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Review Article

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A Promising Approach in the Treatment of Resistant Hypertension: Renal Denervation

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Abstract

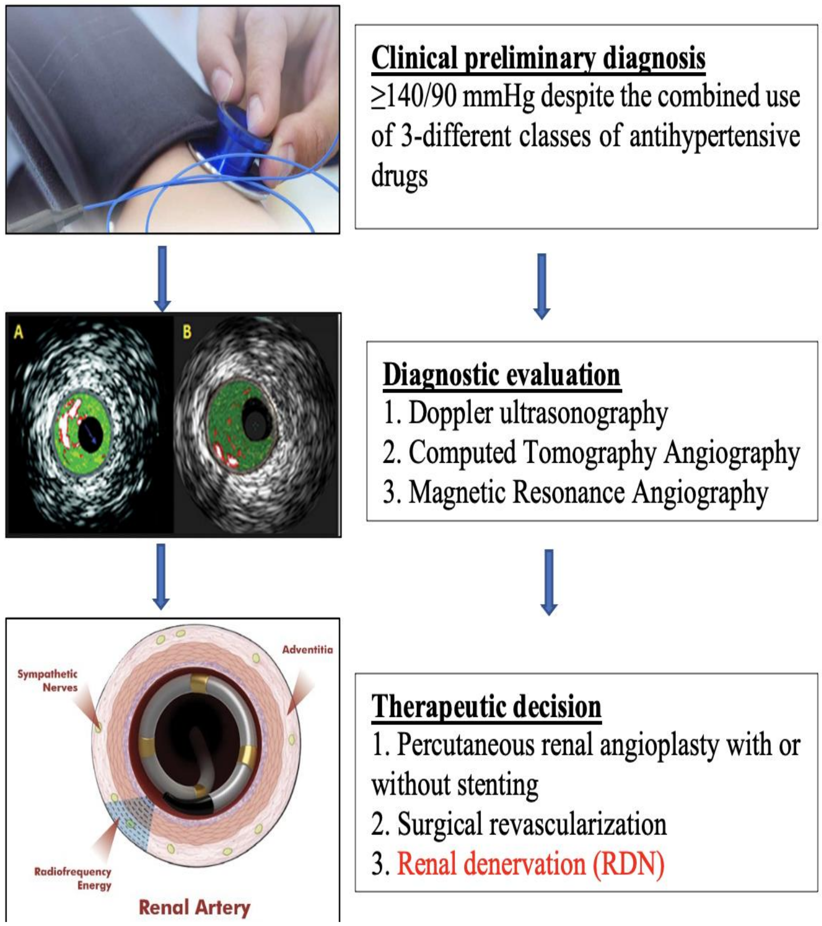
Purpose: *This article highlighted renal denervation (RDN) in the treatment of resistant renal hypertension, with a minor emphasis on other methods.*

Materials and Methods: *Hypertension (HT) remains a major public health problem. The estimated incidence in 2023 among 30-79-year-olds is around 1.28 billion. Kidney disease (KD) and HT are intrinsically linked and severely affect each other. Narrowing of the renal artery, mainly due to the formation of atherosclerotic plaques and secondary to fibromuscular dysplasia, causes an elevation in renal and systemic blood pressure (BP). Despite the combined use of 3 different classes of antihypertensive drugs, the mean blood pressure sometimes remains ≥ 140/90 mm Hg. In these cases, which are called resistant HT, surgical methods such as bypass grafting and endarterectomy or angioplasty with or without a stent are used to achieve renal revascularization. Another promising treatment modality is RDN.*

Results: *Radiofrequency ablation (RFA), ultrasound, or neurotoxin injection are the most commonly used approaches for renal denervation. As INVAMED (Ankara, Turkey), we have developed an RDN device system (Delta® Modulator Renal Denervation for Hypertension).*

Conclusion: *Although there are exceptions in terms of efficacy in reports, RDN systems are rapid and have resulted in safe and sustained reduction in blood pressure.*

Keywords: Resistant Hypertension, Renal Denervation, Renal Artery Stenosis, Renal Hypertension, Delta Modular



Visual Abstract: Approach to the patient with resistant hypertension, from clinical pre-diagnosis to diagnostic evaluation and therapeutic intervention

