

Original Article

Percutaneous Sympathetic Renal Denervation

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ABSTRACT

Arterial hypertension is a highly prevalent disease and is associated with increased cardiovascular risk. Despite great advances in drug therapy, a considerable number of patients do not have an effective control of the disease, despite the use of multiple drugs, usually in high doses. Renal sympathetic denervation (RSD) has proved to be a promising therapy, with high safety and efficacy in preliminary studies in patients with resistant hypertension. The role of the sympathetic nervous system in the physiopathology of hypertension is well known, and is the rationale for the ablation of sympathetic fibers by transluminal delivery of radiofrequency in the renal arteries. In the last few years, results from case series, non-controlled studies and one multicenter randomized trial with a limited number of patients have shown a significant decrease in short and mid-term blood pressure levels. The objective of this review was to gather evidence on the use of RSD in the control of resistant hypertension and describe technical aspects and perspectives of the procedure.

DESCRIPTORS: Hypertension. Drug resistance. Kidney. Review.

RESUMO

Denervação Simpática Renal Percutânea

A hipertensão arterial sistêmica (HAS) é uma doença de alta prevalência e está comprovadamente relacionada a maior risco de eventos cardiovasculares. Apesar dos grandes avanços no tratamento farmacológico, uma parcela considerável dos pacientes não obtém um controle efetivo da doença, a despeito do uso de múltiplos fármacos e em doses elevadas. A denervação simpática renal percutânea (DSRP) tem se mostrado uma terapia promissora, com elevada segurança e eficácia em estudos preliminares em pacientes com HAS resistente. O papel do sistema nervoso simpático na fisiopatologia da HAS é bem conhecido e constitui o racional para a ablação das fibras simpáticas, por meio da aplicação de radiofrequência por via transluminal nas artérias renais. Nos últimos anos, resultados provenientes de algumas séries de casos, estudos não controlados e um estudo randomizado multicêntrico, com número limitado de pacientes, mostraram queda significativa dos níveis tensionais em curto e médio prazos. Esta revisão teve por objetivo reunir as evidências do uso da DSRP no controle da HAS resistente de maneira crítica, assim como descrever aspectos técnicos do procedimento e perspectivas.

DESCRIÇÕES: Hipertensão. Resistência a medicamentos. Rim. Revisão.

Systemic arterial hypertension (SAH) is an endemic disease in Brazil and worldwide, and is considered the main modifiable risk factor in cardiovascular disease prevention. Population studies conducted in

Brazilian cities over the last two decades have shown a SAH prevalence > 30%, expected to increase due to an aging population.¹ The treatment of SAH has proven to reduce the risk of developing cardiovascular

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disease and, despite the advancements in knowledge and therapeutic arsenal, it remains a disease with low control rates.²

The causes of inadequate hypertension control are numerous, such as poor adherence to lifestyle changes and drug treatment, blood pressure (BP) measurement errors, white-coat hypertension, medications that develop or aggravate hypertension, and undiagnosed secondary causes of hypertension. Even after considering these possible causes, a percentage of patients still have difficulties in controlling BP, despite the use of multiple medications. This condition is known as resistant hypertension (RH).

RH is defined as the condition in which BP remains above target ($\geq 140/90$ mmHg) despite the use of three or more different classes of antihypertensive drugs, including a diuretic, at optimal doses.³ Recent epidemiological data have defined the prevalence of RH as approximately 15% of cases of SAH.³ BP control in these patients is a major challenge, requiring the combination of multiple antihypertensive drugs, but still not achieving adequate control. Considering this challenge, new interventional therapeutic options have been studied; among them, percutaneous renal sympathetic denervation (RSD) has gained prominence after demonstrating significant BP reduction in RH cases.⁴

