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Understanding Resistant Hypertension: Pathophysiology and Management Strategies

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ABSTRACT
Hypertension, characterized by persistently elevated blood pressure, poses significant health risks, including cardiovascular and renal complications. Resistant hypertension (RH), defined as hypertension that remains uncontrolled despite treatment with three antihypertensives from different classes, is increasingly prevalent, affecting an estimated 11% of hypertensive patients in certain regions and showing a rising trend over the decades. The pathophysiology of RH involves complex interactions among the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), and various physiological mechanisms, including baroreceptor function and endothelial dysfunction. These factors contribute to increased vascular resistance, sodium retention, and fluid overload, exacerbating blood pressure elevation. Studies indicate that patients with RH face significantly higher risks of adverse cardiovascular events and mortality compared to those with responsive hypertension. Management strategies for RH include pharmacological approaches, typically involving a combination of three antihypertensive agents, and may necessitate the addition of spironolactone in cases of aldosterone excess. Non-pharmacological interventions, such as dietary sodium restriction and lifestyle modifications, also play a crucial role in managing blood pressure. Renal denervation is an innovative catheter-based intervention for patients with uncontrolled hypertension. For patients with uncontrolled hypertension, medication intolerance or those unwilling or unable to commit to lifelong medication regimens, RDN may be an important treatment option to optimize care. The technology could be used as an adjunct to drug therapy and lifestyle modifications. Continued research is essential to deepen the understanding of RH and improve treatment outcomes for affected individuals.

Keywords: Resistant hypertension, antihypertensive therapy, RAAS, vascular resistance, endothelial dysfunction, spironolactone, renal denervation, lifestyle modification, sodium restriction, cardiovascular risk.

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INTRODUCTION

Hypertension (High blood pressure) is characterised by a continuously elevated pressure in the blood vessels. Blood pressure is produced when blood is pumped by the heart and presses up against the walls of blood vessels, or arteries.

High blood pressure (BP), or hypertension, is defined by two levels by 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines elevated BP, with a systolic pressure (SBP) between 120 and129 mm Hg and diastolic pressure (DBP) less than 80 mm Hg, and stage 1 hypertension, with an SBP of 130 to 139 mm Hg or a DBP of 80 to 89 mm Hg [1,2].

Hypertension is a threatening medical condition and can increase the risk of heart, kidney, brain, and other conditions. Approximately 1 in 5 women and 1 in 4 men—roughly a billion people—have the illness, making it a leading cause of premature death globally. Two thirds of cases of hypertension are found in low- and middle-income countries, where the burden of the disease is disproportionately felt. This is largely because these populations have experienced an increase in risk factors in recent decades [3]

Resistant Hypertension

According to 2017 AHA/ACC Hypertension Guidelines, resistant hypertension (RH) is defined as hypertension (HTN) that remains uncontrolled with three anti-hypertensives of different classes commonly including a long-acting calcium channel blocker (CCB), a blocker of the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]), and a diuretic, or blood pressure (BP) that is controlled on four medications. The drugs are administered at maximum or maximum tolerated daily doses [1].

Diagnosis of RH

Diagnosis of resistant hypertension is very important and errors can lead to misdiagnosis of RH. The major factors include preparation of the patient, environmental conditions, cuff size, and technique of BP measurement. BP should be measured according to the guidelines [4].

Prevalence of Resistant Hypertension

In 2021, RH was found in 11% of hypertensive patients in southern part of India [5]. It has been possible to estimate the prevalence of resistant hypertension by using the National Health and Nutrition Examination Survey (NHANES) dataset. Based on information gathered between 2003 and 2008, Persell calculated that 8.9% of US adults with hypertension and, possibly more significantly, 12.8% of US adults receiving treatment for hypertension had resistant hypertension [6]. Egan and colleagues examined blood pressure control trends using NHANES and discovered that over the past few decades, there has been a progressive increase in the estimated prevalence of resistant hypertension [7]. Based on estimates, 5.5% of adult hypertensive Americans had resistant hypertension between 1988 and 1994. There was an 8.5% rate between 1999 and 2004 and an estimated 11.8% rate between 2005 and 2008. Nine million Americans are thought to have resistant hypertension out of the 76 million adult Americans with hypertension who are estimated to have a prevalence rate of nearly 12% [8]. Spanish researchers found that 14.8% of treated subjects had resistant hypertension based on the AHA criteria. This finding was based on an analysis of over 68,000 patients who were being monitored by primary care physicians and specialists and who had been included in an ambulatory blood pressure monitoring registry. White coat resistant hypertension, which is characterised by an elevated clinic blood pressure (> 140/90 mm Hg) but a controlled 24-hour ambulatory blood pressure (< 130/80 mm Hg), was prevalent in this cohort. Of the patients diagnosed with resistant hypertension, 37.5% had elevated clinic blood pressure alone [9]. When these three studies are taken together, they show that 12–15% of patients receiving treatment for hypertension also have resistant hypertension [10, 11].

