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Review Article

Device-Based Therapy for Treatment-Resistant Hypertension: Recent Update

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Abstract

Treatment-resistant hypertension (TRH) remains a significant challenge in clinical practice, despite the availability of multiple antihypertensive medications and contributes substantially to excessive renal and cardiovascular morbidity and mortality. Clinical and experimental evidence suggests that sympathetic nervous system over-activity is the main culprit for the development and maintenance of TRH. Both medical and interventional strategies, targeting the sympathetic over-activation, have been designed in patients with hypertension over the past few decades. Minimally invasive, catheter-based, renal sympathetic denervation (RDN) and carotid baroreceptor activation therapy (BAT) have been extensively evaluated in patients with TRH in clinical trials. The outcomes of those trials have been impressive, however, many of these trials were uncontrolled and in need of validation. Device-based therapy for treatment-resistant hypertension has the potential to provide alternative or adjunctive treatment options to certain groups of patients who are refractory or intolerant of multiple antihypertensive medications. However, more research is needed to prove its long-term efficacy, safety and cardiovascular outcomes in human subjects. In this article, we will review the recent clinical trial evidence for catheter-based renal denervation, carotid baroreceptor activation therapy, and newly emerged central arteriovenous anastomosis trials to pinpoint the weak links and discuss potential alternative approaches.

Keywords: *Device-Based Interventional Therapy; Sympathetic Nervous System Over-Activity; Renal Sympathetic Denervation; Treatment-Resistant Hypertension*

Introduction

Hypertension remains a major public health problem and is the leading cause of mortality worldwide. The prevalence among adults was estimated to be 26% in 2000 and is projected to reach 29% by 2025, representing more than 1.56 billion patients globally [1]. The American College of Cardiology (ACC) and American Heart Association (AHA) 2017 guideline for high blood pressure in adults indicated that 46 % of US adults have hypertension (BP ≥ 130/80 mmHg), representing over 100 million people in the US alone [2]. Moreover, prevalence is continually rising as the population ages. Hypertension is the most common treatable risk factor for cardiovascular morbidity and mortality. However, overall hypertension control rate (BP ≤ 140/90 mmHg) is still unsatisfactory and is approximately only 53% in US [3]. In 2007, hypertension was the highest ranked cause of death in the United States, being responsible for 17.4% of total mortality [4].

There is both experimental and clinical evidence that over-activity of the sympathetic nervous system (SNS) at the level of renal, cardiac, and skeletal muscle has been the main contributor to the pathophysiology of hypertension [5]. Blood pressure exhibits a direct

relationship to sympathetic-nerve activity in patients presenting with severe hypertension [6]. In the 1930 - 1950s, non-selective surgical splanchniectomy effectively reduced both high blood pressure and cardiovascular mortality in patients manifesting severe uncontrolled hypertension [7]. Unfortunately, these benefits were offset by the significant adverse events associated with the procedure. Selective surgical renal denervation yielded mixed results. In some patients, the procedure reduced high blood pressure, but in other patients it did not. When effective antihypertensive medications became available in the late 1950s, surgical denervation was abandoned due to its severe complications [8]. Nonetheless, evidence suggests that sympathetic nerve system over-activity is a major component in the pathogenesis of severe hypertension and remains an important target of interventions in the treatment of hypertension.

In recent years, due to the advancement in technology and a better understanding of the role of SNS in resistant hypertension, interventions have been developed to selectively target the sympathetic nervous system. The most prominent procedures include catheter based renal sympathetic denervation (RDN), carotid baroreceptor activation therapy (BAT) and central arteriovenous coupler therapy (Figure 1). This review is aimed to provide clinical insight into resistant hypertension, the pathophysiologic basis of autonomic modulation as a target for resistant hypertension treatment, and available clinical evidence about device-based therapies for treatment resistant hypertension, including their efficacy and safety. Current limitations and future perspectives will also be discussed.

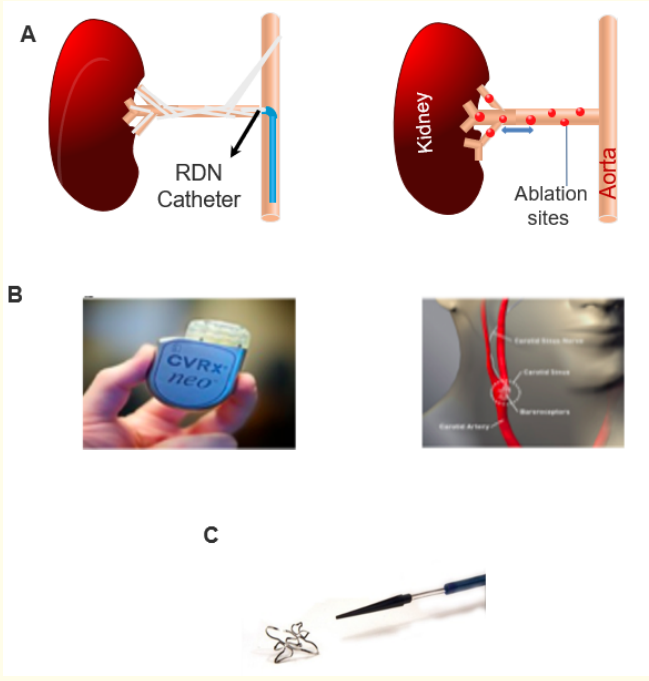

Figure 1: *Device based Therapy: A. Catheter based renal denervation (RDN) (SymplicityTM, Medtronic Inc.). B. Barostim neoTMsystem. C. ROX AV Coupler device.*

Role of sympathetic nervous system over-activity in pathogenesis of treatment resistant hypertension

