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TOPIC HIGHLIGHT

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Transcatheter therapies for resistant hypertension: Clinical review

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Abstract

Resistant hypertension (RHTN) is a commonly encountered clinical problem and its management remains a challenging task for healthcare providers. The prevalence of true RHTN has been difficult to assess due to pseudoresistance and secondary hypertension. Atherosclerotic renal artery stenosis (RAS) has been associated as a secondary cause of RHTN. Initial studies had shown that angioplasty and stenting for RAS were a promising therapeutic option when added to optimal medical management. However, recent randomized controlled trials in larger populations have failed to show any such benefit. Sympathetic autonomic nervous system dysfunction is commonly noted in individuals with resistant hypertension. Surgical sympathectomy was the treatment of choice for malignant hypertension and it significantly improved mortality. However, post-surgical complications and the advent of antihypertensive drugs made this approach less desirable and it was eventually abandoned. Increasing prevalence of RHTN in recent decades has led to the emergence of minimally invasive interventions such as transcatheter renal denervation for better control of blood pressure. It is a minimally invasive procedure which uses radiofrequency energy for selective ablation of renal sympathetic nerves located in the adventitia of the renal artery. It is a quick procedure and has a short recovery time. Early studies in small population showed significant reduction in blood pressure. The most recent Symplicity HTN-3 study, which is the largest randomized control trial and the only one to use a sham procedure in controls, failed to show significant BP reduction at 6 mo.

Key words: Resistant hypertension; Renal denervation; Renal artery stenosis; Renal artery stenting; Transcatheter therapy; Sympathetic autonomic nervous system

Core tip: The aim of this paper is to review resistant hypertension (RHTN), including primary and secondary causes. Renal artery stenosis is one of the secondary cause of RHTN but angioplasty and stenting of renal artery for management of RHTN has failed to show any benefit. Sympathetic nervous system dysfunction is commonly noted in individuals with resistant hypertension. Renal sympathetic nerve denervation is a minimally invasive procedure which may help improve management of RHTN. However, the Symplicity HTN-3 trial failed to show a meaningful reduction in BP and has questioned this approach.

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INTRODUCTION

Resistant hypertension is defined as above goal systolic

blood pressure (SBP) despite therapy with three or more antihypertensive medications of different classes at maximum tolerable doses with one being a diuretic[1]. The definition can be extended to at goal blood pressure (BP) requiring four or more drugs of different classes[1]. The true prevalence of resistant hypertension (RHTN) is difficult to assess due to significant number of patients with poor medical compliance and/or suboptimal treatment regimen[1]. Prevalence of RHTN according National Health and Nutritional Examination Survey (NHANES) is 8.9% within the hypertension population[2]. With rising incidence of obesity, and people living longer, it is likely to become a major public health concern in the upcoming decades[1]. RHTN should be considered after excluding pseudo-hypertension and secondary causes of hypertension. It is associated with significant end organ complications including, coronary artery disease (CAD), stroke and chronic kidney disease (CKD). Prognosis is poor in individuals who have failed therapy with multiple classes of antihypertensives. The degree of reversibility of end organ damage with successful control of BP in these individuals is lacking evidence, but optimal blood pressure control in general has shown to delay onset and progression of end organ complications and it reduces the incidence of major vascular events[1]. RHTN is beginning to become a global issue, which has led to the advent of minimally invasive interventions for optimal BP control.