Prognosis of RH

Hypertension is most important cardiovascular risk factors in the world today. Several studies, have showed that patients with RH have increased risk of myocardial infarction, stroke, peripheral arterial disease, heart failure, and all-cause mortality, chronic kidney disease when compared with patients without RH [4, 11-17].

In a retrospective study of >200 000 patients with incident hypertension, 2.1% cardio vascular deaths occurred in RH group and 1.9% in non-RH group over the median 3.8 years of follow-up. The outcomes such as death, myocardial infarction, heart failure, stroke were more in RH group and there was higher risk of patients developing CKD [11].

Sim 2015 et al in a retrospective, longitudinal cohort study compared end stage renal disease (ESRD), ischemic heart event (IHE), congestive heart failure (CHF), cerebrovascular accident (CVA), and all-cause mortality among 470,386 individuals with resistant and nonresistant hypertension (non-RH). The study showed that the risk of ESRD and CVA and were 25% and 23% greater, respectively, in uRH compared to cRH [12].

Several other prospective studies have shown that patients with resistant hypertension had double the risk of cardiovascular disease events when compared to hypertensive patients who are responsive to the treatment [13-16].

Resistant hypertension has a more adverse physiology and will need better understanding in order to better manage this population.

Pathophysiology of Resistant Hypertension

The development and maintenance of resistant hypertension are attributed to a multitude of factors, one of which is the activation of the sympathetic nervous system (SNS).

Sympathetic Nervous System Activation

The kidney's broad sympathetic innervation plays a key role in the development and physiological regulation of every facet of renal function [18]. Increased renal sympathetic nerve activity (RSNA) results in renal vasoconstriction, with decreased glomerular filtration rate and renal blood flow, and increased

renal vascular resistance; increased renal tubular reabsorption of sodium and water throughout the nephron; and increased renal release of renin and norepinephrine [19].

Neurotransmitters like epinephrine released from adrenal medulla, and norepinephrine released from the nerve terminals along act on the adrenergic receptors and express the sympathetic-blood pressure relationship where the neurotransmitters transfer the effects of the sympathetic nervous system on the vasomotor tone.

Systemic vascular resistance and cardiac output are the two main effector factors in neural blood pressure regulation. The equilibrium between vasoconstrictor and vasodilatory forces determines the arteriolar tone. While β-receptor stimulation enhances cardiac output, α-receptor activation causes vasoconstriction thus raising the blood pressure. The severity of the high blood pressure is closely correlated with the level of sympathetic activity [20-22].

The hormone system known as the renin-angiotensin-aldosterone system (RAAS), which controls blood pressure and fluid balance, is influenced by sympathetic activation. Sodium and water retention are other functions of the SNS [23].

Renin-angiotensin-aldosterone system (RAAS)

An essential function of the renin-angiotensin-aldosterone system (RAAS) is to control blood pressure and fluid balance in the body. Dysregulation of the RAAS may play a role in the pathophysiology of resistant hypertension [24,25].

The first step in the process is the release of renin from the kidney's juxtaglomerular cells. Apart from sympathetic nerve stimulation via beta-1 adrenergic receptors, renin release is dependent on various factors like renal baroreceptor mechanism in the afferent arteriole that senses changes in renal perfusion pressure, low sodium (sensed as Cl^-) by to the macula densa cells of the distal tubule, or blood pressure and angiotensin II levels. One important factor influencing the activity of the RAAS is control over renin secretion. Renin transforms the inactive precursor angiotensinogen produced by the liver into angiotensin I. The angiotensin-converting enzyme (ACE), which is mainly found in the endothelium of lungs, vascular endothelium, and cell membranes of the kidneys, heart, and brain subsequently transforms angiotensin I into angiotensin II.

