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A Review on Renal Denervation: A New Frontier in Hypertension Management

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Renal sympathetic denervation (RSDN) is a minimally invasive endovascular catheter treatment that treats resistant hypertension (high blood pressure that cannot be brought under control with medicines) by employing radiofrequency ablation or ultrasound ablation. Using radiofrequency pulses or ultrasound on the renal arteries destroys nerves in the arterial wall. As a result, there is a decrease in sympathetic afferent and efferent activity in the kidney, which lowers blood pressure. Early results from global clinical studies showing significant drops in blood pressure in individuals with treatment-resistant hypertension without sham controls were encouraging. A catheter-mounted device is advanced into the renal artery during the surgery, which entails endovascular access via the femoral artery. The renal nerves are ablated by the device using ultrasound or radiofrequency. To achieve maximum denervation, several ablations are often administered at various longitudinal and rotational positions. An implant is not required for the

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operation to be permanent. Serious complications are uncommon, but minor access site complications occur in about 5% of patients. Other potential complications include renal artery dissection and stenosis. RDN can reduce office systolic blood pressure by an average of 4–6 mm Hg more than control patients. It can also help reduce target organ damage.

Keywords: Renal denervation; hypertension; Chronic Kidney Disease (CKD); device intervention; blood pressure; drug-resistant hypertension; renal sympathetic nerves; sympathetic nervous system.

1. INTRODUCTION

“The majority of current therapeutic approaches for these conditions are pharmacological and lifestyle-based, but more options are needed to prevent heart failure, chronic kidney disease, and their sequelae from progressing, as well as to control blood pressure. These current approaches are not adequate. Both in preclinical and human tests, the role of renal sympathetic nerve activity in the onset and course of various disease states has been persuasively shown. Renal denervation has proven a beneficial tool for both research and treatment in preclinical models of diabetes-related nephropathy, heart failure, myocardial infarction, and chronic kidney disease” [1–6]. “Therapeutic splanchnicectomy and even radical surgical sympathectomy are options for treating individuals with severe hypertension when there are no suitable medications to lower blood pressure pharmacologically. An even more drastic course of action, such as bilateral nephrectomy, is occasionally contemplated for patients with uncontrollably high blood pressure and end-stage renal disease (ESRD). Reducing renin release, increasing urine output (natriuresis and diuresis), and decreasing sympathetic outflow to the kidneys have all been demonstrated to be achievable with surgical renal denervation without hurting the kidney’s other functions, such as renal blood flow and glomerular filtration rate. The experience with transplantation in humans has unequivocally shown that in free-living individuals, the denervated kidney dependably maintains volume and electrolyte balance. Given these results and the need for alternative therapeutic approaches, focusing on the renal sympathetic nerves, which are important in the etiology of hypertension, kidney disease, and heart failure, is a promising strategy” [1]. “Renal nerve dysfunction is strongly linked to cardiovascular illnesses because these nerves play vital functions in controlling blood pressure and fluid content. Sympathetic efferent and sensory afferent nerves make up renal nerves. Renin secretion, sodium absorption, and elevated renal vascular resistance are brought on by activation of the efferent renal sympathetic neurons, and these processes ultimately result in elevated blood pressure and fluid retention. Renal pelvic wall afferent sensory neurons are highly innervated and project to the brain’s hypothalamic paraventricular nucleus, which regulates sympathetic outflow to the peripheral organs, such as the kidneys, heart, and arterioles. Both efferent and afferent denervation mediate the effects of renal denervation on the cardiovascular system” [2].

“Despite the availability of numerous drugs and nondrug therapies that lower blood pressure, uncontrolled hypertension continues to be a significant health concern. A growing percentage of individuals with uncontrolled hypertension—roughly 2 out of every 5—have drug nonadherence. Device-based techniques that denervate the renal arteries have emerged as a potential adjunct to standard antihypertensive treatments in the hunt for blood pressure-lowering strategies that do not depend on adherence to a regimen requiring daily medication ingestion or repeated physical activity. Research is now being conducted on at least three different methods of renal artery denervation: radiofrequency radiation, ultrasound, and injection of neurolytic drugs into the renal perivascular tissue” [3].

2. EMPIRICAL REVIEW

“Markus P Schlaich, Henry Krum, Paul A Sobotka et al in a study named ‘Renal denervation and hypertension’ concluded that One of the greatest medical problems today is essential hypertension, which has a profound effect on people’s lives as well as society at large. Most people now agree that hypertension is a complex disorder that necessitates therapeutic approaches that address multiple parts of the underlying pathophysiology, with the exception of relatively rare monogenetic types.