Treatment resistant hypertension (TRH) was newly defined by AHA in 2018 [9] as office blood pressure ≥ 130/80 mmHg in patients taking 3 different classes of antihypertensive medications at maximum or maximally tolerated doses, including a long acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin converting enzyme [ACE] inhibitor or angiotensin receptor blocker

[ARB] and a diuretic or using ≥ 4 antihypertensive medications regardless of blood pressure level. This definition of resistant hypertension encompasses patients with apparent TRH, controlled TRH and pseudo-TRH [10]. Among treated adults with hypertension, the prevalence of apparent TRH is around 12 - 15% of population-based and 15 - 18% of clinic-based reports [11]. The newly published data from National Health and Nutrition Examination Survey during 2009 to 2014 showed the prevalence of apparent TRH among American adult population was 19.7% according to the 2018 AHA scientific statement of treatment resistant hypertension. Over 10.3 million US adults have apparent TRH according to the new scientific statement [12]. Ambulatory blood pressure monitoring (ABPM) is crucial in differentiating pseudo-TRH from true TRH. A large cohort of the Spanish Ambulatory Blood Pressure Monitoring Registry included 8295 drug-treated hypertensive patients diagnosed with RH based on office blood pressure measurements. 24-hour BP monitoring confirmed that 62.5% had true TRH and the remaining (37.5%) had pseudo-resistant hypertension [13]. Pseudo-TRH comprised approximately half of the TRH patients, and included those with suboptimal adherence to medication regimens and those with non-representative clinical BP measurements. Other causes of pseudo-TRH include white coat syndrome, excessive dietary salt and alcohol intake, and drugs such as non-steroidal anti-inflammatory drugs (NSAIDS), pseudo-ephedrine, and oral contraceptives. Most TRH cases can be effectively managed by using 4 or 5 antihypertensive drugs, including diuretics, central sympatholytics at optimal doses, and combination therapy. In the absence of an identifiable cause for treatment resistant hypertension, a mineralocorticoid receptor antagonist and/or a vasodilator β-blocker can serve as highly effective add-on therapy. Low-dose spironolactone or eplerenone can be remarkably effective for resistant hypertension regardless of the serum aldosterone level [14].

Increased sympathetic nervous system (SNS) activity has been shown to be one of the main mechanisms responsible for the pathogenesis of hypertension [5]. Direct, as well as indirect approaches, used in studies assessing SNS function, have almost uniformly shown that a sympathetic overdrive is detectable in patients with borderline to severe hypertension. Norepinephrine spillover in kidneys, heart, and brain [5] and skeletal muscle sympathetic-nerve activity [15] are enhanced in hypertensive patients. Blood pressure exhibits a direct relationship to sympathetic nerve activity in patients presenting with severe hypertension. A recent study using microneurography [16] demonstrated the marked increase in sympathetic activation and impaired baroreflex function in true TRH patients compared to the normal control and treated hypertensive patients (Figure 2).

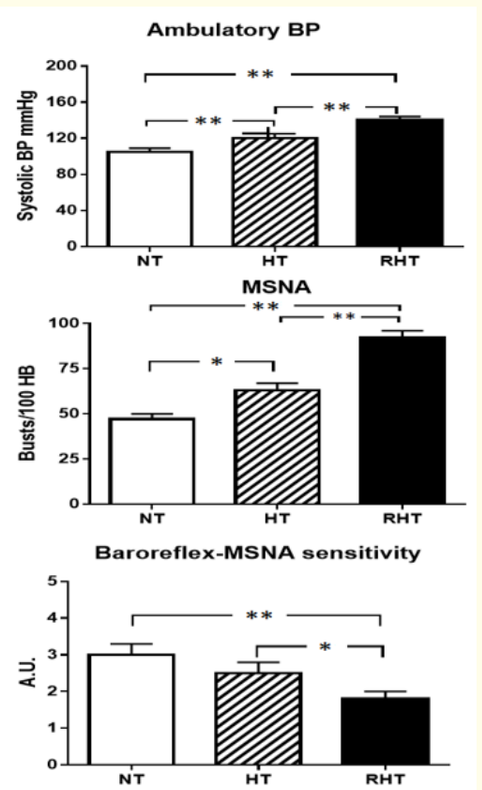

Figure 2: *Marked increase in muscle sympathetic nerve activity and decrease in arterial baroreflex control in true resistant hypertension. Upper panel indicates ambulatory systolic BP differences in resistant hypertension (RHT), well-controlled hypertension (HT), and normotensive control (NT). Middle Panel represents increase in muscle sympathetic nerve activity (MSNA. Busts/100 heart beats) in hypertension. Lower panel indicates decrease in Baroreflex-MSNA sensitivity in hypertensive groups. Values are expressed as mean ± SEM. Asterisks (*P < 0.05, **P < 0.01) refer to the statistical significance between groups. The figure was adapted from publication of Ref. 16 with permission.*

The kidneys play a key role in the long-term blood pressure regulation via two classic mechanisms: the production and release of renin, and fluid volume control by urinary sodium excretion. Both functions are regulated by the SNS. Evidence has accumulated in the past decades on the important role of the renal afferent nerve in inducing an increase in sympathetic discharge at the central level in experimental models of hypertension [17]. Thus, the interplay between the kidneys and the SNS is bidirectional: central sympathetic efferent nerves regulate renal vascular resistance, renin release, and sodium re-absorption, while renal afferent nerves convey sympathoma-excitatory stimuli towards autonomic regulatory nuclei in the central nervous system. Nervous traffic in both directions is increased in hypertension, greatly contributing to its development and maintenance. This pathophysiologic evidence constitutes the clinical basis for renal denervation, which disrupts both renal afferent and efferent nerves [5].