Two well-characterized receptors angiotensin II type 1 (AT1) and angiotensin II type 2 (AT2) mediate the principal physiologic activities of angiotensin II in the kidney. The majority of Angiotensin II's known physiological and pathological effects are mediated by the type 1 (AT1) receptor [18]. These include effects on the kidney (renal tubular sodium reabsorption, inhibition of renin release), sympathetic nervous system, adrenal cortex (production of aldosterone), and cardiovascular system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy) [26]. The AT1 receptor also mediates effects of Angiotensin II on cell growth and proliferation, inflammatory responses, and oxidative stress.

The brain, kidney, and other organs have high concentrations of the type 2 (AT2) receptor throughout foetal life, and these levels sharply decline during the postnatal phase. Despite its modest expression levels in adults, there is some evidence that the AT2 receptor may mediate vasodilation, have antiproliferative, apoptotic, and effects on vascular smooth muscle, as well as limit heart growth and remodelling. It has been suggested that activation of AT2 receptors in the kidney could affect salt reabsorption in the proximal tubules and promote the conversion of renal prostaglandin E2 to prostaglandin F2α. Still, it's unclear how significant are any of these AT2-mediated activities [27].

The RAAS may be overactive in resistant hypertension even in the face of antihypertensive medication. Numerous factors, including increased renin release, elevated levels of angiotensin II, or increased tissue sensitivity to angiotensin II, could be the cause of this. Moreover, RAAS dysregulation can be made worse by genetics, obesity, insulin resistance, and chronic kidney disease [18, 28].

Baroreceptors

Baroreflex plays a crucial role in regulating blood pressure through a feedback mechanism involving specialized receptors called baroreceptors. These baroreceptors are primarily located in the carotid sinus (carotid artery) and the aortic arch. They sense changes in blood pressure and relay this information to the brain, specifically to the medulla oblongata, which is part of the brainstem. When blood pressure increases, the arterial walls stretch, activating the baroreceptors. Afferent fibres from carotid sinus baroreceptors join the glossopharyngeal nerve (ninth cranial nerve) and project to the nucleus tractus solitarii in the dorsal medulla. The efferent fibres project into cardiovascular neurones in the medulla and spinal cord. Stretch-sensitive receptors in the heart and pulmonary veins, together referred to as "cardiopulmonary" receptors, and arterial baroreceptors in the aortic arch make up the extra-carotid baroreceptor population. Cardio pulmonary receptors transmit the afferent information through vagus

nerve to brainstem nuclei. Sympathetic and parasympathetic fibres to the heart and smooth muscles in peripheral blood arteries make up the efferent limbs of the baroreflex loop [29,30].
The increased baroreceptor impulses inhibit sympathetic nervous system and activates the parasympathetic nervous sytem. Inhibion of sympathetic nervous system decreases heart rate, stroke volume and also causes vasodilation. The parasympathetic stimulation decreases heart rate by releasing acetylcholine which acts on pacemaker cells of SA node [31-33].

Fluid retention

A malfunctioning endothelium, or the inner lining of blood vessels, contributes to fluid retention in resistant hypertension. A portion of the vascular permeability that causes fluid to seep into the surrounding tissues is caused by endothelial dysfunction. The combination of vascular leakage and water and sodium retention exacerbates the expansion of blood volume and raises blood pressure levels.
Furthermore, a common feature of resistant hypertension is impaired production of nitric oxide (NO), a vasodilator released by the endothelium. Functional alterations in the microvasculature with a predominately negative constrictive tone are caused by endothelium dysfunction. No facilitates sodium excretion. Vasoconstriction and increased blood vessel resistance are caused by reduced NO levels, which raise blood pressure [34-36].
The dysregulation of these mechanisms is facilitated by obesity, insulin resistance, and inflammation, all of which are frequently linked to resistant hypertension. Fluid retention is further exacerbated by the production of different inflammatory substances by adipose tissue, which affect the RAAS and endothelial function [28].

