

Renal Sympathetic Denervation for Resistant Hypertension Treatment - Current Perspectives

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Abstract

The authors review the concept of resistant hypertension and the involvement of the sympathetic nervous system in hypertension as a rational basis for the technique of renal sympathetic denervation (RSD) performed percutaneously. This revision is the result of an active search for scientific articles with the term “renal denervation” in the Medline and PubMed databases. The techniques and devices used in the procedure are presented, as well as clinical outcomes at six, 12 and 24 months after the intervention with the Symplicity catheter. Significant decreases and progressively higher reductions of systolic and diastolic blood pressure were observed after RSD. The complication rate was minimal. New devices for RSD and its ongoing clinical studies are cited. In conclusion, the RSD presents itself as an effective and safe approach to resistant hypertension. Results from ongoing studies and longer follow-up of these patients are expected to confirm the initial results and put into perspective the expansion of the procedure use in hypertension approach.

Introduction

Blood pressure (BP) is directly related to the risk of death and impairment of cardiovascular and cerebrovascular systems, among others. According to IV Brazilian Guidelines on Arterial Hypertension¹, in Brazil this disease has high prevalence, over 30%, and low control rates, below 20%¹.

Despite the recommendation to carry out a strict and effective control of tensional levels, frequently these goals are not satisfactorily achieved, resulting in greater risk of developing complications and increasing mortality. Many reasons might be involved in obtaining these non-satisfactory results, in a way that only a minority of hypertensive individuals present a proper control of their BP. For these reasons, arterial

hypertension (AH) that is difficult to control is a relevant public health issue¹. Included in this group are individuals with resistant arterial hypertension (RAH). Different studies show the RAH prevalence ranges between 3-30%^{1,2}.

In this scenario, percutaneous approach for bilateral renal sympathetic denervation (RSD) using radiofrequency ablation procedure³ has shown promise among new available therapeutic strategies and is based on the knowledge that, among the many physiopathological mechanisms involved in refractoriness to AH control, the excessive stimulation of renal sympathetic nervous system is distinctive³.

Stimulated by new treatment for RAH, this study aims at reviewing RAH concept, involvement of sympathetic nervous system (SNS) in BP increase, and clinical results with RSD.

Resistant arterial hypertension: definition and associated conditions

Resistant arterial hypertension (RAH) diagnosis is confirmed when there is maintenance of increased BP levels (above adequate BP goals): $\geq 140/90$ mmHg for hypertensive individuals in general and $> 130/80$ mmHg for high risk patients, such as diabetics), despite the use of three or more antihypertensive drugs of different classes, including a diuretic at optimal doses².

Importantly, the diagnosis of true RAH requires the exclusion of secondary causes of AH, in addition to any other associated condition that may interfere in the proper BP control, characterizing pseudo-resistance^{1,2}.

Among the main conditions associated to RAH and subject to specific approach are the inappropriate choice of antihypertensive drugs and/or use of insufficient dosage, failure to measure BP, adherence failure to prescribed medication and/or changes in lifestyle, white-coat effect, AH resulted from a non-identified and/or non-treated secondary cause, and associated conditions that may complicate the BP control, such as obesity, sleep apnea and the use of concomitant medications that increase the BP^{1,2}.

White-coat effect is a particularly important condition and it must be removed through ambulatory blood pressure monitoring (ABPM) before confirming the RAH diagnosis^{1,2}.

More recently, it has been highlighted the association between sleep disorders, including sleep obstructing apnea (SOA), non-controlled AH and cardiovascular complications in adults¹. The prevalence of SOA in adult patients with RAH has been estimated at 84%⁴.

Keywords

Hypertension/therapy; Blood Pressure/innervation; Sympathetic Nervous System; Renal Artery/innervation.

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The role of sympathetic nervous system in context of AH

Stimulation of the sympathetic nervous system (SNS) increases BP in normotensive and hypertensive due to the involvement of baroreceptors and chemoreceptors, through peripheral and central mechanisms that have an effect on the heart, kidneys and peripheral vasculature, leading to a cardiac output, water retention, and increased peripheral vascular resistance, which has a major role in AH pathophysiology^{5,6}.

