RESISTANT HYPERTENSION

Device-based Therapies for Hypertension

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ABSTRACT

Hypertension is a major public health issue and due to poor blood pressure (BP) control rates, worldwide, alternative non-pharmacological therapies are being sought to help improve blood pressure control. There are multiple catheter-based renal denervation (RDN) devices that are available and being studied in various hypertensive populations. The procedure has been shown to be safe, but the efficacy has been variable and enthusiasm for the procedure has been tempered particularly after the negative results from the largest RDN sham-controlled study – SYMPLICITY HTN-3 study. New studies are underway in investigating this technology in patients with less severe hypertension using a dual approach of a group off medication and a group on one to three standard antihypertensive medications. The rationale behind this study design is that in untreated hypertension, this approach will isolate the blood pressure lowering effect of the RDN procedure itself, and in the group assigned to standard antihypertensives, this study design will evaluate the effect of RDN in the presence of a standardized medication regimen. Other innovative noninvasive methods of RDN including a noninvasive ultrasound technology are also being investigated. Baroreceptor inhibition is also continuing to be studied by investigating a newer more patient-friendly device using a unilateral carotid baroreceptor stimulator. Other newer innovative technologies and devices are also discussed including ethanol-based sympathicolysis of the renal nerves and use of an arteriovenous fistula (AVF) device to lower blood pressure. All these methodologies should be considered experimental and cannot be recommended currently for clinical care.

Keywords: Baroreceptor inhibition, Catheter-based renal denervation, Hypertension, Sympathetic nervous system.

INTRODUCTION

Hypertension is a major public health issue with approximately 80 million adults being affected by hypertension in the United States and more than 1 billion people worldwide.[1] Despite the availability of effective pharmacotherapy, data from the 2009 to 2012 National Health and Nutrition Examination Survey (NHANES) revealed that among US adults with hypertension, only 54% were controlled.[1] Lack of blood pressure (BP) control is attributed in part to a high level of noncompliance with medication and less commonly due to true drug-resistant hypertension.[2] Due to the high rates of uncontrolled hypertension, novel innovative approaches to treating hypertension using different devices have been investigated. This review will address updates in renal denervation (RDN) and baroreceptor therapy as well as some of the newer more innovative experimental techniques.

Renal Denervation

The sympathetic nervous system (SNS) has long been recognized to play an important role in the pathogenesis of hypertension. Invasive and nonspecific surgical sympathectomy was performed successfully several decades ago to improve the survival of patients with severe hypertension and related complications. However, after the advent of modern pharmacological therapy for hypertension, surgical sympathectomy was largely abandoned due to the high rates of complications and severe side effects including postural hypotension, impotence, and incontinence. It has recently been possible to perform catheter-based minimally invasive, targeted RDN using a percutaneous femoral catheter approach. The catheter device is able to deliver radiofrequency energy to ablate the renal nerves lying within the outer layer of the artery wall at several discrete sites along the main renal artery. The denervation procedure is minimally invasive and has a short procedure and recovery time. Clinical trials have shown that the procedure is safe; however, the efficacy of the procedure is still being evaluated.

The SNS plays an integral role in maintenance of BP, and sympathetic hyperactivity has been implicated in the pathogenesis of hypertension and increases in parallel to the severity of hypertension.[3-5] The innervation of the kidneys is mostly by the SNS, and the activation of renal SNS is often greater than the other organs in hypertension.[6] There is both efferent and afferent innervation of the sympathetic nerves in the kidneys.[7] The efferent renal sympathetic nerves carry the central sympathetic outflow to the kidneys and the renal efferent sympathetic activity is regulated by central sympathetic outflow, vagal tone (activity of parasympathetic nervous system), and cross-talk between the kidneys. Activation of the efferent renal sympathetic nerves

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results in increased production and release of renal norepinephrine, greater constriction of renal vasculature, increased renin activity, and enhanced sodium and water retention, which all result in increased BP. The afferent renal sympathetic nerves regulate the central sympathetic outflow by sending sensory information from the chemoreceptors and mechanoreceptors located in the kidneys to the central nervous system. Activation of the afferent renal sympathetic nerves due to renal injury including ischemia and hypoxia stimulates sympathetic centers in the brain and increases central sympathetic outflow to the kidneys and the other vital cardiovascular organs including the heart and blood vessels, which also result in an increased BP.[8] Despite the important role the renal SNS plays in BP control, when the sympathetic renal nerves are disrupted, as seen in transplanted kidneys, adequate renal function is maintained. Figure 1 is a schematic depiction of the physiological effects of activating the renal SNS.[9]

