v. 3, n. 50, 2023

International Journal of Health Science

RENAL SYMPATHETIC DENERVATION IN THE MANAGEMENT OF RESISTANT HYPERTENSION: A REVIEW OF CURRENT EVIDENCE

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Abstract: Goal: To evaluate the efficacy and safety of Renal Sympathetic Denervation (RSD) as a therapeutic approach in the management of resistant hypertension, through the analysis of recent clinical and experimental studies. Additionally, it aims to examine current evidence supporting its clinical use, discuss indications and contraindications, and identify areas where further research is needed to improve understanding and clinical practice. **Methodology**: A bibliographic review was carried out through searches in the PubMed Central (PMC) and SciELO (Scientific Electronic Library Online) databases. 196 articles were found and, after applying the inclusion criteria, 24 studies were selected to compose the collection. **Results:** Several types of studies reviewed indicate that Renal Sympathetic Denervation (RSD) is effective and safe in the management of resistant hypertension, both as a stand-alone treatment and as adjunctive therapy. The effects of this treatment demonstrated a reduction in blood pressure for at least 6 months after the procedure, with no complications and no kidney damage for at least 7 years after the intervention. **Final considerations:** Although more research is needed to confirm the long-term results, it is possible to associate Renal Sympathetic Denervation not only as an effective and safe procedure, but also as a relevant intervention for the improvement of cardiovascular morbidity and mortality.
Keywords: Resistant Arterial Hypertension; Renal Sympathetic Denervation; Treatment.

INTRODUCTION

It is estimated that 1 billion people worldwide suffer from systemic arterial hypertension (SAH) (WEBER M.A. et al., 2019). Uncontrolled hypertension remains an important health problem, despite the availability of many drugs and non-pharmacological therapies for its management.

More than 9 million annual deaths can be related to complications of SAH, such as myocardial infarction, stroke and renal failure (WEBER M.A. et al., 2019; BERGO K.K. et al, 2021). Added to this, non-adherence to medication has been increasingly frequent, with approximately 2 out of 5 patients with uncontrolled hypertension (REY-GARCIA, J.; TOWNSEND, R.R., 2022).

There are two main causes in which drugs are not effective for the disease: the first is the patient's non-compliance with the treatment, within a year, due to adverse reactions or the patient's own failure to take the drug regularly. Approximately 50% of diagnosed patients become totally or partially non-adherent to treatment within one year of prescription (SIMONETTI F. et al., 2023). However, in a significant number of patients, the drug approach is ineffective or there is intolerance to specific antihypertensive drugs, which is the second cause of drug ineffectiveness, which is known as resistant arterial hypertension (AHMAD Y. et al., 2021; SIMONETTI F. et al., 2023). Resistant arterial hypertension is characterized by blood pressure levels that remain high despite antihypertensive medication. This condition manifests itself in around 10 to 20% of diagnosed patients (SIMONETTI F. et al., 2023).

Antihypertensive agents are, nowadays, the main means of controlling hypertension, however, drug treatment often may not be efficient as previously mentioned (REY-GARCIA, J.; TOWNSEND, R.R.,2022 ; SIMONETTI F. et al., 2023).

In these cases, device-based blood pressure-lowering therapy such as renal denervation may be a valuable additive or alternative treatment option (AHMAD Y. et al., 2021; SIMONETTI F. et al., 2023; MESSERLI F.H. et al, 2022; BERGO K.K. et al, 2021).

The evolution of renal sympathetic denervation (RSD) over the years has been characterized by periods of ups and downs, with an initial phase of growth followed by a decline attributed primarily to the unfavorable results of a significant randomized clinical trial (SIMONETTI F. et al, 2023). However, recent data from new trials and long-term follow-up of initial trials have confirmed the effectiveness and safety of the procedure, relaunching it in everyday clinical practice. It is important to emphasize that, since RSD is an invasive procedure, the risk-benefit ratio must be clearly defined and its indications for patients with persistent arterial hypertension, in the process of reducing the consumption of several medications, or as a first line of treatment for patients without prior exposure to drugs must be properly evaluated (AHMAD Y. et al., 2021).