TREATMENT

Pharmacological Treatment

Initial 3-Drug Regimens

The basis of RHTN pharmacological therapy is the use of efficacious combinations of at least three antihypertensive drugs. The initial 3-drug regimen should be as standard as possible, with the following components: a long-acting calcium channel blocker (usually amlodipine), a renin-angiotensin system blocker (ACE inhibitor or ARB), and a long-acting thiazide-like diuretic (preferably chlorthalidone or indapamide). However, specific combinations must be tailored based on patient's comorbidities, prior medication intolerances, and financial considerations. The typical three-drug regimen of amlodipine (10 mg), chlorthalidone (25 mg), and ACE inhibitor/ARB combines classes of agents with complementary mechanisms of action that have been demonstrated to be useful in lowering blood pressure, preventing cardiovascular disease (CVD), and preventing death.[1,3] All of the suggested medications are widely well tolerated and are accessible as long-acting formulations and generics. These specific agents have the benefit of being offered in a variety of dual or triple pill combinations, which enables easier regimens, less pills to take, and occasionally lower out-of-pocket expenses (such as copayments) [37]
Due to their effectiveness and tolerability, ACE inhibitors and ARBs are prescribed for RHTN patients and are also used in the prevention and treatment of common comorbidities, such as diabetes mellitus, heart failure, and chronic kidney disease (CKD). When compared to other classes of antihypertensive medications, ACE inhibitors and ARBs both lower the incidence of incident diabetes mellitus by roughly 20% to 30% [38].

Use of Spironolactone as the Fourth Agent

Excess aldosterone is a common cause of RHTN, as shown by a large body of literature [39, 44]. According to numerous studies, about 20% of patients with confirmed RHTN have true, classical primary aldosteronism. More significantly, less severe levels of aldosterone excess that do not meet the rigid requirements for traditional primary aldosteronism may be a factor in the development of resistance to widely prescribed antihypertensive drugs [40]. Overweight and obesity are common comorbidities in patients with RHTN, and they are related to this excess of aldosterone [37].
PATHWAY-2, a double-blind, 4-way crossover study, evaluated spironolactone 25–50 mg daily as add-on therapy for RHTN against bisoprolol (5–10 mg), doxazosin (5–10 mg), and placebo over a 3-month period. Following the observed ingestion of the maximum tolerated doses of the standardised triple-drug regimen, home blood pressure remained uncontrolled, leading to the confirmation of true RHTN. Serum ACE activity measurements and pill counts were used to track adherence throughout the trial. In patients with uncontrolled RHTN, PATHWAY-2 demonstrated that spironolactone was more effective at lowering blood pressure than both a placebo and the two active comparators [41].
Spironolactone, on average, decreased home systolic blood pressure by 8.70 mm Hg more than placebo, 4.48 mm Hg more than bisoprolol, and 4.03 mm Hg more than doxazosin ($P<0.0001$). $P<0.001$ was observed in all groups for the percentage of patients whose blood pressure was controlled: 58.0% for spironolactone, 23.9% for placebo, 43.3% for bisoprolol, and 41.5% for doxazosin. When spirolactone

was administered to PATHWAY-2 study participants with normal renal function (mean estimated glomerular filtration rate of 91.1 mL/min and estimated glomerular filtration rate of >45 mL/min), they did so well. When it came to side effects, such as gynecomastia or hyperkalemia, which could be anticipated to restrict the use of spironolactone, there was overall no difference in their frequency between the treatments [37].

Non-pharmacological Therapies

Dietary sodium restriction

A substantial amount of research consistently showed that dietary sodium restriction lowers blood pressure in hypertensive patients [42]. Given the extensive role that aldosterone-induced sodium and fluid retention play in the development of RHTN, this benefit might be more pronounced in patients with RHTN. A small study comparing high dietary sodium intake (250 mEq/d) to extreme dietary sodium restriction (50 mEq/d) for seven days in the crossover evaluation of twelve patients with confirmed RHTN suggested a significant benefit. When comparing a low to high sodium intake, there was a significant drop in blood pressure, resulting in a 20.1/9.8 mmHg reduction in 24-hour ambulatory blood pressure monitoring. Despite the small sample size of the study, the results are consistent with the well-established role that aldosterone plays in the pathophysiology of RHTN, suggesting that some patients with RHTN may be particularly sensitive to salt and may benefit greatly from intense sodium restriction in terms of blood pressure [43].