To lower overall cardiovascular risk in affected people, all main guidelines recommend a combination of lifestyle modifications and combination medications to achieve target blood pressure (BP) levels. While many patients find success with this method, a significant proportion of them do not comply for a variety of reasons, such as medication intolerance, physician inertia, or noncompliance, putting them at unacceptable risk for cardiovascular disease. Re-evaluating more traditional ideas like renal denervation is part of the ongoing search for new therapeutic strategies to safely and efficiently control hypertension. The development of a unique catheter-based technique that targets and disrupts the renal nerves selectively utilizing radiofrequency (RF) energy has been spurred by recent efforts. It is based on the strong preclinical and clinical findings around the role of renal sympathetic nerves in various aspects of blood pressure management. Based on the limited number of uncontrolled hypertension patients, renal denervation has been conducted. The existing evidence is good, showing that the surgery has a favorable safety profile and is linked to a significant and likely long-lasting drop in blood pressure" [4].

"In a research paper titled 'Renal denervation to treat heart failure' Thomas E Sharp III, David J Lefer et al found that Renal denervation uses chemical, ultrasonic, or radiofrequency ablation to bilaterally ablate the renal sympathetic nerves in a single, minimally invasive catheter procedure. RDN has been demonstrated to have clinically significant benefits in lowering blood pressure in hypertensive patients. Although the results of the early clinical studies were encouraging, they lacked sham controls and were improperly blinded. A later investigation that used a sham treatment arm and appropriately blinded research participants was unable to show that hypertension patients' blood pressure significantly decreased. In recent times, there has been a development of more advanced RDN catheters for clinical application, increased user experience with experimental RDN devices, and adjustments and optimizations made to clinical trial designs to include the most responsive patient populations. It is now evident that in the presence of hypertension, RDN dramatically lowers blood pressure. Although catheter-based RDN therapy is mostly focused on treating resistant hypertension, fundamental research examining this method in the setting of heart failure has gained prominence. The present status of preclinical and clinical research on the application of RDN and alternate autonomic modulatory approaches to treat heart failure" [5].

Roland E Schmieder et al according to a study titled "Renal denervation: where do we stand and what is the relevance to the nephrologist?" concluded that over a billion people globally suffer from hypertension, and the number is rising. Blood pressure (BP) control rates are frequently less than 30%, even in high-income nations with robust healthcare systems. It is frequently necessary to use multiple medication therapies to manage blood pressure, although these regimens may not be adequate for many patients. Furthermore, the intricacy of "Multiple pharmaceutical" treatments hurts treatment compliance and, consequently, control rates, leading to unfavorable consequences. Given this persistent problem, there has been a lot of interest in the use of device-based strategies such as renal denervation as a method to lower blood pressure. A detailed description of the technology and background of renal denervation via catheterization can be found elsewhere. The goal of catheter-based renal denervation is to administer radiofrequency (RF), ultrasound, or injectable alcohol to block the activity of renal afferent sensory and efferent sympathetic nerves. "The viability was demonstrated by early, open-label experiments using first-generation technologies. Though safety was continuously proven, the initial generation of trials had inconsistent efficacy outcomes, and meta-analyses were unable to find any meaningful impact on blood pressure. But recently, several meticulously carried out sham-controlled experiments with improved design and methods, as well as more stringent patient selection, have discovered persistent, implausible, and clinically significant drops in blood pressure in both offices and walks. Both highly targeted ultrasound-based renal denervation and second-generation radiofrequency therapy produced the same effects. Now that renal denervation is once again In the news, nephrologists should take into account several factors. Patients with chronic kidney disease (CKD) and hard-to-treat hypertension present to us every day as possible candidates for an interventional procedure. We are trying to lower the risk of cardiovascular renal protective disease by controlling blood pressure at the office and while walking around, but we also need more instruments to slow down or even stop the progressive loss of renal function. Renal denervation may be especially relevant in some conditions, including chronic kidney disease (CKD), as noted early in the therapy's history" [6].

3. RENAL DENERVATION

In a study titled 'Renal denervation—implications for chronic kidney disease' Roland Veelken, and Roland E Schmieder concluded that There has been a lot of interest in using catheter-based renal denervation to treat patients with chronic kidney disease (CKD) and resistant hypertension. "The majority of observational studies and randomized controlled trials, albeit not all of them, have provided data indicating that the method can effectively lower office and ambulatory blood pressure in patients with primary hypertension without compromising renal function. Renal efferent and afferent nerve disruption appear to be the cause of the purportedly advantageous effects of renal denervation. Global sympathetic tone may decrease in patients with resistant hypertension and chronic kidney disease (CKD) if afferent reflexes are interrupted. The ensuing persistent drop in blood pressure is likely to slow the progression of renal disease. Renal denervation, however, may also have renoprotective benefits for CKD patients by enhancing insulin sensitivity, decreasing renal inflammation, and improving glucose metabolism. To precisely characterize the clinical utility of renal denervation in hypertensive and normotensive patients with chronic kidney disease (CKD), more extensive randomized controlled trials are needed" [7].

