Original Article

# Renal sympathetic denervation with an irrigated-tip catheter: a feasibility study

Rodrigo Vugman Wainstein[a], Luiz Carlos Corsetti Bergoli[a,*], Marco Vugman Wainstein[a], Fernando Pivatto Jr.[a], Gustavo Gonçalves Szortyka[b], Leandro Ioschpe Zimerman[a], Maurício Pimentel[a], Miguel Gus[a], Sandro Cadaval Gonçalves[a], Flávio Danni Fuchs[a]

[a] *Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil*
[b] *Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*

ARTICLE INFO

ABSTRACT

*Background:* Catheter-based radiofrequency renal denervation has emerged as a promising tool for blood pressure control in patients with resistant hypertension. The aim of the present study was to evaluate the feasibility and safety of percutaneous renal sympathetic denervation by radiofrequency ablation using an irrigated-tip catheter in patients with true resistant hypertension.
*Methods:* A saline-irrigated catheter was used for renal sympathetic denervation. The sample consisted of a consecutive series of 11 patients with resistant hypertension based on office blood pressure measurements, confirmed by 24-hour systolic ambulatory blood pressure monitoring (ABPM) ≥ 135 mmHg.
*Results:* After 6 months of follow-up, there was a non-significant reduction of 3.9 mmHg ($p$ = 0.49) and 5.4 mmHg ($p$ = 0.19) in mean systolic and diastolic blood pressures, respectively, as measured by 24-hour ABPM. The mean office systolic blood pressure decreased significantly (182.1 ± 7.4 mmHg to 166.5 ± 7.7 mmHg; $p$ = 0.03), while the mean office diastolic blood pressure did not change significantly (102.4 ± 5.5 mmHg to 99.7 ± 4.0 mmHg; $p$ = 0.54). There was one case of dissection of a branch of the renal artery, which was treated with stent placement.
*Conclusions:* Our study demonstrated the safety and feasibility of renal sympathetic denervation using a saline-irrigated catheter but failed in reducing blood pressure, as measured by 24-hour ABPM, in highly selective patients with true resistant hypertension.

© 2017 Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Denervação simpática renal por cateter com ponta irrigada: estudo de viabilidade

RESUMO

*Introdução:* A denervação renal por cateter de radiofrequência emergiu como ferramenta promissora para o controle da pressão arterial em pacientes com hipertensão resistente. O objetivo do presente estudo foi avaliar a factibilidade e a segurança da denervação simpática renal percutânea com ablação por radiofrequência usando um cateter irrigado em pacientes com hipertensão arterial resistente.
*Métodos:* O cateter irrigado com solução salina foi utilizado para a denervação simpática renal. A amostra foi constituída por uma série consecutiva de 11 pacientes com hipertensão resistente na aferição ambulatorial, confirmada por monitorização ambulatorial da pressão arterial (MAPA) de 24 horas, com pressão arterial sistólica ≥ 135 mmHg.
*Resultados:* Após seguimento de 6 meses, houve redução não significativa de 3,9 mmHg ($p$ = 0,49) e 5,4 mmHg ($p$ = 0,19) na média das pressões sistólicas e diastólicas, respectivamente, avaliadas pela MAPA de 24 horas. Houve redução significativa da pressão arterial sistólica ambulatorial (182,1 ± 7,4 mmHg vs. 166,5 ± 7,7 mmHg; $p$ = 0,03), mas não da pressão arterial diastólica (102,4 ± 5,5 mmHg vs. 99,7 ± 4,0 mmHg; $p$ = 0,54). Também observou-se um caso de dissecção de ramo da artéria renal, tratada com implante de stent.
*Conclusões:* Foram demonstradas a segurança e a factibilidade da denervação simpática renal utilizando cateter irrigado de radiofrequência com solução salina, mas não foi verificada redução da pressão arterial medida pela MAPA de 24 horas em 6 meses em pacientes altamente selecionados com hipertensão resistente verdadeira.