Lifestyle modifications:

Weight loss and regular exercise are two lifestyle modifications that are known to have antihypertensive effects in general hypertensive population, but they have not been sufficiently studied in patients with RHTN. It is obvious that these interventions improve cardiovascular and metabolic health overall. They should also be advised because they are likely to lower blood pressure in RHTN patients to levels that are comparable to or higher than those observed in the general hypertensive population.[31] Current guidelines indicate that achieving weight reduction of > 5 to 10% body weight will help lower BP in individuals who are overweight or obese [5].

Numerous reviews have demonstrated in a similar manner that diet modifications combined with short-term weight loss result in significant and meaningful reductions in systolic blood pressure of 5.7 mmHg. In order to achieve BP reductions of approximately 4.5/3.2 mm Hg, patients with primary hypertension who participated in longer-term randomised control trials and were monitored for at least 24 weeks after the trial reported modest weight losses (~ 4 kg) [45].

Reducing alcohol consumption

Reducing alcohol consumption has also been demonstrated to have positive effects on blood pressure control and management. Reducing alcohol consumption is advised by current ACC/AHA clinical guidelines for the treatment of HTN [1]. Alcohol consumption at any level was linked to a higher risk of HTN in men, according to a meta-analysis with 361,254 participants. The elevated risk of hypertension in females was observed solely at intake levels surpassing two daily drinks (12 g ethanol per drink) [46]. The study revealed that individuals who consume ≥ 6 drinks per day experienced a greater reduction in blood pressure (5.5 mmHg in SBP and 4 mmHg in DBP) when their alcohol consumption was limited [46]. BP control and management may benefit from lowering alcohol consumption, according to these findings.

Recently, there has been increased interest in the use of inspiratory muscle training (IMT) as an intervention to enhance cardiovascular outcomes like blood pressure. In order to receive this kind of training, the patient must breathe through a machine that has a valve adjusted to a preset pressure threshold. The valve opens and air flows through the device when the patient exerts sufficient pressure [47]. IMT protocols are usually performed twice daily in relatively short training sessions (30 breaths) with training loads ranging from 30 to 80% of the patient's maximal inspiratory pressure. Even though there are currently no studies looking into the role of IMT in patients with RHT, there are a number of studies showing that IMT, when used in protocols lasting six to eight weeks, improves blood pressure outcomes [48].

Interventional Therapy

Renal Denervation:

Renal denervation (RDN) is minimally-invasive procedure that employs catheter-based methods to interfere with the signals between the kidney and the brain. This technique disrupts the nerve signals that control blood pressure in the kidneys, leading to a decrease in systolic blood pressure by about 4 to 6 millimeters of mercury (mm Hg) compared to patients who do not receive this treatment [49-52]

Sympathetic nerves surrounding the distal segment of renal artery are mostly post ganglionic neurons are unmyelinated and more vulnerable to axonal damage in the renal denervation [53].

To minimize the risk of complications, it is essential that a deeply experienced interventionalist with a strong background in renal artery interventions carries out the procedure, as indicated by the outcomes of renal artery revascularization studies [54].

Types of renal denervation

Currently there are 3 techniques of renal denervation that use percutaneous femoral access to the renal artery. These are performed using radiofrequency, ultrasound, or alcohol-mediated renal denervation [55].

Renal denervation by Radiofrequency

Radiofrequency ablation (RFA) involves placing electrodes via a catheter, where the electrodes produce heat using medium-frequency alternating current. This heat is toxic to nerves surrounding the renal artery where as it is well tolerated by the arterial wall. The energy field extends up to 7 mm from the lumen of the kidney artery [56].

