

Renal Denervation Using an Irrigated Catheter in Patients with Resistant Hypertension: A Promising Strategy?

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Abstract

Background: Systemic hypertension is an important public health problem and a significant cause of cardiovascular mortality. Its high prevalence and the low rates of blood pressure control have resulted in the search for alternative therapeutic strategies. Percutaneous renal sympathetic denervation emerged as a perspective in the treatment of patients with resistant hypertension.

Objective: To evaluate the feasibility and safety of renal denervation using an irrigated catheter.

Methods: Ten patients with resistant hypertension underwent the procedure. The primary endpoint was safety, as assessed by periprocedural adverse events, renal function and renal vascular abnormalities at 6 months. The secondary endpoints were changes in blood pressure levels (office and ambulatory monitoring) and in the number of antihypertensive drugs at 6 months.

Results: The mean age was 47.3 (\pm 12) years, and 90% of patients were women. In the first case, renal artery dissection occurred as a result of trauma due to the long sheath; no further cases were observed after technical adjustments, thus showing an effect of the learning curve. No cases of thrombosis/renal infarction or death were reported. Elevation of serum creatinine levels was not observed during follow-up. At 6 months, one case of significant renal artery stenosis with no clinical consequences was diagnosed. Renal denervation reduced office blood pressure levels by 14.6/6.6 mmHg, on average ($p = 0.4$ both for systolic and diastolic blood pressure). Blood pressure levels on ambulatory monitoring decreased by 28/17.6 mmHg ($p = 0.02$ and $p = 0.07$ for systolic and diastolic blood pressure, respectively). A mean reduction of 2.1 antihypertensive drugs was observed.

Conclusion: Renal denervation is feasible and safe in the treatment of resistant systemic arterial hypertension. Larger studies are required to confirm our findings. (Arq Bras Cardiol. 2014; 102(4):355-363)

Keywords: Hypertension; Catheter ablation; Kidney / innervation; Sympatectomy / methods; Surgical procedures, minimally invasive.

Introduction

Systemic hypertension (SH) is an important public health problem and a significant cause of cardiovascular mortality. Approximately 1 billion adults have SH and this figure is estimated to reach 1.5 billion in 2025¹. In addition, approximately 12.8% of patients have resistant SH².

Data from clinical studies have demonstrated that antihypertensive therapy reduces the incidence of stroke by 35% to 40%, of myocardial infarction by 20% to 25%, and of heart failure by more than 50%³. Despite the proved efficacy of pharmacological treatment, control of

SH remains inadequate in most of patients: approximately 65% of hypertensive patients are not treated or receive inadequate treatments; studies estimate that 34% to 52% of treated patients do not reach the desired target blood pressure levels⁴.

The high prevalence of resistant SH and low rates of blood pressure control obtained with conventional treatment have resulted in the interest for alternative therapeutic strategies. With the AIM of promoting inhibition or blockade of the sympathetic nervous system (SNS) activity, percutaneous renal sympathetic denervation (RSD) emerged with perspectives of high efficacy and safety in the treatment of patients with resistant SH⁵. However, catheters dedicated to RSD are still unavailable in Brazil. This fact, plus the potential advantages of irrigated catheters in cardiac ablations (ability to reach deeper lesions and lower risk of thrombus formation in the catheter tip, with consequent embolization), corroborated the hypothesis that irrigated-tip catheters can also be beneficial in the context of RSD.

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The objective of this investigation was to evaluate the feasibility and safety of RSD with irrigated catheter in patients with resistant SH.

Methods

Case series

Patients with resistant SH being regularly followed up in the Outpatient Clinic of Arterial Hypertension and Nephrology of the Dante Pazzanese Institute of Cardiology were evaluated for inclusion. The American Heart Association scientific statement for resistant hypertension⁴ criteria were used for the definition of resistance, so that patients either should have systolic blood pressure (SBP) > 140 mmHg, as measured in the office, despite the use of three or more antihypertensive drugs, or controlled blood pressure using four or more synergistic antihypertensive drugs. Diagnosis of resistant SH should have been confirmed by at least one ambulatory blood pressure monitoring (ABPM) performed throughout the follow-up period.

Poor adherence to pharmacological treatment was ruled out by hospitalizing the patients for at least five days prior to the intervention. During the hospital stay, investigation of secondary causes for SH was completed and updated. Patients with a glomerular filtration rate < 45 mL/min; severe liver disease; coagulation disorders; NYHA functional class III or IV heart failure; severe ventricular dysfunction (EF < 0,30); moderate or severe heart valve diseases; severe arrhythmias; acute myocardial infarction or stroke in the past 6 months; unexplained angina and/or myocardial ischemia; renal artery abnormalities (stenosis > 50%, presence of stent or previous angioplasty, solitary kidney); renal artery diameter < 4 mm; history of surgical procedures in the past 2 months; hypersensitivity to the DYE; suspected pregnancy; history of alcohol consumption within less than 1 year; mental disorder that could affect the follow up; and life expectancy shorter than 1 year were excluded from the study.