Kenichi Katsurada, Yukako Ogoyama, Yasushi Imai, et al according to the study titled 'Renal denervation based on experimental rationale' found that "One of the pathophysiological characteristics of heart failure and hypertension is an overabundance of sympathetic nervous system activity. The rostral ventrolateral medulla in the brain stem and the paraventricular nucleus (PVN) of the hypothalamus are important components of the central nervous system that regulate sympathetic outflow to peripheral organs. Through nearby structures with a weak blood-brain barrier, information from the peripheral circulation—such as serum levels of sodium and angiotensin II—is transmitted to the PVN. In addition, signals from baroreceptors, chemoreceptors, and cardiopulmonary receptors as well as afferent input via the renal nerves are all integrated at the level of the PVN. The brain renin-angiotensin system and the balance between nitric oxide and reactive oxygen species in these brain areas also determine the final sympathetic outflow. Additionally, brain inflammatory responses have been shown to modulate these processes. Renal denervation interrupts both the afferent inputs from the kidney to the PVN and the efferent outputs from the PVN to the kidney, resulting in the suppression of sympathetic outflow and eliciting beneficial effects on both hypertension and heart failure" [8].

"Surgeons began using the ancient medicinal idea of denervating the human kidney to improve blood pressure regulation on a bigger scale in the 1920s. Approaches to directly target the sympathetic nerves were largely abandoned with the introduction of potent blood pressure-lowering medications and the advent of modern pharmacology. According to a study by Markus P Schlaich, Dagmara Hering, Paul A Sobotka, Henry Krum, Murray D Esler et al titled 'Renal denervation in human hypertension: mechanisms, current findings, and prospects' But in the last two to three years, there has been a huge resurgence of interest in cutting-edge, minimally invasive device-based strategies that target the renal nerves specifically. Promising outcomes from proof-of-concept research and clinical trials showing compelling blood pressure-lowering effects in the majority of treated patients are what is driving the excitement. Perhaps even more encouraging are findings suggesting possible extra benefits related to common comorbidities of hypertension, such as impaired glucose metabolism, renal impairment, heart failure, ventricular hypertrophy, etc" [9].

Jianzhong Xu, Dagmara Hering, Yusuke Sata, Antony Walton, et al in a study titled 'Renal denervation: current implications and future perspectives' concluded that "A typical characteristic of arterial hypertension is the activation of the sympathetic nervous system (SNS), which has been shown to play a role in the onset and progression of the hypertensive condition. There is compelling evidence that several illness conditions, such as insulin resistance, congestive heart failure, sleep apnea, ventricular arrhythmias, chronic renal failure, and others, are strongly linked to excessive use of social networking sites. Many patients' SNS remains unopposed because sympatholytic drugs, which can be used pharmacologically to treat SNS overactivity, are not frequently employed in clinical practice. Catheter-based renal denervation, a new therapeutic strategy that targets the SNS, has been shown to lower blood pressure in patients with resistant hypertension in a clinically meaningful way. This is likely due to its effects on both efferent and afferent renal nerve traffic. The vascular and renal safety profile of this interventional treatment is favorable, according to the data currently available. Although preliminary findings from small, usually uncontrolled investigations in similar illness conditions that are frequently characterized by excessive SNS activity are encouraging, they need to be confirmed in well-planned clinical trials" [10].

Anna Pisano, Luigi Francesco Iannone, Antonio Leo, et al in a study titled 'Renal denervation for resistant hypertension' found that "the overall hypertensive population has a high prevalence of resistant hypertension, which poses challenges for clinical therapy. Numerous strategies, such as increased antihypertensive medication, lifestyle changes, or a combination of the two, have mostly failed to enhance patient outcomes and lower the risk of cardiovascular disease and kidney damage. Renal sympathetic ablation, or renal denervation, has been suggested as a potential therapeutic alternative to treat resistant hypertension in the past 10 years because renal sympathetic hyperactivity is a primary cause of the disorder. There is insufficient data to conclude that renal denervation improves major cardiovascular outcomes and renal function in people with resistant hypertension. On the other hand, research with a moderate level of certainty suggests that it could enhance 24-hour ABPM and diastolic office-measured blood pressure. To elucidate the value of this technique in this population, further trials measuring patient-centered outcomes rather than surrogate outcomes, with longer follow-up periods, larger sample sizes, and more standardized procedural methodologies, are required" [11].

