Review Article

Catheter-Based Ultrasound Renal Denervation in Patients with Resistant Hypertension: A Systematic Review

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ABSTRACT

Background: The maintenance and development of hypertension are fundamentally dependent on renal sympathetic hyperactivity. Through regulation of the renal sympathetic nerves, catheter-based renal sympathetic denervation has been demonstrated to dramatically lower blood pressure (BP) in patients with resistant hypertension (systolic blood pressure 160 mm Hg on three or more antihypertensive medicines, including a diuretic). This study assessed a catheter-based ultrasound device of the next generation intended to maximize nerve coverage using circumferential ultrasound energy. This study's objective is to describe the results of renal denervation (RDN) in patients with resistant hypertension using a catheter-based ultrasonography device to measure blood pressure and safety. A potential new non-pharmacological therapy for resistant hypertension is renal denervation.

Method: PubMed, Web of Science, Science Direct, Cochrane Library, and Google Scholar were thoroughly searched for relevant material. Throughout this meticulous process, the Rayyan QRCI was used.

Results: our review included 10 studies with parameters including the period of study, age range of patients, office blood pressure, ambulatory blood pressure and the used approach. Clinical studies are required to determine whether this method is effective in treating this resistant hypertension.

Conclusion: In individuals with resistant hypertension, catheter-based ultrasound renal denervation significantly and persistently lowers blood pressure and has no negative effects on renal function or renal artery anatomy.

Keyword: Renal Denervation, Catheter, Ultrasound, Blood Pressure, Ambulatory Blood Pressure, Resistant Hypertension.

Introduction

The prevalence of resistant hypertension has increased worldwide owing to the increasing prevalence of obesity and increased age of the population [1]. An estimated 1.28 billion adults worldwide have hypertension among whom 46% are unaware of having hypertension. Unfortunately, only 42 % are diagnosed and treated and approximately 1 in 5 of them have their hypertension under control [2].

The "hypertension paradox" refers to the rise in uncontrolled BP among persons despite the availability of more treatment choices. Resistant hypertension is characterized by failure to achieve blood pressure control despite giving optimal permissible doses of three antihypertensive drugs of different classes, including a diuretic.