Clinical Trials of RDN

The initial proof of concept study using a catheter-based technique enrolled 45 patients with resistant hypertension and preserved renal function and showed impressive BP reduction after bilateral RDN.[10] The efficacy of the RDN procedure was confirmed by reduction in the renal and overall sympathetic activities, resulting in the lowering of renin and of renal and total body norepinephrine levels, improvement of cardiac baroreflex sensitivity, and decreased muscular sympathetic nerve firing toward the normal level. This study was expanded to enroll 153 subjects with resistant hypertension and preserved renal function (SYMPLICITY HTN-1).[11] This nonrandomized proof of concept study demonstrated significant changes in systolic BP (SBP) and diastolic BP (DBP; –32.0 and –14.4 mm Hg) respectively, at 36 months.[11] One

subject required renal artery stenting, and three deaths unrelated to RDN occurred during follow-up.

A randomized controlled trial (SYMPLICITY HTN-2) was then conducted in Europe, Australia, and New Zealand which enrolled 106 patients with resistant hypertension and preserved renal function.[12] Patients were randomly assigned to RDN plus previous medical therapy or previous medical therapy alone groups. At the end of the 6-month follow-up, the control group was given the option to cross over and receive the RDN procedure. The study showed that RDN significantly reduced office BP from 178/97 mm Hg at baseline to 143/85 mm Hg at 6 months, while BP was unchanged in the control group despite similar baseline characteristics. In addition, significant reductions in home and 24-hour ambulatory BP (ABP) were observed in the RDN group only. Among the pooled patients who underwent RDN and were followed for 36 months, office BP was reduced by 33/14 mm Hg, consistent with the follow-up data from SYMPLICITY HTN-1.[13] No serious procedure or device-related complications or significant changes in renal function were noted.

To gain regulatory approval for this procedure in the United States, the SYMPLICITY HTN-3 study was undertaken. SYMPLICITY HTN-3 was different from the prior trials in that it involved a sham procedure in the control group.[14] The study enrolled 535 patients who met strict entry criteria for resistant hypertension and who were randomized in a 2:1 ratio to either the RDN procedure or the sham procedure. The trial did not meet its primary efficacy endpoint, which was defined as a superiority margin of 5 mm Hg for the difference in office SBP change from baseline to 6 months in the RDN group as compared with the sham control group. Using office-based SBP at 6 months, there were SBP reductions of 14.1 and 11.7 mm Hg in the RDN and control arms respectively. Although each
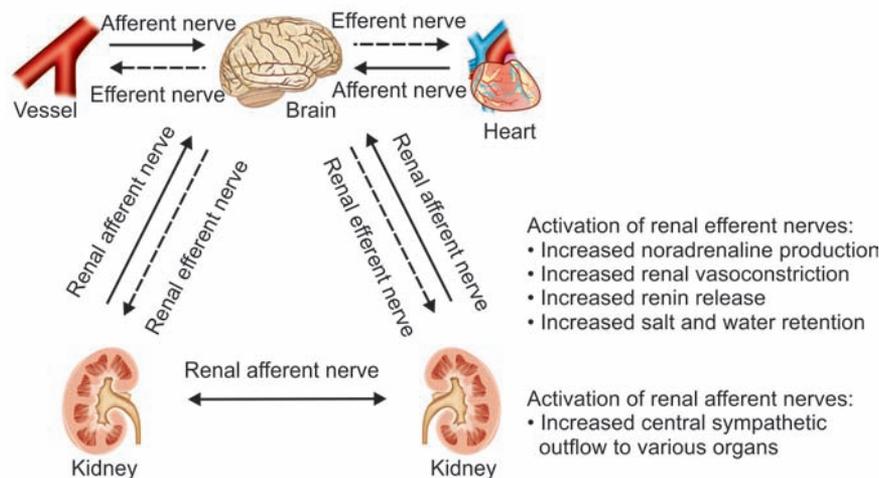