4. RENAL FAILURE

"Renal failure induces an increase in sympathetic nerve activity (SNA) in both experimental animals and people. The kidney has both efferent and afferent nerves, making it a highly innervated organ. According to the study by Yutang Wang, Sai-Wang Seto, titled 'Therapeutic effects of renal denervation on renal failure' In both people and animals, renal denervation has a preventative effect against renal failure. A drop in blood pressure, a drop in renal efferent SNA, a drop in central SNA and sympathetic outflow, and a downregulation of the renin-angiotensin system are some of the underlying mechanisms. Research has shown that while functional re-innervation doesn't happen in people for more than two years following renal denervation, it does occur in animals a few weeks after the injury. In certain circumstances, such as acute kidney injury brought on by ischemia/reperfusion and renal failure caused by bile duct ligation, renal denervation may not be renal protective. Patients with both early and end-stage renal failure have undergone catheter-based renal denervation, and the data that have been published thus far indicate that this treatment is both safe and efficient in lowering blood pressure. More research is required to determine whether renal denervation helps patients with renal insufficiency function better" [12].

In the study titled 'The role of renal denervation in the treatment of heart failure' Paul A Sobotka, Henry Krum, Michael Böhm, et al concluded that under normal circumstances, the interaction between the heart and kidney contributes to the maintenance of circulatory homeostasis through hemodynamics and neurohumoral regulation processes. Congestive heart failure (CHF) causes the normal regulating mechanisms to malfunction, though, and patients with CHF frequently experience severe renal dysfunction. Renin release, water, and salt retention, and decreased renal blood flow—all characteristics of the renal symptoms of congestive heart failure—are brought on by activation of the renal sympathetic efferent neurons. The central nervous system is affected by an increase in global sympathetic tone caused by a rise in angiotensin II plasma levels, which is partly mediated by renal sympathetic activation. Renal sympathetic activity can be measured clinically by renal norepinephrine spillover, and an increase in renal norepinephrine spillover in CHF predicts shorter survival. In addition to efferent sympathetic activation, activation of renal sensory neurons in CHF may generate a reflex increase in sympathetic tone that contributes to higher peripheral vascular resistance and vascular remodeling as well as left ventricular remodeling and dysfunction. It has been demonstrated that surgical renal denervation enhances both ventricular and renal function in animal models of heart failure. While surgical renal denervation has long been recognized as an effective way to control blood pressure and increase survival rates in hypertensive patients, its popularity has been hindered by its intrusive nature and related consequences. Nonetheless, there is a lot of interest in using a brand-new catheter-based device that was just released to treat CHF and hypertension since it precisely inhibits both efferent and afferent renal neurons. The effectiveness and safety of renal denervation in CHF patients are being studied in several ongoing clinical trials [13].

Gerald F Dibona, Murray Esler, et al in a study titled 'Translational medicine: "the antihypertensive effect of renal denervation' found that Catheter-based renal denervation might, perhaps, provide a cure for essential hypertension in selected patients, those with milder hypertension than treated in the current research. This theory has not yet been verified. Extreme safety would be required if the method were to be used for less severe cases of essential hypertension. Noteworthy, a renal artery dissection was brought on by catheter insertion in one of the approximately 100 patients who have been investigated thus far; this condition was managed with stenting (34). Other than this procedural error, no short-term (up to two years) renal artery problems have been Identified; particularly, no cases of renal artery stenosis or aneurysm have been reported. If endothelial damage was discovered after the fact, it could have contributed to the delayed onset of atherogenesis in the renal artery. Regrowth of efferent sympathetic nerves is conceivable, but it's unclear how much this would completely restore sympathetically mediated kidney function and may negate the antihypertensive effect that has been shown. A partial degree of reinnervation occurs 2-3 years following heart transplant surgery, which involves the severing of the heart's sympathetic nerves. Renal afferent nerve regeneration is improbable. Any decrease in blood pressure caused by renal deafferentation is probably going to be long-lasting" [14].

In 'The Current State and Future of Renal Denervation: A Review' Aneel S Maini, Mansi Maini, Tayo Addo, Vivek Koshti et al found that since the U.S. FDA recently approved new, minimally invasive devices, the concept of renal denervation as a treatment option for hypertension that is difficult to control has been around for several decades. Renal denervation may help treat hypertension, but before it is widely used, several issues need to be taken into account. In comparison to sham control, the effect is negligible and largely comparable to the addition of a single blood pressure-lowering drug. Further refining of the approach could potentially yield higher effects. Beyond the direction, advantages, and disadvantages of the renal denervation technologies themselves, important things to think about are patient groups that benefit the most and phenotypes or biomarkers that indicate a higher response. Based on data collected over the last ten years, RDN appears to be a viable technology. When compared to sham treatments, current devices show good safety but only modest BP lowering, suggesting that they could be a beneficial extra tool for high-risk patients to lower blood pressure when standard approaches fail. Furthermore, additional research is necessary to determine the technology's apparent positive effects on several comorbidities. An improved comprehension of renal sympathetic physiology [15].