Faced with such a scenario, the objective of this narrative review is to analyze the efficacy and safety of renal sympathetic denervation as a therapeutic approach in the management of resistant hypertension, examining recent clinical and experimental studies. In addition, review current evidence supporting its clinical use, discuss indications and contraindications, and identify areas where further research is needed to improve understanding and clinical practice.

METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Such a strategy was used for the elaboration of the research through its guiding question: "What is the efficacy and safety of renal sympathetic denervation in the management of resistant hypertension, and what are the current scientific evidences that support its clinical use?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients

with resistant hypertension, the variable would be renal sympathetic denervation, for the outcome of greater safety and efficacy in managing the condition. The searches were carried out through searches in the PubMed Central (PMC) and SciELO (Scientific Electronic Library Online) databases. 3 descriptors were used in combination with Boolean operators: resistant hypertension, renal sympathetic denervation and treatment. The search strategy used was: (resistant hypertension) AND (renal sympathetic denervation) AND (treatment). A total of 186 articles published in the last 5 years were found in the PubMED database and a total of 10 articles in the SciELO database. A total of 196 articles were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Spanish and Portuguese; published in the period from 2016 to 2023 and that addressed the themes proposed for this research, studies of the review, observational and experimental types and made available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, 24 articles were selected from the PubMed database, which were used to compose the collection.

RESULTS

RESISTANT ARTERIAL HYPERTENSION

Hypertension represents a worrying chronic disease that is constantly growing globally. By achieving a systolic blood pressure below 120 mmHg, there is a significant reduction in the risk of death and complications associated with the disease. However, resistant hypertension is an obstacle to achieving this blood pressure target (OREKHOV A.U. et al., 2022). Resistant hypertension is defined as a condition where blood pressure remains above proposed targets even with the use of three different classes of antihypertensive drugs, including calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARB), in addition to thiazide diuretics (ZHANG X. et al., 2016).

The prevalence of resistant hypertension is estimated to be between 10 and 20% of global hypertensive patients, which corresponds to approximately 200 million people. In the United States, about 9% of hypertensive patients have resistant hypertension, while in Brazil this rate is slightly higher, at 11.7%. Variations in blood pressure control are influenced by socioeconomic conditions, with more developed countries having a control of 28.4%, while in less developed countries this rate drops to 7.7%. The prevalence of resistant hypertension is more expressive in the elderly, obese and people of African descent, as well as in patients with diabetes, left ventricular hypertrophy, high alcohol and salt consumption, metabolic syndrome and chronic kidney disease (YUGAR-TOLEDO J.C. et al., 2020).

Several etiologies are indicated for the development of resistant hypertension, which is commonly associated with hypervolemia. The increase in volume can be partially explained by excess aldosterone, added to factors such as obesity, chronic kidney disease and high salt intake. In addition, other mechanisms, such as increased activity of the sympathetic nervous system, are relevant in the pathophysiology of resistant hypertension (VOORA R.; HINDERLITERA A.L., 2018; SYED, M. et al., 2021).

There are also secondary causes for resistant hypertension, categorized as endocrine and non-endocrine (YUGAR-TOLEDO J.C. et al., 2020). Among non-endocrine diseases, renal

parenchymal disease and obstructive sleep apnea stand out, a highly prevalent condition in these patients, especially considering the influence of the sympathetic nervous system on the pathophysiology of the increase in blood pressure induced by apnea (MESSERLI F.H. et al, 2022). Among the endocrine causes, primary hyperaldosteronism, pheochromocytoma, hypothyroidism and hyperthyroidism are relevant (YUGAR-TOLEDO J.C. et al., 2020).

Patients with resistant hypertension have high cardiovascular morbidity and mortality, with a 47% higher risk of developing cardiovascular events compared to hypertensive patients in general. These patients are also more likely to have damage to target organs, making it essential to investigate these injuries for correct risk stratification. In addition, cerebrovascular changes are also common in patients with resistant hypertension, manifesting insidiously with microscopic lesions in the white matter of the brain, progressing to cognitive impairment and vascular dementia (YUGAR-TOLEDO J.C. et al., 2020).