INITIAL DIAGNOSIS OF RHTN

RHTN is a diagnosis of exclusion. The initial step in management of poorly controlled blood pressure would be to rule out pseudo-resistance and secondary causes of HTN. Poor BP measurement technique, and use of improper cuff size can lead to falsely elevated BP readings. This can be avoided by allowing a patient to sit in a quiet room for a few minutes before checking BP, using an appropriately sized cuff and proper technique[1]. Medical noncompliance is another commonly encountered problem and has been noted in up to 40% of newly diagnosed hypertensive patients[1]. White coat hypertension is present in 20% to 30% of individuals and it should be further evaluated with ambulatory BP measurement[1]. Lifestyle factors such as obesity, excessive dietary salt intake, heavy alcohol consumption and certain medications can significantly contribute to elevation of BP, and it must be addressed before giving diagnosis of RHTN[1]. The most common secondary causes of RHTN are RAS, obstructive sleep apnea (OSA), primary hyperaldosteronism and renal parenchymal disease[1]. Fibromuscular dysplasia is a common cause of RAS in middle aged females, whereas atherosclerotic RAS is predominantly seen in the elderly. OSA is a known cause of hypertension and its severity is directly associated with difficulty in controlling BP[1]. OSA is thought to cause sympathetic dysregulation which can lead to RHTN[1]. Primary hyperaldosteronism has a prevalence of 20 percent in individuals with RHTN and its etiology can be often obscure[1]. CKD is commonly the result of long standing poorly controlled HTN and it can lead to RHTN.

RENAL ARTERY STENOSIS AS SECONDARY CAUSE OF RHTN

RAS is often noted in individuals with RHTN. Stenting or angioplasty in addition to optimal medical management for atherosclerotic RAS has failed to show any significant benefit in regards to HTN or CKD in randomized control trials (RTC)[3]. Up to 90% of renal artery stenosis in the elderly population is due to atherosclerosis[1,3,4]. A significant degree of RAS can decrease renal perfusion which leads to the over-activation of the renin-angiotensin-aldosterone axis (RAAS)[4]. RAAS overactivation leads to increase in sodium and water retention, causing elevation in systemic blood pressure[4]. The severity of stenosis required to cause over activation of RAAS is unknown, but use of ACE-inhibitor can cause acute worsening of renal function and should raise suspicion of significant RAS in these individuals[4]. There is also up-regulation of SANS which can further make it difficult to control BP[4]. Such individuals are at high risk of end organ complications including left ventricular hypertrophy, heart failure with recurrent pulmonary edema and CKD[4].

TRANSCATHETER THERAPY FOR ATHEROSCLEROTIC RENAL ARTERY STENOSIS

Theoretically, stenting of the stenotic lesion should resolve RHTN. Initial studies showed significant reduction in SBP and this led to increase in revascularization rates for renal artery stenosis[3,4]. However, recent RCT have shown such revascularization to be futile[3,4]. The "Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis trial", aka. EMMA trial, concluded that previous uncontrolled and unblended studies had overestimated the benefits of renal artery revascularization[5]. No significant difference in mean 24-h ambulatory blood pressure was noted between the control group and angioplasty group at the end of 6 mo[5]. "The Randomized comparison of percutaneous angioplasty *vs* continued medical therapy for hypertensive patients with renal artery stenosis trial" was a randomized study that enrolled patients with renal artery stenosis of 50% or greater and minimum diastolic BP of 95 on at least two antihypertensive medications[6]. Revascularization resulted in modest systolic BP improvement without any change in renal function but, there was significant post-procedural complication noted in the intervention group[6]. "The effect of balloon angioplasty on hypertension in atherosclerotic renal artery stenosis trial", also known as the "Dutch renal artery stenosis intervention cooperative (DRASTIC)" concluded that the benefit of angioplasty was "little" over medical management[7].

Table 1 Renal artery stenting/angioplasty in resistant hypertension

Ref.	Size	Follow up period	Mean SBP reduction with stenting/ angioplasty	Mean SBP reduction with medical therapy	*P* value
Cooper *et al*[3] (Coral trial)	947	43 mo	16.6 ± 21.2	15.6 ± 25.8	0.03
Van Jaarsveld *et al*[7] (DRASTIC trial)	106	12 mo	19	17	0.51
Plouin *et al*[5] (EMMA trial)	49	6 mo	12 ± 20	8 ± 16	0.46
Webster *et al*[6]	135	3-54 mo	34	8	0.018

SBP: Systolic blood pressure.