ROLE OF THE KIDNEY AND SYMPATHETIC NERVOUS SYSTEM IN THE PHYSIOPATHOLOGY OF HYPERTENSION

The renal sympathetic nervous system (SNS) comprises a dense network of post-ganglionic efferent fibers originating in the hypothalamus that reach the kidneys, through the pre- and paraspinal ganglia (T10-T12). Afferent fibers emerge from the renal pelvis and ascend to the autonomic center in the brain, and to the contralateral kidney through the roots of the ipsilateral dorsal ganglia (T6-L4), allowing a cross-regulation between the kidneys and the SNS. Both afferent and efferent fibers travel the path of the renal arteries through the adventitial layer of the vessel.⁵

The renal SNS plays a vital role in the onset and perpetuation of primary SAH, especially in the non-elderly population, as it contributes significantly to the increase in cardiac output and vascular tone. There is evidence suggesting the involvement of the SNS in this population, by demonstration of elevated plasma and urinary norepinephrine levels, and the increased activity of post-ganglionic sympathetic neurons and peripheral alpha-adrenergic receptors.⁶ Sympathetic hyperactivity has also been demonstrated in patients with SAH related to sleep apnea, obesity, diabetes mellitus, and chronic renal failure.⁷⁻⁹

Experimental studies have demonstrated higher renal sympathetic activity in patients with primary hypertension,

confirmed by measurement of norepinephrine released into plasma by the renal sympathetic nerves.¹⁰

The efferent sympathetic activity, for the kidneys, causes renin release, with subsequent activation of the renin-angiotensin-aldosterone system, leading to BP increase, increased tubular sodium retention, and reduction in renal blood flow.^{11,12}

Afferent signaling from the kidneys to the SNS, which is stimulated by reduced renal flow, causes an increase in efferent sympathetic activation to the kidneys, vessels, and heart, perpetuating the process.^{13,14} The rationale of percutaneous RSD therapy is to block this pathway, reducing the role of the SNS in SAH.

RSD FOR CONTROL OF RESISTANT SAH

Denervation of the SNS has been used as anti-hypertensive therapy for over 50 years, through the non-selective thoracolumbar splanchnicectomy. This procedure was able to control SAH and to improve the clinical condition of a significant number of patients, especially in cases of malignant hypertension, whose mortality rate at the time was greater than 50% at five years.¹⁵ However, the procedures had many undesirable side effects and, later, with the emergence of effective and safe antihypertensive medications, and due to the complexity and morbidity of the surgical sympathetic denervation procedure, this treatment modality was abandoned.

Based on the aforementioned physiopathological mechanisms and the evolution of interventional medicine, percutaneous RSD, through transluminal radiofrequency ablation of renal sympathetic fibers, has recently been the focus of attention in the treatment of RH. One of the first prospective studies showed an average reduction in BP of 27 mmHg for systolic and 17 mmHg for diastolic pressure at 12 months in patients with RH, and no major complications have been reported.^{16,17}

PERCUTANEOUS RSD TECHNIQUE

The Symplicity® renal denervation system (Medtronic – Santa Rosa, United States) is the pioneer device in RSD and at present, it is the system that has been most often tested in clinical trials (Figure 1). Before starting the procedure, unfractionated heparin must be administered to maintain activated clotting time (ACT) > 250 seconds. The technique consists of inserting a guide catheter through femoral access compatible with a 6F sheath, followed by the introduction of a catheter with radiofrequency energy emission, which is used four to six times, two minutes each time, using a spiral-shaped application, from the most distal segment toward the ostium of each renal artery. The catheter tip must be in contact with the artery wall to cause a thermal injury, which is predominantly restricted to the sympathetic fibers located in the adventitia, as

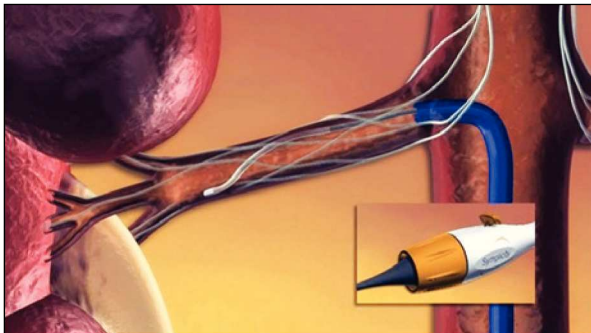


Figure 1 – Symplicity® Renal Denervation System.