SNS is involved in BP acute variations, in situations like exercising and postural variation. However, the mechanisms responsible for the presence of sympathetic hyperactivity in chronic AH and its role in AH maintenance remain unknown⁵⁻⁷. It is known that the increased sympathetic activity and the consequent release of catecholamine by sympathetic nerves, in addition to increasing vascular tone in resistance vessels, in early stages of AH, could also be stimulating trophic mechanisms and vascular hypertrophy in the long-term. It is possible that trophic alterations on vessel walls are maintaining BP increase in the chronic stage of AH⁵⁻⁷.

Noradrenaline serum levels are higher in hypertensive individuals when compared to normotensive ones, primarily in young people, in which sympathetic hyperactivity seems to have a central role in the development of AH^{5,6}.

Reflex mechanisms of the control of an autonomic activity are suppressed in the context of AH. It is probable that the minor baroreflex sensitivity observed in hypertensive patients is the primary determinant of the BP variability observed and, indirectly, of the injuries on associated target organs^{5,6}.

SNS activity is related to increased cardiovascular morbidity and mortality in the early morning hours. In this period, there is an increase in alpha-sympathetic activity, with high BP, of the heart rate and cardiac output present in many hypertensive patients in this period of the day⁵⁻⁷.

Exposure to stress is known to increase the sympathetic activity. This situation could be induced in laboratory animals, developing AH by exposure to stress. In young individuals with genetic predisposition to develop AH, it was observed higher vasoconstrictor response to mental stress or physical exercise tests and higher chance to develop AH⁵⁻⁷.

Plenty of evidence has pointed to the role of sympathetic hyperactivity in the development and progression of cardiovascular and metabolic complications related to increased BP, such as left ventricular hypertrophy, vascular hypertrophy, endothelial dysfunction, heart arrhythmia, and insulin resistance⁵⁻⁷.

Renal sympathetic nervous system

The abundant adrenergic innervation in kidneys and renal SNS appear to modulate the renin release via beta-adrenergic receptors and control renal hemodynamics via alpha-adrenergic receptors. Thus, the increased renal SNS activity could contribute to AH pathophysiology through many mechanisms: increased tubular reabsorption of water and sodium, increased secretion of renin and production of angiotensin II, increased renal vascular resistance, and reduced glomerular filtration. In fact, the increased renal SNS activity has been demonstrated in several models of experimental AH⁵⁻⁷.

Sympathetic efferent innervation of the kidney is carried out through a dense network of postganglionic neurons that innervate the kidneys; axons of these neurons exit chest and lumbar sympathetic trunk and reach the pre-paravertebral sympathetic ganglia. They run throughout the artery and renal hilum, subdividing itself and penetrating the cortex and juxtaglomerular area. Stimulating the renal sympathetic nerve increases the production and release of noradrenaline, while interrupting the sympathetic nervous stimulation results in reducing its production and release. When renal sympathetic nerves are stimulated, beta-1 receptors increase renin secretion and alpha-1 receptors increase renal reabsorption of sodium and fluids, promote renal vasoconstriction and reduce renal blood flow^{3,5-7}.

Triggering afferent renal sympathetic nerves results in signals that reach the cardiovascular and renal regulation centers in the central nervous system. Thus, afferent sympathetic fibers appear to strongly contribute in the regulation of the systemic vascular resistance and BP control^{3,5-7} and, therefore, antihypertensive treatment must consider the effective inhibition of sympathetic activity⁵.

Thus, mechanisms through which RSD reduces BP are fascinating, although not yet completely understood. Probably there is a reduction of efferent sympathetic nervous fibers and an additional reduction of afferent sensory fibers. Evidence suggests the possibility that sensory afferent sympathetic nervous fibers also participate in AH genesis and its denervation has therapeutic effects^{3,5-7}.

Renal sympathetic denervation

Interventional methods more recently implemented, such as baroreflex stimulation or renal sympathetic denervation³, have been pointed out as new strategies to treat RAH^{3,8}.

Technique and devices

Invasive procedures for the treatment of AH had already been tried before. Lumbar sympathectomy performed six decades ago⁹ in 1,266 hypertensive patients with malignant AH resulted in relevant and effective decrease of BP, but the increased incidence of complications, such as postural hypotension, syncope and impotence, limited the use of this technique in clinical practice. The development of effective antihypertensive medications also contributed to stop using this technique.

