Interventional Therapy in Refractory Hypertension: An Update

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Abstract
Hypertension represents a major public health issue, affecting about 26% of the world's population. It is the most common cardiovascular risk factor worldwide, with a prevalence that continues to grow. Among this hypertensive population, a critical subgroup is that of patients with resistant hypertension. For subjects with truly resistant hypertension, the next step after nonpharmacological interventions and drug therapy is represented by interventional treatment. However, implementing an interventional approach in resistant hypertension represents a real challenge. The decision needs to be undertaken in multidisciplinary teams, which must include a specialist in hypertension, and it is not routinely recommended. The main device-based therapies for hypertension are represented by carotid baroreceptor stimulation, renal denervation, and the creation of an arteriovenous fistula. Until 2018, there was an important controversy on the beneficial effects of renal sympathetic denervation. One cannot ignore, however, the positive results of interventional therapy for treatment-resistant hypertension obtained in different trials conducted on a large number of patients. A significant reduction in blood pressure values and an improvement in cardiovascular outcomes could be attained with interventional therapy through a rigorous selection of patients.

Keywords
hypertension, resistant, interventional, renal sympathetic denervation

Rezumat
Hipertensiunea arterială reprezintă o problemă majoră de sănătate publică, afectând aproximativ 26% din populația lumii. Este cel mai frecvent factor de risc cardiovascular la nivel mondial, cu o prevalență în continuă expansiune. Un subgrup critic al populației hipertensive este cel al pacienților cu hipertensiune arterială rezistentă. Pentru subiecții cu hipertensiune arterială rezistentă, următoarea resursă terapeutică (după optimizarea terapiei non-farmacologice și suplimentarea medicației antihipertensive) este reprezentată de terapia intervențională. Cu toate acestea, implementarea unei astfel de decizii terapeutice la cazurile cu hipertensiunea arterială rezistentă reprezintă o adevărată provocare. Decizia trebuie luată în echipe multidisciplinare, care trebuie să includă obligatoriu și un specialist în hipertensiune arterială, nefiind recomandată de rutină. Principalele metode de tratament intervențional în hipertensiunea arterială sunt reprezentate de procedura de denervare simpatică renală prin ablația pe cateter cu radiofrecvență a ramurilor simpatice de la nivelul arterelor renale, electrostimularea baroreceptorilor de la nivelul sinusului carotidian și crearea de anastomoze arterio-venoase. Până în anul 2018, datele privind beneficiile denervării simpatice renale, precum și ale celorlalte terapii intervenționale, erau contradictorii. Cu toate acestea, nu putem ignora rezultatele pozitive ale terapiei intervenționale în hipertensiunea arterială rezistentă, obţinute în diferite centre, pe o serie mare de pacienţi. Concluzionând, printr-o selecție riguroasă a pacienților înainte de adresarea acestora pentru terapia intervențională a hipertensiunii arteriale, s-ar putea obține o reducere semnificativă a valorilor tensionale și o îmbunătățire a prognosticului cardiovascular.

Cuvinte cheie
hipertensiune arterială, rezistentă, intervențional, denervare simpatică renală

Introduction

Hypertension represents a major public health issue, affecting about 26% of the world's population. It is the most common cardiovascular risk factor worldwide, with a prevalence that continues to expand [1]. It is more prevalent in low- and middle-income countries than in high-income countries, with population-level interventions (e.g., increasing the availability and accessibility of fresh fruits and vegetables and lowering the sodium content of processed, packaged, and prepared foods) being of extreme importance [2].

Hypertension is a disease characterized by office systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or both. It affects about 1.13 billion subjects worldwide [3,4]. Among this hypertensive population, a critical subgroup is that of patients with resistant hypertension. Resistant hypertension is defined as blood pressure values above target despite the control of risk factors and good compliance with treatment, with at least three antihypertensive drugs, in the maximum tolerated doses, one of which is a diuretic [5]. Regarding the prevalence of resistant hypertension, based on the National Health and Nutrition Examination Survey, between 2007 and 2014, 15.95% of the U.S. adults with treated hypertension had treatment-resistant forms when the 2017 high blood pressure guideline criteria were applied [6].