"Cardiovascular outcomes in renal atherosclerotic lesions trial (aka, CORAL)" was an NIH funded, open-label, unblinded and a multicenter randomized study[3]. It compared stenting *vs* medical therapy in atherosclerotic renal artery stenosis[3]. This trial randomized 947 individuals with elevated SBP and/or CKD with estimated GFR of 60 mL/min per 1.73 m^2 of BSA as per MDRD formula and RAS of at least 60%[3]. Patients were randomized to either only medical therapy or medical therapy plus renal artery stenting group[3]. The primary endpoint of this study was a major cardiovascular or renal event[3]. Over a 43-mo median follow up, there was no significant difference in regards to the primary endpoint between the 2 study groups[3]. SBP was noted to be reduced in the stenting plus medical therapy group by 16.6 ± 21.2 mmHg and in the medical therapy only group by 15.6 ± 25.8[3]. There was only a modest SBP lowering in stenting group compared to medical therapy group (-2.3 mmHg) with a Confidence Interval (CI) of -4.4 to -0.2 and *P* value of 0.03[3]. Once again revascularization for renal artery stenosis was proven to be futile, putting another nail into its' coffin (Table 1).

Earlier trials had a smaller sample size and the patients had clinically insignificant RAS, which question their validity. The sample size was 49 in the EMMA trial and the DRASTIC trial had 106 participants, which is too small to detect a significant difference between the study groups[5,7]. This increases the chance of a type 2 statistical error. They enrolled patients with mild RAS when a lesion of at least around 70% is deemed to be hemodynamically significant by many experts[8,9]. A crossover rate to therapy group was 44% in DRASTIC study which further obscures outcomes[7]. Earlier trials assessing effect of revascularization on RHTN used angioplasty of stenotic lesions that may not be as effective as stenting[8-10]. CORAL was one of the largest randomized trial with 947 participants comparing medical therapy *vs* endovascular stenting in addition to medical therapy for RHTN. It also included stricter criteria in regards to the degree of stenosis required to be eligible for participation, which was not seen in earlier studies. CORAL trial seems of have addressed some of the common issues with previous studies and provides the most statistically significant data.

SYMPATHETIC THEORY OF RHTN

Sympathetic autonomic nervous system (SANS) dysfunction is seen in 50% of hypertensive individuals, which makes it a promising therapeutic target[11]. The sympathetic fibers densely innervate the kidneys and are mainly located in the adventitial layer of the vascular wall of the renal arteries[12]. Activation of the afferent limb of the Renal SANS stimulates the posterior hypothalamus, the autonomic centers in the medulla oblongata and the mid brain[13,14]. All messages are integrated into the autonomic centers and are relayed back to the kidneys *via* the thoraco-lumbar paravertebral ganglia, the superior mesenteric ganglia and celiac prevertebral ganglia[13,14]. Increase in efferent sympathetic tone leads to vasoconstriction of the renal vasculature by activation of the alpha-1a receptors which leads to a decrease in blood flow to the kidneys[15]. It accelerates alpha-1b adrenergic receptor mediated tubular reabsorption of sodium and water[15]. It also causes over activation of the RAAS through the beta-1 adrenergic receptors located on the juxtaglomerular cells[15]. Sympathetic over-activity on the heart increases cardiac output and its effect on blood vessels increases peripheral vascular resistance in an effort to increase renal perfusion[13]. These pathophysiologic changes make an individual susceptible to RHTN which can lead to end organ complications over time[13,16].