Recently, efforts have been directed to conduct a bilateral approach of renal nerves, initially through a percutaneous interventional technique using a catheter embedded to a radiofrequency device. Radiofrequency pulses are fired on the arterial wall in several points, from the distal part to the proximal part of both arteries, in spiral. The procedure can be conducted in renal arteries with ≥ 4 mm diameter and at least 20 mm length, before any bifurcation of the main branches^{3,10,11}.

Pre-clinical studies demonstrated that this technique is safe, efficient and minimally invasive, associated with little incidence of side effects and short recovery time^{3,10}. In pigs, the radiofrequency application causes acute transmural lesion with coagulation, loss of endothelial surface and thrombus formation, but without impairment of the renal perfusion.

In 10 days, it was observed a reendothelization of arterial luminal surface¹². Histopathological evaluation of pigs, six months after the procedure, primarily revealed renal nerves fibrosis. Findings for renal artery have shown 10-25% fibrosis of medial and adventitial layer with mild ruptures of the external elastic lamina, without changes on smooth muscular layer, without thrombosis or arterial stenosis. No changes on kidneys or bladder were found¹³.

To date, clinical results are very positive and encouraging. Systematic review, including 19 studies and 683 individuals, concluded that RSD promoted decreases of systolic BP (SBP) which varied between 18-36 mmHg and diastolic BP (DBP) ranging between 9-15 mmHg. In five studies, it was observed a BP-lowering effect sustained in 12 months of follow-up. There was no worsening of renal function and there were very few side effects related to the procedure, such as pseudo-aneurysm of renal artery, hypotension and bradycardia¹⁴.

Several devices have been developed to conduct RSD⁸. What presents clinical results with larger number of patients and longer follow-up period is the Symplicity (Medtronic Inc., Minneapolis, Minnesota) catheter system, which fires radiofrequency pulses. Radiofrequency RSD is also possible with other devices, in ongoing development, some have already been tried in human beings and approved for use in Europe, such as the catheters EnligHTN (St. Jude Medical Inc., St. Paul, Minnesota), Vessix V2 (Vessix Vascular Inc., Laguna Hills, California), and One Shot (Maya Medical Inc., Campbell, California) catheter. The radiofrequency catheters Thermocool (Biosense Webster Inc., Diamond Bar, California) and Chilli II (Boston Scientific Inc., San Jose, California) are being used for human beings, but have not been approved for use yet. New technology involving ultrasound ablation is also available with Paradise (ReCor Medical Inc., Ronkonkoma, New York) catheter, already in experimental clinical use⁸.

Simplicity studies: results and limitations

RSD technique was initially tested in an open-label pilot clinical study, Symplicity HTN-1¹¹, conducted with 45 patients with RAH, with preserved renal function. Patients administered, in average, 4.7 antihypertensive drugs and had mean baseline BP of 177/101 mmHg. Primary outcomes of the study were procedure safety and decrease of casual BP. Secondary outcomes were procedure effects on the production of renal noradrenaline (spillover) and renal function. Patients' follow-up occurred with one, three, six, nine and twelve months, without adjusting the quantity of antihypertensive medications, unless necessary¹¹.

BP decreases were significant in all periods of the follow-up. Thus, with one month of follow-up, the observed SBP and DBP decrease was of -14/-10 mmHg, respectively, reaching -27/-17 mmHg with 12 months after procedure. Six of the 45 patients (13%) had SBP reduction < 10 mmHg, being considered as non-responsive, while the five patients with RAH who were not subjected to the procedure (control group) had BP increased in subsequent evaluations. Twelve months after the procedure, 38% of patients had BP controlled (SBP < 140 mmHg) and 28% had BP partially controlled (SBP 140-159 mmHg)¹¹ - Table 1.

In this pilot, the presence of intercurrents was minimal, such as the occurrence of periprocedural diffuse abdominal pain, relieved with analgesics. The procedure proved to be safe and free from complications in 43 of the 45 patients (one patient had renal artery dissection that was treated and resolved by interrupting the RSD procedure and another patient had pseudo-aneurysm at the injection site and was treated conservatively). Angiographies conducted after the procedure in 18 patients have not demonstrated any abnormality of renal arteries; thus, magnetic resonance conducted after six months in 14 patients had not demonstrated complications related to the procedure¹¹.

The efficiency of the RSD procedure was also evaluated by the decreased noradrenaline release (spillover): in 10 study patients, this decrease was of 47%, and these patients had a decreased mean BP after six months of -22/-12 mmHg, similar to the group as a whole. Heart rate remained unaltered at all moments¹¹.