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In subjects who appear to have resistant hypertension, it is essential to assess the patient's compliance to treatment, which describes an inverse proportional relationship with the number of daily recommended drugs. Pseudo-resistance also refers to the physician's inertia to increase the dose of antihypertensives or to add a new class. Furthermore, screening for the most common causes of secondary hypertension should be considered [7].

Thereafter, two distinct entities have to be distinguished in the truly resistant hypertensive population, namely controlled resistant hypertension and refractory hypertension. The controlled resistant hypertension group includes the patients who meet the criteria for resistant hypertension but achieve blood pressure control targets with at least four antihypertensive drugs at maximum tolerated doses. Usually, to optimize blood pressure control in these patients, it is recommended to add a low dose of mineralocorticoid receptor antagonist (spironolactone 25–50 mg q.d. or eplerenone 50 mg q.d.). This recommendation is based on the observation that secondary hyperaldosteronism is common among hypertensive patients [3]. On the contrary, the refractory hypertension group includes the subjects who meet the criteria for resistant hypertension and persist in having uncontrolled blood pressure despite receiving maximum tolerated doses of four antihypertensive classes [8,9]. Thus, for the second category of patients, with refractory hypertension, the next step after nonpharmacological interventions (e.g., dietary sodium restriction, weight reduction, regular physical activity, smoking cessation) and drug therapy is represented by interventional therapy [10].

However, implementing an interventional approach in resistant hypertension represents a real challenge. The decision needs to be undertaken in multidisciplinary teams, which must include a specialist in hypertension, and it is not routinely recommended. The main device-based therapies for hypertension are represented by carotid baroreceptor stimulation, renal denervation, and the creation of an arteriovenous fistula [11].

Renal Sympathetic Denervation

The idea of renal denervation emerged from the remark that sympathetic hyperactivation plays a vital role in the etiopathogenesis of hypertension. Nerve signaling between the kidneys and the central sympathetic nervous system is bidirectional and occurs through the renal afferent and efferent nerves. Renal sympathetic denervation reduces both renal and central sympathetic activity, and thus blood pressure, in patients with resistant hypertension. Clinical and experimental data suggest that the modulation of sympathetic activity may also reduce the incidence of heart rhythm disorders, such as atrial fibrillation and ventricular arrhythmias. Reduction of left ventricular hypertrophy and improvement in diastolic function have also been observed after renal denervation, indicating that this technique could help treat heart failure with preserved ejection fraction.

Three different endovascular renal denervation techniques have been used in clinical trials: the delivery of radiofrequency or ultrasound energy and the injection of neurotoxic agents such as alcohol. Regarding the radiofrequency renal denervation technique, the ablation catheter is commonly placed in the distal segment of the renal arteries under fluoroscopic guidance, and the radiofrequency energy is delivered. Each radiofrequency application is succeeded by a retraction of a minimum 5 mm and a rotation of 90 degrees of the catheter tip. Thus, the radiofrequency energy is applied in approximately eight circumferentially ablation points to cover the renal artery's entire circumference [12].

Another endovascular renal denervation technique uses the Peregrine catheter, which releases small doses of absolute alcohol, a powerful neurolytic agent, in the perivascular space of the renal artery, achieving in this way the perivascular ablation of the afferent and efferent sympathetic nerves. Preclinical studies have shown that the Peregrine System infusion catheter is safe and effective in delivering absolute alcohol at all assessed doses (0.15–0.60 mL/artery) [13].

The Paradise Renal Denervation System is a minimally invasive, catheter-based procedure that uses ultrasound energy to ablate renal nerves. Two to four circumferential ultrasound emissions of seven seconds duration are delivered along both renal arteries, while a cooling balloon with circulating water protects the renal artery wall from heat.

