal studies to reduce renal norepinephrine levels and histology assessment revealed successful circumferential artery injury with evidence of permanent nerve damage. The first in-human study commenced in 2013 with 18 patients treated alongside 17 swine.²⁵ There were no procedural complications and minimal patient discomfort. Six-month blood pressure reductions were significant at 23/14 mmHg. Further clinical evaluation is ongoing to assess the potential value and clinical role chemical ablation may have for resistant hypertension.

The Future

Trials remain ongoing to evaluate the role of radiofrequency ablation. Boston Scientific are currently undertaking the Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension (REDUCE-HTN:REINFORCE) trial and believe variables in medications and high-risk patients clouded results of previous investigations. Medtronic are conducting trials with their Spyral device on and off medications including a sham procedure. Certainly, the initially promising field has slowed down in the setting of negative outcomes from SYMPLECTICITY-3 but there are lessons to be learned. A first-generation device was used with significant operator and procedure variability. More recent devices with multiple electrodes may increase procedural success from a complete denervation perspective and subsequently clinical outcomes. Thermal ablation RDN catheters have shown excellent safety profiles, largely due to controlled thermal energy to the renal blood vessels. Better penetration into the adventitia either through optimal catheter contact or higher energy is required to achieve nerve deactivation.

Anatomically, information from the IVY trial in preclinical models has shown better response when the side branch and main trunk are ablated, instead of the main trunk and the side branches alone. It is now advocated that more dense innervation is present in the distal renal artery and side branches, and better clinical outcomes can be achieved by distal ablations. This is contrary to the earlier belief of ostial ablations. The role of ultrasound and chemical ablation with ethanol warrants further evaluation and may lead to more positive clinical outcomes.

A current limiting factor in RDN is the lack of awareness of procedural success at the time of intervention. There is no confirmatory method to ensure the renal nerves have been successfully ablated. Research

into peripheral markers may permit overcoming this obstacle in the future. There remains a population of patients who are likely to be more adrenergic driven than others and may benefit more from RDN than others. These patients deserve to be identified, given the serious mortality and morbidity associated with uncontrolled hypertension.

Baroreceptor Activation Therapy

Baroreceptor activation therapy (BAT) is another exciting investigational area for an interventional role in treatment of hypertension. This was also initially evaluated in the 1950s and 1960s, prior to the development of the wide array of antihypertensive medications currently available. At that time electrical stimulators were used to activate the afferent pathway of the baroreceptor reflex to treat angina initially, then hypertension.^{26,27} However they were limited by procedural complications, surpassed by medications and became a defunct procedure.

Current understanding of the pathophysiology allows attention to be drawn back to a possible role for carotid body stimulation in hypertension. Baroreceptors are located at the carotid sinus, at the level of the bifurcation of the carotid artery and the aortic arch. Stretch mechanoreceptors are activated by pressure in the arterial wall and information transmitted via the glossopharyngeal nerve to the nucleus tractus solitarius in the medulla of the central nervous system. There, it is integrated with other afferent and cortical inputs and efferent pathways are modulated to regulate blood pressure with alteration of sympathetic or parasympathetic activation of the heart, vasculature and kidneys as appropriate. Activation of baroreceptors in the setting of high blood pressure causes upregulation of the parasympathetic system while hypotension and reduced baroreceptor stimulation activates the sympathetic nervous system. Previously, it was thought that the baroreceptor reflex has only a short-term role in blood pressure regulation to protect from extremes. However animal studies and human observational studies suggest it also has a longer term role with possible resetting of response levels, in the setting of prolonged hypertension.²⁸

Devices

The Rheos System® Hypertension Therapy System, CVRx Inc

CVRx Inc developed the first device for baroreceptor stimulation, the Rheos system, with first implantation in 2005. This requires surgical insertion with bilateral electrodes being tested intra-operatively to ensure correct positioning and activation of the right and left carotid sinus with leads connecting the electrodes to a generator device, placed usually in the right infraclavicular area. It is activated one month after implantation, animal studies suggest earlier activation interferes with skin healing. It electrically activates the carotid sinus to simulate hypertension in the central nervous system and downregulate the sympathetic nervous system. Two feasibility trials initially assessed the Rheos system, the Device Based Therapy of Hypertension Trial (DEBUT) in Europe and US Feasibility trial enrolling 61 patients.²⁹ Two-year follow-up showed a sustained reduction in baseline blood pressure of systolic 30 mmHg and diastolic 15 mmHg, with reduced use of antihypertensive medications.