Positive results of this initial pilot study stimulated the proposal for a new study: the Symplicity HTN-2¹⁵, randomized, prospective, multicenter study. In this study, 106 patients with RAH were randomized for RSD (n = 52, initial mean BP of 178/96 mmHg) or maintenance of the previous drug therapy (n = 54, initial mean BP of 178/97 mmHg), having as main outcome the modification of casual BP in six months and as secondary outcomes the procedure safety, occurrence of cardiovascular outcomes, and additional measures of BP after six months.

At the end of the sixth month of follow-up, casual BP in the RSD group was reduced in -32/-12 mmHg in relation to baseline. In the control group, BP had no decrease (+1/0 mmHg). Thus, the difference of BP between RSD and control groups after six months was of 33/11 mmHg. Significant decreases were also observed in residential measurement and ABPM and BP at six months, although smaller in absolute numbers to decreased casual BP observed¹⁵ (Table 1).

Ten patients (20%) reduced the number of medications administered in the group subjected to intervention against three (6%) in the control group. Four patients (8%) increased the number of drugs used in the RSD group against six (12%) in the control group¹⁵.

At the end of six months, 41 patients (84%) who were subjected to RSD showed a decreased SBP \geq 10 mmHg and were considered responsive, against only 18 patients (35%) in the control group. The procedure had not complications or side effects¹⁵. The patients who, during the first six months, continued administering medications and had an unsatisfactory control of BP, were submitted to RSD, and the follow-up was extended to one year, with BP results similar to those who underwent the intervention at baseline¹⁶. One-year results of the follow-up of patients who underwent RSD in Symplicity HTN-2 study showed decrease maintenance of SBP (-28.1 mmHg), value similar to that observed with six months of follow-up (-31.7 mmHg)¹⁶ - Table 1.

However, in Symplicity HTN-1¹¹ and Symplicity HTN-2 (HR11)¹⁵ studies, we observed important limitations that need to be considered: a) possible mechanisms responsible for reducing BP at RSD were not investigated in any of the

Table 1 – Main characteristics and results of Simplicity HTN-1 e HTN-2 studies^{11,15,16}

Study	Characteristics	Main results
Simplicity HTN-1 ¹¹	Open-label, non-randomized study N = 45 Mean age 58±9 years; 56% male; 31% diabetics Initial BP: 177/101 mmHg Outcomes: decreased casual BP at 12 months and procedure safety	↓ casual BP at 12 months: -27/-17 mmHg 12 months: 38% SBP < 140 mmHg; 28% SBP 140-159 mmHg and 13% decreases < 10 mmHg (non-responsive) Procedure free from complications
Simplicity HTN-2 ¹⁵	Randomized, nonblinded study N = 106 Mean age 58±12 years; 58% male; 67% diabetics Initial BP: 178/97 mmHg (intervention) and 178/98 mmHg (control) Outcomes: decreased casual BP at 6 months and procedure safety	↓ casual BP at 6 months: -32/-12 mmHg ↓BP ABPM* at 6 months: -11/-7 mmHg 6 months after the procedure: 84% decrease of SBP < 10 mmHg; 10% had no decreases SBP (non-responsive) Procedure free from complications
Simplicity HTN-2 Extension to 1 year ¹⁶	Patients in Simplicity HTN-2 control group who maintained the unsatisfactory control of BP (SBP > 160 mmHg) underwent the RSD procedure with 6 months of follow-up Follow-up extended to 1 year	↓ casual SBP at 12 months (for group early treated with RSD): -28.1 mmHg ↓ casual SBP at 12 months (for group late treated with RSD): -23.7 mmHg Procedure free from complications

*ABPM was conducted in only 20 patients of the procedure group. RSD: renal sympathetic denervation; ABPM: ambulatory blood pressure monitoring; BP: blood pressure; SBP: systolic arterial pressure..

studies^{6,11,15,17,18}; b) there was no control group for Symplicity HTN-1¹¹, reducing the relevance of its results; c) at Symplicity HTN-2¹⁵, due to the complexity of the tested procedure (invasive intervention), the study could not be blind, thus creating a possible evaluation bias^{6,11,15,17,18}; d) in both studies, patients were not properly evaluated for the possibility of secondary AH (it is known that up to 10% of patients with RAH have primary aldosteronism and, in these patients, RAH invasive treatment could be considered; e) only a small number of patients was administering the appropriate clinical therapy for RAH treatment, such as the restriction of salt in diet and use of spironolactone, raising the question whether these patients were really treatment-resistant. Thus, it is believed that more rigorous inclusion and exclusion criteria must be applied in future studies in order to test this RAH treatment technique^{6,11,15,17,18}.