1. Introduction

Despite the availability of effective pharmacological treatments, hypertension (HT) remains an important public health problem [1,2]. According to the 2023 World Health Organization data, an estimated 1.28 billion adults aged 30-79 years worldwide have hypertension [3]. It is the most frequently diagnosed condition during outpatient visits and is a major risk factor for heart failure, myocardial infarction, stroke, and chronic kidney disease [4]. Most HT cases are not related to another known medical condition, primary HT. Other conditions, secondary HT, are related to another medical condition, usually the kidneys, arteries, heart, or endocrine system [5,6]. Kidney disease (KD) and HT are intrinsically linked. The presence of HT is the leading cause of KD and kidney failure (end-stage kidney disease). On the other hand, as renal function decreases, the incidence and severity of HT increase [7]. KD can also cause a type of high blood pressure (BP) called renal hypertension (RHT) [8].

The main purpose of controlling HT is to reduce BP in order to protect the organs, especially the kidneys [9]. In addition to the lifestyle changes recommended for RHT, the three therapeutic options are medical therapy, percutaneous renal angioplasty without (PRA) or with a stent (PRA-S), and surgical revascularization [10]. On the other hand, renal denervation strategies have recently been gaining more and more attention [2]. This review article aims to highlight denervation of the renal arteries, which will open a new horizon in the treatment of renal hypertension, with minor emphasis on other methods.

1.1. Pathophysiology of Renal Hypertension

The mechanisms of hypertension are complex and multifactorial [11]. One of the causative factors is hypertension of kidney origin. In the pathogenesis of hypertension of renal origin and renal damage, the renin-angiotensin-aldosterone system (RAAS) plays a crucial role [12,13]. Restriction of blood flow to the kidney, at least 75% reduction in the diameter of the renal artery, causes the release of renin in the contralateral kidney due to stimulation of the renal nerve [14].

The kidneys are richly innervated by sympathetic autonomic fibers, and they lack parasympathetic innervations. Of the sympathetic fibers, some end in the renal vasculature, where stimulation causes vasoconstriction, resulting in decreased renal blood and plasma flow and glomerular filtration rate. The others innervate the granular cells of the juxtaglomerular apparatus and cause renin secretion, triggering the renin-angiotensin II-aldosterone cascade, and causing further vasoconstriction and sodium retention by the kidneys. A third group of sympathetic fibers stimulates cells in the convoluted tubule proximal to reabsorb sodium and water (Figure 1) [4].