THE SURGICAL APPROACH TO SYMPATHETIC DENERVATION FOR RHTN

Surgical sympathectomy was the treatment of choice for malignant hypertension before antihypertensive medications were available[11,16]. Five-year mortality from malignant hypertension was estimated to be 100%[17,18]. Thoracolumbar splanchnicectomy was first introduced in 1938[18]. Treatments ranging from radical subdiaphragmatic splanchnicectomy to less aggressive interventions such as sympathetic ganglionectomy resulted in reduced blood pressure and favorable end organ changes[11,19]. However, they were associated with undesirable adverse effects such as, orthostatic hypotension, sexual dysfunction, incontinence, anhydrosis and tachycardia[11,19]. The surgery was typically performed as a one or two step procedure and required extended hospital stay[17]. Surgical sympathectomy became a second line treatment after introduction of antihypertensives for patients whose BP was uncontrolled despite medical management[17]. Surgical sympathectomy increased sensitivity of antihypertensive drugs and had lower mortality compared to medical management alone[17]. As newer and more potent antihypertensive medications of different classes became available, this radical approach phased out due to its undesirable adverse effects. However, suboptimal control of blood pressure on maximal medical therapy, the increasing prevalence of RHTN and evidence of renal sympathetic nerve over-activity in hypertensive

individuals has sparked interest in catheter based renal sympathetic denervation as a promising therapeutic option[16,20,21].

TRANSCATHETER RENAL DENERVATION

Transcatheter renal sympathetic nerve ablation is a minimally invasive procedure. It complements the BP lowering effects of the former radical approach without its adverse effects and has a much faster post-procedural recovery time[13]. The post-operative mortality in patients treated with the surgical approach was as high as 11% compared to relatively none with RDN[18]. Contraindications to RDN mainly include GFR < 45 mL/min per 1.732 m^2, past interventions such as angioplasty or stenting, abnormal anatomy, Diabetes type 1, age less than 18 years and pregnancy[22]. One of the devices widely studied in RCT is the Symplicity Renal Denervation System by Medtronic. This device consists of a low power radio frequency generator and a disposable catheter[13]. The procedure is performed under conscious sedation through percutaneous access. The catheter tip is an opaque platinum electrode. It is hand guided into the renal artery, adjacent to the dense neural site located near the renal hilum[13]. The design of the catheter allows safe delivery of low level radio frequency energy across the arterial wall to ablate the nerves located in the adventitia of the renal artery[13]. Multiple ablations are delivered in a circumferential pattern every few millimeters within both renal arteries to ensure complete ablation. The procedure takes less than an hour and the patient is usually observed for a day after the procedure[13].

Many other catheter designs are currently being investigated. The ST. Jude's Enlig HTN Renal Denervation System uses a multi-electrode catheter which delivers the ablation in a specific circumferential pattern, eliminating the need for catheter manipulation and administering multiple ablations[22]. The EnligHTN 1 trial was a non-randomized study which evaluate the efficacy and safety of this device in 46 patients whose mean office BP was 176/96 mmHg[22]. Office BP reduced by 26/10 at 6 mo with a *P* value of < 0.0001 without any complications[22]. The Vessix V2 renal denervation system uses an over the wire balloon catheter with electrodes in a specific pattern to deliver RF energy and it is currently being evaluated in the REDUCE-HTN trial expected to complete in December 2014[23].

Catheter based ultrasound renal denervation is a newer technique which uses intravascular ultrasound for selective denervation of the renal nerves in the adventitia of the artery[24]. The device uses a catheter-based transducer, which delivers high frequency sound waves in a circumferential manner[24]. The transducer has an inflatable balloon with a water circuit that keeps the walls of the arterial lumen cool when energy is being delivered[24]. This prevents thermal damage to the vessel wall while selectively ablating the renal nerves[24]. The circumferential delivery of energy is not dependent on the position of the catheter which allows for a consistent post procedural outcome[24]. This devise is currently being evaluated in 50 patients in the ACHIEVE study, which is anticipated to be complete in February 2015[25]. Chemical renal nerve ablation is the latest technique which uses peri-adventitial dehydrated ethanol injection administered in a circumferential pattern[26]. Most of the newer devices are "energy based" and can lead to thermal injury of the vessel wall which is an advantage of chemical RDN[26]. This approach has been successful in lowering renal parenchymal norepinephrine levels at 2 wk in swine models which is a measure of reduced sympathetic activity[26]. Randomized control trial in human model is needed to evaluate its safety and efficacy.