Still with limitations, in both studies some patients had their medication changed during the follow-up, reducing the impact of the procedure on BP decrease^{6,11,15,17,18}. Another aspect was the wide variability of hypotensive response observed at the end of six months with different methods of BP measurement used in both studies, making the efficacy analysis of the procedure quite heterogeneous^{6,11,15,17,18}. It is worth noting that in both studies, only part of the patients was subjected to ABPM, and this supplemental method is crucial to remove the white-coat effect. In this cohort, BP decrease in ABPM was of approximately 1/3 from that obtained for casual BP, suggesting the RSD effects may not be as significant as they initially appeared^{6,11,15,17,18}.

A concern with this technique is related to safety and durability of hypotensive effect in the long-term, due to the regenerative ability of the nervous tissue^{6,11,15,17,18}. However, the follow-up of 24 months after the procedure of 153 patients with RAH in the study Symplicity HTN-1¹⁹ showed progressively greater decreases of casual BP after procedure,

reaching -32/-14 mmHg at 24 months. The authors concluded that RSD resulted in substantial decrease and sustained of BP with two-year follow-up, without significant adverse events.

It is worth noting that about 20% of patients initially selected for the procedure did not participate in the study Symplicity HTN-2¹⁵ for difficulties in renal anatomy that prevented the procedure from being carried out, which could limit the clinical use of this therapy on a large scale^{6,11,15,17,18}.

Ultimately, not all patients subjected to the procedure managed to reduce the BP. If we consider that RSD had a mean decrease of SBP of 20-25 mmHg and DBP of 10-15 mmHg, at the end of 12 months of follow-up, similar decreases in SBP and DBP were also observed in patients administering spironolactone as the fourth drug in RAH treatment.

For this reason, it is important to try to identify factors that may predict the therapeutic success of the intervention. Univariate analysis in Symplicity HTN-1¹¹ did not identify any pre-procedure condition capable of predicting RSD success, while in Symplicity HTN-2¹⁵ the highest SBP values and use of central sympatholytic agents were capable of predicting the procedure success^{6,11,15,17,18}.

Due to the nature of the procedure, a more detailed analysis on renal function of patients undergoing RSD is mandatory¹⁷. Extended results of Symplicity HTN-1 for 24 months of follow-up¹⁹ observed a significant decrease of TGF (-16 ml / min/1,73 m²) in 10 patients; smaller decrease, but also significant (-7,8 ml / min/1,73 m²) was observed in five patients who were not administering spironolactone or any other diuretic in the first year after procedure. It is worth noting that, even with TGF decrease, no patient showed increase in serum creatinine or evolution to renal insufficiency or need for dialysis, and this TGF decrease was also lower than that estimated if patients had maintained BP unchanged from the protocol start¹⁹.

Clinical studies with other devices

EnligHTN is a multi-electrode catheter with a basket and, when it opens inside the renal artery, it allows energy release simultaneously in four points of the arterial endoluminal surface. It was the catheter used in ARSENAL study, which preliminary results were presented in 2012, reporting a BP decrease of $-28/-10$ mmHg, one month after the intervention, with 78% of patients showing a decreased systolic BP > 10 mmHg. Adverse events occurred in very few cases ($n = 6$): bruising on the arterial puncture site, vasovagal response on sheath withdrawal and bradycardia after procedure. Study final results will be recognized in 2013, after the six months follow-up of 47 patients treated with RSD using EnligHTN⁸ catheter.

Vessix V2 system of DSR has a catheter with a low-pressure balloon, with bipolar radiofrequency electrodes on the balloon surface, and it is being tested in the REDUCE-HTN study, with closure of results scheduled for August, 2014. Preliminary results in 10 patients showed BP decreases of $-30/-11$ mmHg⁸.