Another mechanism is that of the baroreceptor reflex which buffers acute rises and falls of blood pressure. When blood pressure rises suddenly, the increased stretch-sensitive baroreceptor firing sends inhibitory signals to the nucleus tractus solitarius (NTS) in the brain stem. This triggers a reflex increase in vagal efferent activity and decrease in sympathetic efferent activity. The end result is a decrease in heart rate, contractility and vascular tone which reduces blood pressure (Figure 3).

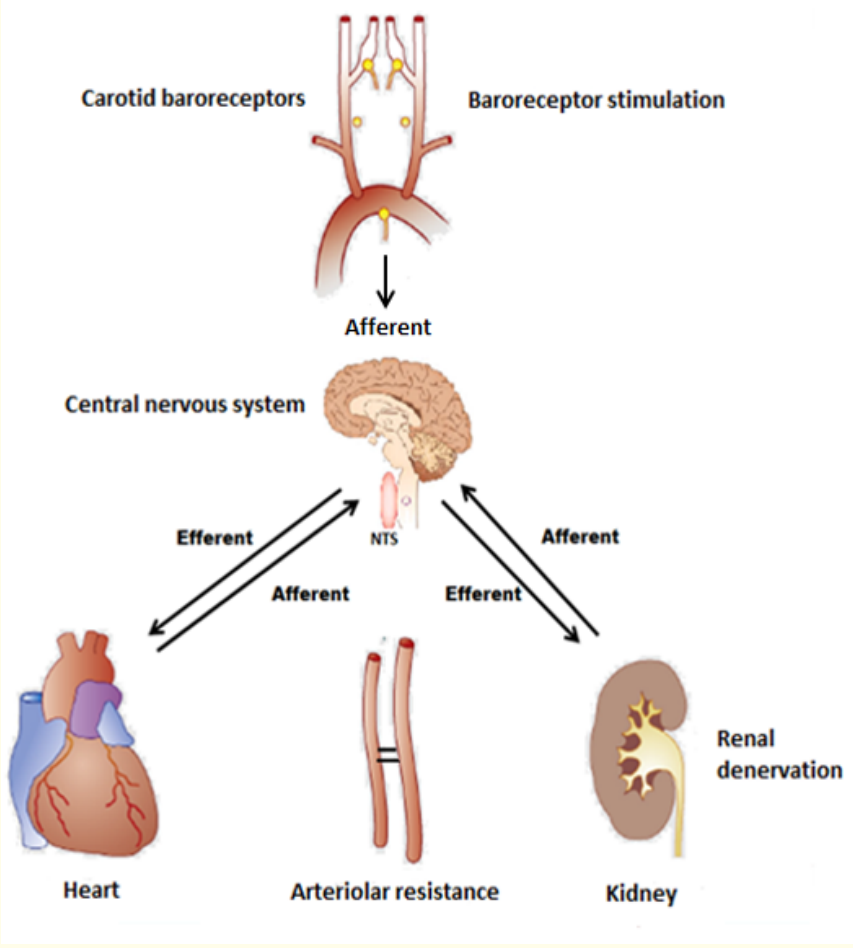

Figure 3: *Therapeutic targets of the sympathetic nervous system in hypertension. The figure was adapted from Ref. 5 and 6 with permission.*

The baroreceptors are believed to play a permissive role in chronic hypertension, and they reset to defend sustained hypertension. Grassi., *et al.* [16], have demonstrated that marked inhibition of baroreflex function exists in true TRH patients (Figure 2). Desensitization of baroreflex receptors to blood pressure fluctuations induced by arterial wall stiffening and circulating angiotensin II and aldosterone have been proposed as a leading mechanism of chronic sustained hypertension [18].

Catheter based renal denervation (RDN) in patients with treatment-resistant hypertension

Renal sympathetic denervation has been performed through the years, both in animal models and in humans, by the surgical interruption of renal nerves. With advancements in technology and the advent of transcatheter techniques, several types of devices have been made clinically available for transvascular renal sympathetic denervation [19,20]. Most of the sympathetic fibers are located 2 - 3 mm from the renal artery lumen and they are thus amenable to catheter-based thermal ablation [21]. Catheter-based RDN delivers transvascular energy through the renal artery wall to disrupt both afferent and efferent sympathetic fibers that are coursing in the adventitia of the vessel [22]. Radiofrequency (RF) energy has been the preferred source of energy so far in most studies. Currently used systems can create discrete lesions of about 2 - 3 mm in diameter and depth, depending on the target temperature. It has been determined therefore that certain numbers of lesions are needed in order to achieve complete denervation [23,24]. These lesions need to be distributed in suitable patterns, so as to achieve complete fiber interruption, but at different distances from the origin of the artery so as to avoid cross-sectional lesioning, which may predispose to renal artery stenosis.

The first in-human feasibility, safety, and proof of concept study (SYMPLICITY HTN-1) [19] included 50 patients with treatment-resistant hypertension. Of those, 45 patients were eligible for RDN and composed the treatment group. Five patients declined the procedure and were followed up as the control group. Office BP reduction with RDN was significant, smaller in the first month (-14/-10 mmHg) and more pronounced office BP reduction was demonstrated at 6 months (-27/-17 mmHg). Ambulatory BP monitoring (ABPM) was done in a small subset of patients and showed much less BP reduction (-11 mmHg for SBP). SYMPLICITY HTN-2 [20] was performed in a larger sample of 106 patients with TRH. RDN was performed in 52 patients plus standard antihypertensive medications and the remaining 54 patients remained on standard therapy as control group. BP was reduced significantly in the first month in the active RDN group (-20/-7 mmHg) but was much greater at 6 months (-32/-12 mmHg). No change in BP was observed in the control group (0/-1 mmHg) over 6 months. BP reduction was significantly less in a smaller group of 20 patients who underwent ambulatory BP measurement (-11/-7 mmHg).