The relationship between resistant hypertension and chronic kidney disease is well established, with hypertensive nephrosclerosis being the common denominator between both conditions, resulting from hemodynamic changes that lead to glomerulosclerosis. The profile of patients with resistant hypertension can be distinguished from those with non-resistant hypertension, given the presence of specific characteristics, such as: obesity, high salt intake, advanced age, chronic kidney disease, target organ damage, black race and female gender. (YUGAR-TOLEDO J.C. et al., 2020; MESSERLI F.H. et al., 2022).

RENAL SYMPATHETIC DENERVATION (RSD)

The renal function of regulating blood pressure becomes particularly relevant when changes occur in blood pressure in afferent arterioles, which leads to adjustment of renal function in favor of controlling systemic blood pressure. Renal sympathetic nerves play a crucial role in the onset and maintenance of hypertension (SYED, M. et al., 2021). For years, attempts have been made to deal with the consequences of the action of the sympathetic nervous system on hypertension. Approximately 100 years ago, radical surgical sympathectomy was applied with relative success in the treatment of hypertensive patients, as well as surgical renal denervation was performed in a limited number of patients and presented varied results (STAVROPOULOS K. et al., 2020).

Renal Sympathetic Denervation (RSD) is being investigated as a non-pharmacological therapeutic option, which can function both as a stand-alone treatment and as an adjunctive therapy. Over the last decade, several studies have evaluated the effectiveness of DSR in the management of hypertension (SYED, M. et al., 2021; ZEIJEN V. J. M. et al., 2022). Recent studies have revealed the absence of long-term complications from the procedure and no functional or anatomical or functional kidney damage, 7 years after the intervention (BERGLAND O.U. et al.,2021).

Recently, the implementation of catheter-based techniques, use of radiofrequency or thermal energy highlighted the concept of renal denervation within cardiology. The first proof-of-concept study reported a highly significant reduction in blood pressure in patients, while the largest placebo-controlled study (SYMPLICITY HTN-3) failed to find similar results (STAVROPOULOS K. et al., 2020).

There are three different approaches for renal sympathetic denervation: radiofrequency, ultrasound and injection of neurotoxic substances. In the radiofrequency

approach, electrodes are placed that generate heat to deprive the surrounding nerves of the renal artery. The ultrasound technique involves a catheter with an inflatable balloon and four ultrasounds, which deliver ablation energy to a specific depth to disrupt the perivascular sympathetic nerve fibers of the renal artery. The third technique involves the injection of neurolytic agents infiltrated by a small catheter with microneedles, which penetrate the perivascular space of the renal artery and inject the neurotoxic liquid (REY-GARCIA, J.; TOWNSEND, R.R.,2022).

With regard to the most recently used techniques - radiofrequency and ultrasound -, contemporary research seeks to evaluate the effects of ablation using these different modalities of renal sympathetic denervation. Ultrasound denervation occurs via full circumferential thermal ablation to a depth of approximately 6 to 7 mm, which corresponds to the predicted location of the sympathetic nerves in the main renal artery. 2018). Radiofrequency, in turn, can be performed in two ways: ablation of the main renal artery (RFM-RDN) or ablation of the main renal artery, branches and accessories (RFB-RDN), the latter being performed on branches and accessories due to the smaller distance between the lumen and the sympathetic fibers compared to the main renal artery (FENGLER K. et al., 2019a).

Effective destruction of sympathetic fibers is crucial for the success of renal sympathetic denervation in patients with resistant hypertension. Thus, theoretically, ultrasound and radiofrequency techniques for ablation of the main renal artery, branches and accessories present a greater possibility of completely reaching the renal nerves and obtaining the effectiveness of the procedure (REY-GARCIA, J.; TOWNSEND, R.R., 2022).

