

Renal Denervation – a Modern Option for Treating Resistant Hypertension

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ABSTRACT

Hypertension is one of the main cardiovascular risk factors, and it remains an important health problem, demonstrating an increasing incidence despite new treatment methods. Numerous risk factors that can lead to the development of difficult-to-treat or resistant hypertension have been described in the literature in recent years. In this type of hypertension, an important role is played by the sympathetic nervous system. Especially in these cases, with a sympathetic overactivation, renal denervation has proven its efficacy and safety in lowering blood pressure. In this brief clinical update, we present the results of the main studies regarding the efficacy and safety of the renal denervation technique used in the treatment of resistant hypertension.

Keywords: resistant hypertension, renal denervation, sympathetic nervous system

INTRODUCTION

Although there are various new therapeutic techniques, hypertension remains one of the major cardiovascular risk factors. Numerous antihypertensive therapeutic strategies, including pharmacological agents such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, anti-renin drugs, antiadrenergic or new molecules such as fribastat or empagliflozin, are available on the market, but renal ablation/denervation remains one of the most important and successful therapeutic options for resistant cases of hypertension. However, due to its invasive nature, this therapeutic method is not routinely recommended.^{1,2}

An important role in the etiology of hypertension is played by the genetic factor interconnected with environmental, behavioral, and social factors. Globally, more than 1 billion people are suffering from hypertension, which contributes to 218 million disability-adjusted life years. According to the World Health Organization, uncontrolled hypertension produces 9.4 million deaths per year.^{1,3,4}

Resistant or difficult-to-control hypertension is defined as a constant high blood pressure (above 140/90 mmHg) which is uncontrolled despite the phar-

macological use of three antihypertensive agents, including a diuretic, for at least one month without any interruption. This state of resistance is caused by numerous metabolic factors such as obesity, diabetes mellitus, sleep apnea syndrome, alcohol intake, volume overload, thyroid disease, or even chronic kidney disease. It is estimated that up to 40% of patients with chronic kidney disease will develop uncontrolled hypertension. Also, these patients are at an increased risk of developing coronary or peripheral artery disease, stroke, or vascular dementia.^{1,5-7}

Pseudo-resistant hypertension is defined as uncontrolled hypertension due to either inadequate measurements, atherosclerosis or poor adherence to treatment, or insufficient drug doses. In some cases it was associated with white coat hypertension or non-adherence to treatment.^{5,8} The identification of these factors is very important in order to reduce the risk of adverse events related to renal denervation.⁹

The prevalence of hypertension varies significantly; in clinical studies, it was found to be around 12–18%, but after excluding the pseudo-resistant cases, the real prevalence was established at 5% in the general population and slightly higher in hypertension centers.^{3,10}

Recent studies have proved that the incidence of hypertension varies by race and gender, being higher in the non-Hispanic black population and in women, especially the non-dipping blood pressure forms. Besides race, gender, or associated comorbidities, one of the most important contributors to the development of resistant hypertension is the sympathetic nervous system.¹

The renal sympathetic nerves are located within and adjacent to the renal artery wall,⁹ and the sympathetic nervous system plays an important role in renal physiology. Sympathetic activation triggers renal arterial vasoconstriction, which leads to the stimulation of renin secretion with increased sodium and water reabsorption and increased blood pressure.^{2,5} This overexpressed sympathetic activation is more pronounced in the younger population.⁸

Current guideline recommendations regarding the use of renal denervation/ablation as a therapeutic strategy are controversial. The 2017 guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA), and the 2018 guidelines of the Canadian Cardiovascular Society do not recommend this procedure effective in reducing blood pressure, and the 2018 guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) do not recommend it for the routine treatment of high blood pressure due to the lack of necessary evidence regarding safety and efficacy (recommendation class III, level B). However,

these guidelines assert that invasive therapeutic methods, including renal denervation or the stimulation of baroreceptors, can be used as effective therapeutic approaches in case of pharmacological failure (recommendation class II, level B).¹

EFFECTIVENESS OF RENAL ABLATION – WHAT DO WE KNOW AND WHAT IS NEW?

Renal ablation represents an invasive technique used as an alternative for the treatment of resistant hypertension. In the last decade, several studies have analyzed its efficacy in the treatment of resistant hypertension. However, the results vary widely, from a significant reduction of ambulatory systolic blood pressure to an insignificant effect on blood pressure reduction.² These differences can be explained by incorrect blood pressure measurement techniques, the different classes and doses of the drugs used to treat hypertension, and the different response of each patient to drug therapy.^{1,2}

The most important clinical trials that have studied the efficacy of renal ablation are SYMPLICITY HTN-2, HIT-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO.^{1,2}

Results from the SYMPLICITY HTN-2 study, performed on a sample of 106 patients, have shown a reduction in blood pressure of 31/12 mmHg in patients with renal denervation, compared with 0/–1 mmHg in patients using only drug therapy.⁵

SYMPLICITY HTN-3 (2014), the first renal denervation trial, did not reveal significant differences between the invasively treated group (renal ablation procedure) and the control one. However, further analyses have exposed not only significant problems regarding the study design (non-homogeneous study population), but also a low level of experience in the study centers, with uncontrolled adherence to treatment and uncontrolled changes in the pharmacological treatment, as well as the use of a wide range of antihypertensive classes and several types of ablation catheters.^{1,8}