Most catheter-based RDN studies that followed, and implemented similar protocols to the early SYMPLICITY (HTN-1 and 2) trials, remained unblinded and included a single arm, and most of them presented reductions in office SBP in the range of 20 - 30 mmHg [25]. Those earlier studies created a great deal of enthusiasm for a promising breakthrough therapy for the treatment of resistant hypertension, but they were accompanied by a number of questions and inconsistencies.

SYMPLICITY HTN-3 was the first randomized, single-blinded, sham-controlled RDN study [26] and enrolled 535 patients with TRH in a 2:1 ratio to optimal medical therapy plus RDN or to optimal medical therapy plus sham procedure. The study was conducted in over 90 centers throughout the US and, for the first time, included 25% African American hypertensive patients in an RDN trial. The study met its primary safety endpoint: a composite of all-cause mortality, end stage renal disease, embolic events resulting end organ damage and vascular complications, hypertensive crisis, or renal artery stenosis. The study, however, failed to meet the primary efficacy endpoint. Results indicated that there was no significant difference in office BP or ABP between groups. At 6 months, office BP decreased by 14.1 ± 24 mmHg in the RDN group and by 11.7 ± 26 mmHg in the sham control group ($p = 0.255$). The average 24-hour ambulatory SBP decreased by 6.75 ± 15.11 mmHg in the RDN group and by 4.79 ± 17.25 mmHg in the sham control group for a difference of 1.96 mmHg ($p = 0.979$). The failure of SYMPLICITY HTN-3 raised significant doubts about the efficacy of RDN and challenged the concept of renal denervation as an effective interventional therapy for treatment resistant hypertension.

Other studies also reported negative results in the RDN trials. In a small study of 12 patients with difficult-to-control hypertension [27], there was no change of BP, heart rate, and resting muscle sympathetic never activity (MSNA) after RDN at 5 months follow up. One explanation for the negative results is patient selection. Patients had lower baseline office BP (157/85 mmHg) and more importantly, many of them (5/12, 42%) had normal BP (SBP < 140 mmHg), and furthermore, there was no evidence of sympathetic over- activation in these patients (normal baseline MSNA and HR). This study raises a question regarding patient selection in the early RDN trials. In another recently published study, 65 patients with apparent TRH were referred for RDN. Of those, 46 patients were excluded due to white coat hypertension, secondary hypertension, and poor medication adherence [28]. Patients with true TRH underwent RDN (n = 9) or clinically adjusted drug treatment (n = 10) and the trial was stopped early because RDN had uncertain BP-lowering effects in both office and ambulatory BP compared to the adjusted drug treatment group. This study was flawed by antihypertensive medication selection and dose adjustment as trial confounders and there were small numbers of patients studied.

SYMPLICITY HTN-3 and other negative trials left many valuable questions unanswered and created an urgent need for further research in the role of renal denervation in treatment of resistant hypertension. Post-hoc analysis of SYMPLICITY HTN-3 trial revealed that a higher number of renal artery ablations (≥ 12 ablations) is associated with consistent and significant reduction in BP and that many patients had incomplete renal denervation in this trial [23]. Only 68 (18%) RDN treated patients received one four-quadrant ablation either in the right or left renal artery, while 19 patients (5%) received four-quadrant ablations in both arteries, and they achieved the greatest BP reduction. Most patients (69%) in the RDN group had 0 four-quadrant ablations. Therefore, the main reason for failure of the SYMPLICITY HTN-3 trial appears to be incomplete renal denervation. Other confounding factors included patient BP medication adherence and adjustment in both groups, as there were 38% of patients who required an anti-hypertensive medication change during follow-up which could have contributed to the unexpected outcomes of the trial. Furthermore, the newly designed second generation ablation catheter (SYMPLICITY Flex catheter) which was different from the previous SYMPLICITY trials (HTN-1 and 2) was used in SYMPLICITY HTN-3 trial and was another potential cause of the failure.

To address much controversies created in recent renal denervation trials [29], a newly designed proof of concept trial was warranted to address the important question whether the catheter-based RDN alone could indeed lower BP in patients with hypertension in the absence of antihypertensive medications. SPYRAL HTN -OFF MED study was a multi-center, international, randomized, single-blind, and sham controlled trial to assess BP lowering effects of RDN in patients with mild to moderate hypertension who were either drug naïve or who agreed to have their medication withheld for a period of time [30]. 80 patients with office SBP (≥ 150 and < 180 mmHg) and DBP (≥ 90 mmHg) and a mean 24 h ABP ≥ 140 and < 170 mmHg were randomly enrolled in the RDN group (n = 38) and sham control group (n = 42). At 3 months follow up, 24h ABP was reduced 5.5/4.8 mmHg and office BP was decreased 10/5.3 mmHg respectively in RDN group (Both $P < 0.05$) and change in both 24 h ambulatory and office BP in sham control group was very minimal and was not different from baseline at 3 months.

The SPYRAL HTN-OFF MED study provided robust evidence that RDN alone effectively lowered blood pressure in patients with hypertension. This novel trial differs substantially from the previous renal denervation trials in term of the renal denervation techniques used, the hypertensive population enrolled and the absence of concomitant antihypertensive medications. The newly invented third generation Symplicity SPYRAL multielectrode catheter (Medtronic, Galway, Ireland) produced circumferentially all four-quadrant ablations in main renal arteries, branch vessels and accessary arteries. Average number of ablations per patient obtained in SPRRAL HTN OFF MED was 4-fold higher (43.8 ± 13.1) than SYMPLICITY HTN-3 (11.2 ± 2.8), indicating that more complete denervation was achieved. SPYRAL HTN-OFF MED selected a patient population with combined systolic/diastolic hypertension. Despite these differences, one third of the patients still had no BP reduction after RDN. Medication adherence, which has been the most relevant confounding factor affecting the outcome of antihypertensive trials, was expected to be eliminated by the absence of BP medication use and informed medication monitoring in this trial. However, about 10% patients in both groups still took antihypertensive medications.