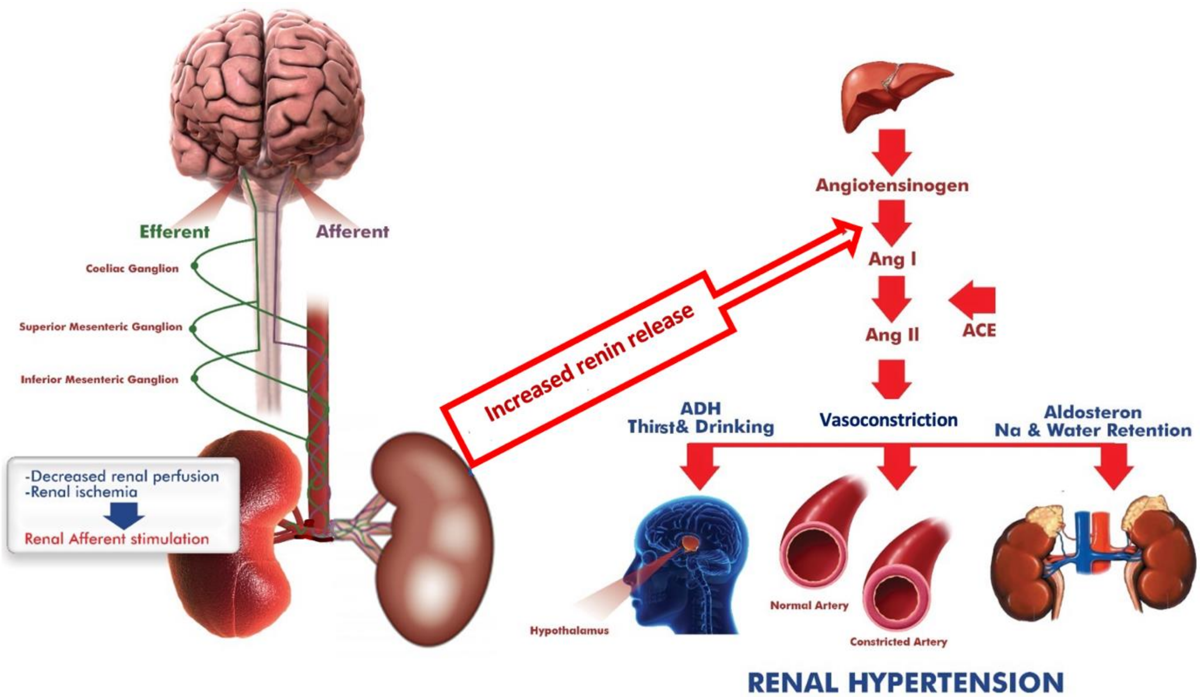


Figure 1: The renin-angiotensin-aldosterone system and blood pressure relation [4,5]. The renal artery stenosis-stimulated renin release, which leads to impaired renal perfusion, triggers a series of events that lead to angiotensin II production. These chemical events process cause vasoconstrictions due to increase in sympathetic tone, sodium and water retention because of increased aldosterone level, and thirst and drinking a lot of water due to increased antidiuretic hormone. These events result in systemic and intrarenal hypertension

RHT caused by occlusion or narrowing of the renal arteries accounts for 3-8% of all HT cases. This renovascular disease causes decreased blood flow to the kidney that results in end-stage kidney disease, also known as chronic kidney disease, and elevated systemic BP [15]. The formation of an atherosclerotic plaques is the predominant lesion detected in RHT patients. It often affects the ostium and proximal one third of the main branch of the renal artery. Although not common, the second most common cause is fibromuscular dysplasia. It is a non-inflammatory, non-atherosclerotic vascular disease that preferably affects small to medium sized arteries [14]. In some cases, while systemic BP remains normal, hypertension can occur in the renal vessels and complicates the diagnosis of RHT [16].

1.2. Diagnosis

Duplex Doppler ultrasound is an excellent initial imaging modality that provides both functional evaluation of the renal arteries and some anatomical information. CT and magnetic resonance angiography are used in the evaluation of anatomical characteristics [17,18]. In addition, some screening tools, such as renin activity or blood flow to each kidney, are used to evaluate physiological parameters [10,14].

1.3. Assessments of Therapeutic Options

Controlled BP is crucial for protecting organs, especially the kidneys, from HT [2]. Dietary and lifestyle changes and a two-drug regimen can be expected to reduce BP in the vast majority of patients [18]. When angiotensin converting enzyme (ACE) inhibitors are part of treatment, patients with RHT have a higher survival rate than those without ACE inhibitors [19].

However, in some patients with HT encountered in routine clinical care, BP cannot be controlled despite combined therapy. Resistant HT is mentioned when the mean blood pressure remains ≥ 140/90 mm Hg despite the combined use of three different classes of antihypertensive drugs [2,8]. In cases such as this and progressive kidney failure, an interventional procedure may be recommended to improve blood flow to the kidney in certain people [19]. In these cases, angioplasty (PRA or PRA-S) or surgical methods (bypass grafting or endarterectomy) are used to provide revascularization [20].

It is difficult to reveal the superiority between interventional and medical treatment in RHT and to determine the treatment of choice for all cases of RHT due to factors such as clinical characteristics of the patients and differences in treatment indications [19-21]. Some studies comparing different modalities such as EMMA (Essai Multicentrique Medicaments vs Angioplasty), DRASTIC (the Dutch Renal Artery Stenosis Intervention Cooperative), ASTRAL (the Angioplasty and Stenting for Renal Atherosclerotic Lesions), CORAL (the Cardiovascular Outcome for Renal Artery Lesions), and STAR (the Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function) with medical treatments failed to demonstrate the superiority of renal artery revascularization over pharmaceutical treatment in controlling blood pressure and preserving kidney function [22-26].

In light of current study data, it is not necessary to perform a surgical or other interventional revascularization approach, including angioplasty or newer renal denervation, for HT that can be controlled with lifestyle changes and medical treatment options recommended by the guidelines. Furthermore, currently, revascularization is only recommended for conditions such as progressive worsening of renal function and rapid increase in antihypertensive need in patients with previously well-controlled hypertension [10]. More properly designed studies are needed to determine which patient populations are likely to benefit from renal revascularization. In addition to medical treatment, PRA or PRA-S was considered the most effective treatment in renovascular diseases because it would lead to the restoration of blood flow [21,27]. In practical terms, angioplasty can also limit overall hospital stays, avoid general anesthesia, and minimize tissue trauma.