Recently, other new, noninvasive methods of renal denervation have been imagined, namely stereotactic radiotherapy, at doses of 25, 35, and 45 Gy. Of note, this method is currently in the preclinical evaluation stage, proving its usefulness in porcine models [14].

Renal sympathetic denervation can be performed only after the firm confirmation of the diagnosis of resistant hypertension and, therefore, the exclusion of secondary causes of hypertension. The evidence that contributed to the introduction of this therapy in the guidelines for the management of arterial hypertension (as interventional therapy in resistant hypertension) originated in two large trials that aimed to evaluate the efficiency of the procedure (SYMPLICITY HTN-1 and SYMPLICITY HTN-2) [15].

SYMPLICITY HTN-1 was the first trial to prove that renal sympathetic denervation effectively achieves blood pressure control. A total of 153 patients with systolic blood pressure >160 mm Hg, despite treatment with at least three antihypertensive drugs at the maximum tolerated doses, one of which was a diuretic, were included in this study. Excluded from the trial were patients with an increased risk of bleeding (e.g., thrombocytopenia, bleeding diathesis, anemia), chronic kidney disease (an eGFR < 45 mL/min /1.73m^2), Type 1 diabetes, previous renovascular interventions, abnormalities or anatomical variations of the renal arteries, or pregnancy. In these subjects with resistant hypertension, renal sympathetic transcatheter denervation substantially reduced blood pressure, with no recorded significant adverse events. Importantly, this effect was consistent for up to two years [16].

In SYMPLICITY HTN-2, patients with resistant hypertension and no exclusion criteria were randomized to either renal sympathetic denervation or pharmacological treatment for the first six months. The primary outcome was the reduction in blood pressure at six months. At six months, blood pressure decreased by 32/12 mm Hg in the immediate intervention group, compared to the initial values

of 178/96 mm Hg, whereas there was no significant reduction in blood pressure in the control group. Subsequently, the patients in the control group also benefited from renal sympathetic denervation and were evaluated for another 6 to 30 months. After renal sympathetic denervation, these patients had a similar decrease in blood pressure as patients in the immediate intervention group [17].

The results of these two trials, SYMPLICITY HTN-1 and SYMPLICITY HTN-2, pointed toward powerful benefits of renal sympathetic denervation. Thereupon, out of the need of confirming these outcomes on a higher number of patients, followed for a more extended period, by comparison to a control group, SYMPLICITY HTN-3 was born. This trial compared the evolution of patients undergoing renal denervation with those in whom a fictive procedure was performed. A total of 535 subjects were randomly assigned to one of the previously mentioned procedures. The study results were negative and did not reach statistical significance, meaning that no significant differences in the systolic blood pressure value at six months were recorded between the renal-artery denervation group and the sham control group. For this reason, the SYMPLICITY HTN-4 trial (ongoing at the time that the SYMPLICITY HTN-3 results were released) was prematurely stopped [18].

Other trials that provided important information on renal sympathetic denervation were the DENERHTN and PRAGUE 15 trials. The peculiarity of the DENERHTN trial lies within the fact that 106 patients were randomized (1:1) to receive either renal sympathetic denervation plus an optimal antihypertensive treatment (renal denervation group) or the same singular antihypertensive treatment (control group). A total of 101 subjects were included in the final analysis (48 in the renal denervation group and 53 in the control group). At six months, in patients with resistant hypertension, renal denervation plus optimal medical therapy decreased the ambulatory blood pressure values more than the antihypertensive treatment alone [19].

On the contrary, the PRAGUE-15 trial documented similar effects between renal sympathetic denervation and optimized pharmacotherapy (mainly by the addition of spironolactone) in terms of the effectiveness in lowering blood pressure. However, optimized antihypertensive treatment was associated with a greater incidence of adverse events and higher rates of medication discontinuation [20].