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The prevalence of resistant hypertension is 9.4%in all hypertensive people and 7.4% in treated hypertensive people. True resistant hypertensive individuals are at 2.94 time's higher risk of developing cardiovascular disease than controlled hypertensive individuals [1]. It is well known that blood pressure is regulated primarily by renin-angiotensin-aldosterone system sympathetic nervous system (SNS) [3]. One of the earliest surgical interventions for resistant hypertension treatment is that of Smithwick and Thompson (1955) who made thoracolumbar sympathetic splanchiectomy and followed up patients for 5 years. The surgery lowered both SBP and DBP and decreased the all-cause mortality in comparison to medically treated control group. This technique had many side effects as orthostatic hypotension, peripheral vasoconstriction and gastrointestinal dysfunction. This technique was extinct for its serious side-effects and the emergence on new effective antihypertensive drugs [4]. It is important to control hypertension because those who have untreated hypertension or those who have uncontrolled hypertension are at increased risk of all-cause, cerebrovascular disease, cardiovascular disease, and heart disease mortality. Whereas those who are controlled hypertensives are at lower risk of mortality [5]. Ineffective management of hypertension may be caused by medication non-adherence, and prescription. This emphasizes the shortcomings of primarily pharmaceutical methods for the efficient control of hypertension [6]. Renal denervation using a catheter has become a promising therapy for individuals with resistant hypertension over the past 10 years. In proof-of-concept studies, individuals who underwent radiofrequency renovascularization via a catheter experienced significantly reduced systolic pressure [7]. The randomization unaltered outcomes, SYMPLICITY HTN-3 study with a sham control, however various confounding variables were revealed that might explain the study findings [8]. However, proof-of-concept and sufficiently powered experiments Kidney denervation devices using second-generation radiofrequency and ultrasound technology have showed potential. [9]. SYMPLICITY HTN-3's key efficacy objective was not achieved, the SYMPICITY HTN-JAPAN [10] study was terminated early [7]. Due to the fact that Asian patients [11] have different cardiovascular risk factors and hypertension phenotypes from Caucasians, here is a lack of information about the use in Asian individuals with renal denervation [12]. The renal denervation treatment for anti-hypertension patients from Japan and South Korea was evaluated in the sham-restricted the effect of renal denervation on the 24-Hour BP Control by Ultrasound in Resistant Hypertension (REQUIRE) experiment [13]. Deeper research has been done on Pathogenesis is influenced by the functions of the compassionate adrenergic technique and the renin-angiotensin method in pathogenesis, development, significant organ damage caused by high blood pressure. These studies have also given rise to new perspectives on the aims of hypertension management. By treating anti hypertension with catheter-based radiofrequency renal denervation (RDN), Krum as well as colleagues demonstrated that RDN has been demonstrated to lower patients' blood pressure (BP) over time. This procedure was risk-free and had no clear drawbacks [14]. The outcomes of the DENERHTN research, a multicenter, open-label trial, were published in early 2015, a randomized controlled clinical study comparing standardized stepped-care AHT (SSAHT) with a blinded end goal was conducted. SSAHT alone was compared to SSAHT with renal denervation in 106 RHTN patients, showed that the renal denervation group experienced at six months, a further 5.9 mm Hg drop ambulatory in the middle of the day blood pressure in systole (ASBP). Furthermore, the renal denervation group had a higher rate of managed HTN. These findings showed that under the careful treatment supervision of hypertension professionals, renal denervation might drop ambulatory blood pressure in RHTN patients. Importantly, there was no difference in medication compliance between the two groups (Renal denervation in conjunction with SSAHT, as well as SSAHT alone), indicating that this did not affect the results [15]. Interestingly, despite care at hypertension centers, Medication adherence was frequently insufficient. (50% of patients took less medication than prescribed or none at all). This implies that drug adherence still contributes to inadequate BP control 50% of patients took half the amount of medicine advised or none at all [16]. This systematic review investigates those effects in refractory hypertension individuals, catheter-based ultrasonography renal denervation was studied.

Methods

The PRISMA acronym stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The criteria were followed in this systematic review.

Study Design and Duration: This systematic review was carried out in August 2023.

Strategy for searching: A complete search was conducted in five significant databases, such as

Google Scholar, Web of Science, PubMed, and Science straight, and EBSCO, to find the pertinent studies. Our search was restricted to English, and we took into consideration the specific requirements of each database. In order to discover relevant research, the next keywords were changed into terms for PubMed Mesh: "Sickle cell, Malaria, Plasmodium falciparum, Hemoglobin." To match the key phrases, the Boolean operators "OR" and "AND" were applied. Publicly accessible articles, human trials, and publications the search results met everything in English.

Selection criteria

Inclusion criteria, for this review, we took consideration of the following factors:

• Any research investigates the renal denervation by catheter in hypertensive patients
• There were no restrictions on age.
• Accessible, free articles.

Exclusion criteria:

• We excluded participants with an unsuitable renal artery anatomy, chronic kidney disease, secondary hypertension, inflammatory bowel disease, a history of major cardiovascular events, or other chronic conditions are.
• Case reports, letters to the editors, and replies to conflicts were excluded.
• Non-English language.

Data extraction: In the search strategy's output, duplicates were found using Rayyan (QCRI). The researchers filtered the combined search results using a set of inclusion/exclusion criteria to assess the relevancy of the titles and abstracts. Each paper that meets the requirements for inclusion has been examined carefully by the reviewers. The writers presented additional methods for resolving disputes after serious thought. The authors were able to get information on the studies' titles, authors, research year, country, participants, gender, diagnostic tool, main findings, and conclusion.