Fig. 1: The physiological effects of activating efferent and afferent renal sympathetic nerves

group's BP reduction from baseline was statistically significant, the between-group differences were not statistically significant. Blood pressure was also assessed using 24-hour ABP monitoring. The change in 24-hour ABP was –6.8 mm Hg in the denervation group and –4.8 mm Hg in the sham procedure group, which was not statistically significant. There were no significant differences in safety between the two groups. Twelve-month follow-up data from SYMPLICITY HTN-3 study were available for 319 of 361 RDN subjects and 48 of 101 noncrossover subjects; 6-month denervation follow-up was available for 93 of 101 crossover subjects.[15] In the subjects undergoing RDN, the decrease in office SBP was greater at 12 months than at 6 months (–15.5 and –18.9 mm Hg respectively; p = 0.025), but 24-hour ABP data did not show a significant difference at 12 months. The noncrossover group had a significant decrease in SBP at 6 months of –32.9 mm Hg, but the reduction was less at 12 months with mean SBP reduction of 21.4 mm Hg. The lesser BP reduction observed in the noncrossover group was attributed possibly to nonadherence with medication.[15]

Several key variables have been identified *post hoc* that were predictive of SBP response to RDN including total number of ablation attempts and energy delivery in a four-quadrant pattern, higher baseline office SBP ≥ 180 mm Hg, use of an aldosterone antagonist, preserved kidney function at baseline, and nonuse of vasodilators. Caucasian patients who underwent RDN had a significantly greater change in office SBP than those receiving sham: –15.2 and –8.6 mm Hg respectively (p = 0.012).[16] Further evaluation has also shown that conflicting results from the three SYMPLICITY studies may be due to a number of issues including differences in study design, patient characteristics, medication adherence, or efficacy of the RDN procedure itself. Although SYMPLICITY HTN-2 and HTN-3 studies were both randomized controlled trials, HTN-2 had a less rigorous study design without a sham procedure arm.

The potent placebo or Hawthorne effect in the control group of HTN-3 is also a potential explanation for this negative study. Other factors include the large percentage of patients whose antihypertensive medications were changed during the follow-up period. Specifically, there were slightly more increases in dose or number of medications in the sham group and more decreases in dose or number of medications in the RDN group.[16] The HTN-3 trial was also performed in a US cohort consisting of a higher proportion of African-Americans than that of other trials; however, there were no racial differences in response to the RDN procedure in HTN-3, but African-Americans had a more potent response to the sham procedure than non-African-Americans, which needs further exploration.[16]

Another area of focus in explaining the varied results of these trials pertains to the RDN procedure itself and the anatomic distribution and density of sympathetic nerves within the renal artery wall. The knowledge of renal nerve distribution and reduction in sympathetic activity has been obtained from studies using a porcine model, which has shown that the number of renal nerves is greatest in the extrarenal branches and in the main artery compared with the ostium, and the average distance from the lumen was greatest for nerves at the ostium and least at the branches. Renal denervation lowered renal norepinephrine levels to a greater extent when performed in branches of the renal artery closer to the kidney, most likely due to greater number of nerves located in the distal renal artery and branch arteries.[17] Due to a greater concentration of nerves in the proximal and middle segments of the renal artery and the nerves in the distal segment lying closer to the lumen, the distal segments are more susceptible to ablation.[18,19] The circumferential distribution of nerves along the renal artery is also not uniform and there are more nerves in the ventral than dorsal regions. Therefore, asymmetric delivery of radiofrequency energy is necessary for complete ablation as shown in Figures 2A to C. In the
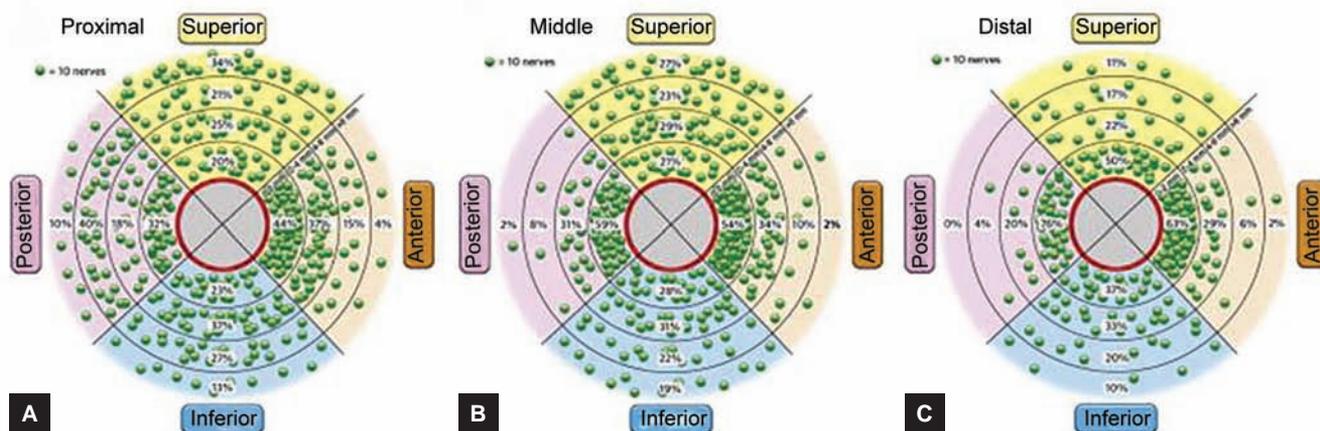
Figs 2A to C: The distribution of renal sympathetic nerves within and along the renal artery wall. Each green dot represents 10 nerves. Percentages denote the relative number of nerves according to distance from the lumen in each cross-sectional segment of the artery wall and in (A) proximal; (B) middle; and (C) distal locations