However, randomized studies have indicated that response rates do not differ significantly between the approaches performed (ultrasound, radiofrequency of the main renal artery and radiofrequency of the main renal artery, branches and accessories). This observation can be attributed to other factors, such as the time of evaluation after treatment and the inclusion of patients with isolated systolic arterial hypertension, which may have other possible causes for resistant hypertension, especially the reduction in compliance of the arterial wall (FENGLER K. et al., 2019; LI L. et al., 2023).

For Stavropoulos K., et al (2020), renal denervation resulted in a significant improvement in organ damage caused by resistant hypertension. The main benefits observed included a reduction in left ventricular thickness, improvement in renal function and a decrease in urinary albumin levels (KORDALIS A. et al., 2018). These results suggest that renal denervation may be an effective approach to reducing organ damage associated with resistant hypertension and thus could supposedly improve cardiovascular morbidity and mortality. Accordingly, Stoiber L. et al. (2018) also proves the restoration of aortic distensibility.

It must also be noted that there is a greater indication of the procedure for patients with high sympathetic dependence, since there was a demonstration of a more relevant antihypertensive effect in this group, when compared to the study with other animal models. In this context, when dealing with the risks and benefits of RSD, there is an acceptable safety profile, with rare serious adverse effects and no more frequent than those occurring in placebo procedures. Data collected from blinded, randomized, placebo-controlled studies comprehensively show that renal denervation is safe and provides a significant reduction in blood pressure for at least 6 months after the procedure. If this result persists in the long term, the technique

can result in a 10% relative reduction in the lifetime risk of serious cardiac events and a 7.5% relative reduction in mortality from other causes (SHAH R.T.; WANG B.X., 2022).

According to Kario, K. et al. (2022), one month after the procedure, home SBP decreased significantly from baseline in the renal denervation versus sham control group, but between-group differences in change from baseline were no longer statistically significant at months two and three. The reduction from baseline in 24-hour ambulatory and office systolic blood pressure at 3 months was also not statistically significant between the renal denervation groups (sham control vs denervation), and the same applies day and night ambulatory BP.

Renal sympathetic denervation is an effective and safe option for the treatment of resistant hypertension, with long-term benefits in lowering blood pressure, although the antihypertensive burden index, the estimated number of defined daily doses of antihypertensive drugs and the estimated number of antihypertensives five years after RSD has not changed. It is also important to emphasize that more research is needed to confirm these results and to evaluate the durability of the effects of renal sympathetic denervation (PANCHAVINNIN P. et al., 2022; ZEIJEN V. J. M. et al., 2022).

CONCLUSION

SAH is a multifactorial disease recognized as a significant contributor to cardiovascular morbidity and mortality. Despite the availability of several highly effective pharmacological options for the treatment of hypertension, resistant SAH represents a considerable challenge in its management. In this context, the role of the sympathetic nervous system in the pathophysiology of hypertension stands out, which has stimulated the development of new technologies. Among them, Renal Sympathetic Denervation (RSD) emerges as a promising therapy, with several techniques being used (ultrasound, radiofrequency of the main renal artery, and radiofrequency of the branches and accessory vessels of the renal artery), although without significant differences between them. The future success of DSR is intrinsically linked to technological advances that can guarantee a complete, or at least almost complete, lesion of the renal sympathetic fibers, as well as the evidence of long-term cardiovascular benefits in patients with resistant hypertension and/or other conditions. It is necessary to conduct new studies that not only consider blood pressure levels as parameters, but also include target organ damage markers. This approach is fundamental for advancing in this area of research.

REFERENCES

AHMAD, Yousif et al. Randomized blinded placebo-controlled trials of renal sympathetic denervation for hypertension: a meta-analysis. **Cardiovascular Revascularization Medicine**, v. 34, p. 112-118, 2022

AHMAD, Yousif et al. Renal denervation for hypertension: a systematic review and meta-analysis of randomized, blinded, placebo-controlled trials. **Cardiovascular Interventions**, v. 14, n. 23, p. 2614-2624, 2021.

AZIZI, M. et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. **The Lancet,** v. 391, n. 10137, p. 2335-2345, 2018.

BERGLAND, Ola Undrum et al. The randomised Oslo study of renal denervation vs. Antihypertensive drug adjustments: efficacy and safety through 7 years of follow-up. **Blood pressure**, v. 30, n. 1, p. 41-50, 2021.