The research protocol and the written informed consent form were duly approved by the Research Ethics Committee of the Dante Pazzanese Institute of Cardiology in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Clinical endpoints

The primary endpoint of the study was the procedure safety, as assessed by the quantification of the rate of periprocedural adverse events (vascular complications in the puncture site and in the renal artery); analysis of the renal function (comparison between baseline and 6 months after the intervention); and occurrence of renal arterystenosis/aneurysm at 6 months after the intervention, as assessed by arteriography.

The secondary endpoints comprised the changes in office BP levels at 6 months after the procedure, and the analysis of the effect of the procedure on the number of antihypertensive drugs used. The changes in BP of patients who had ABPM recorded within up to 1 month prior to the

procedure were also analyzed by this method throughout the study.

All BP measurements were taken using an automated brachial sphygmomanometer, in accordance with the recommendations of the VI Brazilian Guidelines of Arterial Hypertension⁶. The choice of the pharmacological treatment for the control of blood pressure levels was left to the discretion of the attending physician, according to the patient's tolerance profile and associated comorbidities. Adherence to treatment was encouraged in all medical visits.

Description of the procedure

Two arterial lines were placed, according to the method standardized by the team; one was in the right femoral artery, and the other, in the left femoral artery. A catheter was inserted in the left renal artery for injection of DYE to perform renal arteriography. The right femoral artery was used for insertion of a sheath, through which the ablation catheter (Therapy Cool Path[®], St Jude Medical[®], Minneapolis, Minnesota, USA, or Celsius Thermocool[®], Biosense-Webster Inc[®], Diamond Bar, California, USA) was introduced and positioned in the renal artery. After vascular line placement, unfractionated heparin was administered at a dose of 100 u/kg for anticoagulation. Aortography at the level of the renal arteries was performed after administration of intravenous nitroglycerin (200 mcg), and followed by catheterization and selective renal arteriography for the evaluation of the anatomy and positioning of the ablation catheter distally in the renal artery. Four to six sequential deliveries of radiofrequency were made along both renal arteries, with the purpose of promoting renal denervation. The catheter was pulled 5 mm and rotated after each delivery, thus producing a spiral configuration of the ablations (Figure 1).

Due to the severe visceral pain generated by ablation, sedation and analgesia with narcotic and opioid drugs were performed in all cases. At the end of the procedure, a control renal arteriography was performed to evaluate the vascular integrity, also after administration of intravenous nitroglycerin (200 mcg).

Post-procedural assessment and clinical follow-up

The introducers were removed when the activated clotting time reached values < 200 seconds. Manual compression hemostasis was performed for at least 20 minutes, followed by a compressive dressing. The patient was allowed to walk 4 hours after resting, provided there was no bleeding in the puncture site. After the procedure, attention was focused on the occurrence of vascular complications such as hematomas and pseudoaneurysms in the site of femoral lines. Medications were adjusted and the patients were instructed on the need for a periodic follow-up.

The first follow-up visit occurred 7 ± 2 days after the procedure and its purpose was to evaluate complications in the puncture site, renal function, hemoglobin/hematocrit, and to readjust the dosage of the antihypertensive drugs.