SYMPLICITY trials, the RDN procedure was performed by starting in the distal segment of the artery, with successive ablations applied to the wall after rotating the catheter tip circumferentially and withdrawing proximally. In SYMPLICITY HTN-3, only 19 patients received ablations in all four quadrants bilaterally.[16] In this small group of patients, BP reduction was similar to that observed in prior trials. Given the complicated network of nerves, there is likely a certain minimum number of ablations needed for the procedure to be effective, and in SYMPLICITY HTN-3, the number of ablation attempts during the procedure was associated with a greater BP response to RDN, and a higher number of ablations did not increase the risk of adverse events.

Other RDN Studies

The European Network COordinating research on Renal Denervation (ENCOReD) database has published data on predictors of response to RDN.[20] They identified 109 extreme BP responders (first quintile) and nonresponders (fifth quintile) (as defined by ABP) to RDN defined according to office or 24-hour ABP in their network. They compared the baseline characteristics and BP changes 6 months after RDN in both subsets. In extreme responders, baseline BP and BP changes 6 months after RDN were similar for office and out-of-office BP; however, when they were defined according to office BP, there was a huge white coat effect at baseline, with dramatic decrease in effect at 6 months. Extreme responders were more frequently found to be women, had higher baseline office BP, and higher estimated glomerular filtration rate (eGFR) when compared with nonresponders. When defining extreme responders and nonresponders, the single relevant difference between both subsets was baseline ABP. This suggests that ABP readings should be used as a baseline to select the appropriate subjects for RDN studies due to the large white coat effect when using office BP. The authors also suggest that a greater response in females may reflect drug compliance.

A randomized study from Europe assessed the effects of RDN in milder hypertension in 71 patients with resistant hypertension with mean daytime ambulatory SBP of 143 to 144 mm Hg.[21] Patients were assigned to RDN *vs* sham procedure. Data were analyzed for both the intention-to-treat (ITT) analysis and the per protocol analysis. The mean change in 24-hour SBP in the ITT cohort was not significantly reduced at 6 months in the RDN *vs* sham group (–7.0 *vs* –3.5 mm Hg respectively; p = 0.15 respectively). However, in the per protocol cohort, 24-hour SBP was significantly reduced at 6 months in the RDN *vs* sham group (–8.3 *vs* –3.5 mm respectively; p = 0.042), indicating efficacy of RDN in patients with mild resistant hypertension who completed the treatment protocol per study design.