SYMPLICITY HTN-1 Study

This study is registered with ClinicalTrials.gov, numbers NCT00483808, NCT00664638, and NCT00753285. It was an open-label study where 86 patients treated with SYMPLICITY FLEX catheter were followed for 36 months. A drop of 10 mmHg was reported in 69% at 1 month, 81% at 6 months, 85% at 12 months, 83% at 24 months, and 93% at 36 months. One patient underwent stenting for renal artery stenosis and three deaths unrelated to the renal denervation occurred during the follow-up. Thus, the study showed substantial lowering of blood pressure in patients with treatment-resistant hypertension without any major safety issues. Also, the effects of lowering blood pressure were consistent across different age groups, baseline renal function, and diabetes status [52, 57].

SYMPLICITY HTN-2 Study

After the proof-of-principle trial, SYMPLICITY HTN-1 established the feasibility of this procedure and indicated that individuals suffering from severe, treatment-resistant hypertension saw a substantial and lasting reduction in blood pressure over a minimum period of 3 years, the SYMPLICITY HTN-2 randomized clinical trial (NCT00888433) then evaluated the safety and efficacy of renal denervation combined with medical management versus medical management alone (control group) in patients with severe treatment-resistant hypertension [58].

A total of 70 patients were included in the long-term follow-up where 40 patients from the original renal denervation treatment group followed up to 36 months' post-randomization, and 30 control subjects who crossed over to renal denervation treatment at 6 months' post-randomization were followed up to 30 months after the procedure. At baseline, all treated subjects had a mean blood pressure of 184/99 mmHg. At 30-month post-procedure in cross over patients, systolic blood pressure decreased 34 mmHg (95% CI: -40, -27, P <0.01) and diastolic blood pressure decreased 13 mmHg (95% CI: -16, -10, P<0.01). In the initial renal denervation group, systolic and diastolic blood pressure reductions at 36 months were -33 mmHg (95% CI: -40 to -25, P<0.01) and 14 mmHg (95% CI: -17 to -10, P<0.01), respectively.

Periprocedural complications included one hematoma and one renal artery dissection before energy delivery, necessitating renal artery stenting were observed in original renal denervation therapy group and crossover group, respectively. Later complications included acute renal failure in 2 patients, which fully resolved, 15 hypertensive events that required hospitalization, and death in 3 patients unrelated to the device. The mean eGFR remained unchanged, and there were no reported renal vascular complications [58].

SYMPLICITY HTN-3 Study

Symplicity HTN-3 which is a multi-center, prospective, single-blind, randomized, controlled study examined the safety of renal denervation in people with uncontrolled hypertension (NCT01418261). Bilateral renal denervation was performed using the Symplicity Catheter. Primary outcome of the study was the change in office systolic blood pressure for the renal artery denervation group compared with the sham control group at 6 months. The primary safety endpoints included the incidence of all-cause mortality, end stage renal disease, significant embolic event, renal artery perforation or dissection requiring intervention, vascular complications, hospitalisation for hypertensive crisis unrelated to non-adherence to medications, or new renal artery stenosis of more than 70% within 6 months.

Out of 364 (68%) patients who received renal artery denervation (mean age 57.9 years) and 171 (32%) who received the sham control (mean age 56.2 years), 36-month follow-up data were available for 219 patients (original renal artery denervation group), 63 patients (crossover group), and 33 patients (non-crossover group). The change in office systolic blood pressure at 36 months was –26.4 mm Hg (SD 25.9) in the renal artery denervation group and –5.7 mm Hg (24.4) in the sham control group (adjusted treatment difference –22.1 mm Hg [95% CI –27.2 to –17.0]; P≤0.0001). The change in 24 h ambulatory

systolic blood pressure at 36 months was −15.6 mm Hg (SD 20.8) in the renal artery denervation group and −0.3 mm Hg (15.1) in the sham control group (adjusted treatment difference −16.5 mm Hg [95% CI −20.5 to −12.5]; P≤0·0001) at 36 months. The rate of the composite safety endpoint, including all-cause death, new-onset end-stage renal disease, significant embolic event resulting in end-organ damage, vascular complication, renal artery re-intervention, and hypertensive emergency was 15% (54 of 352 patients) for the renal artery denervation group, 14% (13 of 96 patients) for the crossover group, and 14% (10 of 69 patients) for the non-crossover group at 48 months [59].