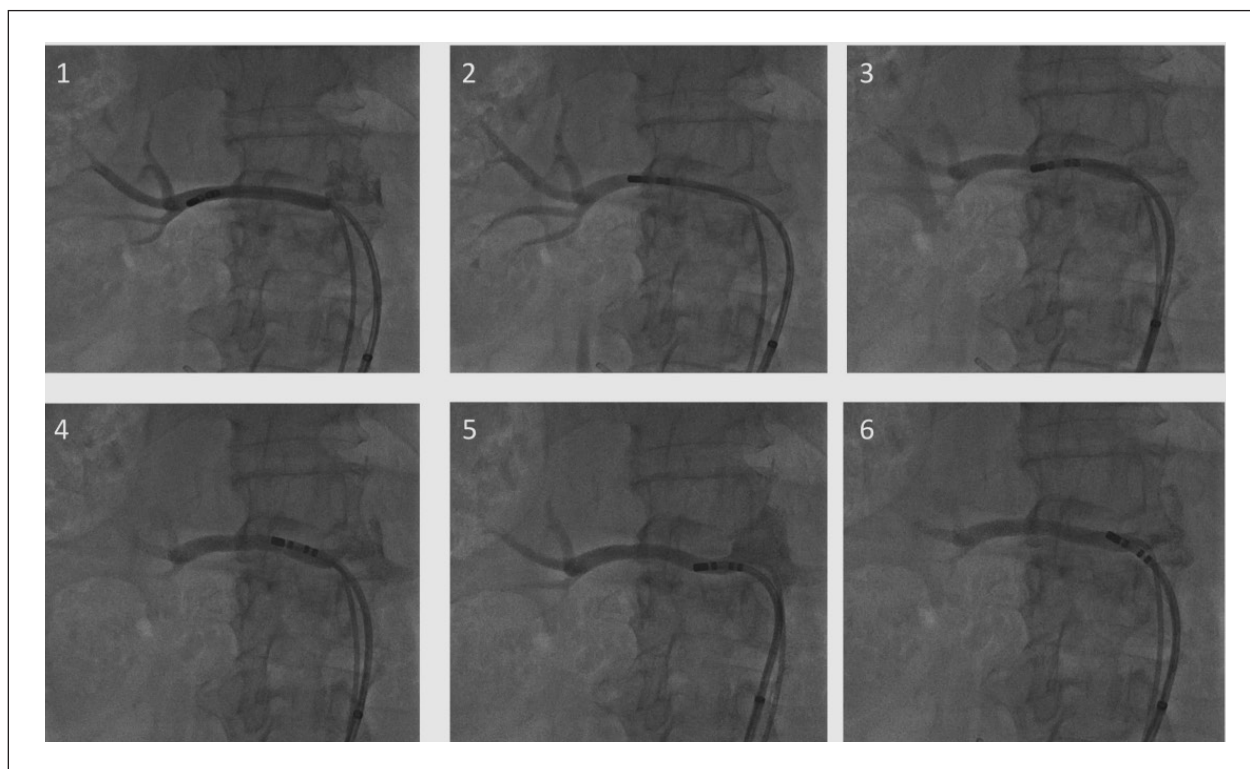


Figure 1 - Sequential radiofrequency lesions in right renal artery. Deliveries started at the distal segment of the renal artery; the catheter was pulled and rotated after each delivery to promote sequential lesions with a spiral configuration.

Further follow-up visits occurred at 30 ± 7 , 90 ± 10 , and 180 ± 10 days (Figure 2). BP was measured as described for the preprocedural assessment. Laboratory tests and ABPM were requested in all visits. Angiography of the renal arteries was repeated at 6 months of follow-up.

Statistical analysis

Continuous variables were expressed as mean and standard deviation and compared using the Student's t test, considering the normal data distribution. Categorical variables were expressed as absolute and relative frequencies and compared using the chi square test. For all parameters compared, p values ≤ 0.05 were considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences® (SPSS) version 16 program (software for Windows®, SPSS Inc®, Chicago, Illinois, USA).

Results

Baseline characteristics

Ten patients (nine women) underwent RSD. Their mean age was $47.3 (\pm 12)$ years. The mean time of SH was 18.3 ± 10.7 years. The mean office SBP and diastolic blood pressure (DBP) were 187.1 ± 35.7 and 104.1 ± 18.5 , respectively. Eight patients had undergone ABPM within 30 days prior to the procedure. The mean BP levels measured by ABPM were 179.2 ± 23.2 and 109.4 ± 22.7 for SBP and DBP, respectively.

The mean number of antihypertensive drugs used before the procedure was 7.6 ± 1.3 . The patients' baseline characteristics are summarized in Table 1.

Angiographic characteristics

The mean diameters of the right and left renal arteries were 4.9 ± 0.4 mm and 5.0 ± 0.7 mm, respectively. The mean length of the right and left renal arteries were 35.3 ± 8.4 mm and 27.6 ± 10.5 mm, respectively. The individual measurements are shown in Table 2.

In one case, the presence of a polar artery was observed on the left side; in another case, the presence of three polar arteries was observed, two of them on the left and one on the right. Two patients had mild proximal renal artery stenosis.

Technical characteristics of the procedure

All procedures were performed via the transfemoral approach according to the protocol described here. On average, 79 mL of DYE were used and 19.7 ± 5.8 minutes of fluoroscopy were spent. The mean number of radiofrequency deliveries was 5.1 ± 0.7 on the right renal artery and 4.3 ± 1.6 on the left renal artery (Table 2).

Procedure safety

The procedure was performed uneventfully in 90% of cases. In the first case of this series, dissection of the renal artery was