The Renal Denervation for Hypertension (DEN-ERHTN) trial from France assessed the efficacy, safety, and cost-effectiveness of RDN in resistant hypertension when added to a standardized stepped-care antihypertensive treatment as compared with standardized stepped-care treatment alone.[22] The standardized treatment consisted of use of a combination of a diuretic, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB), and dihydropyridine calcium channel blocker (indapamide 1.5 mg, ramipril 10 mg (or irbesartan 300 mg), and amlodipine 10 mg daily). Patients were recruited from 15 French tertiary care hypertension centers with physicians experienced to perform RDN using the Medtronic catheter. After 4 weeks of the standardized triple therapy, 106 patients with ABP-confirmed resistant hypertension were randomly assigned to the RDN (n = 53) or the control group (n = 53). After randomization, spironolactone 25 mg/day, bisoprolol 10 mg/day, prazosin 5 mg/day, and rilmenidine 1 mg/day were sequentially added from months 2 to 5 in both groups if home BP was ≥135/85 mm Hg. At 6 months, the RDN group in combination with standardized triple therapy had a significantly greater reduction of daytime and nighttime SBP as measured by ABP (6 mm Hg). The number of antihypertensive drugs and drug adherence at 6 months were similar between the two groups, and there were three minor RDN-related adverse events including lumbar pain in two patients and mild groin hematoma in one patient. A mild and similar decrease in eGFR rate from baseline to 6 months was observed in both groups.

A study from Europe analyzed the effects of RDN on isolated systolic hypertension.[23] Sixty-three patients with isolated systolic hypertension and 63 patients with combined hypertension (SBP ≥ 140 and DBP ≥ 90) were enrolled. Patients had office and ABP measurements at 3, 6, and 12 months. Renal denervation significantly reduced office SBP and DBP at 3, 6, and 12 months in both isolated systolic and combined hypertension, but there was less reduction in the patients with isolated systolic hypertension at all time points. Mean 24-hour ABP was significantly reduced at all time points in combined hypertension, but the SBP was only significantly reduced at 3 and 12 months and only at 12 months for DBP in patients with isolated systolic hypertension using ABP. This study demonstrates that RDN appears to be less effective for isolated systolic hypertension as compared with patients with combined hypertension.

Global SYMPLICITY Registry

The Global SYMPLICITY Registry (GSR) is a prospective, open-label, multicenter registry of patients at 245 international sites who have had the RDN procedure using the SYMPLICITY catheter without being enrolled in a trial.[24]

The only inclusion criteria are age ≥18 years and eligibility for RDN as defined by local regulations for use of the SYMPLICITY RDN system. Office and 24-hour ABP change, laboratory values, and protocol-defined safety events are collected. One-year results in the first 1,000 enrolled patients are now available. In the first 1,000 consecutive patients enrolled, the mean age was 61 ± 12 years, 61% were male and mean body mass index was 30 ± 6 kg/m^2. Comorbidities included diabetes mellitus (42%), renal dysfunction (eGFR <60 mL/min/1.73 m^2; 23%), obstructive sleep apnea (11%), and history of cardiac disease (51%). Baseline office BP was $165/89 \pm 24/16$ mm Hg and baseline 24-hour BP was $154/86 \pm 18/14$ mm Hg. One-year office SBP change in 740 patients was -13.0 ± 26.3 mm Hg ($p < 0.001$) and 24-hour SBP change (n = 390) was -8.3 ± 17.8 mm Hg ($p < 0.001$). In patients with more severe hypertension (baseline office SBP of at least 160 mm Hg plus an ambulatory 24-hour SBP of at least 135 mm Hg while taking three or more antihypertensive medications), the office SBP change was -21.5 ± 25.6 mm Hg ($p < 0.001$) and the 24-hour SBP change was -11.4 ± 17.9 mm Hg ($p < 0.001$). At 1 year postdenervation, there were seven cardiovascular deaths, new renal artery stenosis >70% occurred in two patients, and new-onset end-stage renal disease occurred in three patients. The GSR demonstrates that in a large real-world population RDN resulted in significant BP reductions 1 year postprocedure. There were no long-term safety concerns following the denervation procedure. Updated data with 2-year follow-up should be available soon.[25]

In the GSR, 59% of the operators had performed >15 RDN procedures even before the registry started in contrast to SYMPLICITY HTN-3 trial where 50% of operators performed ≤2 renal procedures during the study. The average number of complete 120-second ablations in the severe hypertension cohort in the registry was 13.7, whereas it was only 9.2 in SYMPLICITY HTN-3 trial. This may account for the differences in efficacy between the registry data and HTN-3.