5. VASCULAR AND RENAL MORBIDITY

Due to its role in cardiovascular death, vascular and renal morbidity, and financial burden, hypertension is a major global public health concern. Therefore, it is crucial to take advantage of the chance to impact clinical outcomes through hypertension control. According to the study by David E Kandzari, Deepak L Bhatt, Paul A Sobotka et al titled 'Catheter-based renal denervation for resistant hypertension: rationale and design of the SYMPLICITY HTN-3 Trial' Despite adherence to several current medical therapies, a considerable minority of individuals experience persistent blood pressure increase, a condition dubbed resistant hypertension. With the recent identification of the renal sympathetic and somatic nerves as key players in blood pressure regulation and the creation of a novel technique that targets and eliminates these sources of resistant hypertension, there is a chance to offer a clinically significant benefit to a broad range of patient populations. Early clinical testing of catheter-based, selective renal sympathetic denervation in patients with resistant hypertension has shown clinically significant, long-lasting blood pressure reductions and mechanistically correlated sympathetic efferent denervation with decreased renal norepinephrine spillover and renin activity, increased renal plasma flow, and reduced renal norepinephrine spillover. The SYMPLICITY HTN-3 Trial is a pivotal study that aims to assess the safety and efficacy of catheter-based bilateral renal denervation for the treatment of uncontrolled hypertension despite adherence to at least three antihypertensive medications of different classes (at least one of which is a diuretic) at maximally tolerated doses. The trial is designed as a prospective, randomized, masked procedure, single-blind trial. The change in office-based systolic blood pressure from baseline to six months is the major efficacy goal [16].

Despite the availability of combination therapy, resistant hypertension continues to pose a significant therapeutic challenge. Given that it is closely linked to obesity and advanced age, its occurrence is expected to rise over the coming decades. Patients with resistant hypertension are more likely to experience cardiovascular problems, thus receiving adequate antihypertensive therapy will have a positive impact on their health. According to the study by Mario Santos, Henrique Carvalho et al titled 'Renal sympathetic denervation in resistant hypertension' The interaction between the sympathetic nervous system and kidneys plays a critical role in hypertension. It affects several pathophysiological processes, including sodium balance, systemic neurohumoral activation, and central sympathetic tone. Indeed, research employing several animal models showed that renal denervation prevented and reduced hypertension in various animal species. Significant drops in blood pressure were also noted in patients with malignant hypertension undergoing sympathectomy procedures. On the other hand, the rates of periprocedural complications and incapacitating adverse events associated with these methods were unacceptable. Recently, a novel approach to treating sympathetic activation without the use of drugs has been effectively created. An endovascular technique called renal sympathetic percutaneous denervation employs radiofrequency energy to kill the autonomic renal nerves that run through the adventitia of the renal arteries. This technique offers a fresh and potentially effective take on the tactic of blocking the sympathetic nervous system [17].

In a research paper titled 'Renal Denervation in Resistant Hypertension and Obstructive Sleep Apnea' Ewa Warchol-Celinska, Aleksander Prejbisz et al found that in refractory hypertensive patients with obstructive sleep apnea (OSA), renal denervation may reduce blood pressure and ameliorate the severity of OSA. Individuals who have OSA and resistant hypertension are at a higher risk of cardiovascular disease. Renal denervation decreased office and ambulatory blood pressure in resistant hypertensive individuals with OSA in a randomized controlled experiment. The clinical severity of OSA Improved along with the blood pressure reduction in resistant hypertensive patients [18].