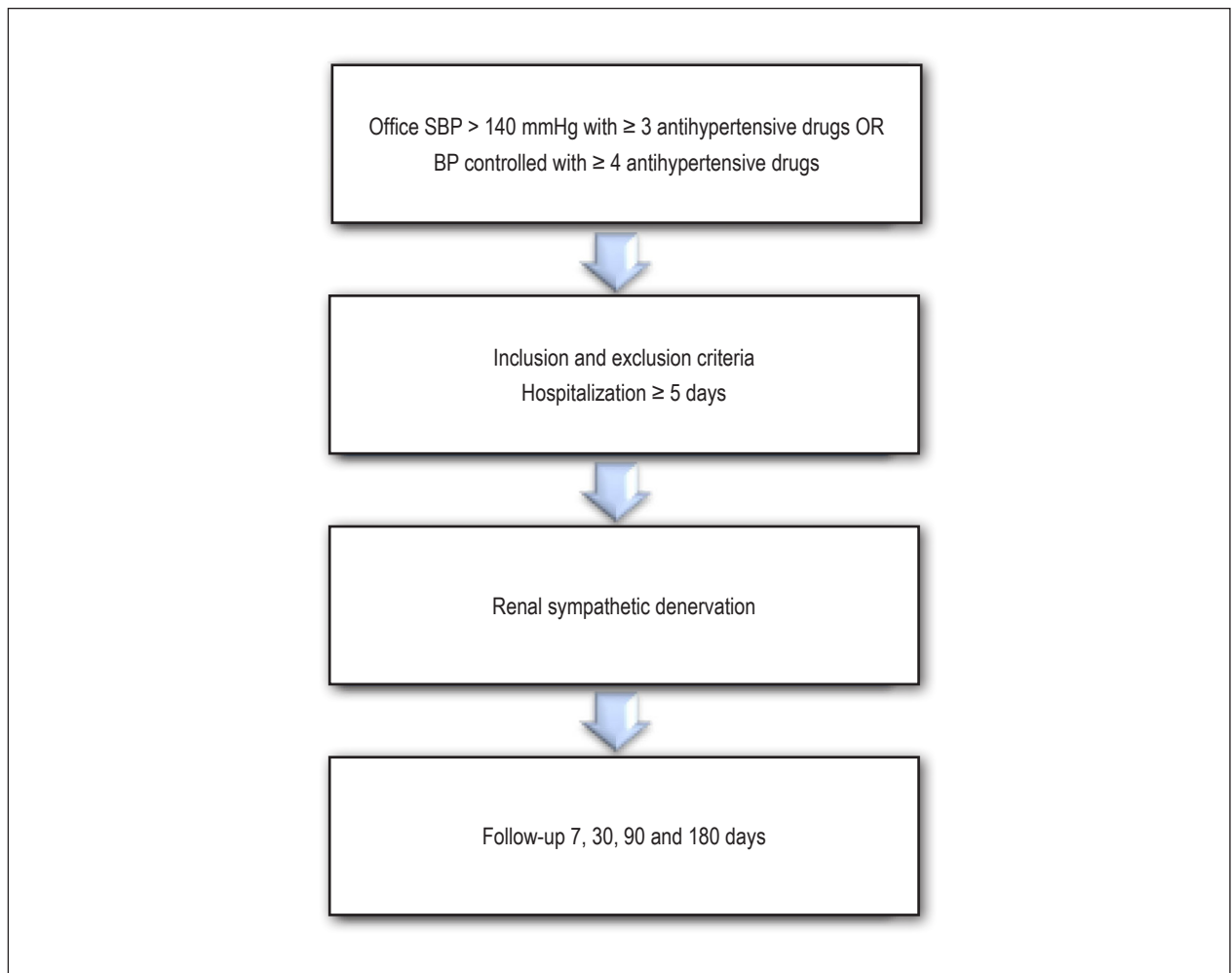


Figure 2 - Study flowchart. SBP: systolic blood pressure; BP: blood pressure.

Table 1 - Baseline characteristics

Variable	
Female gender, n (%)	9 (90)
Age, mean (SD)	47.3 (12)
Body mass index, mean in kg/m ² (SD)	29.6 (3.8)
Diabetes mellitus, n (%)	3 (30)
Dyslipidemia, n (%)	7 (70)
Cigarette smoking, n (%)	0 (0)
Alcohol consumption, n (%)	0 (0)
Previous myocardial infarction, n (%)	0 (0)
Previous stroke, n (%)	0 (0)
Peripheral vascular disease, n (%)	0 (0)
Family history of SH, n (%)	9 (90)
Baseline creatinine, mean in mg/dL (SD)	0.94 (0.29)

SD: standard deviation; SH: systemic hypertension.

Table 2 - Angiographic and technical characteristics of the procedure

Patient	Diameter RRA (mm)	Diameter LRA (mm)	Length RRA (mm)	Length LRA (mm)	Deliveries RRA (n)	Deliveries LRA (n)
1	4.2	4.3	24.0	10.9	5.0	0
2	5.1	5.0	40.3	30.0	5.0	5.0
3	5.5	6.0	41.0	30.0	6.0	5.0
4	5.5	4.5	35.0	17.5	6.0	4.0
5	4.8	4.3	30.0	36.0	5.0	5.0
6	5.2	6.1	27.0	27.0	4.0	6.0
7	5.2	4.3	26.0	13.0	5.0	5.0
8	4.4	5.5	50.0	39.0	4.0	4.0
9	4.8	5.2	40.0	33.0	5.0	4.0
10	4.8	5.0	40.0	40.0	6.0	5.0
Média (DP)	4.9 (0.4)	5.0 (0.7)	35.3 (8.4)	27.6 (10.5)	5.1 (0.7)	4.3 (1.6)

SD: standard deviation; RRA: right renal artery; LRA: left renal artery.

detected after ablation due to mechanical damage caused by the sheath. This was treated with stent implantation, with no subsequent complications or increase in the length of hospital stay. At 6 months, a control renal arteriography showed a patent stent with no significant intrastent hyperplasia.

Focal parietal irregularities were observed in some cases immediately after radiofrequency delivery; they were attributed to spasm and/or edema. None was considered to limit the blood flow at the end of the procedure.

No complications related to the femoral puncture were observed during the periprocedural period. There was no elevation in serum creatinine levels, thus denoting preserved glomerular filtration rate during the follow-up (Figure 3).