The first reported RDN in humans was done by Schlaich and Colleagues in 2009[27]. The subject was a 59-year-old male patient with history of two TIA, untreated OSA secondary to intolerance to CPAP, and RHTN who was on seven antihypertensive medications[27]. He underwent this procedure without any complications[27]. Reductions were noted in renal norepinephrine spillover and mean office blood pressure, while the renal blood flow increased[27]. "The Catheter-based renal sympathetic denervation for resistant hypertension" was a multicenter safety and proof-of-principle cohort study, which evaluated the BP lowering effect and safety of renal denervation in 50 patients from Europe and Australia[28]. Eligible patients had an office SBP ⩾ 160, and were on three or more antihypertensive agents of which one was a diuretic with no previous ablations, stenosis, and bilateral kidneys with an anatomy that was conducive to the procedure[28]. Out of the 50 patients, 45 underwent the procedure and 5 were disqualified primarily due to dual renal artery anatomy[28]. Patients who underwent the procedure had a mean office blood pressure reduction of 27/17 at 12 mo with one complication of renal artery dissection during the procedure[28].

The Symplicity HTN-1 trial was a major open label study with a total of 153 patients enrolled at centers in the United States, Europe and Australia[29]. They were followed for 24 mo and were noted to have a mean BP reduction of 32/14[29]. Statistically, *P* value for the reduction was noted to be < 0.0001 for SBP and diastolic BP (DBP) at intervals of 1, 3, 6, 12 and 18 mo, except for *P* value of = 0.002 for DBP at 24 mo[29]. The complication rate was three percent with three patients experiencing groin access site pseudoaneurysm and one patient experiencing renal artery dissection[29]. A final 3 year report evaluated follow up data of only 88 of the 153 patients and noted a mean SBP reduction of 32 mmHg with a 95%CI of -35.7 to -28.2[30]. Complications over the three year period were one new renal artery stenosis which needed stenting and three unrelated deaths[30].

The Symplicity HTN-2 was the first multicenter, prospective RCT that evaluated the effectiveness of transcatheter renal denervation. Primary end point was change in seated SBP at the six month point[12]. A total of 106 eligible participants aged 18 to 85 years who had SBP ⩾ 160 mmHg or ⩾ 150 mmHg if patient was a type 2 diabetic despite compliance with treatment on ⩾

Table 2 Renal nerve denervation in resistant hypertension

Ref.	Sample size	Follow up duration	Mean SBP reduction in RDN group (in mmHg)	Mean SBP reduction in control group (in mmHg)	*P* value
Worthley *et al*[22] (EnilgHTN 1 trial)	46	6 mo	26	No randomized control group	0.0001
[a]Krum *et al*[28]	45	12 mo	27	No randomized control group	0.001
Simplicity HTN-1 investigators[b]	153	24 mo	32	No randomized control group	0.0001
Esler *et al*[12] (Simplicity HTN-2)	106	6 mo	32 ± 23	+ 1	0.0001
Bhatt *et al*[32] (Symplicity HTN-3)	535	6 mo	14.13 ± 23.93	11.74 ± 25.94	< 0.001

[a]Follow up data available for *n* = 9 at 12 mo; [b]Follow up data available for *n* = 18 at 24 mo. SBP: Systolic blood pressure; RDN: Renal denervation; HTN: Hypertension.