they are more sensitive to heat than the surrounding tissues. The impedance of the catheter tip in contact with the artery is measured in real time, so that when the tissue temperature rises during each application, there is the reduction in the system impedance. An absolute reduction of 10% or more in the impedance is a marker of successful ablation.⁵

The procedure can be performed while the patient is awake; however, in most cases, systemic analgesia and conscious sedation are required, due to intense back pain during radiofrequency application; it may even require deeper sedation with airway protection. Edema and spasm of the arterial wall may occur as a result of thermal injury, shown as parietal irregularities on angiography (Figure 2) without hemodynamic involvement, and spontaneous resolution after the procedure is the usual outcome.¹⁸ Immediate reversal can be attempted with intra-arterial vasodilators, such as nitroglycerin and verapamil. The use of the radial approach has been reported with success.¹⁹

The Symplicity HTN-2 study is the only randomized controlled trial published to date, and represents the greatest clinical evidence for percutaneous RSD use in patients with resistant primary SAH.⁴ It was a multicenter study (24 centers in Europe, Australia, and New Zealand), in which 106 adult patients were randomized (aged 18 to 85 years) with essential hypertension and systolic BP > 160 mmHg (or > 150 mmHg in diabetics), measured in the office, and in regular use of at least three classes of antihypertensive drugs. Individuals with previous renal intervention, those with unfavorable kidney anatomy (luminal diameter < 4 mm, length of renal artery < 20 mm, or significant renal anomalies), type 1 diabetes, renal failure with glomerular filtration rate < 45 mL/min, severe valvular stenosis and acute myocardial infarction, unstable angina, or stroke within the last six months were excluded. These subjects were randomized to percutaneous RSD and to a control group with medication only, with the primary endpoint of BP reduction at six months. At the end of the study, the intervention group showed a significant

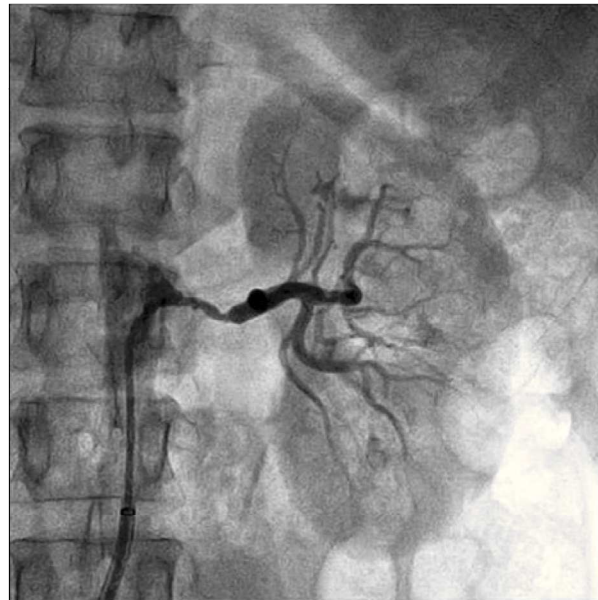


Figure 2 – Arterial spasm and edema after sympathetic denervation.

decrease in BP measured in the office when compared to the control group ($-33/-11$ mmHg, $P < 0.0005$). The percutaneous RSD resulted in a reduction ≥ 10 mmHg and ≥ 20 mmHg of systolic BP in 75% and 63% of patients, respectively.