The PRA or PRA-S remains the treatment of choice for renal artery fibromuscular dysplasia [21,28]. With good long-term medical outcomes, PRA and PRA-S are also the standard of care for renal artery stenosis in kidney transplant recipients [29]. In a study comparing PRA and PRA-S, the primary success rate of PRA-S was found to be higher (57% vs 88%) [30]. In some studies, comparing angioplasty and surgical bypass, renal functional recovery and renal artery patency were dramatically better in the surgical group after four years of follow-up [31,32]. Revascularization may not result in restoration of kidney function due to the damage that occurs during the period of reduced blood flow [33]. However, Ritchie et al. reported that percutaneous revascularization significantly reduces the risk of death and cardiovascular events in high-risk subgroups such as sudden pulmonary edema, rapidly declining kidney function, or refractory hypertension undergoing revascularization [34].

1.4. Treatment of RHT

HT is the leading cause of heart attack, stroke, and death [2,18,28]. The main goal of the various options for the treatment of renovascular hypertension is to reduce BP [35]. However, uncontrolled high BP continues in a large proportion of patients despite pharmacological treatment and nonpharmacological approaches such as lifestyle changes and diet. If these approaches are not sufficient to control BP, therapy may be extended to other interventions, such as revascularization methods and renal denervation [36].

1.5. Pharmacological Treatment

Even when primarily associated with renal artery stenosis, high BP can commonly be successfully treated with medication [9,10]. Of the medications, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers generally work better to control blood pressure [12]. In addition to these, diuretics, beta-blockers, alpha-beta blockers, and calcium channel blockers are frequently used drugs [8]. If the underlying cause is atherosclerosis, a combination therapy that includes antihypertensive, antiplatelet, and lipid lowering agents may be required [27].

1.6. Treatments for Revascularization

In some hypertensive patients, revascularization procedures may be recommended to restore blood flow to the kidney. PRA or PRA-S is performed to open a narrowed or blocked artery to allow blood flow to the kidney (Figure 2).

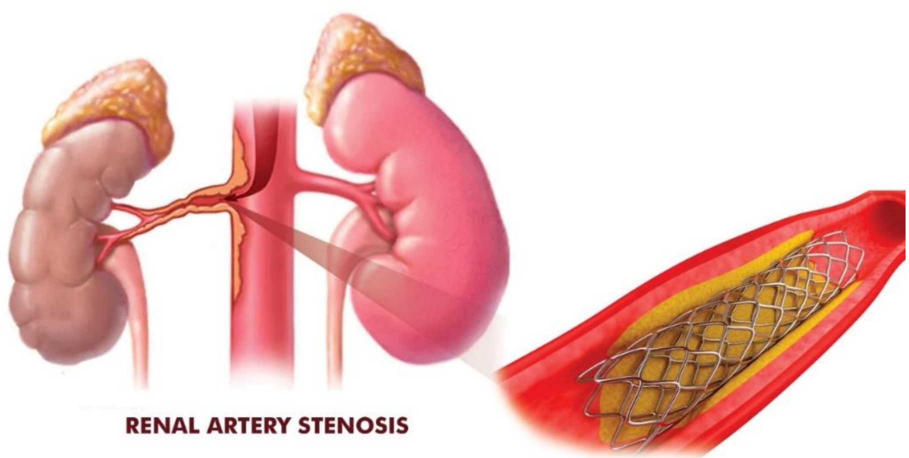


Figure 2: Schematic Illustration of the stenting in patients with overt renal artery stenosis [3]

If these less invasive methods fail, surgical revascularization may be necessary to bypass the narrowed or blocked site of the artery [21,28]. Sometimes this is done by connecting the renal artery to the artery of an extrarenal organ such as the liver and spleen [32]. Rarely can nephrectomy be recommended as a treatment for people with unilateral renovascular diseases.

1.7. Renal Denervation

Another potential treatment modality is renal denervation [21]. In experimental animal models, surgical denervation of renal nerves prevented the onset or reduced the severity of hypertension [37]. Three approaches are more commonly used for renal denervation. These approaches use radiofrequency ablation (RFA), ultrasound, or a neurotoxin injected through the wall of the renal artery into the perivascular space. The most widely used RFA uses a catheter to position heat generating electrodes using medium frequency alternating current [38].