SPYRAL HTN-ON MED trial [31] was conducted to evaluate the effects of renal denervation on blood pressure in the presence of antihypertensive medications. This was an international, multicenter, randomized, single-blind, sham controlled trial in patients with uncontrolled hypertension who were on 1, 2 or 3 BP medications at a stable dose for 6 weeks. 80 patients with office SBP between 150 - 180 and DBP ≥ 90 mmHg, and 24h systolic ABP between 140 - 170 mmHg were randomly enrolled into RDN (n = 38) and sham control group (n = 42). The same denervation protocol implemented in SPYRAL HTN-OFF MED was used in this trial. Office and 24h ambulatory blood pressure decreased significantly from baseline to 6 months in the renal denervation group (-9.4/-5.2 and -9/-6 mmHg) as compared to sham control. More importantly, hourly BP reduction was sustained throughout 24h in the renal denervation group. Medication adherence was about 60% and varied for individual patients throughout the study. No major adverse events occurred in either group. Worthley., *et al.* recently reported the 6-month data from the first-in-human trial, EnligHTN-I [32]. This study evaluated 46 patients with resistant hypertension and baseline characteristics similar to the early SYMPLICITY trial population. All patients underwent RDN using a newly invented multi-electrode catheter aiming to achieve more complete renal denervation. Office BP was reduced significantly in the first month (-28/-10 mmHg) and remained at the same level for 6 months. Ambulatory BP measurements were performed in all patients in this study and demonstrated average 24-hour SBP reduction of -10/-5 mmHg as compared to office BP reductions. BP reduction remained similar up to 12 months follow-up in the same patients [33].

Analysis from the previous trials indicated that patients with younger age, combined systolic/diastolic hypertension, and higher arterial stiffness index are more responsive to RDN [30,34,35]. No effective and practical screening or diagnostic tests predict good candidates for RDN with RF. While radiofrequency energy (RF) ablation was the most used in the recent trials, it may have accounted for the 15-30% non-responders when compared to sham groups, possibly from incomplete or partial denervation. Other technologies include ultrasound energy, cryoenergy and perivascular chemical denervation may provide a more optimal and complete denervation for patients with TRH.

Endovascular ultrasound renal denervation has been developed to thermally ablate the renal sympathetic nerves. Chernin., *et al.* [35] first reported effects of ultrasound energy induced RDN using the Therapeutic Intra Vascular UltraSound (TIVUS) (Cardiosonic ,Tel Aviv, Israel) system in patients with TRH. 39 patients with office SBP> 160 mmHg were enrolled this multicenter and single arm study. Mean reduction of office SBP after RDN was -26.1 ± 9.6, -28.0 ± 9.9 and -30.6 ± 14.1 mmHg at 1, 3, and 6 months follow up. Mean reduction of systolic ABP was 6.8 ± 15.1 mmHg. More importantly, all patients had BP reduction after the procedure in this cohort and patients with isolated systolic hypertension had a significant smaller reduction in office SBP after 6 months compared with patients with combined systolic/diastolic hypertension (-16.2 ± 18.5 vs -49.9 ± 33.4 mmHg). RADIANCE-SOLO [36] was a multicenter, international, single-blind, sham controlled trial to investigate whether endovascular ultrasound renal denervation reduces ambulatory blood pressure in patients with hypertension in the absence of antihypertensive medications (Paradise renal denervation system, ReCor Medical, Palo Alto, CA, USA). 146 patients with 24 h ABP ≥ 135/85 and < 170/105 mmHg after 4-week discontinuation of up to two antihypertensive medications, were randomized to undergo renal denervation (n = 74) or a sham procedure (n = 72). This study was powered for efficacy and the reduction in daytime ABP was greater with renal denervation (-8.5 ± 9.3 mmHg) than with the sham procedure (-2.2 ± 10 mmHg) at 2 months. No major adverse events were reported in either group. The RADIANCE-SOLO and SPYRAL HTN -OFF MED trials enrolled largely similar patient population, and yielded consistent results, demonstrating that catheter based renal denervation, using either ultrasound or RF energy, lowers blood pressure among patients who are off antihypertensive medications. The results of both trials will inform the design of future studies in this population to provide additional safety and long-term efficacy data, which will be important to establish the role of renal denervation in the treatment of hypertension.

Transvascular catheter-based cryoablation was recently developed for RDN. Prochnau., *et al.* [37] first investigated whether RDN with cryoenergy can serve as an alternative option in a small single arm study. Ten patients with resistant hypertension who were non-responders to renal denervation with RF were treated with cryoablation for RDN. (Freezor® Xtra; Medtronic, Minneapolis, MN, USA). Mean reduction of office SBP (-41/-47/-61) and Systolic ABP (-38/-35/-52) were significant in all patients studied and no short-term procedure related complications occurred. This small study qualified RDN with cryoenergy as an effective second-line therapeutic option

in patients with TRH. Large, randomized, blinded, and sham controlled trials are needed to validate the efficacy and safety of RDN with cryoablation.