Data syntheses and analyses: To give a qualitative summary of the research's results and main elements, utilizing information from pertinent studies, summary tables were created. Once the data from the systematic review was retrieved, the most effective way to use the data from the included study articles was determined.

Risk of bias evaluation: For non-randomized treatment studies, the risk of bias assessment approach ROBINS-I was utilized, the quality of the included studies was evaluated. The seven topics evaluated were perplexing. Participant recruitment for the study, Intervention categorization, variations from intended interventions, missing data, appraisal of results, and choice of stated result.

Results

Explore results: After removing 50 duplicates from the search results, 210 study papers remained. Title and abstract screening was performed on 160 publications; 70 were found to be research-worthy and 90 were rejected. Out of the 70 reports that were requested for retrieval, only 35 items could not be located. Final screening for full-text review involved 35 publications; 15 were rejected owing to inaccurate study findings, and 10 were rejected because they used the wrong population type. In this systematic review, 10 relevant study articles were included.

Characteristics of the research included

(Table 1) summarizes the socio-demographic characteristics of the studies considered. Our results included ten studies. One of them is conducted in Japan and Korea [17], one in China [21], one in Poland [20] and three of them in Europe [22, 23, 24]. The patients investigated varied in age from 18 to 80 years old on average [17- 26]. These investigations involved 24-hour ambulatory systolic blood pressure was more than 135 mm Hg [20] or more than 140 mmHg [17, 23]. The blood pressure in the workplace was more than 140 mm Hg [20, 26], more than 150/90 mmHg [17, 23] and more than 160 mmHg [21].

(Table 2) summarizes the clinical features of the studies included. The investigations investigated whether using the RDN technology was practical and secure. Patients with resistant hypertension had significant blood pressure drops [18- 20, 23, 24] and a reduced urine protein excretion rate, both of which had no negative effects on renal function or renal artery anatomy [21]. No reno-vascular problems developed either [22]. Stroke volume was decreased because of RDN [25]. According to another research, even while the fall in blood pressure following renal denervation was comparable to that observed in other sham-controlled studies, the decline in the study's sham group was much greater [17]. Another research found that the reduction in the highest 24-hour ambulatory blood pressure was seen in people with smaller renal arteries and had nothing to do with length of the renal arteries, supplementary arteries, or renal arterial disease [26].

Discussion

The effectiveness of renal denervation has been examined in the context of ideal research designs and procedural approaches, including strategies for more thorough ablation [27]. There exists indications suggesting denervation of the kidneys might be effective in lowering blood pressure into hypertensive individuals who do not rely on blood pressure-reduction medications, indicating that additional research in this patient population is warranted [28].

Table (1): Socio-demographic characteristics of the included participants.

Study	Country	Study design	Patients	Age range	Period of study	Blood pressure	24-hour ambulatory systolic blood pressure
Kario, Kazuomi et al. 2022 [17]	Japan and South Korea	randomized, controlled REQUIRE trial	143	20–75 years	Between January 12, 2017 and March 31, 2020.	≥150/90 mmHg	≥140 mmHg
Bhatt, Deepak L et al. 2014 [18]	---	prospective, single-blind, randomized, sham-controlled trial	535	18 to 80 years of age	---	---	---
Chernin, Gil et al. 2018 [19]	---	multicenter, single-arm trial	39	---	6 months	---	---
Warchol-Celinska, Ewa et al. 2018 [20]	Poland	prospective, phase II, proof-of-concept, randomized, nonsham design, open-label trial	60	18 and 70 years	during 2012 to 2015	≥140 mm Hg	≥135 mm Hg
Zhang, Zhi-Hui et al. 2014 [21]	China		77	61.713.5 Years.	from October 2011 to February 2013	≥160 mm	---