Device (Company)	Ablation modality	Electrode	Balloon	Cooling	Delivery	Guidewire size (Fr)	Ablation time (s/ artery)	Clinical trial program(s)
Simplicity Flex (Medtronic Inc)	Monopolar RF	Single	No	Blood	Deflectable tip	6	540	Simplicity HTN
PARADISE (ReCor Medical Inc)	USG	Single	Yes	Close irrigation	OTW	6	50-150	REALISE
Vessix (Boston Scientific Corp)	Bipolar RF	Multiple	Yes	None	OTW	8	30	REDUCE-HTN
EnligHTN (St Jude Medical)	Monopolar RF	Multiple	No	Blood	Deflectable tip	8	90	EnligHTN
EnligHTNment								
OneShot (Covidien-Maya)	Monopolar RF	Single	Yes	Blood	OTW	6, 7	240	RAPID
Iberis (Terumo)	Monopolar RF	Single	No	Blood	Deflectable tip	4	540	ALLEGRO-HTN
Delta (Invamed)	Monopolar RF	Single	No	Blood	OTW	6	240	INVA-RDN**
Abbreviations: RF: Radiofrequency; USG: Ultrasound. *Ongoing. **Adapted from References [4,36,39,40].								

Table 1: Some Selected Renal Denervation Systems

There are several denervation systems used for renal denervation (Table 1). As INVAMED (Ankara, Turkey), we have also developed a newer renal denervation device system (Delta® Modulator Renal Denervation for Hypertension) for the treatment of resistant hypertension. The system consists of a catheter connected to a generator (Figure 3).

Figure 3: Schematic illustration of Delta® Modulator Renal Denervation.

Using fluoroscopic guidance, entering the kidneys from the inguinal artery through a 0.014" guiding catheter, the denervation catheter is placed at the ostium of the renal artery. During renal denervation, the catheter delivers controlled radiofrequency (RF) energy to weaken the renal sympathetic nerve that causes RHT. This energy generates heat that creates a thermal injury to the wall of the renal artery. The primary target is the sympathetic nerves located in the adventitia of the artery. With the cooling effect of blood flow during the procedure, intima damage is minimized. It provides precisely controlled RF energy by creating 360-degree ablation according to a programmed algorithm (Figure 4). The catheter is also designed to reach the main arteries, branches, and accessory arteries in a wide variety of diameters (3-8 mm) to treat a wide variety of patients.

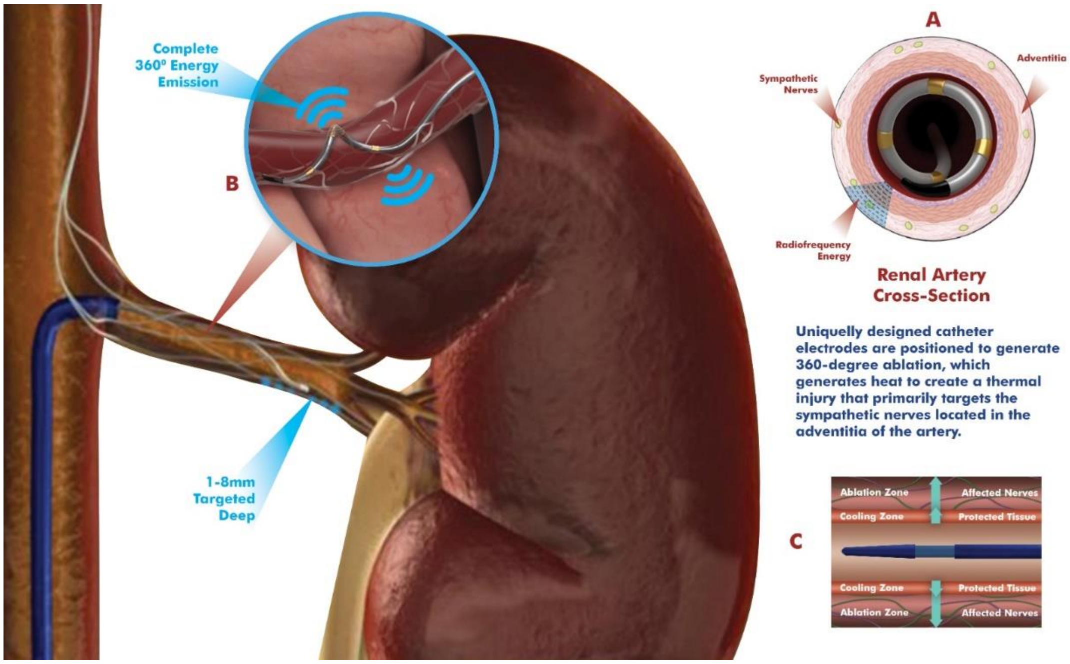
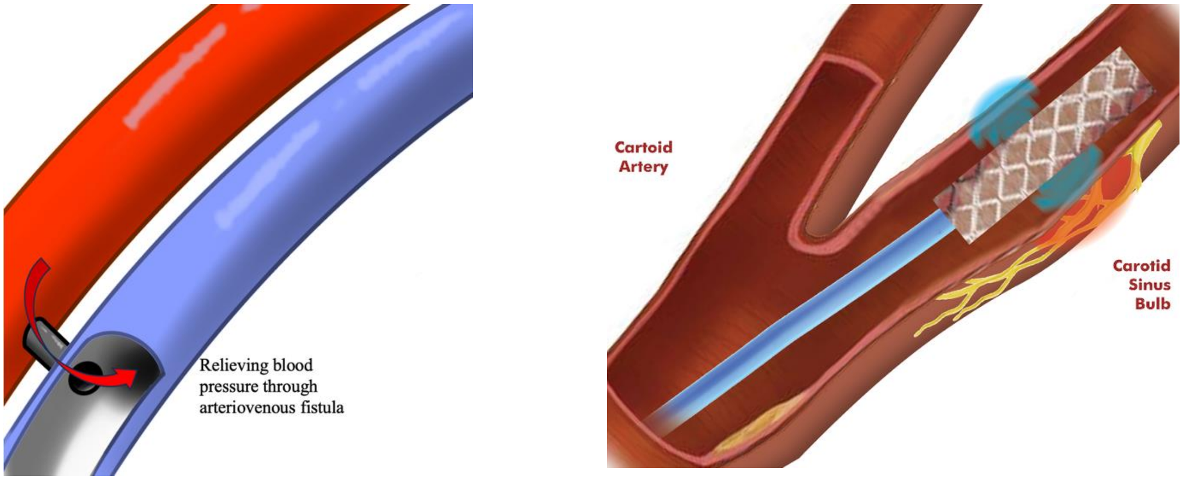