3 antihypertensive medications were screened[12]. A total of 52 patients were randomized to renal denervation group at 24 participating centers in Australia, Europe and New Zealand[12]. BP in the intervention group was reduced by 32/12 mmHg (SD ± 23/11 mmHg) from a baseline of 178/97 mmHg (*P* value < 0.0001) compared to change of -1/0 mmHg from baseline of 178/97 mmHg in control group (*P* value = 0.77 for SBP and 0.83 for DBP) with no significant post procedural complications[12]. Thirty six month data was recently presented which showed a reduction in BP by an average of 33/14 (*P* value < 0.01) in 40 of the study participants[31].

The Symplicity HTN-3 is the largest sham controlled, single blinded trial to recruit 535 patients. Inclusion criteria were SBP ⩾ 160 mmHg on stable antihypertensive regiment with ⩾ 3 medications of different classes at full tolerated doses with one being a diuretic[32]. The primary endpoint was change in office SBP measurement at 6 mo and a secondary endpoint assessed 24 h ambulatory BP[32]. Patients were randomized in a 2:1 fashion between RDN group and control group[32]. Within the RDN group, SBP was reduced by 14.13 mmHg with a mean SD of ± 23.93 and in the control group, SBP was reduced by 11.74 mmHg with a mean SD of ± 25.94 at 6 mo (*P* value < 0.001 for change for baseline for both groups)[32]. With ambulatory BP monitoring, RDN group showed a reduction in SBP by 6.75 mmHg with mean SD of 15.11 and in the control group, SBP was reduced by 4.79 mmHg with a mean SD of 17.25[32]. The trial did meet its safety end point[33]. Compared to former studies, Symplicity HTN-3 is the largest and the only blinded RTC which included a sham procedure in the control group. It is the first trial to show that there was no significant difference between the RDN when compared to medical management alone. Symplicity HTN-4 was also a RCT which was estimated to enroll 580 patients but was suspended after release of data from the Symplicity HTN-3 trial[34]. It was similar to Simplicity HTN-3, but its eligibility criteria required participant to be on ⩾ 3 antihypertensive medications of different classes with one of them being a thiazide or a thiazide like diuretic and SBP ⩾ 140 mmHg but less than 160 mmHg[35] (Table 2).

DISCUSSION

The long term benefits of optimum BP control on end organ prognosis is beyond doubt. Newer antihypertensive agents are increasingly selective and efficacious but the prevalence of RHTN is still a public health burden. This prevalence is likely to increase with increasing incidence of obesity and longevity. RHTN is essentially a diagnosis of exclusion and should be considered in individuals after pseudoresistance and secondary causes of HTN are ruled out. Angioplasty and stenting can successfully treat RHTN in individuals with renal artery stenosis due to fibromuscular dysplasia but it has proven to be futile in atherosclerotic RAS. Renal denervation for RHTN may be an excellent therapy with low complication rates. Rare complications such as RAS requiring stenting, renal artery dissection and access site pseudoaneurysm have been noted[28,30]. The current safety profile of RDN is limited to 3 years and it appears to be fairly acceptable[36]. However, long term safety of such intervention is currently unknown[28,30]. Earlier trials presented promising results but the data from Symplicity HTN-3 trial may have brought RDN to a screeching halt for the time being. In comparison to former trials, Symplicity HTN-3 is the largest RTC, and it is the only one to include a sham group which underwent an angiography instead of denervation. Most trials used office BP reduction as primary endpoint that can vary significantly and is not as accurate as ambulatory BP monitoring. This was also addressed in Symplicity HTN-3 trial and it didn't show a meaningful SBP reduction between the two groups, thus, providing us with the most objective data on RDN. Nerve regrowth has been documented in individuals after renal transplant, questioning the durability of RDN, which is currently unknown[28]. RDN also does not completely eliminate the need for medical management and most patient still need to continue on an oral antihypertensive medications. In the meanwhile, RDN continues to be an option after failure with lifestyle and medical management in approved markets[36]. Is there a sub group of individuals with RHTN that may benefit from RDN? Future studies are need to address this question. Much has to be established about the efficacy and long term safety of RDN.

Any conclusions based on currently available data may be premature.

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