© 2017 Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista.
Este é um artigo Open Access sob a licença de CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

Hypertension remains a major global concern and ranks among the leading risk factors for cardiovascular complications, such as myocardial infarction and stroke.[1] In 2000, an estimated 1 billion people worldwide had hypertension, and this global burden is predicted to increase to 1.56 billion by 2025.[2] Approximately 8 to 10% of all hypertensive patients have resistant hypertension, a condition that confers substantial additional risk for cardiovascular disease.[3-6]

Renal denervation with radiofrequency catheter ablation (RFA) has emerged as a promising tool for blood pressure control in patients with resistant hypertension. The concept of sympathetic nerve ablation, which provided the background for the development of renal denervation in the treatment of hypertension, is based on three ideas. The first idea is the activation of the renal sympathetic outflow in hypertensive patients, the second is the blood pressure-lowering effect of surgical renal denervation demonstrated in experimental models of hypertension, and the third is the anatomy of the renal sympathetic nerves in their passage to the kidneys.[7,8] Initial clinical trials of renal denervation in patients with resistant hypertension have shown promising office blood pressure reduction.[9,10] However, a large randomized controlled trial with a sham control group failed to meet its primary efficacy endpoint,[11] and the efficacy of the procedure has been brought into question. Even so, some questions must be answered in future trials, such as the identification of responders, how to monitor intraprocedural success and quantification of device-related differences in the effectiveness of renal ablation.[12]

In this scenario, a number of new catheter systems and treatment modalities for renal denervation are under development. The potential advantages of using an irrigated-tip catheter for cardiac ablation, such as the ability to reach deeper lesions and reduce the risk of thrombus formation at the catheter tip, support the hypothesis that irrigated-tip catheters can also be beneficial in the setting of renal denervation.[13,14]

The aim of the present study was to evaluate the feasibility and safety of renal denervation using a saline-irrigated RFA catheter in patients with true resistant hypertension.

## Methods

### Study design

We conducted an experimental, prospective study to assess the feasibility and safety of renal denervation in a consecutive series of patients with resistant hypertension.

### Study patients

Patients were recruited from the Hypertension Clinic at *Hospital de Clínicas de Porto Alegre* (HCPA) after review of self-reported medication adherence. Eligible participants were all adults aged 18 to 75 years with a diagnosis of resistant hypertension, defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg as measured in the office, despite the use of three or more antihypertensive drugs in adequate doses, one of which was a diuretic.

Patients who met the eligibility criteria underwent 24-hour ambulatory blood pressure monitoring (ABPM). To confirm the diagnosis of resistant hypertension (24-hour SBP ≥ 135 mmHg), ABPM was performed using a Spacelabs 90207 ABPM monitor (SpaceLabs Inc, Wokingham, UK) programmed for measurements every 15 minutes between 7 a.m. and 11 p.m. (day period) and every 20 minutes from 11 p.m. to 6 a.m. (night period).

All patients were screened for secondary causes of hypertension and submitted to pharmaceutical assistance in order to help with antihypertensive drug therapy adherence.

Patients were included only after poor adherence to medication was excluded. The exclusion criteria were a glomerular filtration rate of less than 45 mL/min/1.73 m², pregnancy, mental disorder that could affect follow-up, or a life expectancy of less than 1 year. Patients with myocardial infarction, unstable angina or stroke within 6 months of treatment were also excluded. Anatomic exclusion criteria were renal artery stenosis of more than 50%, prior renal artery stenting, multiple renal arteries, a renal artery of less than 4 mm in diameter, or a treatable segment of less than 20 mm in length.

The study was approved by the Ethics Committee of HCPA. All procedures were performed after obtaining written informed consent.

### Study treatment

Renal denervation was performed under conscious sedation with local anesthesia and analgesia. Systemic anticoagulation with intravenous heparin was achieved after femoral artery puncture and sheath insertion. A 45-cm long 8 F sheath was positioned in the abdominal aorta, and a pigtail catheter was advanced to perform non-selective renal angiography. Contrast was injected to locate the ostia of the renal arteries and assess the presence of any anatomic exclusion criteria.