Figure 4: Application of Delta® Modulator Renal Denervation for Hypertension procedure.
A. 1. Denervation of the nerve with radiofrequency energy following catheter positioning; 2. Clinical effects of denervation of the nerve. B. The 360-degree ablation of the arterial nerve fibers; C. Damage to the adventitia where the nerves are located. Adapted from References [5,11,36,41].

1.8. Promising Experimental Approaches

Based on this principle, arteriovenous fistulas created to reduce vascular resistance, it has been revealed that the placement of a shunt between the iliac artery and the iliac vein (arteriovenous coupling) relieves arterial pressure hemodynamically (Figure 5) [42].



A. Arteriovenous Fistula B. Carotid Artery

Figure 5: A. Creating a central arteriovenous anastomosis between the iliac artery and vein
B. Placing carotid sinus baroreceptors simulator [41].

Electrical stimulation of the carotid sinus baroreceptors is another approach to reducing sympathetic tone to help control blood pressure [43]. Initial studies have shown that a significant reduction in blood pressure is maintained over a 6-year follow-up period [44].

2. Discussion

The efficacy and safety of a new methodology to be used in a treatment are the basic evaluation approach. Trials have yet to prove the superiority of PRA or PRA-S, which are the treatment of choice for renal artery fibromuscular dysplasia, in the treatment of atherosclerotic RHT [38]. Considering current studies such as those selected in Table 1, a newer minimally invasive strategy, RDN, appears to be successful in achieving a significant and sustained reduction in BP in the majority of cases of RHT.

As stated in the meta-analysis study by Sardar et al., not only the efficacy, but also the safety profile has generally remained at an acceptable level to date, including follow-up for some up to 36 months [45]. In addition to being effective and safe, the procedure is also quick, with an ablation time of 4 minutes and a procedure time of approximately 50 minutes from first arterial access to closure [46]. The patient is allowed to eat and drink 2 hours after the procedure [47].

In SYMPLICITY HTN studies, phase I and II clinical trials have revealed that the RDN procedure is effective and safe in the treatment of resistant RHT [48,49]. However, the largest study to date, SYMPLICITY HTN-3 (phase III), did not demonstrate a significant effect on BP lowering with renal denervation compared to medical therapy compared to sham control. Fortunately, the result of SYMPLICITY HTN-3, as in other studies, showed that the procedure was safe.