Renal vascular safety

Renal arteriography was performed in all patients at 6 months of follow-up. In one case, there was evidence of left renal artery stenosis of significant magnitude (70%). Although with no clinical implication, it was treated with stent implantation, uneventfully.

Effects on blood pressure and on the number of antihypertensive drugs

After six months of follow-up, RSD reduced office BP measurement by a mean of 14.6/6.6 mmHg ($p = 0.4$ for both SBP and DBP). A progressive reduction in blood pressure levels was observed throughout the follow-up, with a slightly greater benefit on the 3rd month in relation to the 6th month (Figure 4). The mean ABPM BP reduction ($n = 8$) was 28/17.6 mmHg ($p = 0.02$ and 0.07 for SBP and DBP, respectively) (Figure 5). A mean reduction by 2.1 antihypertensive medications prescribed was observed at 6 months (Figure 6).

A significant variation in the antihypertensive response was observed among the patients. While no antihypertensive effect or reduction in the number of medications was observed in

three patients, other three significantly benefited from the procedure, with reductions of up to 62 mmHg in SBP and of up to six antihypertensive drugs at 6 months of follow-up.

Discussion

This was a Brazilian study conducted in a tertiary-care center, in which an irrigated catheter was used for radiofrequency delivery in the context of RSD in patients with resistant hypertension. The results showed that renal sympathetic activity ablation using an irrigated catheter is feasible and safe.

The procedure reduced office SBP and DBP by 14.6 mmHg and 6.6 mmHg, respectively, on average. There was a mean reduction by 2.1 antihypertensive drugs used. A reduction of up to six antihypertensive drugs and up to 62 mmHg in SBP was observed during follow-up. Results of ABPM in eight patients were even better, with a significant reduction by 28 mmHg and 17.6 mmHg in SBP and DBP, respectively. The difference between ABPM and office BP reductions shows the white-coat effect in our population. We should point out that changes in blood pressure levels as assessed by ABPM were not reported in two patients. In one patient, due to the poor quality of the preprocedural ABPM, and, in another, due to bruise/hematoma resulting from low platelet count during the performance of the baseline ABPM; for this reason, it was decided not to repeat the test during the follow-up.

Overall, the reduction in BP as measured by ABPM in our study is similar to that measured in the office by the Symplicity catheter. In the Symplicity HTN-2 study, renal denervation reduced office SBP and DBP by 32 mmHg and 12 mmHg, respectively, after 6 months of follow-up. However, there are some differences between the two studies. First, our patients required a greater number of antihypertensive drugs at baseline (7.6 versus 5.2). Second, because of our smaller number of patients, we could confirm resistant SH by means of hospitalization, whereas in the Symplicity HTN-2