Another beneficial effect of catheter-based renal sympathetic denervation therapy that is worth mentioning is represented by the improvement of glucose metabolism, as emphasized by a pilot study that enrolled 50 patients with therapy-resistant hypertension. In this study, 37 patients were assigned to bilateral renal denervation and 13 subjects to the control group. Systolic and diastolic blood pressures, fasting blood glucose, insulin, C-peptide, hemoglobin A1c, HOMA index (homeostasis model assessment-insulin resistance), and glucose levels during the oral glucose tolerance test were evaluated before, one month, and three months after the treatment. At one and three months, blood pressure values were significantly reduced ($p < 0.001$) in the treatment group without any modifications in concomitant antihypertensive medication. In addition, at three months after the intervention, fasting blood glucose, insulin levels, and C-peptide levels were significantly reduced, as were the HOMA index and the blood glucose levels recorded during the oral glucose tolerance test. These significant changes in blood pressure values and glucose metabolic markers were not recorded in the control group [21].

Thus, we can conclude that until 2018, there was an important controversy on the beneficial effects of renal sympathetic denervation. However, one cannot ignore the positive results obtained in different trials conducted on a large number of patients, to which are added the results of other subsequent studies, the results of which were published later.

Subgroup analyses of the Global Simplicity Registry (Global Prospective Registry for Sympathetic Renal Denervation in Selected Indications Through 3 Years) totaling 2,652 patients with resistant hypertension illustrated that the decrease in blood pressure via sympathetic renal denervation is similar and consistent among patients with high-risk comorbidities, including patients with diabetes mellitus, atrial fibrillation, and isolated systolic hypertension. Blood pressure reduction was sustained for up to three years after the intervention, demonstrating the durability of renal sympathetic denervation in different subgroups, especially in patients with high atherosclerotic cardiovascular disease (ASCVD) risk scores [22].

The SPYRAL HTN-OFF MED Pivotal was the first trial to assess the efficacy of renal sympathetic denervation in the absence of hypertensive medication. Hypertensive patients with systolic blood pressure values greater than 150 mm Hg and lower than 180 mm Hg were randomly assigned (1:1) to either a renal denervation procedure or a simulated procedure, with 331 patients being included in this analysis. Blood pressure values were reassessed at three months. This study has revealed the superiority of renal denervation over a sham procedure in safely lowering blood pressure values in patients with no antihypertensive medication [23].

The secondary analyses of SPYRAL HTN-OFF MED Pivotal revealed that plasma renin activity and serum aldosterone concentrations were significantly reduced at three months in patients randomized to renal sympathetic denervation when compared to baseline levels as well as to the control group. At the same time, higher initial levels of plasma renin activity were associated with a significantly greater reduction in systolic blood pressure values [24]. Another secondary analysis of SPYRAL HTN-OFF MED Pivotal disclosed that the decrease in mean office, 24-hour, daytime, and nighttime systolic blood pressure at three months following the procedure was more significant in the subgroup of subjects with renal sympathetic denervation and baseline heart rate > 70 beats per minute. This finding supports the linkage between baseline heart rate and reduction in blood pressure values after renal sympathetic denervation [25].

As previously mentioned, renal sympathetic denervation has also been described as an effective neuromodulatory treatment for recurrent malignant ventricular arrhythmias and arrhythmic storms, although randomized evidence is lacking. The use of renal sympathetic denervation as an auxiliary therapy for refractory ventricular arrhythmias is limited to case reports and small studies. A recent systematic review sought to examine the safety and efficacy of renal sympathetic denervation for the therapeutic management

of refractory ventricular arrhythmias. It has included seven studies and 121 patients, and it has demonstrated a significant beneficial effect of renal sympathetic denervation in decreasing the number of ventricular arrhythmias and thus reducing the need for shock therapy and antitachycardia pacing in patients with implantable cardioverter-defibrillators [26].