Alcohol induced perivascular renal denervation

Renal sympathetic fibers have been identified as far as 8 - 10 mm away in depth from the vessel lumen in humans, and anatomy varies from patient to patient [38]. Energy-based, transvascular radiofrequency nerve ablation has inherent limitations related to thermal injury to the media and inadequacy of depth of denervation. Fischell., *et al.* [39] developed a novel, next generation perivascular renal artery denervation device (Peregrine™), applying a catheter-based chemical neurolysis of renal sympathetic nerves, with selective micro-infusion of alcohol (ETOH) into the peri-adventitial space to achieve predictable, sustained nerve injury. The pre-clinical study revealed that transluminal perivascular denervation using micro injection of alcohol significantly reduces renal tissue norepinephrine levels (68 - 88%) with histopathologic evidence of marked, deep, and circumferential renal nerve injury at depths of up to 13.4 mm from the intimal surface. In contrast to the catheter-based radiofrequency nerve ablation which, in animal models, followed with re-innervation of renal nerves [40], nerve injury in the alcohol-treated vessels after 3 months was characterized by vacuolization, loss of internal architecture, and the development of peri-neuro fibrosis. Alcohol-induced nerve injury appeared pathologically permanent, with damage to the peri-neural sheath that would prevent nerve regeneration. Whereas, pathological examination did not show evidence of device-related or alcohol-induced injury to the intimal layer of treated vessels. There were no thrombi, dissections, aneurysms, perforations, hematomas, neointimal formation, negative remodeling or other device-related pathology. The first feasible human study using perivascular ETOH denervation [41] evaluated 18 patients with resistant hypertension with the vast majority of patients (16/18) achieving significant, sustained office BP reduction at 6 months (mean -24/-12 mmHg). The reduction in BP was associated with a decrease in the number of anti-hypertensive medications patients were taking (average1.4 medications per patient). No patients in this trial required an increase in the number of antihypertensive medications and no major adverse effects occurred during the trial period. The authors concluded that the procedure was safe and effective and serves as a promising alternative approach for renal denervation. Large, randomized, controlled trials are undergoing to validate the safety and efficacy of the device in patients with resistant hypertension.

Beyond the long-term reduction of BP in patients with resistant hypertension, catheter-based RDN also improves left ventricular mass, glucose metabolism, insulin resistance, health-related quality of life, arrhythmia, and the obstructive sleep-apnea index [42-44]. Furthermore, the procedure may benefit congestive heart failure patients, but this is still under investigation [45].

Summary of available devices

In the SYMPLICITY HTN trials and other earlier trials, RDN was performed using the first and second generation of single electrode catheter [19-20,26] (Symplicity, Medtronic). Complete renal denervation can be difficult to achieve with a single electrode catheter, seen on a two-dimensional screen, attempting to create lesions in a three-dimensional artery. The RDN procedure creates imprecise lesions with no practical and immediate measure of procedural success. Operator's specific experience of ablation system used can therefore be a crucial determinant of achieving adequate denervation [22]. The newly designed, next generation of multi-electrode catheters is aimed to deliver RF energy to sympathetic nerves located at the renal artery adventitia in a pre-determined pattern and to achieve the desired pattern of lesions (four-quadrant ablations) with less manipulation and operator training. The St Jude's multi-electrode ablation system (EnligHTN) has 4 electrodes mounted on a basket that can easily achieve circumferential distribution of lesions [32]. The third generation Symplicity SPYRAL catheter has 4 electrodes mounted on a catheter, positioned to apply RF energy circumferentially in all four quadrants of the renal artery and branch vessels [30,31]. Other CE approved systems include, Vessix V2 system (Vessix Vascular-Boston Scientific) [46]; and the Oneshot system (Covidien) which is currently off the market [47], both have the electrodes mounted on a balloon. The Iberis system (Terumo) has 4-French shaft that enables radial access [48]. The paradise system using ultrasound as energy source has been approved for use in Europe (ReCor Medical) [36]. RDN was achieved with catheter based cryoablation (Freezor® Xtra, Medtronic, Minneapolis, MN, USA) in patients with resistant hypertension [37]. In addition, Peregrine system infusion (Ablative Solutions) achieved

perivascular denervation by peri adventitial microinjection of ETOH [41]. Many those devices have been evaluated in small, unblinded, single arm studies in which BP reduction has been sustained over 3 - 12 months in patients with drug-resistant hypertension (Figure 4).

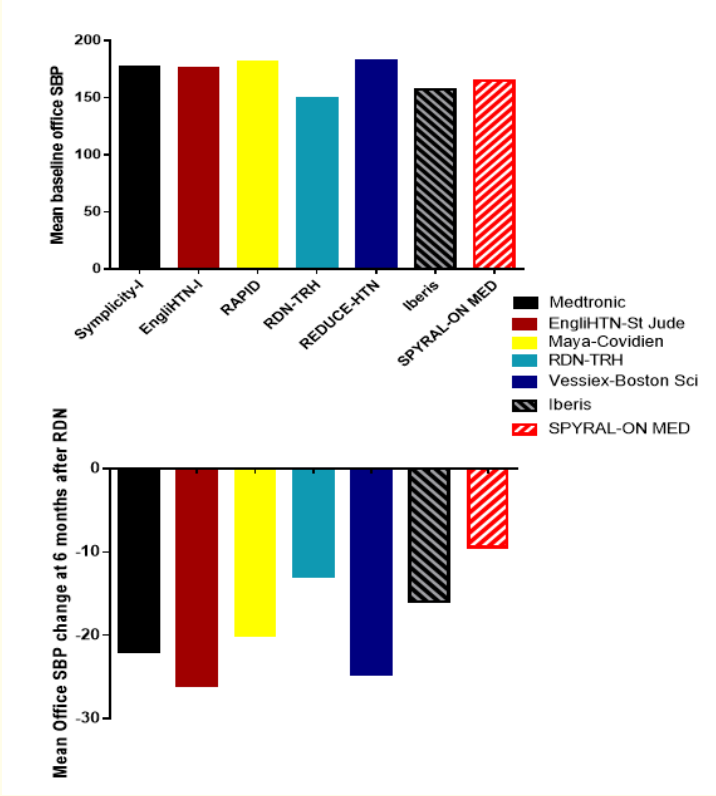

Figure 4: *Reduction of systolic blood pressure by renal denervation using different types of catheters in single-arm, open-label studies.*

Limitations and future directions of renal sympathetic denervation

The SYMPLICITY HTN 1 and 2 trials, along with earlier single-arm RDN trials demonstrated the safety, efficacy and sustained long-term blood pressure lowering effects using renal denervation in resistant hypertension. However, their results are questioned due to lack of randomization, sham control and blindness in those trials [24]. The degree of renal denervation achieved in Simplicity HTN-1 trial was 25 - 47% as expected, and incomplete denervation occurred frequently with treatment failure between 15 - 50%. Patient selection and follow up were compromised by the underuse of 24-hour ABPM and lack of monitoring medication adherence by checking serum or urine drug level of antihypertensive medications. Many patients with white coat syndrome, or secondary hypertension, such as pheochromocytoma, were enrolled into RDN studies and underwent the procedure mistakenly [19-20,26].