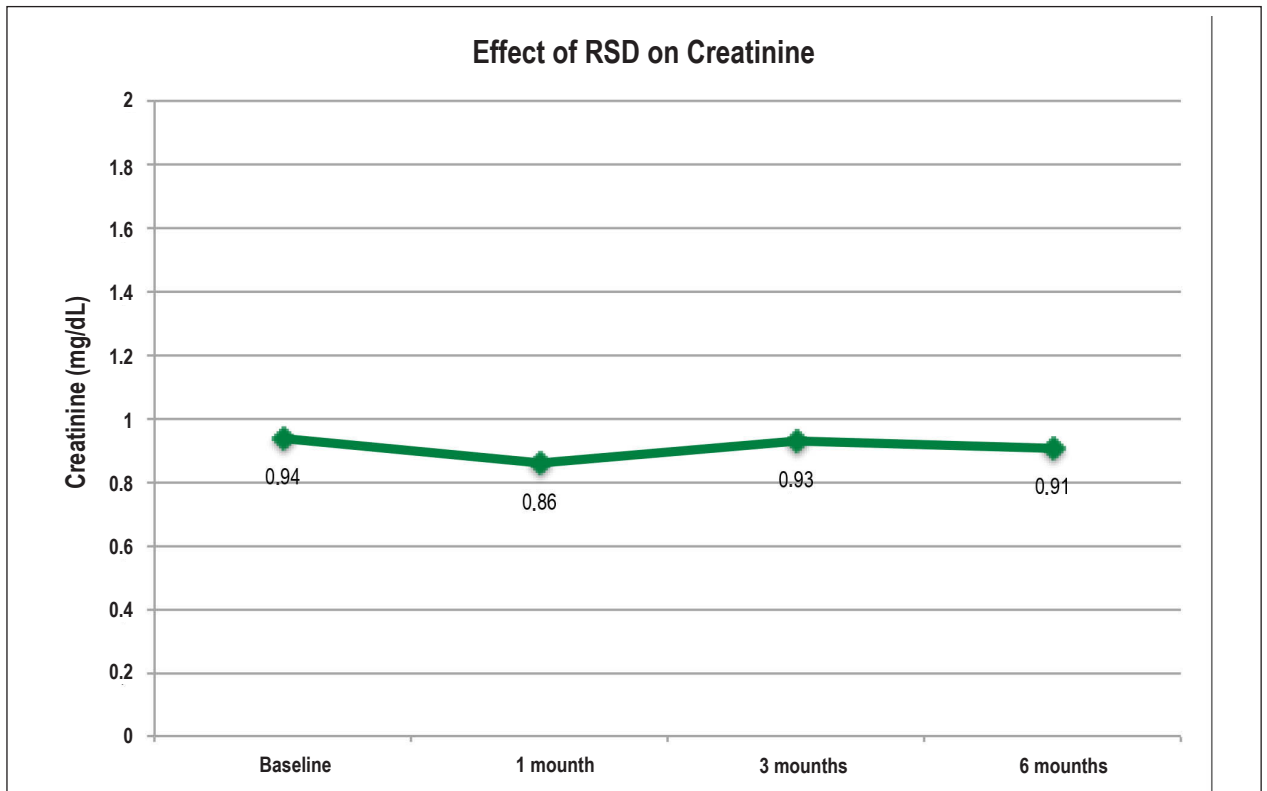


Figure 3 - Effects of renal sympathetic denervation (RSD) on serum creatinine levels. BP: blood pressure; SBP: systolic blood pressure.

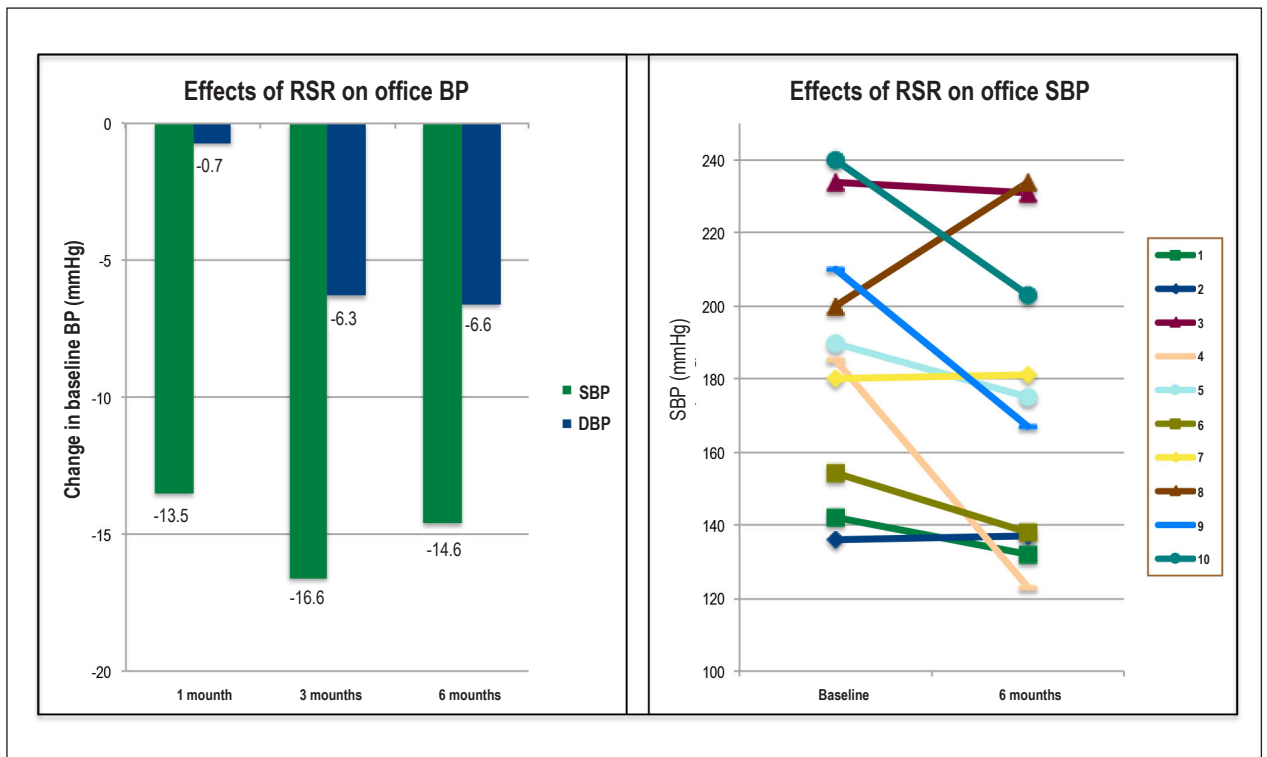


Figure 4 - Left: mean effect of renal sympathetic denervation (RSD) on blood pressure (BP) measured by ambulatory blood pressure monitoring (ABPM). Right: effect of RSD on systolic blood pressure (SBP) measured by ABPM in 10 patients undergoing the procedure.