If the anatomy was suitable, a large-curve, open irrigated-tip, deflectable 7 F RFA catheter with a 3.5-mm tip (ThermoCool, Biosense Webster, Waterloo, Belgium) was placed in the right renal artery and advanced distally under fluoroscopic guidance, with the tip directed upward.

Radiofrequency energy was delivered using a radiofrequency generator (Abcontrol, Biotronik, Berlin, Germany) at a power of 15 W, flow rate of 17 mL/minute, and controlled temperature (not exceeding 43°C). If the temperature exceeded this limit, the generator immediately stopped the application.

Each energy application lasted 90 seconds, and the catheter was not moved during the procedure. At the end of each application, the catheter was moved proximally and curved to the anterior portion (clockwise rotation) for a new application. The goal was to perform four applications in the right renal artery (depending on its length), always moving the catheter proximally and rotating clockwise (1/4 turn each time). This procedure was intended to avoid circumferential energy delivery, which could increase the chance of creating renal artery stenosis.

Upon reaching the ostium of the renal artery, energy application was stopped. The catheter and sheath were pulled back into the abdominal aorta. Then, from this position, the left renal artery was cannulated with the RFA catheter, and the same ablation procedure was repeated. At the end of all applications, aortography was performed to exclude acute complications. The catheter and sheath were then removed, and hemostasis was achieved by manual compression.

Patients returned for their first follow-up visit 7 days after the procedure for evaluation of puncture site complications and renal function. After the first visit, follow-up assessments occurred every 30 days over the first 6 months after intervention. Each visit included measurement of office blood pressure, heart rate, review of antihypertensive medications, and assessment of adverse events.

ABPM was required at 6 months for all patients. After the study began, we decided to include ABPM at 30 days after the procedure and analysis of baseline and 30-day epinephrine, norepinephrine and dopamine levels.

Adherence to treatment and lifestyle changes were encouraged at all medical visits. Automated brachial sphygmomanometer was used for blood pressure measurements at each office visit. Antihypertensive drugs were prescribed at the discretion of the attending physician according to the patient's tolerance and associated comorbidities.

*End points*

The primary safety outcomes were acute procedural complications, defined as vascular or renal artery injuries of percutaneous renal denervation, and clinically meaningful changes in renal function after 6 months of follow-up. The primary efficacy outcome was reduction in mean 24-hour ABPM at 6 months compared with baseline.

Secondary efficacy outcomes included a reduction in office systolic and diastolic blood pressure from baseline to 6 months, change in ambulatory daytime and nighttime blood pressure from baseline to 6 months and reduction in plasmatic catecholamine levels after 30 days. The reductions in 24-hour ABPM at 30 days were also evaluated, compared to baseline and considered a secondary efficacy outcome.

*Statistical analysis*

Parametrically distributed continuous variables were expressed as the mean and standard deviation (SD) and compared using a generalized estimating equation model. The Wilcoxon test was used to compare non-parametrically distributed continuous variables, such as plasma catecholamine levels, before and after intervention. Categorical variables were expressed as absolute and relative frequencies and compared using the Chi-square test. Descriptive statistics were used for baseline demographics and medications. For all comparisons, a *p*-value < 0.05 was considered statistically significant. Sample size was decided arbitrarily because it is a feasibility and safety study. All statistical analyses were performed using IBM Statistical Package for Social Science (SPSS), version 18.