Krum, Henry et al. 2009 [22]	Australia and Europe	proof-of-principle trial	50	---	between June, 2007, and November, 2008	---	---
Daemen, Joost et al. 2019 [23]	Europe	prospective, multicenter, nonrandomized, postmarket study	96	mean age 63.9 year	---	176.2/95.0 ± 20.6/16.0 mmHg	156.2/88.4 ± 15.4/12.7 mmHg,
Mauri, Laura et al. 2018 [24]	United States and Europe.	clinical study	131	---	---	---	---
Lurz, Philip et al. 2020 [25]	---	randomized cohort	162	---	---	---	---
Lauder, Lucas et al. 2018 [26]	---	---	150	≥18 years	between March 2009 and June 2013	≥140 mmHg	---

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Method	Outcomes
Kario, Kazuomi et al. 2022 [17]	Renal artery anatomical eligibility was assessed using computed tomography or magnetic resonance angiogram, and verified by renal artery angiography at the time of surgery.	the renal denervation and sham control groups both saw comparable drops in 24-hour ambulatory BP
Bhatt, Deepak L et al. 2014 [18]	Renal denervation or a sham operation was randomly allocated to patients with severe resistant hypertension in a 2:1 ratio.	Between the two groups, there were no discernible differences in terms of safety.
Chernin, Gil et al. 2018 [19]	The cohort was divided into 4 groups: recurrent severe resistant hypertension, severe resistant hypertension treated with a unidirectional catheter; moderate resistant hypertension treated with a multidirectional catheter; and severe resistant hypertension treated with a multidirectional catheter.	significant blood pressure drops were seen, however more slowly in individuals with isolated systolic hypertension. The RDN technology could be used safely and effectively.
Warchol-Celinska, Ewa et al. 2018 [20]	---	In individuals with resistant hypertension and obstructive sleep apnea, RDN reduced both office and ambulatory blood pressure.
Zhang, Zhi-Hui et al. 2014 [21]	using 64-detector computed tomography (CT)	demonstrating the efficiency of RDN treatment of resistant hypertension

Krum, Henry et al. 2009 [22]	Office blood pressure and safety information were the main objectives before the procedure and at the 1, 3, 6, 9 and 12-month marks. A magnetic resonance angiogram was performed six months after the surgery, and renal angiography was performed before, right away after, and 14–30 days thereafter.	There were no renovascular complications.
Daemen, Joost et al. 2019 [23]	A catheter-based ultrasound device that uses circumferential ultrasonic energy to maximise nerve coverage.	The approach seemed secure and produced long-lasting reductions in office BP and 24-hour ambulatory BP.
Mauri, Laura et al. 2018 [24]	---	REQUIRE is intended to assess individuals who are on standard-of-care medication for resistant hypertension. At three months, the reduction in 24-hour ambulatory systolic blood pressure will be evaluated.
Lurz, Philip et al. 2020 [25]	In patients with hypertension receiving RDN and compared to sham therapy, cardiac magnetic resonance imaging was performed to evaluate the impact of RDN on heart function.	When compared to sham, RDN reduced the volume of the stroke in individuals with resistant hypertension.
Lauder, Lucas et al. 2018 [26]	A monoelectrode radiofrequency catheter was utilised for bilateral RDN.	Patients with smaller renal artery diameter had the greatest reduction in blood pressure over the course of 24 hours.