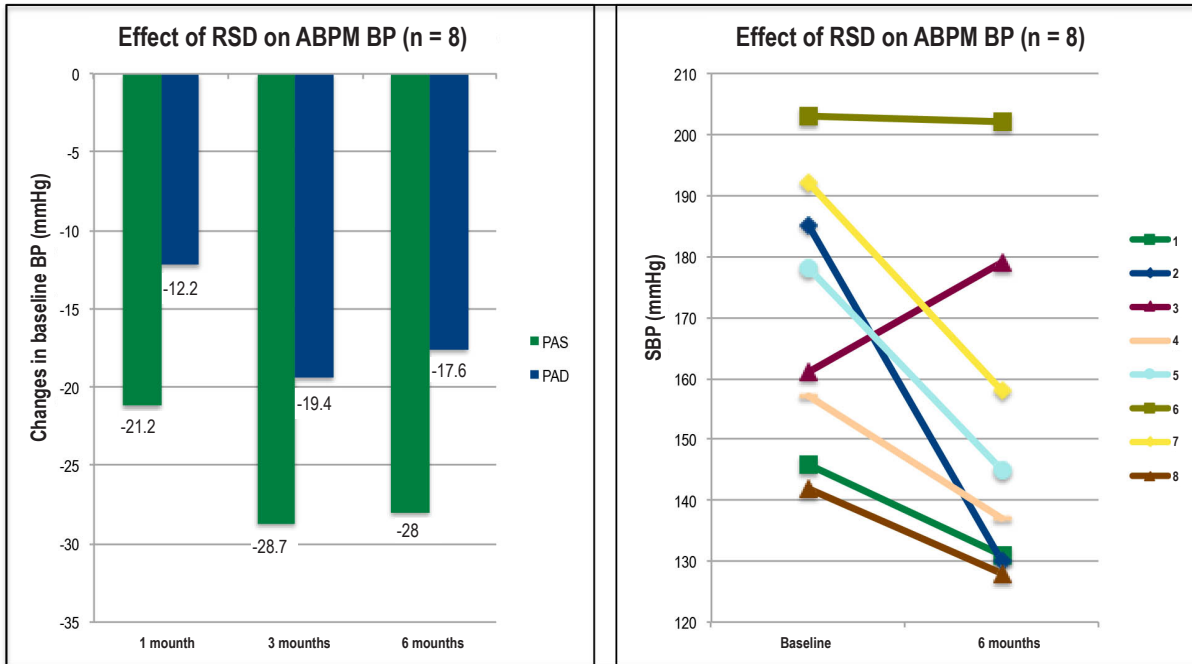


Figure 5 - Left: mean effect of renal sympathetic denervation (RSD) on blood pressure (BP) measured by ambulatory blood pressure monitoring (ABPM). Right: effect of RSD on systolic blood pressure (SBP) measured by ABPM in 8 patients undergoing the procedure.

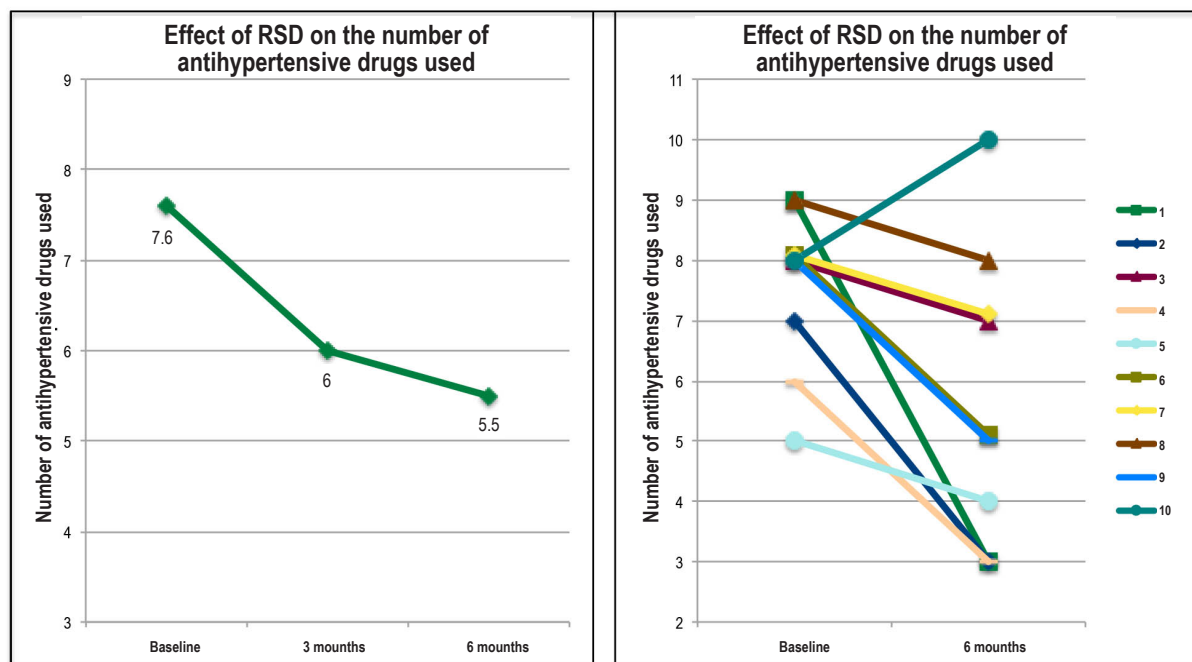


Figure 6 - À esquerda: efeito da DSR sobre a média do número de anti-hipertensivos. À direita: efeito da DSR sobre o número de anti-hipertensivos em cada um dos 10 pacientes submetidos ao procedimento. DSR: Denervação simpática renal.