Sandeep Nathan, George L Bakris et al in the study titled 'The future of renal denervation in resistant hypertension' found that increased cardiovascular morbidity and mortality are associated with resistant hypertension, which is characterized as insufficient blood pressure management even with three or more antihypertensive drugs used at maximally tolerated levels. A key factor in the pathobiology of resistant hypertension appears to be increased renal afferent and efferent sympathetic activity, which is carried by neurons that arborize the adventitia of the renal arteries. Based on past experiences, individuals with malignant hypertension often saw a significant reduction in blood pressure following surgical denervation and/or sympathectomy. In the last ten years, a percutaneous variation of surgical denervation called catheter-based radio-frequency renal denervation has been created. In the last ten years, a percutaneous variation of surgical denervation called catheter-based radio-frequency renal denervation has been created. Thus far, non-randomized and unblinded trials have shown that percutaneous renal denervation employing a range of methods can significantly lower office-based blood pressure but has a less significant effect on ambulatory blood pressure. However, the only adequately powered, blinded, sham-controlled study on renal denervation that has been carried out to date was unable to achieve its main goal, raising questions about the efficacy of the treatment. Although further research is needed, ancillary benefits of renal denervation have been linked to illnesses like heart failure, diabetes mellitus, and sleep apnea [19].

In the study titled 'Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study' Henry Krum, Markus Schlaich, Rob Whitbourn et al concluded that Catheter-based renal denervation causes substantial and sustained blood-pressure decrease, without serious adverse effects, in individuals with resistant hypertension. Investigations on the efficacy of this method in the treatment of this ailment require prospective randomized clinical studies [20].

In 'Renal sympathetic denervation in patients with treatment-resistant hypertension (The Simplicity HTN-2 Trial): a randomized controlled trial' Simplicity HTN-2 Investigators et al found that Patients with essential hypertension have sympathetic outflow to the kidneys stimulated, and renal sympathetic nerves play a role in the development and maintenance of hypertension. Renin release is stimulated, tubular salt reabsorption is increased, and renal blood flow is decreased by efferent sympathetic output. Kidney afferent signals influence central sympathetic outflow, which in turn causes neurogenic hypertension. Non-selective surgical sympathectomy was effectively used as a treatment of severe hypertension before antihypertensive drugs became generally available. Recently developed endovascular catheter technology enables selective denervation of the human kidney, with radiofrequency energy delivered in the renal artery lumen, accessing the renal nerves located in the adventitia of the renal arteries. A first-in-man study of this approach showed successful renal denervation with reduction of sympathetic activity and renin release in parallel with reductions of central sympathetic outflow. Safety and feasibility trials of this procedure identified substantial reductions in blood pressure without substantial procedure-related complications [21].

In a research paper titled 'Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study' Felix Mahfoud, Markus Schlaich, Ingrid Kindermann found that Insulin resistance and poor glucose metabolism are linked to hypertension. Both conditions may be exacerbated by persistent sympathetic nervous system activation. In patients with resistant hypertension, we looked at the impact of renal sympathetic denervation via catheterization on blood pressure regulation and glucose metabolism. Renal denervation considerably lowers blood pressure and enhances insulin sensitivity and glucose metabolism. This improvement, meanwhile, didn't seem to be connected to adjustments in pharmacological therapy. Therefore, in patients with resistant hypertension and metabolic diseases at high cardiovascular risk, this innovative treatment may offer protection [22].

Christian Ott, Roland E Schmieder et al in a study titled 'Renal denervation for resistant hypertension: past, present, and future' Just five years ago, renal denervation (RDN) as a therapy for resistant hypertension was first proposed. The method's widespread adoption, at least in Europe, has been encouraged by a clear pathophysiological role for renal sympathetic activity in the development and maintenance of hypertension, as well as encouraging results demonstrating a significant and long-lasting drop in blood pressure (BP) following RDN. However, no appreciable decrease in blood pressure was seen in a crucial experiment with a sham-control group. Subsequently, it was evident that methodological problems as well as subpar performance and implementation of the intervention had hindered the outcomes of the Simplicity HTN-3 study, severely restricting its validity. The rebirth of RDN has now started in 2015, and new randomized prospective clinical trials have commenced or are in the process of commencing. As a last resort for treatment-resistant hypertension, it could be prudent to consider all prior research in the meantime. A new scientific age began, with modifications to the interventional strategy and patient selection that may maximize the benefits of RDN [23].

In a study titled 'Renal Sympathetic Denervation for Resistant Hypertension' Michael Froeschl, Adnan Hadziomerovic, Marcel Ruzicka, et al concluded that Resistant hypertension is an increasingly widespread health issue associated with major unfavorable cardiovascular effects. The renin-angiotensin II–aldosterone system and the sympathetic nervous system both work more than usual in the pathophysiology of this illness. A vital connection between these two systems is the network of sympathetic fibers that runs through the renal artery adventitia. These nerves can be targeted by transferring radiofrequency radiation from the lumen of the renal arteries to renal artery walls (percutaneous renal sympathetic denervation [RSD]), a method that has gained tremendous interest. The health of Canadians is increasingly at risk from hypertension, and more especially from resistant hypertension. Although there are encouraging data to support the use of RSD in resistant therapy, much more research needs to be done before this treatment is widely used [24].