**Results**

Seventeen patients were selected, but only 11 were included in the analysis (Figure 1). Table 1 shows the patient characteristics. Three patients withdrew their consent to undergo the procedure. At the beginning of the procedure, immediately after abdominal angiography, three other patients were excluded: one patient had severe unilateral renal artery stenosis, which was treated with stent placement; one patient had small-caliber renal arteries (< 4 mm); and one patient showed a very high impedance on the catheter, precluding the safe application of radiofrequency energy. The mean number of antihypertensive drugs used was 6.0 ± 1.3. At baseline, mean office systolic and diastolic blood pressures were 182.1 ± 7.4 mmHg and 102.4 ± 5.5 mmHg, respectively. In 24-hour ABPM, mean systolic and diastolic blood pressures were 151.1 ± 2.9 mmHg and 90 ± 3.3 mmHg, respectively (Table 2). Nocturnal systolic and diastolic blood pressure dip was present in two and six cases, respectively. Four patients had blood samples collected at baseline and 30 days after the procedure for analysis of catecholamine levels. Only 5 of 11 patients underwent 24-hour ABPM at 30 days. The number of antihypertensive drugs from baseline to 6 months was similar.

In all cases, intervention was performed via the femoral artery. Bilateral renal RFA was performed in all patients, and the mean number of applications was 4.9 ± 0.9 in the right renal artery and 4.8 ± 0.8 in the left renal artery. All patients were discharged home 1 day after the renal denervation procedure.

There was one case of periprocedural dissection of a branch of the left renal artery. The lesion was stented with good angiographic result, restoring normal blood flow in the vessel. There was no perforation or embolization that required interventions involving the renal vasculature. There were no vascular complications or other major adverse events requiring prolonged hospital stay. Serum creatinine levels remained stable from baseline to 6 months after intervention (0.8 ± 0.25 mg/dL to 0.87 ± 0.28 mg/dL ; *p* = 0.67).
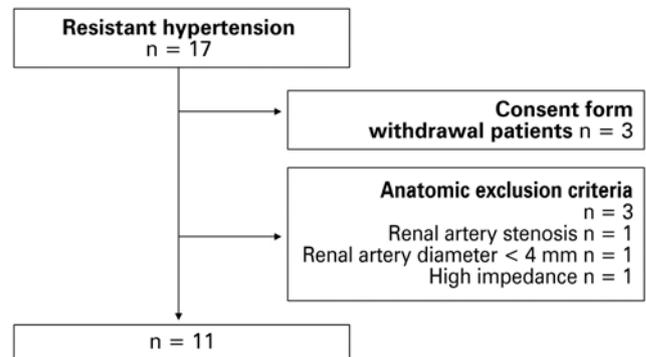


**Figure 1.** Study flowchart.

**Table 1**
Baseline characteristics

| Variable | n = 11 |
|---|---|
| Age, years | 56.5 ± 10.5 |
| Male, n (%) | 3 (27.3) |
| Body mass index, kg/m$^2$ | 31.1 ± 3.8 |
| Obesity, n (%) | 7 (63.6) |
| Type 2 diabetes mellitus, n (%) | 4 (36.4) |
| Smoker, n (%) | 2 (18.2) |
| Coronary artery disease, n (%) | 0 |
| Previous stroke, n (%) | 0 |
| Heart failure, n (%) | 0 |
| Ejection fraction, % | 63.4 ± 5.2 |
| eGFR, mL/min per 1.73 m$^2$ | 90.6 ± 24.6 |
| Number of antihypertensive drugs | 6.0 ± 1.3 |
| Thiazide diuretics, n (%) | 11 (100) |
| Potassium-sparing diuretics, n (%) | 7 (63.6) |
| ACEI only, n (%) | 10 (90.9) |
| ARB, n (%) | 2 (18.2) |
| ACEI/ARB associated, n (%) | 1 (9.1) |
| Calcium channel antagonist, n (%) | 10 (90.9) |
| Beta-blockers, n (%) | 10 (90.9) |
| Nitrate and other vasodilators, n (%) | 9 (81.8) |
| Centrally acting antihypertensive, n (%) | 5 (45.5) |

eTFG: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

**Table 2**
Baseline blood pressure measurements

| Baseline blood pressure | Systolic | Diastolic |
|---|---|---|
| 24-hour ABPM, mmHg | 151.1 ± 2.9 | 90.0 ± 3.3 |
| Daytime ABPM, mmHg | 152.6 ± 2.9 | 92.1 ±3.4 |
| Nighttime ABPM, mmHg | 146.0 ± 3.8 | 83.1 ± 3.0 |
| Office, mmHg | 182.1 ± 7.4 | 102.4 ± 5.5 |

ABPM: ambulatory blood pressure monitoring.