SAFETY OF RDN

Renal denervation in the hands of experienced operators appears to be safe. In SYMPLICITY HTN-3,[1] the study did meet its primary safety endpoint. Renal function was not adversely affected. Patients with preexisting renovascular abnormalities were excluded from the SYMPLICITY trials, but there have been a number of reports of *de novo* renal artery stenosis discovered during follow-up that were not originally reported in the results of the trials.[26-28]

The Future of RDN

There are other catheter-based systems being developed with at least four RDN studies underway using different technologies and catheter designs but utilizing an almost identical study design.[29] There is an off medication and an on medication group in most of these ongoing studies. Subjects are being randomized to RDN *vs* a sham procedure based on HTN-3 design. Medtronic is conducting the SPYRAL HTN Global Clinical Trial in the USA, Europe, Australia, and Japan. The trial is underway and consists of two randomized, sham-controlled trials: SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED.[30] Patients will be followed for 3 years after RDN. The HTN-OFF MED study is designed to isolate the BP-lowering effect of the RDN procedure, and the HTN-ON MED study will evaluate the effect of RDN in the presence of a standardized antihypertensive medication regimen consisting of a one-, two-, or three-drug regimen consisting or an ACE inhibitor or ARB, a thiazide, a calcium channel blocker, or a beta-blocker being prescribed at minimum 50% of maximum prescribed dosage. This study is also utilizing a newer, multielectrode catheter (SPYRAL) to reduce procedure duration and to allow for the simultaneous and uniform delivery of radiofrequency energy in all four quadrants. It also has the ability to ablate both distal segments and branch renal arteries. The trial will include patients with more moderate hypertension with an entry office SBP of 150 to 180 mm Hg in both the on and off medication groups. This is likely based on data from the two randomized controlled trials that have demonstrated a benefit of RDN in patients with less severe hypertension.[21,22] The results of the BP responses in RDN studies to date and ongoing trials are shown in Graph 1.[29]

Other Approaches for RDN

Ethanol-based Sympathicolysis of Renal Nerves

A novel noncatheter-based approach to RDN has been developed using image-guided percutaneous circumferential injection of dehydrated ethanol around the renal artery to achieve renal sympathetic denervation. This has been demonstrated in an adult porcine model. A novel three-needle delivery device is introduced into the renal arteries using fluoroscopic guidance. Ethanol is injected bilaterally with one injection per artery using the three needles into the adventitial and periadventitial space, using three different ethanol doses with a saline injection as a sham control. Three swines received ethanol and seven received saline injections. The mean renal parenchymal norepinephrine concentration at 2 weeks was reduced by 54 to 88% in a dose-dependent manner. Histological examination revealed circumferential renal nerve injury at depths of 2 to 8 mm from the intimal surface. There were no device-related or ethanol-induced injuries. Angiography at 45 days demonstrated normal appearing renal arteries with no detectable stenoses (n = 8).[31] This
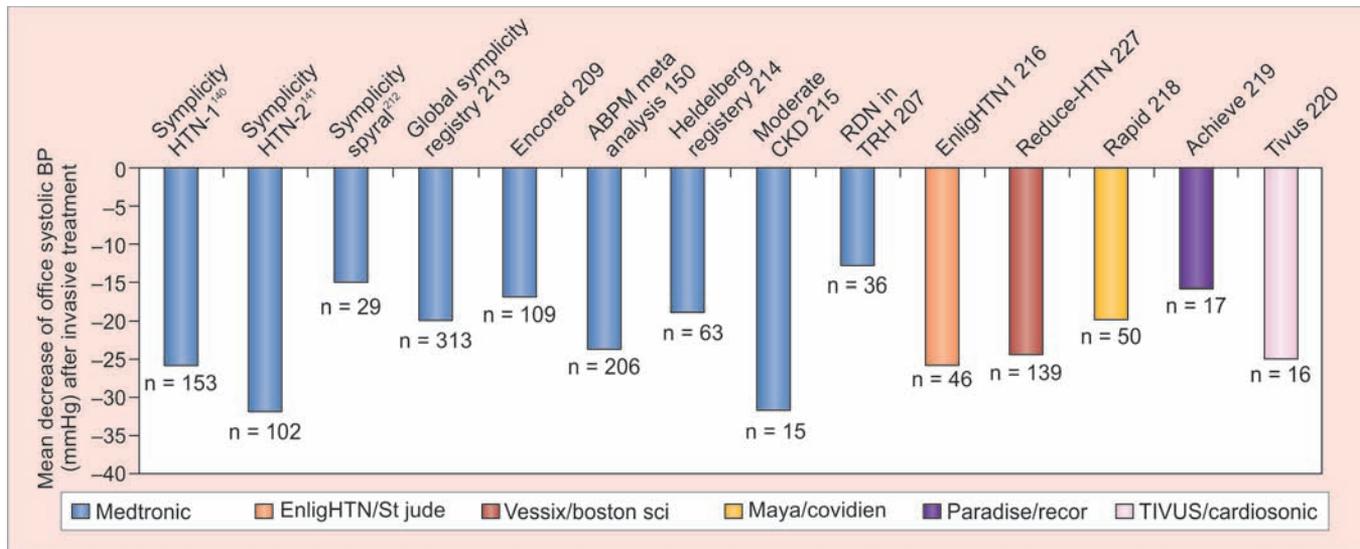
Graph 1: Recent studies of the effects of renal denervation with various catheters on blood pressure