At the 12-month follow-up, patients in the intervention group maintained a substantial reduction in BP without further complications and without associated worsening of renal function.²⁰ Of the 51 patients in the control group, after the initial six months, there was a crossover to percutaneous RSD in 31 of them, who also showed a significant reduction in BP. Recently, the three-year results of the HTN-1 study were presented, the longest clinical follow-up to date, showing maintenance of BP reduction results in the three-year evolution.²¹

Regarding the safety profile of the procedure, in the Symplicity HTN-2 study, the complications related to percutaneous RSD were rare. There was one case of pseudoaneurysm of the femoral artery; one case of significant decrease in BP after the procedure, requiring reduction of antihypertensive drugs and prolonged hospitalization for observation of lower-limb paresthesia; and one case of persistent low back pain requiring analgesia, which improved after 1 month.

During the procedure, seven patients had bradycardia. One of the concerns of the study regarded the possible worsening in renal function caused by hemodynamic changes and renal autoregulation. However, there was no difference between the groups regarding glomerular filtration rate and levels of cystatin C. The implementation of percutaneous RSD therapy in patients with more advanced stage of chronic renal failure was

tested in a pilot study,²² in which 15 patients with a mean glomerular filtration rate of 31 mL/min and RH were assessed. After a 12-month follow-up, there were significant reductions in BP without impaired renal function.

With the results reported by the Simplicity HTN-1 (Phases 1 and 2) and Simplicity HTN-2 (Phase 3) studies in 2010, the Symplicity® device for percutaneous RSD received approval for its clinical use in Europe (CE marking). Currently, four other devices have been approved in Europe, namely: the EnligHTN® renal denervation system, by St. Jude Medical (St. Paul, United States); the Vessix V2® renal denervation system, by Boston Scientific Corporation (Natick, United States); the OneShot® system, by Covidien (Mansfield, United States); and the Paradise® system, by ReCor Medical (Menlo Park, United States). In Brazil, only the Simplicity catheter has been approved by the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária – ANVISA), but its generator is still awaiting approval. None of the systems have been approved by the Food and Drug Administration (FDA) to date, and the Simplicity HTN-3 study is forthcoming, which included a placebo procedure for comparison.

The use of radiofrequency catheters with irrigated tip, designed for ablation of cardiac arrhythmia, has been tested as an alternative to the catheters specifically used for percutaneous RSD, with positive results in preliminary studies.^{23,24}

INDICATION OF PERCUTANEOUS RSD

The treatment of RH through percutaneous RSD has been an attractive alternative to exclusive drug therapy. Despite the positive and promising results of the Simplicity studies and its approval in Europe, some considerations should be made before its clinical indication. As mentioned above, to date there has been only one randomized, controlled trial, whose primary endpoint did not include clinical events, the number of patients was not significant, the control group was not submitted to any additional treatment, and the study was not double-blind. Moreover, there is no long-term follow-up to ensure efficacy and safety of this therapy over an extended period. It is possible that, over time, there is a regeneration of renal sympathetic fibers,²⁵ a fact already described in renal transplant grafts, reducing the long-term effects of percutaneous RSD. With the increasing number of cases, new complications not yet observed in earlier studies may arise. There have been reports of renal artery stenosis post-RSD,²⁶ possibly caused by vascular injury in the renal artery submitted to radiofrequency thermal injury, with consequent scarring and luminal narrowing of the vessel.

Not all patients undergoing percutaneous RSD show a significant reduction in BP. Further studies are

necessary to identify markers of good response to the procedure and to avoid exposure of individuals who will not benefit from an invasive procedure.

In the Simplicity HTN-2 study, it was observed that BP reduction in the intervention group was less significant in 24-hour ambulatory blood pressure monitoring (ABPM) than in the measurements made during medical consultations. This is another issue that needs to be clarified.

Much has been debated about the definition of RH and, despite the difficulty to control the disease, in most cases BP levels can be reduced with a combination of four or more drugs. Some studies have shown significant BP reduction in cases of RH with the association of spironolactone.^{27,28} However, increasing the number of prescribed drugs brings a higher risk of adverse events and hinders drug therapy adherence – a major cause of hypertension treatment failure. Thus, the percutaneous RSD may possibly be considered an option for cases where there is difficulty in adherence to therapy with multiple drugs.