For 24-hour ABPM at 6 months (Figures 2 and 3), the mean SBP was 147.2 ± 6 mmHg (135.3 to 159.1 mmHg), with a mean reduction of 3.9 mmHg compared with baseline (*p* = 0.49). The mean diastolic blood pressure was 84.6 ± 3 mmHg (78.5 to 90.7 mmHg), with a mean reduction of 5.4 mmHg from baseline (*p* = 0.19). In the 24-hour ABPM at 6 months, there was a mean reduction in daytime SBP of 4.0 mmHg (152.6 to 148.6 mmHg; *p* = 0.52) and of 1.1 mmHg

in nighttime SBP (146.0 to 144.9 mmHg; *p* = 0.82). The mean daytime and nighttime DBP decreased by 5.3 mmHg (92.1 to 86.8 mmHg; *p* = 0.24) and 3.0 mmHg (83 to 80 mmHg; *p* = 0.42), respectively. For ABPM at 30 days, the mean SBP and DPB were 144.5 ± 8.1 and 83.3 ± 6 mmHg, respectively. The mean reduction in blood pressure was numerically greater at 30 days than at 6 months (6.6 mmHg for SBP and 6.7 mmHg for DBP) but not statistically significant (*p* = 0.68 and *p* = 0.38, respectively).

At the end of 6 months, the mean office SBP decreased from 182.1 ± 7 to 166.5 ± 7.7 mmHg (*p* = 0.03), and the mean office diastolic blood pressure decreased from 102.4 ± 5.5 to 99.7 ± 4 mmHg (*p* = 0.54) (Figure 3). There were no changes in the levels of serum epinephrine (*p* = 0.22), norepinephrine (*p* = 0.68) or dopamine (*p* = 0.27).

## Discussion

Our case series included 11 patients with resistant hypertension and showed that sympathetic denervation of the renal arteries using a saline-irrigated RFA catheter might be safe and feasible but not effective in reducing 24-hour ABPM. There was a statistically significant decrease of approximately 15 mmHg in office-based SBP measurements at the 6-month follow-up. We did not observe any significant change in neither the 6-month follow-up blood pressure measured by ABPM or in the serum epinephrine and dopamine levels. The absence of a reduction in serum catecholamine levels should be viewed with caution since only four patients were included to this analysis. It is worth noting that our sample consisted of patients with true resistant hypertension.

Despite the promising results demonstrated in the Symplicity HTN-2 Trial, the noticeable methodological flaws prompted further studies with more rigorous methodology. The Symplicity HTN-3 Trial included 535 patients who were randomized 2:1 to renal sympathetic denervation or a sham procedure, with efficacy endpoints assessed by 24-hour ABPM. Similar to other studies, including ours, efficacy endpoints were not met when blood pressure measurements with 24-hour ABPM were analyzed at 6 and 12 months.[11,15] The mechanisms that could explain the disparity between the follow-up office



**Figure 2.** Mean 24-hour baseline, 1-month and 6-month systolic and diastolic pressures from ambulatory blood pressure monitoring. *p*-values were 0.68 and 0.38 for all comparisons of systolic and diastolic blood pressure, respectively.