study, this diagnosis was defined in outpatient visits, and this may have led to overestimated findings. Third, in Symplicity HTN-2, changes in the dosage of the antihypertensive drugs were only allowed if the patient showed symptoms related to hypotension. In the present study, drug dosage was changed with the aim of achieving control, as recommended by the VI Brazilian Guideline of Arterial Hypertension. Fourth, the non-responders rate, defined as a SBP reduction < 10 mmHg, was greater than that of Symplicity. This finding may have resulted from a higher complexity, smaller number of patients assessed in the present study, and, mainly, from the fact that, in some patients, baseline BP was controlled with four or more antihypertensive drugs and, in these cases, no significant reduction was observed in BP, but rather in the number of drugs used during follow-up. Still, the percentage of non-responders to RSD in this study is consistent to data of the literature, whose rates reach values of up to 37%^{5,7}. Finally, the irrigated-tip catheter designed for cardiac ablation – a non-dedicated catheter for RSD, was used.

Recently, the effects of three different catheters generally used for cardiac ablation in an *in vitro* study with porcine renal arteries were published⁸. When a 5F catheter with solid tip and 8W energy is used (a catheter with similar characteristics and same energy as used in Simplicity HTN-2), more significant neural renal lesions were observed when delivery was extended to up to 120 seconds (same delivery duration as used in Simplicity HTN-2). The 7F solid-tip catheter (generally used for cardiac ablations) caused significant neural lesions, regardless of the energy (8W or 15W) or duration of radiofrequency delivery (30, 60, or 120 seconds). Additionally, the 7F irrigated catheter (generally indicated for ablations of the left cardiac chambers, such as in atrial fibrillation and ventricular tachycardia) caused complete destruction of the nerves and mid-layer damage when 15W were delivered, as from 60 seconds. These observations translate the rationale that 5F solid-tip catheters cause neural lesions; however, radiofrequency deliveries with 7F catheters, especially the irrigated catheters, result in deeper and more intense lesions. Based on these data, we conclude that, in the cases in which electrophysiology catheters are used for RSD, the differences among them should be respected, same for the standardization of radiofrequency delivery for each type of catheter, aiming at an adequate delivery of energy to the tissue in terms of efficacy and safety of the procedure. Little energy may be insufficient for an appropriate nerve ablation, and excessive energy may cause acute and/or mid- and long-term side effects such as renal artery stenosis or aneurysm⁸.

Lesion by radiofrequency depends on several factors, among which an adequate electrode-tissue contact, the energy used, delivery duration, and the catheter type stand out. In clinical situations such as ventricular tachycardia, it is mandatory that the lesion is deep enough to penetrate the myocardial tissue. However, the excessive temperature in the catheter tip may result in the formation of a clot, which, in turn, limits energy release and reduces lesion extension. Based on these facts, efforts have been made to optimize energy

delivery to the tissue without substantially increasing the catheter tip temperature. Currently, catheters with continuous irrigation systems are commonly used in the treatment of cardiac arrhythmias with the purpose of increasing the depth of radiofrequency tissue penetration. Considering the location of the renal nerves in the vessel adventitia – sometimes more than 4 mm beyond the intima layer, we hypothesize that irrigated catheters may also be beneficial in the setting of RSD. Our findings were consistent with those published in Ahmed et al⁹ study, in which ten patients with resistant SH underwent RSD with irrigated catheter. The authors demonstrated reductions in SBP and DBP by 21 and 11 mmHg, respectively, at 6 months of follow-up, and absence of severe complications⁹. Renal artery dissection resulting from damage by the sheath occurred in our first case. After technical adjustments, no other subsequent event was observed, thus suggesting a learning curve effect. Complications such as infarction, renal failure or thrombosis and pulmonary edema were not reported. One case of stenosis was diagnosed at 6 months of follow-up in an asymptomatic patient. In this case, stent implantation was performed successfully and uneventfully. We should point out that this patient was on eight antihypertensive drugs prior to RSD, and at 12 months of follow-up his blood pressure levels were controlled with the use of only three antihypertensive drugs.

Among the major limitations of this study, we point out its non-randomized design, the small sample, and the absence of a control group. Despite these limitations, the results seem promising and are consistent with data from the literature. Further randomized studies are necessary to confirm the present findings.

Author contributions

Conception and design of the research: Armaganijan L, Staico R, Moraes A, Abizaid A, Moreira D, Amodeo C, Sousa M, Armaganijan D, Sousa JE; Acquisition of data and Analysis and interpretation of the data: Armaganijan L, Staico R, Moraes A; Statistical analysis: Armaganijan L, Staico R; Writing of the manuscript: Armaganijan L; Critical revision of the manuscript for intellectual content: Staico R, Moraes A, Abizaid A, Moreira D, Amodeo C, Sousa M, Armaganijan D, Sousa JE, Sousa A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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