Study	Method	Result	Reference
SPYRAL HTN- OFF MED Pivotal	Radiofrequency	-RDN: ↓5 mm Hg -Sham: ↓1 mm Hg	[50]
SPYRAL HTN-ON MED Pilot	Radiofrequency	-RDN: ↓9 mm Hg -Sham: ↓2 mm Hg	[51]
RADIANCE-HTN SOLO	Ultrasound	-RDN: ↓7 mm Hg -Sham: ↓2 mm Hg	[52]
RADIANCE-HTN TRIO	Ultrasound	-RDN: ↓8 mm Hg -Sham: ↓3 mm Hg	[53]

Table 2: Some Selected Studies Investigating the Efficacy of RDN on Systolic BP

Table 2 shows that RDN, >135 mm Hg for 24 hours at baseline, produces a mean reduction in ambulatory systolic BP of 5-7 mm Hg in the absence of antihypertensive medication (RADIANCE-HTN SOLO, SPYRAL HTN-OFF MED). In the presence of antihypertensive medication (RADIANCE-HTN TRIO, SPYRAL HTN-ON MED Pilot), RDN provides an average reduction of 8-9 mm Hg of ambulatory systolic BP.

Despite the disappointing results of SYMPLICITY HTN-3 in terms of efficacy, the RDN strategy is still an alive and active area of research. Data from these studies provide excellent evidence of safety, with the absence of serious adverse events related to devices or procedures that affect renal arteries or renal function [11,49,54]. The lesson from SEMPLICITY HTN-3 has become to address the utility of the redesigned and validated version of this system with strongly designed sham-controlled, blinded, randomized clinical trials, rather than an approach that will jeopardize its future use [36,47]. For example, the SYMPLICITY-HTN 3 study used first-generation single-ended electrode radiofrequency ablation catheter technology, which requires significant operator manipulation with point-to-point ablation [54]. In fact, a SYMPLICITY HTN-3 subgroup analysis showed that a stronger response was associated with more lesions and a four-quadrant positioning. The multi-electrode systems such as Delta® (Invamed) and OneShotTM (Covidien) can be placed once and deliver up to four lesions prior to movement [47]. Besides BP reductions, several analyzes have also supported the association between RDN and a reduced need for antihypertensive drugs [2,46,55,56].

2.1. Limitation of the Study

This study has some limitations. Although there are several devices used for renal denervation in resistant hypertension, the well-designed studies are less. Some of them have shown controversial results that confuse the feasibility of the strategy. There are differences between the technology of the devices, the groups of patients, and the experience of the operating personnel.

3. Conclusion

If drug-based therapy is not sufficient to control blood pressure, therapy may be extended to include a procedure known as renal denervation. With exceptions, the renal denervation system has resulted in a safe, rapid, and sustained reduction in blood pressure. It significantly reduces or eliminates the need for medication. The future of RDN must evolve around the improvement of its technology and further well-designed studies to evaluate its long-term efficacy and safety. However, interventional procedures are not always successful in terms of clinical outcome in all patients and are not complicated as a procedure. The assumption that recovery of renal artery patency always preserves the kidney is not correct. Physicians making clinical decisions and performing interventions should know that restoring renal blood flow is clinically effective for certain subsets of patients, but not all.

Home Message

• Hypertension is a major public health problem with approximately 1.28 billion adults aged 30-79 years worldwide.
• Kidney disease and hypertension are intrinsically linked, the presence of each triggering the other.
• In some cases, hypertension remains 140 / 90 mm Hg despite the combined use of 3 different classes of antihypertensive drugs. This is defined as resistant hypertension.
• The narrowed renal artery is the leading cause of resistant hypertension. Therefore, revascularization procedures may be recommended to restore blood flow to the kidney.
• For resistant hypertension, another potential treatment modality is renal denervation.
• The renal denervation system resulted in a safe, rapid, and sustained reduction in blood pressure. It should be considered as an alternative option for the treatment of resistant hypertension.

Statement of Ethics

This manuscript, which is a review article, does not include studies with human or animal participants.

Conflicts of Interest Statement

Rasit Dinc is the president of INVAMED (Ankara, Turkey).

Authors' Contributions

Rasit Dinc designed, conceptualized, searched for data, wrote and finalized.

Data Availability Statement

The authors confirm that data supporting the findings of this study are available in the article.

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