In the future, large, randomized, blinded, and sham-controlled trials are needed to validate the efficacy of RDN in patients with treatment-resistant hypertension. The complete interruption of renal sympathetic nerves with RDN is essential for its success, and attention, therefore, need to be paid to systems that can provide predictable, and reproducible results. The RDN systems need to be easy to use, less operator dependent, and require minimal manipulation to achieve complete fiber interruption. A clinically practical marker that can confirm the immediate success of complete renal denervation during the RDN procedure is urgently needed [49].

Baroreceptor activation therapy (BAT) for treatment of resistant hypertension

Baroreflex modulation has long been regarded as an appropriate site for intervention to reduce sympathetic nerve activity and high blood pressure. Carotid sinus electrical stimulation enhances carotid sinus firing and decreases heart rate and blood pressure by sympathetic inhibition in patients with resistant hypertension. Long-term clinical data, however, is scarce and has only in recent years been tested in the context of clinical trials. The Rheos Baroreflex Hypertension Therapy system (CVRx Inc., Minnesota) is the first implantable device for BAT in the treatment of resistant hypertension and has been tested in two small earlier trials and 2 large clinical trials [50,51].

The DEBuT-TH (Device Based Therapy in Hypertension trial) was the first-in-man, European, proof of concept, prospective, single arm feasibility study [50]. The primary end-points were to assess the safety and efficacy of the Rheos device over a 3-month period. A total of 45 patients with resistant hypertension were enrolled during years 2004 - 2007 and were followed up over the next 2 years. They had a mean baseline office BP of 179/105 mmHg and were on 5 antihypertensive drugs. A total of 10 patients who declined device implantation were used as a control group. After 3 months of BAT, mean office BP was reduced by 21/12 mmHg and ABP was reduced by 6/4 mmHg. At the 1 and 2 year follow up, mean office BP was reduced to 30/20 and 33/22 mmHg respectively. A similar trend was observed with ABPM where BP was decreased by 13/8 at 1 year and 24/13 mmHg at 2 years. An obvious limitation of this study was the fact that it was not randomized and involved medication changes during the study period. Some serious adverse events were also reported; three infections required the device to be explanted; one perioperative stroke with minimal residual effects probably due to intra-operative injury to the hypoglossal nerve, and one device-related migration of the implantable pulse generator requiring repositioning.

The Rheos Pivotal Trial [51] was the first double-blinded, randomized, placebo controlled, device trial conducted in centers in Europe and the US. The primary endpoints were safety and efficacy of BAT in resistant hypertension. All 265 patients were implanted with the device and subsequently randomized (2:1) either into group A with BAT for the first 6 months or to group B with delayed BAT initiation following the 6-month visit. The primary endpoint was BP change at 6 months. The trial met three of the five co-primary endpoints: sustained efficacy (reduction in SBP of at least 10 mmHg at 12 months, 88% responders), BAT safety (40 % rate reduction in hypertensive events in group A), and device safety (2.3% hypertension-related stroke). At 6 months, there was 54% responders in group A and 46% in group B, (P = 0.97). There was no significant difference between patients having the device on and those having the device off. Thus, the study failed to meet its primary end point. Procedure safety (4.4 % transient nerve injury, 4.8% permanent nerve injury, 4.8% general surgical complication, and 2.8 % respiratory complaint) was poor. Long-term follow up of BAT treated resistant hypertensive patients suggested long term BP reduction was sustained up to 4 to 6 years. With improvement in technology in BAT, a less invasive procedure emerged, limiting the excessive procedure-related complications. A second-generation Rheos implantable BAT device [52] has been evaluated in a single arm, open label study (Barostim neo trial). The new BAT device was designed to work with a single electrode implanted unilaterally, making the surgical procedure much simpler. Thirty patients with resistant hypertension were enrolled in the trial in 7 centers across Europe and Canada and had baseline mean office BP of 172 ±/100 mmHg. The mean office BP reduction was 26/12 at 6 months. More interestingly, in a subset (n = 6) of patients who failed prior RDN, office BP was decreased by 22/10 mmHg after BAT. In a recently published study, fifty-one patients from the Barostim neo trial prospectively underwent ABPM before and after BAT for 6 months. ABP was significant reduced by chronic stimulation of the carotid sinus using the BAT neo device (148 ± 17/82 ± 13 to 140 ± 23/77 ± 15, p < 0.01) [53]. At 1 year follow up, 45 patients treated with Barostim Neo device had significant blood pressure reduction [54]. Only 3 minor procedure–related complications occurred within 30 days of implantation of the device and all complications were resolved without long term sequelae and adverse effects were similar to the procedure of pacemaker implantation.