6. CATHETER-BASED RENAL DENERVATION

In '*Catheter-based renal denervation* in the treatment of resistant hypertension' GA Stouffer, GF DiBona, A Patel, P Kaul, AL Hinderliter, et al found that according to clinical studies, systolic blood pressure (BP) can be lowered by about 30 mm Hg by catheter-based renal denervation (RD), which involves cutting off the afferent and efferent sympathetic nerves that supply the kidney. For individuals with resistant hypertension—a disease in which blood pressure stays high even when a sensible drug regimen is followed—this technology is presently being investigated as a treatment alternative. Numerous studies on humans and animals that highlight the significance of the sympathoadrenal axis in the etiology of hypertension served as the foundation for the development of this innovative therapeutic strategy. The kidneys affect central sympathetic drive through afferent neurons, while sympathetic efferent signals to the kidneys increase blood pressure by inducing renin release and salt retention. However, RD has demonstrated advantages in clinical trials long before the processes are completely known, as is the case with many therapeutic advancements. More research is required to determine whether afferent sympathetic nerve interruption contributes to the BP reductions seen with RD, to assess the extent and importance of re-innervation after RD, to clarify the factors that may cause some patients to not respond to RD, to ascertain whether RD's modulation of the sympathetic nervous system can have positive effects apart from BP reduction, and to create techniques to gauge RD's efficacy in real-time [25].

Bo Liang, Yi Liang, Rui Li, Ning Gu, et al in a study titled 'Effect of renal denervation on long-term outcomes in patients with resistant hypertension' found that although there are still many issues to be resolved, RDN may be one of the most successful strategies for lowering blood pressure in people with RH. The first is that the research must be double-blind and sham-controlled. Additionally, ambulatory blood pressure must be the primary method used for blood pressure evaluation. Lastly, a rigorous comparison of the ongoing antihypertensive effect of RDN in various RDN systems is also necessary. Nevertheless, there is hope for the future. Renal denervation is a minimally invasive surgery that is increasingly being shown to be a promising new non-drug treatment option for patients with resistant hypertension. However, there is currently insufficient research on the long-term effects of renal denervation on blood pressure control in patients with resistant hypertension [26].

Several significant clinical disorders, such as essential hypertension, heart failure, chronic kidney disease, and insulin resistance, are characterized by increased central sympathetic drive. Increased sympathetic outflow to the kidney and other organs is vital for cardiovascular regulation, and afferent signaling from the kidneys has been found to play a significant role in heightened central sympathetic drive. According to the study by Markus P. Schlaich, Dagmara Hering, Paul Sobotka, Henry Krum, Gavin W Lambert, Elisabeth Lambert, et al titled 'Effects of renal denervation on sympathetic activation, blood pressure, and glucose metabolism in patients with resistant hypertension' found that Further negative effects of prolonged sympathetic activation, such as insulin resistance, which is frequently linked to hypertension, may be facilitated by increased sympathetic outflow to other vascular beds, even though the ensuing effects on renal hemodynamic parameters, sodium and water retention, and renin release are particularly relevant for both acute and long-term blood pressure regulation. The sympathetic link between insulin resistance and hypertension has been further revealed by recent clinical studies that used catheter-based radiofrequency ablation technology to achieve functional renal denervation in patients with resistant hypertension. These studies also identified the renal nerves as a therapeutic target. This unique strategy may certainly offer a safe and effective therapeutic alternative for resistant hypertension and some other conditions, according to preliminary evidence from two clinical trials and several smaller mechanistic clinical studies [27].

In a research paper titled 'Renal sympathetic denervation for treating resistant hypertension' Alberto Polimeni, Antonio Curcio, Ciro Indolfi et al found that Due to its role in cardiovascular death, vascular and renal morbidity, and economic burden, systemic hypertension is a major global health concern. As such, its effects are felt strongly on public health around the globe. Therefore, improving the management of high blood pressure is essential to affecting clinical outcomes. A considerable percentage of people experience persistently elevated blood pressure despite adhering to various current medical therapies; this condition is known as "resistant hypertension" By upsetting regulatory processes, renal sympathetic innervations contribute to antihypertensive medications' inability to work. While renal afferent signals are integrated in the central nervous system and augment sympathetic nerve discharge, renal afferent nerve fibers are in charge of sympathetic activation and play a role in blood pressure control. Thus, a novel approach that targets and eliminates these components of hypertension offers a new avenue for treatment. Renal sympathetic denervation may now be induced with a catheter, and this technique is now routinely used. Clinical assessment of selective renal sympathetic denervation has proven clinically significant, long-lasting blood pressure decreases in patients with resistant hypertension [28].