At the same time, experimental data displayed that renal sympathetic denervation targets important etiopathogenic links of heart failure with reduced ejection fraction. Reducing renal sympathetic activity and inhibiting the renin-angiotensin system decreases the amount of left ventricular fibrosis and improves left ventricular and coronary artery function. These cardioprotective mechanisms act synergistically. Ultimately, renal sympathetic denervation stopped the progression of heart failure with reduced ejection fraction after myocardial infarction in an experimental swine model, where a significant increase in circulating levels of B-type natriuretic peptides has also been noticed [27].

Regarding the effects of renal denervation on blood pressure values and long-term results, it has been appreciated that it takes a median period of two months for subjects who undergo this procedure to have a greater decrease in office and ambulatory blood pressure values than those who do not. Importantly, the efficacy of this procedure appears to be sustained for up to three years [28].

In addition, identifying the candidates for renal denervation therapy is probably the biggest challenge. It has been hypothesized that high baseline plasma renin activity, increased renal noradrenaline spilover rate, high baseline plasma catecholamines, baroreflex dysfunction (the loss of the baroreflex-mediated sympathetic inhibition), an increase in blood pressure during radiofrequency energy delivery, and the extent of positive change could potentially predict the procedural success of renal denervation therapy [29].

Table 1 summarizes the main indications and contraindications of renal denervation, and Table 2 illustrates the design and the results of the first trials that evaluated the safety and efficacy of this technique.

Table 1 - Main indications and contraindications for renal denervation

Indications	Contraindications
Refractory hypertension (after the exclusion of secondary forms of hypertension, pseudo-resistance, and “white coat” hypertension	Renal arteries abnormalities (e.g., aneurysms, stenosis, diameter < 4 mm) Past interventions on the renal arteries (e.g., angioplasty, stent implantation) Bleeding diathesis Chronic kidney disease (eGFR < 45 mL/min/1.73 m^2) Type 1 diabetes Pregnancy Age < 18 years

Carotid Baroreceptor Stimulation

The idea of carotid baroreceptor stimulation or baroreflex amplification therapy is derived from the observation that the electrical stimulation of the carotid sinus increases its afferent activity from the carotid baroreceptors to the brain, therefore leading to a long-term reduction in central sympathetic activity and an increase in cardiac parasympathetic activity. The first-generation system developed for carotid baroreceptor stimulation compelled for bilateral electrical stimulation of the carotid sinus, presenting several procedural and long-term safety shortcomings. The second-generation system was designed with a better safety profile, and it consists of unilateral carotid sinus stimulation [30]. There is no randomized clinical trial with the second-generation device [3].

In the Rheos Pivotal Trial, which has used a first-generation bilateral device, carotid baroreceptor stimulation or baroreflex activation therapy (BAT) has proven its efficacy in reducing blood pressure in patients with resistant hypertension. The sample of 265 patients were 2:1 randomized to either immediate BAT (181 subjects) or delayed BAT after six months (84 subjects). A mean decrease in systolic blood pressure of up to 35 mm Hg at the 12-month visit was recorded in all individuals enrolled in the trial. However, the procedure is complex in the sense that BAT involves the surgical implantation of a device that obliges the recipient to periodic checks and maintenance (battery replacement). Additionally, the cost is higher than in the case of renal denervation, and the evidence to support the safety and efficacy of this procedure is still being evaluated [31].

Other advantageous effects of carotid baroreceptors stimulation are represented by the reduction of heart rate and adverse cardiac remodeling, the improvement of kidney function, with an increase in diuresis, and decreased renin release [32].

Creation of an Arteriovenous Fistula

Central iliac arteriovenous anastomosis consists of the formation of a fixed-caliber communication of low resistance between the arterial and the venous circulation through the use of a stent-like nitinol device (ROX arteriovenous coupler) [3]. This therapeutic approach addresses mainly the mechanical features of the cardiovascular system, as opposed to primarily targeting the sympathetic nervous system with either renal sympathetic denervation or carotid baroreceptor stimulation. It will cause an immediate, significant reduction in blood pressure values and in the systemic vascular resistance because of an instant decrease in the effective arterial volume [33].