novel three-needle delivery device has now been studied in 18 subjects with refractory hypertension. Procedural success was achieved in 100% of subjects (n = 18) and arteries (n = 37) without any study-related adverse clinical events at follow-up. One death of a subject was recorded but determined to be nonstudy related. There were no angiographic observations of renal artery stenosis, aneurysms, or other renal artery abnormalities at 6 months (32 renal arteries). Sixteen of the 18 subjects had a 6-month follow-up. The mean office SBP decreased from 175 ± 17 to 151 ± 26 mm Hg (–24 mm Hg). There was an average decrease in antihypertensive medications from baseline of 3.4 to 2.0 per subject at 6 months.[32]

Extracorporeal High-intensity Focused Ultrasound

Noninvasive RDN using extracorporeal high-intensity (Kona ultrasound-based RDN) focused ultrasound has been tested in dogs using a sham control. This technology showed reductions in both BP and norepinephrine concentrations when compared with baseline, with no significant change observed in the sham control group. Histopathologic examination also demonstrated nerve fiber disruption at day 28 after RDN.[33] This technology has now been tested in humans. A total of 10 patients underwent the noninvasive high-frequency ultrasound-based RDN and finished the follow-up visits. The baseline values of 24-hour ABP and office BP were 159.1/90.7 and 169/91.0 mm Hg respectively. The mean reductions in the 24-hour ABP from baseline to 1, 3, and 6 months were –13.1/–7.6; –14.9/–9.0; and –11.4/–4.8 mm Hg respectively. The mean reductions in office BP were –25.6/–10.2; –29.9/–12.2; and –29.2/–11.2 mm Hg at the 1, 3, and 6-month time points respectively.[34]

BAROREFLEX ACTIVATION THERAPY

Previous trials have shown substantial BP reductions using baroreflex activation therapy (BAT) in patients with resistant hypertension;[35,36] however, BAT has not been met with wide clinical enthusiasm. The Rheos device requires bilateral surgeries with bilateral implantation of electrodes around both carotid arteries at the location where the greatest response on stimulation is observed. This invasiveness of the procedure, the short battery life, and the procedure complication rate make this a potentially unattractive option for patients. A second-generation system of BAT (Barostim neo™) has been designed requiring implantation of a single electrode at one carotid site, therefore reducing the surgical procedure and possible complications. The Barostim device also has a smaller battery with an extended lifespan of about 3 years. A nonrandomized proof of concept study using this device enrolled 30 patients with treatment-resistant hypertension and showed a 26/12.4 mm Hg BP reduction at 6 months. There were three perioperative and one long-term procedure-related complications.[37] There is a new study, i.e., currently enrolling using the new device call the Barostim Hypertension Pivotal Trial (NCT01679132). A recently published study explored whether unilateral BAT stimulation would produce comparable BP reductions as bilateral stimulation using the data from patients enrolled in the Rheos Pivotal trial.[36] This trial enrolled treatment-resistant hypertensive patients who were randomized to receive either immediate BAT or deferred BAT, 6 months after implantation. During the trial, parameters were adjusted to achieve optimal baroreflex activation. Unilateral stimulation was applied unless bilateral stimulation resulted in a greater BP reduction. The 6-month data were pooled