The first experience in human beings with One Shot system was reported. It is a catheter with an irrigated balloon and electrodes mounted helically, in a way that radiofrequency pulse can be conducted only once, making the procedure faster and more accurate, without the need of handling the catheter. BP decreases observed one month after intervention were similar to those observed in the Symplicity²⁰ study.

ThermoCool catheter is being used in SWAN HT study and intends to include 800 hypertensive patients. Pilot study results with 10 patients have shown decreases in BP and in markers of sympathetic activity. This same catheter and Chilli II system are being implemented in SAVE study, which also aims at including a relevant number of individuals - 500 patients⁸.

Paradise catheter is being tested in REALISE study. Preliminary results of 15 patients have shown BP decrease of $-32/-16$ mmHg with three months of follow-up and were presented in congress in 2012⁸.

Clinical studies that conducted RSD with irrigated radiofrequency ablation catheters, generally used for ablation in heart tissue, have also demonstrated positive results.

Ten patients subjected to RSD with this type of device were followed-up for six months. Mean BP decreases observed were significant ($-21/-11$ mmHg) and all patients reduced their BP in 10 mmHg or more by the end of this observation period. There were no complications on renal artery, such as aneurysms or stenoses, and there were no renal function impairments²¹.

Another experiment with this type of catheter confirmed the effect on BP, evidencing decreases in mean BP of 24h on ABPM of $-24/-14$ mmHg, three months after the procedure, without changes on renal function or albuminuria and without vascular complications²².

RSD effects besides the decreased peripheral arterial pressure

RSD positive impact on the central hemodynamics and arterial rigidity was recently reported. Evaluation of 110 patients who underwent RSD showed a decrease in central aortic BP

from 167/92 mmHg at baseline to 141/85 mmHg in six months. In this same period, the augmentation index presented a decrease of 5.3% and the carotid-femoral pulse wave velocity decreased from 11.6 ± 3.2 m/s to 9.6 ± 3.1 m/s. Improvements in central hemodynamics and arterial rigidity may be important prognostic implications, particularly in patients with cardiovascular high-risk, such as patients with RAH²³.

RSD was also capable of reducing the sympathetic activity measured through muscle sympathetic nerve activity (MSNA) after three months from procedure, with mechanisms not yet elucidated. RSD results were more evident for single sympathetic vasoconstrictor fibers, demonstrating substantial and rapid decrease of its activity²⁴.

The association between increased renal sympathetic activity and components of metabolic syndrome (MS) was already demonstrated. A group of 50 patients was evaluated²⁵, with 37 being subjected to RSD and 13 maintained under conservative treatment. Initial mean BP in both groups was of 178/96 mmHg. After three months of procedure, we observed significant decreases in BP ($-32/-12$ mmHg), fasting blood glucose (from 118 mg/dl to 108 mg/dL), of insulin levels (from 20.8 UI/ml to 9.3 UI/ml) and levels of C-peptide (from 5.3 ng/ml to 3.0 ng/ml). Authors also tested the impact on insulin sensitivity, calculated through homeostasis model assessment-insulin resistance (HOMA-IR), and observed the decreased level of insulin resistance with RSD (from 6 to 2.4). Glucose, after two hours of stimulation, also improved after the procedure, with a decrease of 27 mg/dl compared to baseline. There were no changes on BP and metabolic parameters in the control group²⁵.

RSD impact on renal hemodynamics and urinary excretion of albumin was assessed in a study with 100 patients: 88 were subjected to RSD and 12 constituted the control group. There was a decrease in resistivity index with three and six months of procedure, but there was no change in urinary excretion of albumin or C-cystatin values. However, the number of individuals with microalbuminuria or macroalbuminuria was reduced with RSD. There were no changes in these parameters in the control group²⁶.

Another study²⁷ evaluated the role of RSD in 10 patients with RAH and sleep apnea. At the end of six months, it was observed a decrease in BP ($-34/-13$ mmHg) and improvement in sleep apnea (from 16.3 to 4.5 events/hour).