BERGO, K.K. et al. Renal sympathetic denervation lowers systemic vascular resistance in true treatment-resistant hypertension. **Blood pressure**, v. 30, n. 1, p. 31-40, 2021.

FENGLER, K. et al. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). **Circulation**, v. 139, n. 5, p. 590-600, 2019a.

FENGLER, K. et al. Renal denervation in isolated systolic hypertension using different catheter techniques and technologies: insights from a randomized trial. **Hypertension**, v. 74, n. 2, p. 341-348, 2019.

KARIO, K. et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial. **Hypertension Research,** v. 45 p. 221–231, 2022.

KORDALIS, A. et al. Regression of organ damage following renal denervation in resistant hypertension: a meta-analysis. **Journal of Hypertension,** v. 36, n. 8, p. 1614-1621, 2018.

LE, L. I. et al. Effect of renal denervation for patients with isolated systolic hypertension: a systematic review and meta-analysis. **Journal of Geriatric Cardiology**: JGC, v. 20, n. 2, p. 121, 2023.

MESSERLI, F.H. et al. Renal denervation in the antihypertensive arsenal–knowns and known unknowns. **Journal of hypertension,** v. 40, n. 10, p. 1859-1875, 2022.

OREKHOV, A. U.; SABITOV, Yersyn T.; KARAZHANOVA, Ludmila K. Renal denervation in resistant hypertension treatment. **Bratislavske lekarske listy**, v. 123, n. 10, p. 710-715, 2022.

PANCHAVINNIN, P. et al. Long-term outcome of renal nerve denervation (RDN) for resistant hypertension. **Hypertension Research**, v. 45, n. 962-966, abril, 2022.

REY-GARCÍA, J.; TOWNSEND, R.R. Renal denervation: a review. **American Journal of Kidney Diseases**, v. 80, n. 4, p. 527-535, 2022.

SHAH, Riya Tejas; WANG, Brian Xiangzhi. Effectiveness of renal denervation in the treatment of hypertension: a literature review. **Clinical Hypertension**, v. 28, n. 1, p. 11, 2022

SIMONETTI, F. et. al. Renal denervation and long-term results. European Heart Journal Supplements, v. 25, n**. Supplement B**, p. B85-B89, abril, 2023.

STAVROPOULOS, K. et al. Efficacy and safety of renal denervation for the management of arterial hypertension: A systematic review and meta-analysis of randomized, sham-controlled, catheter-based trials. **The Journal of Clinical Hypertension**, v. 22, n. 4, p. 572-584, 2020.

STOIBER, L. et al. Renal sympathetic denervation restores aortic distensibility in patients with resistant hypertension: data from a multi-center trial. **Clinical Research in Cardiology**, v. 107, p. 642-652, 2018.

SYED, M. et al. The state of renal sympathetic denervation for the management of patients with hypertension: a systematic review and meta-analysis. **Catheterization and Cardiovascular Interventions**, v. 97, n. 4, p. E438-E445, 2021.

VOORA, Raven; HINDERLITER, Alan L. Modulation of sympathetic overactivity to treat resistant hypertension. **Current Hypertension Reports**, v. 20, p. 1-11, 2018.

WEBER, M.A. et al. Renal denervation for treating hypertension: current scientific and clinical evidence. **JACC: Cardiovascular Interventions**, v. 12, n. 12, p. 1095-1105, 2019.

YUGAR-TOLEDO, J.C. et al. Posicionamento brasileiro sobre hipertensão arterial resistente–2020. **Arquivos Brasileiros de Cardiologia,** v. 114, p. 576-596, 2020.

ZEIJEN, Victor J. M. et al. Long-term follow-up of patients undergoing renal sympathetic denervation. **Clinical Research in Cardiology,** v. 111 p. 1256–1268, 2022.

ZHANG, X. et al. The effects of renal denervation on resistant hypertension patients: a meta-analysis. **Blood pressure monitoring**, v. 21, n. 4, p. 206-214, 2016.