for the group with immediate BAT and the 12-month data for the group with deferred BAT. Data showed that 80 patients were stimulated bilaterally and 215 patients had been stimulated on one side only (127 at the right side and 88 at the left side).[38] Pooled data results show that BP and heart rate did not differ between the two groups at baseline; however, BP and heart rate were significantly lower in the unilateral than in the bilateral group after the 6-month period. They also compared the effects of right-sided stimulation with the effects of either left-sided or bilateral stimulation. Right-sided stimulation was found to be the most effective. The authors concluded that BAT produced a greater effect with unilateral than with bilateral stimulation in treatment-resistant hypertension and right-sided unilateral BAT appeared to be more effective than bilateral or left-sided BAT. These data suggest that the left and right carotid system may behave differently, and therefore, future research is needed to assess whether both sides act in concert with each other or independently.

Arteriovenous Fistula for Hypertension

A novel mechanistic approach to BP reduction uses a self-expanding device that creates a 4 mm arteriovenous fistula (AVF) between the iliac artery and vein and generates a sustained calibrated shunt volume of approximately 800 mL/min within a short period of time.[39] This is called the ROX coupler system (ROX Medical Inc., San Clemente, CA). The anastomosis reduces vascular resistance and increases arterial compliance, resulting in immediate and substantial reduction of both SBP and DBP.[40] The ROX coupler system was originally developed for treatment of patients with chronic obstructive pulmonary disease (COPD) and is commercially available for use in Europe. The proposed mechanism of action includes a reduction in total systemic vascular resistance (SVR) and an increase in cardiac volumes and reduction in afterload, resulting in an overall reduction in cardiac work despite increased CO. Improvements in arterial oxygen content may accompany this increase in CO resulting in an increase in tissue oxygen delivery and therefore reducing the hypertensive actions of a number of neurohumoral mechanisms including peripheral and renal chemoreceptors that drive sympathetic overactivation. The reduction in SVR and decrease in effective arterial volume seen after ROX system is implanted result in improved vascular compliance with a reduction in the reflected pulse wave contributing to reducing cardiac work.[29] Initial positive results in COPD patients extended the indication to patients with COPD and superimposed arterial hypertension and showed that BP was reduced in subjects with COPD; however, no BP reduction was seen in the normotensive patients with COPD.[39] Based on this

retrospective analysis, eight non-COPD patients with treatment-resistant hypertension were enrolled to receive the ROX coupler system in a nonrandomized study. Both office and 24-hour ABP were significantly decreased at 6 months.[40] A subsequent prospective nonblinded randomized study from Europe called the multicenter ROX CONTROL-HTN study was performed in 100 non-COPD patients who had treatment-resistant hypertension on drug therapy. The trial also included patients who had failed RDN. Patients were randomly assigned in a 1:1 ratio to undergo implantation of the arteriovenous coupler device plus current antihypertensive medication *vs* maintenance of antihypertensive therapy alone. The primary endpoint was mean change from baseline in office and 24-hours ambulatory SBP at 6 months. Forty-four patients received the AVF coupler therapy and 39 were continued on their usual care. Mean office SBP was reduced by 27 mm Hg in the arteriovenous coupler group ($p < 0.0001$) and by 3.7 mm Hg in the control group ($p = 0.31$). Mean 24 hours ambulatory SBP was reduced by 13.5 mm Hg ($p < 0.0001$) in the arteriovenous coupler group and by 0.5 mm Hg ($p = 0.86$) in the control group. The AVF coupler, however, was associated with late ipsilateral venous stenosis in 12 of the 42 patients and was treated with venoplasty or stenting. Five admissions occurred in 3 of the 39 patients in the control group compared with none in the arteriovenous coupler group ($p = 0.0225$).[41] This represents a novel approach to resistant hypertension when other treatment options have been exhausted as this is associated with a fairly high incidence of complications at 6 months, and long-term consequences of having a chronic AVF need to be evaluated.

CONCLUSION

Hypertension remains a major public health issue and innovative nonpharmacological therapies are being sought due to the continued high rates of poor BP control most likely due to poor compliance with medication and less commonly due to true drug-resistant hypertension. All these methodologies are currently under clinical evaluation and cannot be recommended until we have more information from these ongoing trials.

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