The Symplicity HTN-3 trial was failed to demonstrate that a mono-electrode radiofrequency (RF) catheter device was beneficial in reducing blood pressure after six months when compared to a sham procedure. Few methodological limitations of this trial included frequent medication changes, limited training experience, likely incomplete circumferential ablation in most patients [52].

Renal denervation by Ultrasound

This method uses the ultrasound energy circumferentially, causing renal denervation. Sources that generate ultrasonic waves That are mounted on catheter with an inflatable balloon system which is positioned within the main renal arteries centred by an integrated low-pressure, saline-filled cooling balloon to achieve a circumferential ring of ablation [51,55].

RADIANCE-HTN SOLO, 2018

RADIANCE-HTN SOLO was a multicentre, international, single-blind, randomised, sham-controlled trial which compared the blood pressure lowering efficacy of endovascular ultrasound – the PARADISE System (ReCor Medical) renal denervation system with a sham procedure in two separate cohorts: patients with mild-to-moderate hypertension, who underwent randomisation while off antihypertensive medications (SOLO cohort), and patients with uncontrolled hypertension despite receiving three antihypertensive medications (TRIO cohort). When compared to the placebo treatment, renal denervation led to a greater decrease in daytime ambulatory systolic blood pressure (-8.5 mm Hg, SD 9.3); the baseline-adjusted difference between the groups was −6.3 mm Hg, with a 95% confidence interval of −9.4 to −3.1, P=0.0001). In both groups, no notable adverse events were observed. The study concluded that the endovascular ultrasound renal denervation, without the use of medication, lowered ambulatory blood pressure after two months in individuals with combined systolic and diastolic hypertension compared to a placebo treatment [60].

RADIANCE-HTN TRIO, 2021

RADIANCE-HTN TRIO was a randomised, international, multicentre, single-blind, sham-controlled trial which include 136 patients who were randomly assigned to receive renal denervation by PARADISE System (ReCor Medical) (n=69) or a sham procedure (n=67). Renal denervation resulted in a more significant reduction in daytime ambulatory systolic blood pressure than the sham procedure, with a median decrease of −8.0 mm Hg (interquartile range −16.4 to 0.0 mm Hg) compared to −3.0 mm Hg (−10.3 to 1.8 mm Hg) for the sham group. The median difference between the two treatments was −4.5 mm Hg (95% Confidence Interval [CI] −8.5 to −0.3 mm Hg; adjusted p-value of 0.022). For patients with complete ambulatory blood pressure measurements, this difference was −5.8 mm Hg (95% CI −9.7 to −1.6 mm Hg; adjusted p-value of 0.0051). Safety outcomes were comparable between the two groups [61].

REQUIRE 2022

This study investigated the blood pressure-lowering efficacy of renal denervation in patients with resistant hypertension from Japan and South Korea. The multicentre, randomized, single-blind, sham-controlled trial included 143 patients (72 renal denervation with PARADISE, 71 sham control). The decrease in 24-hour ambulatory systolic blood pressure from baseline at 3 months was similar between the renal denervation group (−6.6 mmHg) and the sham control group (−6.5 mmHg), with a difference of −0.1 mmHg (95% confidence interval: −5.5 to 5.3; P=0.971). Changes from baseline in home and office systolic blood pressure (differences of −1.8 mmHg [p = 0.488] and −2.0 mmHg [P=0.511], respectively) and medication load were not significantly different between the two groups. No major adverse events related to the procedure or device were observed. This study did not reveal a significant difference in ambulatory blood pressure reductions between renal denervation and a sham procedure in patients with resistant hypertension. Although the reduction in blood pressure after renal denervation was similar to that seen in other sham-controlled trials, the sham group in this study showed a substantially greater reduction [62].

Alcohol-mediated renal denervation system

This procedure of chemical denervation involves the targeted delivery of alcohol, typically ethanol, into the renal arteries to ablate the nerves.