In the ROX CONTROL HTN trial, 83 patients with resistant hypertension were randomized in a 1:1 ratio to receive either standard antihypertensive treatment or iliac arteriovenous anastomosis plus standard antihypertensive therapy. At six months, mean office systolic blood pressure values and mean systolic 24-hour ambulatory blood pressure values were significantly lower in the group with iliac arteriovenous anastomosis. In contrast, there was no statistically significant change in the control group. The same therapeutic effect was recorded in the subgroup of patients who had a previous history of renal sympathetic denervation, suggesting that creating an arteriovenous fistula could be beneficial in cases where sympathetic modulation has failed. Nevertheless, at six months

Table 2 - Major clinical trials on renal denervation

Trial	SYMPLICITY HTN-1	SYMPLICITY HTN-2	SYMPLICITY HTN-3	DENERHTN	SPYRAL HTN-OFF MED
Design	Open-label, proof of concept	Prospective, randomized trial	Prospective, single-blind, randomized, sham-controlled trial	Prospective, open-label randomized controlled trial with blinded endpoint evaluation in patients with resistant hypertension	Randomized, single-blind, sham-control trial
Subjects	153 subjects with an elevated office systolic blood pressure (SBP; ≥160 mm Hg) despite taking ≥ 3 antihypertensive drug classes, 1 of which was a diuretic	106 subjects with a baseline SBP of 160 mm Hg or more despite taking three or more antihypertensive drugs were randomly allocated to renal denervation (n = 52) or control (n = 54) group (maintaining previous medical treatment alone)	535 patients with severe resistant hypertension underwent randomization in a 2:1 ratio to renal denervation or a sham procedure	106 subjects with resistant hypertension were randomly assigned in a 1:1 ratio to either renal denervation plus an antihypertensive regimen (renal denervation group) or the same antihypertensive treatment alone (control group)	331 hypertensive subjects were randomly assigned to either renal denervation (n = 166) or a sham procedure (n = 165)
Follow-up	At 1, 3, 6 12, 18, and 24 months	Primary endpoint was assessed at 6 months	6 months	6 months	Primary endpoint (baseline-adjusted change in 24-hour SBP) was evaluated at 3 months
Mean change in blood pressure (BP) values	92% of patients had an office BP reduction of ≥ 10 mm Hg	84% of the patients who underwent renal denervation had a reduction in SBP of 10 mm Hg or more, compared to 35% of controls (p < 0.0001)	No significant reduction of SBP in patients with resistant hypertension at 6 months after renal-artery denervation when compared with the control group	Renal denervation plus standardized treatment decreased ambulatory blood pressure more than the same treatment alone	At 3 months, the mean difference between the two groups for the primary endpoint was −3.9 mm Hg

postintervention, ipsilateral venous stenosis was observed in 29% of subjects. It was, however, successfully treated in all patients with venoplasty, stenting, or both [34].

Conclusions

Therefore, one can conclude that both the diagnostic algorithm and the therapeutic management of resistant hypertension are challenging. Lifestyle modification and treatment optimization are paramount in reducing the increased cardiovascular risk conferred by hypertension. Ensuring compliance to prescribed dietary and pharmacological regimens is mandatory for excluding pseudo-resistance. Patients with confirmed resistant hypertension should be referred to a specialist in hypertension who is more skilled to decide on interventional therapy. The results of multiple studies support the benefits of interventional therapy in resistant hypertension. However, a rigorous selection of patients is required before choosing between renal sympathetic denervation, carotid baroreceptor stimulation, or baroreflex amplification therapy and creation of an arteriovenous fistula.

Compliance with Ethics Requirements

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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