In a randomized controlled trial, the effects of RDN on office as well as ambulatory blood pressure were shown to be dissimilar Trials highlight the need of identifying groups in whose renal sympathetic activity may or may not have a role in the development of hypertension. The majority of nerves are, in fact, distributed circumferentially and closer to the lumen in the distal area of the main renal arteries, within 6 millimeters of the kidney artery lumen, according to research on the renal neural architecture of humans and animals. As a result, better technology which transmit energy is distributed circumferentially around the renal artery at specified places have been developed in order to potentially accomplish more successful nerve ablation. To achieve this more thorough method of denervation, many novel denervation catheters have been developed and are presently undergoing clinical testing [29]. The clinical investigation of renal denervation as a possible therapy for hypertension is still ongoing, and it is endorsed by regulatory agencies in the US, Europe, and Japan, among others. If rigorous standards are followed, a number of Scientific Statements and consensus statements issued in 2015, advocated for the continuation of research on renal denervation [30]. Renal Denervation System Using Catheters (Palo Alto, California-based ReCor Medical) will be evaluated the RADIANCE-HTN Clinical Trial (REQUIRE Clinical Study (Japan and Korea) as well as the REQUIRE Clinical Study (North America and Europe).using lessons learned Symplicity HTN-3 and DENERHTN are both available. The blinded, randomized, sham-controlled RADIANCE-HTN as well as REQUIRE Clinical studies comply to the requirements of the consensus standards [31]. In order to treat resistant hypertension between the 1940s and the 1950s [32], the chest, stomach, and pelvic nerves were purposefully eliminated by certain researchers, which had the desired effect. This approach could not be used in clinical settings any more due to side effects such orthostatic hypotension, small intestine and bladder malfunction, and surgical trauma. Recent research has demonstrated that RDN can inhibit the route stimulation of the renal sympathetic nerve, Restriction of renin and angiotensin release, as well as ablation of sympathetic nerve between the renal artery endothelia, there are afferent and efferent fibers [33]. For example, multicenter, more clinical research Following 6 months of RDN therapy, both Symplicity HTN-1 and Symplicity HTN-2 demonstrated that, The blood pressure of patients with resistant hypertension fell considerably with no negative repercussions. However, the control group's blood pressure did not alter. Additionally, RDN was remained safe and efficient after After three years of monitoring in Symplicity HTN-1, according to a recent study by Krum and colleagues [34]. Our study findings supported the efficacy of RDN in treating resistant hypertension, which was also supported by the findings of other studies conducted abroad. The necessity to identify populations in randomized controlled studies, the differing effects of RDN on office and ambulatory BP revealed that renal sympathetic activity may or may not contribute to the development of hypertension. Renal sympathetic nerve activity serves as a link between these two elements as the kidney is a target organ for hypertension as well as a key cause of hypertension. Renin is released as a result of sympathetic nerve activation in the kidneys, promotes the constriction of renal blood vessels, it hastens the reabsorption of water and sodium ions in the distal convoluted tubules, resulting in high blood pressure or possibly resistant hypertension. Renal events occur more frequently when there is resistant hypertension. Kidney injury from hypertension is predicted by decreased GFR and higher urine protein excretion. RDN is a minimally invasive local manipulation that takes just a short time to perform. It's crucial to ascertain, though, if probable tissue injury and modifications to renal sympathetic nerve activity following ablation will have an impact on renal function and renal artery morphology. Animal studies show that the renal blood flow peak, and renal index, the renal blood flow velocity did not change after RDN. Furthermore, RDN had a deleterious acute and long-term effect on renal blood flow. [35]. According to a clinical study done Mahfoud and his colleagues [36], without affecting renal function, RDN may increase the renal artery resistive index while lowering the rate of protein release in urine. The results of international investigations explained this by a rise in renal parenchyma perfusion resulting from a decrease in renal sympathetic nerve activity. Future studies will need to determine if the hemodynamic effects of RDN shown have an influence on clinically significant end points, such as heart failure hospitalization or even death. Beyond treating hypertension, this would provide RDN access to an entirely new field. Future trials may include hemodynamic parameters in addition to BP reduction as a measure of response to RDN if a relationship between the two can be proven.

Conclusion

RDN had no negative effects on renal function or the anatomy of the renal arteries while significantly and consistently lowering blood pressure and the rate at which proteins were excreted in the urine in individuals with resistant hypertension. There is a need for more research with a bigger sample size and longer follow-up.

Conflict of Interest

None

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None

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