The Rheos PIVOTAL trial³⁰ was a follow-on double-blind study with 181 patients having device activation at month 0 (one month after surgery) and 84 having activation at month 6 (7 months after surgery). The trial met three out of five endpoints, failing to show a significant

6-month blood pressure reduction in treatment versus controls, but did have a significant sustained response at 12 months. It confirmed BAT efficacy and long-term device safety. Short-term procedural adverse events did not reach target endpoint with 9.2 % of patients sustaining nerve injury, 4.4 % had surgical complications and 2.6 % had respiratory complications. Long-term data suggests favourable regression of left ventricular hypertrophy and significant reductions in cardiac dimensions following BAT.³¹

Barostim Neo™ CVRx Inc

CVRx Inc has developed a second-generation device, the Barostim neo system. It is smaller with a longer lasting battery and only one electrode being implanted into the right carotid sinus. Previous trials have suggested that unilateral stimulation may be sufficient to achieve a chronic BP response.³² The initial XR-1 Verification Study³³ of 30 patients showed average blood pressure reduction was 26 mmHg systolic and 12 mmHg diastolic at 6 months and 43 % of patients had SBP <140 mmHg. The neo PIVOTAL trial of 310 patients with the new device is currently underway. BAT is also being investigated for use in heart failure as a reduction in sympathetic activity is postulated to have beneficial effects haemodynamically. A recent study has shown improvements in functional capacity, quality of life and proBNP in patients with New York Heart Association class III heart failure and this area is undergoing further active investigation.

The role of RDN alongside BAT is not yet understood. It is possible that they may have a complimentary role in the setting of resistant hypertension, or perhaps one is superior to the other. Studies in dogs show further reduction in blood pressure with BAT following RDN. Both treatments reduce blood pressure and renin levels and BAT reduces systemic levels of norepinephrine. RDN only reduces renal venous levels of norepinephrine. Six patients who had the Barostim neo device placed in the initial trial had previously undergone RDN and had an average blood pressure reduction of 21/11 mmHg, suggesting BAT has a role in non-responders to RDN. Given advancements remain underway in both fields and we have not yet reached a time when a head-to-head comparison would be feasible.

Arteriovenous Shunts

Patients with advanced chronic obstructive pulmonary disease underwent studies of arteriovenous (AV) shunt creation with the theory to improve oxygenation, cardiac output and functional capacity. Large and unexpected blood pressure reductions were noted³⁴ suggesting that this may be a treatment option for resistant hypertension. Creating a shunt reduces total systemic vascular resistance by moving blood into the high capacity venous system, thus reducing blood pressure.

Rox Medical developed The Coupler, a paperclip size device inserted angiographically between the iliac artery and vein, creating a 4-mm shunt. The Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (ROX CONTROL HTN)³⁵ trial published in the *Lancet* in 2015 evaluated 83 patients with resistant hypertension. Of the 83 patients, 44 underwent implantation of a Coupler device alongside medication and 39 continued on medical treatment. Patients who received the Coupler device had significant blood pressure reductions with a systolic blood pressure drop of 26.9 mmHg versus 3.7 mmHg in the control arm and 24-hour ABPM drop of 13.5 mmHg versus 0.5 mmHg in controls. Ten patients in the active arm had prior unsuccessful RDN, with good response to AV shunt treatment.

There were 25 procedure or device related complications, two were serious and all resolved without consequences. However, 28.6 % of patients experienced issues with lower limb edema 2–9 months following the procedure and were diagnosed with iliac vein stenosis proximal to the anastomosis. Eleven patients required venoplasty and stenting and one required just venoplasty. Concerns also exist regarding the potential for high output cardiac failure and lack of a sham procedure in this trial. However, further studies need to be undertaken to fully evaluate the role AV shunt creation may play in the treatment of resistant hypertension, and to elucidate the patients that would benefit most from this procedure in the future.

Conclusion

Resistant hypertension remains a serious unmet need, prompting the current vogue of research into an intervention to improve clinical outcomes for this patient population. RDN initially appeared to be a very successful adjuvant to medication in the treatment of resistant hypertension, but this excitement was tempered with SYMPLICITY-3. The

addition of a sham procedure and rigorous controls found no clinical benefit from the procedure, but did prove safety. This was a strong blow to the field and has dampened enthusiasm, however clinical trials remain ongoing and researchers have returned to the drawing board to understand and answer many questions regarding the role of RDN. We believe that RDN can reduce blood pressure in the right patient phenotype and if the device is used appropriately, especially in terms of anatomical placement of catheters and number of ablations.

Baroreceptor activation therapy may also have a future role for these patients, however the current device is too invasive and requires vascular surgical cut down in an operating theatre. Further iteration and complete percutaneous implantation may see an important clinical role for this therapy. Other targets under evaluation include targeted splanchnic denervation and carotid body ablation. An interventional procedure with sustained blood pressure reduction resulting in improved clinical outcomes would be a very welcome addition to the cardiology field in the management of resistant hypertension. ■

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