Considering these facts, the European Society of Hypertension published a position regarding the appropriate indication of percutaneous RSD (Table 1).²⁹

FOLLOW-UP AFTER PERCUTANEOUS RSD

There is no consensus regarding the care of patients undergoing percutaneous RSD. The use of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel for a short period may be beneficial in reducing thrombotic events.³⁰ Initially, the patient should be assessed monthly for BP reevaluations and antihypertensive medication adjustment. Routine assessment with renal artery imaging to identify possible complications, especially stenosis, remains controversial. It appears reasonable to perform a Doppler ultrasound of the renal arteries within six months.¹⁷ Other methods, such as magnetic resonance angiography and computed tomography angiography, are alternatives.

PERSPECTIVES

The future of percutaneous RSD looks promising for the treatment of both the most resistant forms of hypertension and some specific clinical situations. New therapeutic options are always welcome against a disease with high prevalence and impact on the population, such as SAH. New cryoablation techniques for renal denervation induced by ultrasound, use of local neurotoxic drugs, and new radiofrequency denervation catheters are being developed and researched.³¹ Recently, a study on safety and efficacy has been published with positive results of the radiofrequency catheter with multiple electrodes (EnligHTN® renal denervation system, Figure 3), which are geometrically positioned to reduce

TABLE 1
Recommendations for the indication of percutaneous renal sympathetic denervation (RSD)
in resistant hypertension (RH)

First step	Confirm RH and rule out the following situations:	Pseudoresistant hypertension with ambulatory blood pressure monitoring and home blood pressure monitoring. Secondary hypertension. Causes that maintain high blood pressure and can be corrected, such as sleep apnea, severe obesity, use of medications that increase blood pressure, and high salt intake.
Second step	Optimize antihypertensive therapy with at least three classes of drugs, with one diuretic, at maximum tolerated doses. Consider the association of aldosterone antagonists (with renal function and hyperkalemia monitoring) and evaluate the response with ambulatory blood pressure monitoring.	
Third step	Assess contraindications of the procedure:	Solitary kidney, renal artery with a diameter < 4.0 mm and length < 20 mm, multiple renal arteries, significant stenosis, previous interventions such as renal artery angioplasty, estimated glomerular filtration rate < 45 mL/min/1.73m ² .
General recommendations		Perform the procedure in centers of excellence in the treatment of hypertension. Use devices that have demonstrated efficacy and safety in clinical trials.

the need for catheter manipulation inside the renal artery and, consequently, the risk of complications.³² With technology improvement, based on results of new studies, there is a trend of increase in the efficiency and safety of the procedure, expanding its indication.

As the sympathetic system has direct involvement in the physiopathology of other diseases, new possibilities for percutaneous RSD use have emerged. Improved glycemic control and reduced insulin resistance have been demonstrated in individuals with impaired glucose metabolism submitted to percutaneous RSD.³³ The use of RSD in patients with heart failure, cardiac arrhythmias, and sleep apnea has also been the object of investigations.³⁴⁻³⁷

CONCLUSIONS

Percutaneous RSD is a new invasive therapeutic modality, whose results demonstrated initial significant reduction in blood pressure in patients with resistant hypertension. The procedure has been shown to be safe and of low complexity. Despite these promising results, this is a new therapy, with limited long-term follow-up and whose clinical evidence is still scarce; therefore, its indication must be made with caution.



Figure 3 – EnligHTN® Renal Denervation System.

In addition to the treatment of resistant hypertension, other diseases may benefit from percutaneous renal sympathetic denervation therapy, such as heart failure, arrhythmia, sleep apnea, and metabolic diseases. Currently, there are several ongoing lines of research and studies in these areas.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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