TARGET BP 1 and TARGET BP OFF-MED

After successful results of first-in-human, and open-label clinical trials which intended to test the safety of a Peregrine System Infusion Catheter, Ablative Solutions, Inc which is a novel 3-needle-based delivery device to perform chemical renal sympathetic denervation in patients with refractory hypertension, with the use of microdoses (0.3 ml per renal artery) of dehydrated alcohol as the neurolytic agent, TARGET BP I (NCT02910414) and TARGET BP OFF-MED (NCT03503773), to further investigated the efficacy and safety of this treatment [63,64].. The trials are randomized, blinded, and sham-controlled, with one trial (TARGET BP OFF-MED) evaluating the treatment without antihypertensive medications and the other (TARGET BP I) evaluating it in addition to prescribed medications. The primary endpoints are changes in 24-hour ambulatory systolic blood pressure at 8 weeks and 3 months' post-procedure. The trials aim to provide robust evidence on the safety and efficacy of this novel RDN method [64].

FUTURE ASPECTS OF RENAL DENERVATION

Improved patient selection: Researchers are working on identifying better predictors of response to renal denervation. This could involve genetic markers, imaging techniques, or other biomarkers that could help determine which patients are most likely to benefit from the procedure.

Advanced technologies: New catheter designs and energy modalities are being developed to improve the efficacy and consistency of the denervation procedure. These may include multi-electrode catheters, ultrasound-based systems, and chemical denervation techniques.

Expanded indications: While renal denervation has primarily been studied for resistant hypertension, researchers are exploring its potential benefits in other conditions such as heart failure, chronic kidney disease, and metabolic disorders.

Combination therapies: Future research may focus on combining renal denervation with other interventions or medications to achieve better blood pressure control and overall cardiovascular outcomes.

Long-term follow-up studies: As more patients undergo renal denervation, longer-term studies will be crucial to assess the durability of the blood pressure-lowering effect and any potential long-term complications.

Cost-effectiveness analyses: As the procedure becomes more refined, studies will likely focus on its cost-effectiveness compared to lifelong medication regimens for hypertension management.

Personalized medicine approach: Future research may aim to tailor the denervation procedure to individual patient characteristics, potentially improving outcomes.

Non-invasive renal denervation: Some researchers are exploring the possibility of achieving renal denervation through non-invasive means, such as focused ultrasound or other external energy sources.

Reinnervation studies: Understanding the potential for nerve regrowth after denervation and its clinical implications will be an important area of future research.

Global accessibility: Efforts to make the technology more widely available and affordable in different healthcare systems around the world may be a focus in the coming years.

CONCLUSION

Resistant hypertension (RH) represents a significant challenge in the management of hypertension, characterized by persistent high blood pressure despite treatment with multiple antihypertensive medications. The rising prevalence of RH, underscores the need for improved diagnostic and therapeutic strategies. This condition is associated with an increased risk of severe cardiovascular events and mortality, emphasizing the importance of early identification and tailored management. Based on the available evidence, renal denervation (RDN) has demonstrated a blood pressure reduction comparable to that achieved by many individual antihypertensive drugs. Despite being an invasive procedure, RDN has maintained a generally acceptable safety profile in studies conducted thus far. The magnitude of blood pressure decrease observed with RDN is in line with what one might expect from adding a single antihypertensive medication to a patient's regimen. Importantly, while RDN involves a minimally invasive intervention, the reported adverse events and complications have remained within tolerable limits, suggesting that its risk-benefit profile may be favorable for appropriately selected patients with resistant hypertension. Ongoing research is critical to enhance our understanding of RH and its underlying mechanisms, which may lead to more effective interventions and improved outcomes for patients. Addressing RH not only has the potential to reduce individual health risks but also to alleviate the broader public health burden associated with uncontrolled hypertension. In conclusion, renal denervation represents a promising interventional approach for managing resistant hypertension. While initial results are encouraging, continued research is necessary to optimize patient selection, refine

techniques, and establish long-term efficacy and safety. As our understanding of this therapy evolves, RDN may play an increasingly important role in the management of hypertension and related cardiovascular disorders. Recent high-quality, sham-controlled trials have provided evidence supporting the safety and blood pressure (BP) reducing effectiveness of both radiofrequency and ultrasound RDN techniques. As a result, RDN has emerged as a viable treatment option for adults with resistant hypertension that remains uncontrolled despite medication, as confirmed by ambulatory BP monitoring.

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