**Figure 3.** Changes in office and 24-hour ambulatory systolic and diastolic blood pressure at 6 months. BP: blood pressure; ABPM: ambulatory blood pressure monitoring.

and ABPM variation are not well understood.[16] We believe that even in a highly selective sample of true resistant hypertensive patients, the office measurement is a method more prone to be influenced by placebo effect, regression-to-the-mean or to the Hawthorne effect.[17]

The present results are consistently similar to the findings of the Symplicity HTN-3 Trial, which is the most important study on renal sympathetic denervation published to date. Some authors have suggested that renal sympathetic denervation may be more effective in patients with less severe resistant hypertension in whom the sympathetic drive is less pronounced and therefore better controlled after the procedure. The rationale for this hypothesis has been recently tested in a randomized, controlled trial.[18] This trial included 71 patients with day-time SBP 135 to 149 mmHg and DBP 90 to 94 mmHg on 24-hour ABPM for renal sympathetic denervation or a sham procedure and showed no significant changes in blood pressure levels measured by ABPM in the intention-to-treat analysis. Nevertheless, there was a slight but significant reduction in daytime SBP (8.3 mmHg vs. 3.5 mmHg; *p* = 0.04) in the intervention group when evaluating only patients included in the per protocol analysis. However, the clinical applicability of this trial is difficult to interpret due to conflicting results from a much larger randomized trial, the Symplicity HTN-3 Trial.

Despite the negative results of the Symplicity HTN-3 Trial, investigators strongly recommend the publication of preclinical data from studies that try to answer questions about renal denervation.[19,20] Unlike studies using a solid-tip dedicated catheter,[9-11] we used a saline-irrigated electrophysiology catheter. The broad experience with electrophysiology from ablation of cardiac arrhythmias describing some potential advantages of using an irrigated-tip catheter have increased the interest of many research groups in investigating its use in renal denervation. Continuous saline irrigation at room temperature results in a significant decrease in catheter tip temperature and, consequently, allows us to more effectively achieve the adventitial layer of the renal artery without causing much discomfort to the patient. Furthermore, excessive temperature at the catheter tip may lead to clot formation, thus limiting the amount of energy delivered and lesion extension, which in turn reduces the efficacy of energy application.[12,13] The potential advantages of the saline-irrigated electrophysiology catheter were demonstrated in a study in a canine model, which confirmed that the use of this device results in more extensive neural degeneration of the adventitia due to deeper penetration of radiofrequency energy and less extensive intimal hyperplasia than the use of non-irrigated electrophysiology catheters.[19]

In contrast to our results, a case series study using a saline-irrigated RFA catheter that included ten patients showed a reduction in blood pressure measured by 24-hour ABPM. Decreased metanephrine, normetanephrine and aldosterone levels were also described in five patients who had blood samples analyzed.[21] Armaganijan et al., in a series of ten cases, reported a statistically significant reduction in systolic and diastolic blood pressure (28/17.6 mmHg) as measured by 24-hour ABPM after 6 months of follow-up.[22] However, the study included almost exclusively women (90% of the sample), and 24-hour ABPM was not an inclusion criterion. The 24-hour ABPM results after 6 months of follow-up were reported only for eight patients, and four of them were considered non-responders (SBP reduction < 10 mmHg). Kiuchi et al., in a series of 24 non-dialysis patients with renal failure, also reported a significant reduction in blood pressure as measured by 24-hour ABPM after a 3-month follow-up.[23] However, a proper comparison with our study is hindered by the fact that a glomerular filtration rate < 45 mL/min/1.73 m² was one of our exclusion criteria, and their follow-up period was reduced to 3 months.