Another interesting evidence related to RSD was recently published, demonstrating the capacity of this technique to reduce left ventricular hypertrophy (LVH) and improve ventricular systolic and diastolic functions in patients with RAH. The study²⁸ included 46 patients who underwent RSD and echocardiogram in three stages (baseline, one month and six months after the procedure), with 18 patients comprising the control group. There was decrease in BP ($-22.5/-7.2$ mmHg after one month and $-27.8/-8.8$ mmHg after six months from procedure) and LVH parameters: reduction of the width of interventricular septum, left ventricular mass index from 53.9 ± 15.6 g/m^{2.7} (112.4 ± 33.9 g/m²) to 47.0 ± 14.2 g/m^{2.7} (103.6 ± 30.5 g/m²) and 44.7 ± 14.9 g/m^{2.7} (94.9 ± 29.8 g/m²) in one and six months, respectively. The improvement of systolic and diastolic functions was evidenced by the reduction of

E/E_c mitral scale and for the increase in ejection fraction from $63.1 \pm 8.1\%$ to $70.1 \pm 11.5\%$ at the end of six months²⁸.

RSD has also shown a relevant improvement in scores evaluating the quality of life three months after procedure. In the study, the subjective evaluation on the quality of life of resistant hypertensive patients before the procedure, was quite negative. It is worth noting that the improvement in the quality of life was not directly associated with the magnitude of BP decrease²⁹.

Cost-effectiveness studies and estimates on clinical benefits in the long-term

Based on the results of the study Symplicity HTN-2¹⁵, it was carried out an analysis of RSD cost-effectiveness and its clinical impact in the long-term. Compared to conventional treatment, RSD reduced the probability of cardiovascular and renal outcomes (relative risk - RR - in 10 years/lifetime: 0.70/0.83 for CVA; 0.68/0.85 for AMI; 0.78/0.90 for all coronary events; 0.79/0.92 for heart insufficiency and 0.72/0.81 for renal disease in the final stage). Estimated mean survival in RSD group was of 18.4 years and in conventional treatment group was of 17.1 years. The ratio of discounted incremental cost-effectiveness was of U\$3,071 per quality-adjusted life-year (QALY), and was, therefore considered a cost-effective strategy for RAH³⁰.

Another analysis revealed the cost-effectiveness in men and women of different ages, and RSD resulted in a gain of 0.98 QALYs for men and 0.88 QALYs in women aged 60, with an additional cost of €2,589 and €2,044, respectively, compared to drug therapy. The younger the patient, the greater the gain in QALYs and the lower the cost. This study pointed out that RSD would be cost-effective until 78 years old for men and 76 years old for women³¹.

Study limitations

This review is a result of an active research of scientific articles named "*renal denervation*" at Medline e PubMed databases, considering a limited number of published original articles and ongoing clinical trials. It represents an exploratory phase of this new intervention method and, therefore, a knowledge theme still in construction.

Future perspectives with RSD

The initial success of RSD technique on RAH, using radiofrequency stimulated the appearance of other types of device, with very promising proposals and more simplified handling and with a more homogeneous performance of RSD^{8,32}. Other interesting techniques, such as renal intra-arterial infusion of guanethidine, or renal periarterial infusion of ethanol³³, or periarterial vincristine injection with

Bullfrog micro-infusion catheter⁸ are still being tested for clinical use. Using non-specific catheters, used in ablation techniques for heart arrhythmias, may represent lower cost to RSD procedure, however, it has not yet been validated for its full scientific use^{22,23}. Among future challenges, is the possibility of performing a non-invasive denervation treatment, using Doppler pointed at renal artery.

Another demand for the future concerns the development of indicators for immediate evaluation of the success of RSD procedure.

Conducting robust, randomized, blinded studies in centers specialized in AH is required to evaluate the long-term efficacy and safety and the possible impact on the reduction of morbidity and mortality. Symplicity HTN-3³⁴ ongoing study must contribute this matter.

Development of knowledge with the use of RSD for RAH could suggest potential use in other conditions concurrent with sympathetic hyperactivity, such as: isolated systolic hypertension, diabetes, chronic renal disease, heart insufficiency, heart arrhythmias, sleep apnea and cirrhosis⁶.

On the basis of limitations of clinical study results with RSD up to this moment and the absence of more comprehensive studies on cost-effectiveness of the procedure, its application in large scale is not yet to be recommended; currently, it must be indicated only for true resistant hypertensive patients, group of very high cardiovascular risk³⁵. It is worth noting that, regardless of a positive clinical result of RSD for RAH, the medical treatment must be based on the combination of continued administration of medications, weight loss and change of lifestyle for all patients^{1,2}.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Brandão AA, Campana EMG, Magalhães MEC, Ferreira E.

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