The more recent clinical trials, SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO, have all considered these parameters, and their results have demonstrated a statistically significant diminution in ambulatory blood pressure and systolic office blood pressure.¹

SPYRAL HTN-ON MED is a global multicenter, blinded (patient and evaluator), randomized, chess-controlled study that evaluated not only the efficacy of renal ablation, but also the safety of this technique in the treatment of un-

controlled hypertension despite maximal treatment with antihypertensive agents.¹ The trial, conducted between July 2015 and June 2017, included 80 patients from 25 clinical centers. The results concluded that renal denervation is associated with a statistically and clinically significant reduction of blood pressure between the groups, three months after the procedure. Also, the trial did not report any adverse safety effects associated with renal denervation.^{1,2}

SPYRAL HTN-OFF MED is a multicenter, single-blind, randomized controlled study regarding the efficacy of renal denervation, conducted in 21 centers. There were 353 patients enrolled, aged between 20 and 80 years, and one of the particularities of the study was the continuation of oral drug therapy for at least three months. The results showed a significant blood pressure reduction in the group treated interventionaly.¹¹

RADIANCE-HTN SOLO is also a global multicenter, single-blind, randomized, sham-controlled trial that aimed to evaluate the efficacy of renal denervation using the endovascular ultrasound technique.¹ Between March 2016 and December 2017, 146 patients aged 18–75 years, with a proper renal anatomy for this technique (renal anatomy was assessed using CT angiography or magnetic resonance before randomization), were enrolled from 21 centers.¹ The main purpose of the study was to demonstrate the effectiveness of this therapeutic technique for the treatment of uncontrolled hypertension without concomitant medication. The results proved that endovascular denervation reduces significantly the systolic and diastolic blood pressure at two months following the procedure. It was also observed that this effect was not influenced by age, gender, ethnicity, geography, or baseline blood pressure variations. The average reduction of systolic blood pressure was 8.5 mmHg, 6.3 mmHg greater than the reduction in the controlled group. However, efficacy and safety of this treatment should be established beyond a period of two months, especially regarding the safety of discontinuing antihypertensive drugs for longer periods.^{1,2,12}

RADIOSOUND-HTN was the first trial in which renal denervation has been performed using three different procedural approaches – denervation at the main renal arteries, at the main renal arteries and side branches, and ultrasound denervation. The results have strengthened previous research, proving once again that renal denervation is able to decrease blood pressure significantly.¹¹ Regarding the most efficient invasive technique, endovascular ultrasound-based renal denervation was found to be superior to the other two techniques. Still, long-term follow-up has shown no comparable differences between

the groups regarding the rate of response to renal denervation.¹³

The experimental study performed by Fink *et al.* on animals did not find a significant clinical pattern of blood pressure reduction after bilateral renal denervation.¹⁴ These results were also confirmed by Grisk O., who concluded that the use of new techniques may reduce the degree of renal re-innervation, but the beneficial effects of bilateral renal denervation may be due to over-sensitivity to denervation.¹⁵

In a study conducted on hypertensive mice with chronic renal disease, Nishihara *et al.* have proved that renal denervation has an antihypertensive effect by increasing urinary sodium excretion in the early phase, followed by increased GABAergic input into the hypothalamic paraventricular nucleus in the late phase. These results were also sustained in diabetic rats or with renal kidney disease.¹⁶

RENAL DENERVATION: PROS AND CONS

Given the controversial results of clinical studies, several questions were raised regarding the efficacy and safety of the renal denervation technique. Preclinical studies on animal models have shown that renal denervation is effective in reducing high blood pressure, and the reduction is maintained several weeks after surgery. On the other hand, this beneficial effect could not be sustained, even in younger mice. Moreover, studies have shown that renal denervation has beneficial effects also on target organs including systolic left ventricular function, bioavailability of nitric oxide, or carbohydrate metabolism.²

The efficacy and safety of renal denervation were also demonstrated in a meta-analysis performed by Dahal *et al.*; however, the authors consider the short follow-up periods of the included studies a major limitation.⁶

A closer analysis of the studies in which renal denervation has not proven his effectiveness suggests that treatment with oral antihypertensive drugs must be continued after the procedure in order to achieve an adequate level of systolic blood pressure. In addition, patients with moderate uncontrolled blood pressure are not suitable for this type of treatment.²

Another main disadvantage of renal denervation is the fact that its blood pressure-reducing effect is not uniform among hypertensive patients. Also, it was observed that being part of a non-African population, age under 65 years, a more efficient glomerular filtration rate at the baseline, or the use of aldosterone antagonists increase adherence to treatment. According to the Austrian Transcatheter Renal Denervation Registry, female and non-diabetic patients are also more responsive to the treatment.^{4,17}

Furthermore, an important factor that can modify the efficiency of renal denervation is the number of performed ablations. i.e. the operator's experience.⁷

Results of the studies performed so far have shown a possible efficacy of renal denervation in case of heart failure or arrhythmias, but further studies are needed to validate these results.¹⁸

CONCLUSIONS

Although, initially, renal denervation had been highly appreciated, further clinical trials have considered it insecure due to the lack of evidence regarding its efficiency and safety. In the present, there are numerous promising data that underscore the advantages of using this technique. Still, current guidelines do not recommend to perform this technique as routine, and the therapeutic decision is based on the operator choice and experience, respectively on the patient's profile.

CONFLICT OF INTEREST

Nothing to declare.

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