Although results of BAT studies are impressive and complications are minimal, the procedure was still invasive and costly, and the battery needs to be changed every few years. A novel alternative, less invasive approach to target carotid baroreceptor has been developed. The MobiusHD (Vascular Dynamics, CA, USA) [55] is an endovascular stent that activates the baroreceptor by causing pulsatile stretch of the carotid sinus. Recently, Spiering et al reported the Controlling And Lowering blood pressure with the MobiusHD, First In Man, in EUrope (CALM-FIM-EUR) trial. It was a prospective, open label study that investigated the safety and efficacy of this endovascular baroreflex

amplification (EVBA) device in patients with resistant hypertension. 30 patients with resistant hypertension was enrolled and underwent successful implantation. Mean office blood pressure was 184/109 mmHg at the baseline and was reduced by 24/12 at 6 months and mean 24 h ambulatory blood pressure was 166/100 at baseline and was reduced by 21/12 mmHg at 6 months. Five serious adverse events had occurred in 4 patients (13%) including hypotension (n = 2), worsening hypertension (n = 1), intermittent claudication (n = 1) and wound infection (n = 1). EVBA is less invasive and substantially lowers blood pressure with acceptable safety profile.

Limitations and future directions of baroreceptor activation therapy

The results of the DEBut-HT and Rheos Pivotal study, the first studies testing the BAT safety and efficacy, had several limitations. The DEBut-HT study was not randomized nor controlled, whereas the Rheos Pivotal study had a robust randomized controlled design, with a control group having "sham intervention" (device implantation without BAT delivering for six months) , but failed its primary endpoint [51]. There was an unexpected BP reduction after device implantation between pre-implant and 1 month after implantation and at 6 months in group B. Likely, the surgical manipulation of the carotid sinus during implantation of electrodes, along with sham or placebo effects, played a role in decrease of BP, making it difficult to draw clear conclusions from these results. The other significant limitation is the occurrence of surgically-related complications. Fortunately, the second-generation BAT device, Barostim neo only requires implantation on one side leading only to minimal surgical complications. MobiusHD stent is implanted on only one side of internal carotid artery and is much less invasive. Both trials were non- randomized, single arm studies without sham control. Phase III trials testing Barostim neo and EVBA device are underway in Europe and US. BAT also has therapeutic potential in heart failure and chronic kidney disease [56]. Results from randomized, double-blind, and sham controlled studies are definitively needed before these technologies can be applied to clinical practice.

Novel central arteriovenous coupler therapy in resistant hypertension

Arterial hypertrophy in response to chronic hypertension is associated with a reduction in arterial compliance. The central aorta and iliac vessels serve as conduits for blood, but their elasticity also acts as a buffer to end organs against the highly pulsatile energy generated by the heart and cardiac cycle, which decreases cardiac afterload and myocardial stroke work. The ROX coupler (ROX Medical Inc, CA) creates a therapeutic 4-mm arteriovenous fistula (AVF) between the iliac artery and vein with a controlled shunt flow (about 800 ml/min). A large low resistance vascular bed can be added to systemic circulation. As a result, the total systemic vascular resistance is decreased. Originally, the procedure was developed to treat patients with chronic obstructive pulmonary disease (COPD) by increasing cardiac output and oxygen delivery to tissues. Incidentally, BP was found to be reduced in COPD patients with hypertension, but not in patients without hypertension by the AVF created using ROX coupler [57]. The concept was further elucidated in a small, non-randomized, open-label study comprising 8 patients with resistant hypertension, but without COPD. After creation of the AVF, both significant office BP and ABP reductions were sustained at 6 months.

More recently, a multicenter, prospective, open-label, randomized, controlled trial (the ROX CONTROL HTN study) was conducted in Europe to evaluate the safety and efficacy of arteriovenous coupler therapy [58]. Eighty-three patients with resistant hypertension were enrolled in arteriovenous coupler therapy group (n = 44) and control group (n = 39). Both groups received standard antihypertensive care during the trial period. Mean office SBP reduced by 26.9 ± 23.9 mmHg ($p < 0.001$) in the arteriovenous coupler group and by 3.7 ± 21.2 mmHg ($p = 0.31$) in the control group compared to baseline at 6 months. The BP reduction was confirmed by ABPM with comparable BP reduction. Mean systolic ABP reduced by 13.5 ± 18.8 mmHg ($p < 0.001$) in arteriovenous coupler recipients and by 0.5 ± 15.8 mmHg ($p = 0.86$) in controls. 39/44 patients treated with AV coupler along with control patients underwent long term follow up and BP reduction of AV coupler therapy was sustained. Mean office SBP was reduced by 25.1 ± 23.3 mmHg and mean systolic ABP was reduced by 12.6 ± 17.4 mmHg (both $p < 0.001$). Implantation of arteriovenous coupler was associated with late ipsilateral venous stenosis in 14 of 42 (33%) patients and was resolved with venoplasty or stenting [59].

Limitations and future directions

The central arteriovenous coupler therapy is a minimally invasive and reversible interventional procedure for resistant hypertension and BP reduction was sustainable with substantial but treatable side effects. It is still in early stage, and there is only one randomized, controlled trial with limited TRH patients (n = 83). Large, long-term, blinded, randomized, sham-controlled trials are needed to test its efficacy and safety in the future. Furthermore, long term effects on cardiovascular mortality remains to be evaluated, notably the risk of high output heart failure and Left ventricular hypertrophy in setting of secondary elevation in Renin- angiotensin levels.

Conclusion

Treatment resistant hypertension remains important predictors of increased mortality and in need for more potent targeted therapies. Minimally invasive device-based therapy is now made possible with the advancement in technology and may offer an alternative or adjunctive option to current medical treatments. Renal sympathetic denervation appears to be the most promising device-based treatment, but further investigations are needed to better define the degree of denervation and select the patient population that would benefit the most from the procedures. Baroreceptor activation therapy is among the most evaluated device-based therapy for resistant hypertension, however more randomized and validated data are needed with an improvement in safety profiles. Promising outcome data have been published; however randomized, blinded, well-controlled studies have failed to prove efficacy beyond a reasonable doubt. Long-term efficacy, safety and cardiovascular outcome trials are certainly needed before these procedures can be recommended for clinical use.

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