In the study titled ‘Renal denervation: a new treatment option in resistant arterial hypertension’ WL Verloop, M Voskuil, PA Doevendans et al found that One of the most common risk factors for cardiovascular disease is hypertension. Even with the wide availability of potent medications and their high prevalence, a sizable fraction of patients fail to meet their treatment objectives. This can be partially explained by patient non-compliance or secondary causes of hypertension. However, “resistant hypertension” may be identified in a subset of people. The initiation and advancement of systemic hypertension are recognized to be significantly influenced by the activation of the sympathetic nervous system. In this case, radiofrequency energy has been created as a percutaneous, catheter-based method to disrupt renal sympathetic nerves. In this case, radiofrequency energy has been created as a percutaneous, catheter-based method to disrupt renal sympathetic nerves. The fact that there was no vascular or renal damage in the initial experiments demonstrated the safety of this method. More importantly, blood pressure was significantly lowered using catheter-based renal nerve ablation in addition to conventional medical therapy. In addition to the favorable outcomes revealed on hypertension, a good influence of this intervention in other disorders, marked by sympathetic overactivation, may be expected. Even though this method seems promising, further research is required to determine the long-term safety and effectiveness of renal denervation in conditions other than hypertension [29].

In ‘Renal denervation: a potential new treatment for severe hypertension’ Yonghong Huan, Debbie L Cohen et al found that despite the existence of potent antihypertensive medications, drug-resistant hypertension is nevertheless often encountered. With no major procedure- or device-related problems so far, the recently developed catheter-based renal denervation method has demonstrated excellent blood pressure reduction and a positive safety profile. While the regeneration of afferent renal sympathetic nerves is still unclear, efferent renal sympathetic nerves are known to regenerate rather quickly. One of the main factors contributing to cardiovascular morbidity and death is hypertension. Despite the availability of multiple classes of effective antihypertensive medications, drug-resistant hypertension continues to be frequent. Long acknowledged as a primary cause of resistant hypertension, sympathetic hyperactivity was removed from radical sympathectomy several decades ago because of severe adverse effects. Recent trials have demonstrated the significant blood pressure reductions and excellent safety profile of the newly designed, minimally invasive, catheter-based renal sympathetic denervation treatment in drug-resistant hypertension. While the long-term safety and effectiveness of renal denervation are yet unknown, new information indicates that renal denervation may offer advantages beyond blood pressure regulation [30].

7. CONCLUSION

A major and expanding global health concern is chronic renal disease, heart failure, and hypertension. The majority of current therapeutic approaches for these conditions are pharmacological and lifestyle-based, but more options are needed because blood pressure control rates and efforts to stop heart failure, chronic kidney disease, and their aftereffects from progressing are still insufficient. Both in preclinical and human tests, the role of renal sympathetic nerve activity in the onset and course of various disease states has been persuasively shown. Renal denervation has proven a beneficial tool for both research and treatment in preclinical models of diabetes-related nephropathy, heart failure, myocardial infarction, and chronic kidney disease. During the 1930s, patients with severe hypertension were treated with therapeutic splanchnicectomy or even a drastic surgical sympathectomy when there were no suitable medications to lower their blood pressure. An even more drastic course of action, such as bilateral nephrectomy, is occasionally contemplated for patients with uncontrollably high blood pressure and end-stage renal disease (ESRD). Reducing renin release, increasing urine output (natriuresis and diuresis), and decreasing sympathetic outflow to the kidneys have all been demonstrated to be achievable with surgical renal denervation without hurting the kidney’s other functions, such as renal blood flow and glomerular filtration rate. The experience with transplantation in humans has unequivocally shown that in free-living individuals, the denervated kidney dependably maintains volume and electrolyte balance. Targeting the renal sympathetic nerves, a key participant in the pathogenesis of hypertension, kidney disease, and heart failure, is an appealing therapeutic approach in light of these results and the need for alternative treatment alternatives. The history of renal denervation is not clear. Early trials showing dramatic drops in blood pressure following renal artery denervation were followed by neutral results when denervation was compared against a sham treatment. Renal denervation is not yet a recognized clinical therapy, despite a strong pathophysiological foundation for blocking the renal sympathetic nervous system as a treatment for hypertension. This is due to insufficient trial results. Nephrologists are particularly interested in renal denervation because it may improve hypertensive patients with chronic kidney disease (CKD), which is often accompanied by sympathetic hyperactivity. Renal denervation in this challenging-to-manage group is safe and effective, according to an increasing amount of clinical evidence. Furthermore, studies in preclinical and clinical settings suggest that CKD patients may benefit from nephroprotective effects.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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