In the present study, there was no reduction in the number of antihypertensive drugs from baseline to 6 months. We encouraged our patients to keep taking the same medications and at the same doses prescribed at enrollment to avoid bias. In the Symplicity HTN-3 Trial,
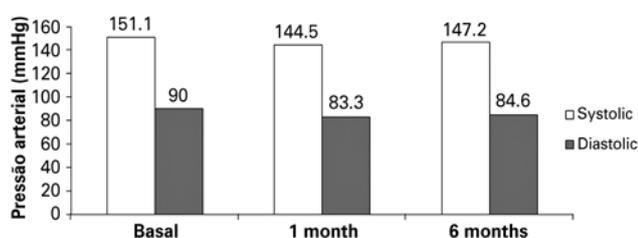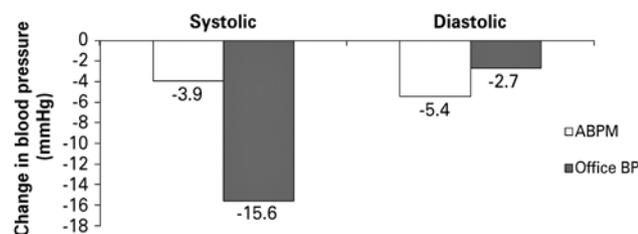
for example, approximately 40% of patients had changes in medication between inclusion and analysis at 6 months.

Another pitfall in renal denervation is the absence of a reliable and practical test, which can be preferably used at the bedside, for immediate evaluation of the results of the procedure. The objective of renal denervation should be to normalize renal sympathetic activity in individuals with sympathetic hyperactivity or reduce it to the lowest physiologically tolerable level. It has been known for several decades that norepinephrine spillover to plasma is increased in essential arterial hypertension.[24,25] However, there is no reliable clinical or laboratory parameter for evaluation of the efficacy of renal denervation in order to show the proportion of injured afferent and/or efferent nerve fibers, resulting in hypoactivity and decreased production of catecholaminergic substances. In our study, only four patients had blood samples collected at baseline and 30 days after the procedure for analysis of catecholamine levels. In this very small sample, no differences in catecholamine values were observed, although the relevance of this finding remains uncertain. In the Symplicity HTN-1 observational study, there was a reduction in norepinephrine spillover in ten patients in whom radiotracer dilution methodologies were applied.[9] However, additional data demonstrated a mild but highly variable reduction when norepinephrine spillover was used as a surrogate marker of sympathetic activity.[26,27] Muscle sympathetic nerve activity assessed by microneurography is a marker of sympathetic activity in skeletal muscle circulation and an important factor in blood pressure control.[28] Its use in the identification of individuals with resistant hypertension and increased adrenergic tone may allow a more appropriate selection of candidates for renal sympathetic denervation and subsequent evaluation of the efficacy of the procedure. In addition to representing a non-immediate evaluation of procedural success, the difficult applicability of this method in daily practice limits its use.

Although many advances have occurred in recent years, a better understanding of sympathetic nervous system pathophysiology and of the precise anatomical distribution of renal sympathetic innervation is needed to improve efficacy. In this respect, Sakakura et al. demonstrated higher density of peri-arterial renal nerves in the proximal and middle segments of renal arteries and predominance of efferent over afferent nerve fibers.[29] The study also showed that the distance from the arterial lumen to the nerve is shorter in distal segments. Such advances may help shape the development of new technologies and technical improvements.

The selection of ideal candidates with true resistant hypertension and sympathetic hyperactivity based on reliable parameters and on accurate assessment of the efficacy of renal denervation procedures is fundamental to the consolidation of this method in a population that can really benefit from it. Nonetheless, any new technological development in the area of renal denervation will need to be submitted to well-designed, sham-controlled trials with 24-hour ABPM. The search for new therapies and development of new technologies should occur in parallel with the medical community's efforts to encourage greater medication adherence and nonpharmacological care, key measures for achieving optimal blood pressure control.

Our case series has limitations inherent in open-label uncontrolled studies with a small sample size. Similar to most studies of renal denervation, we failed to confirm good medication adherence, although our patients had been previously seen by a hypertension specialist and medication adherence was reviewed at each outpatient follow-up visit. Inclusion of urinary analysis may be a useful alternative to confirm medication adherence in small studies such as ours. Operators responsible for the procedures were interventional cardiologists and electrophysiologists. Despite extensive experience in endovascular procedures and familiarity with the use of irrigated-tip catheters, we had no experience with the renal denervation technique. Although circumferential ablation using a unipolar catheter is

dependent on the skill of the operator, in the Symplicity HTN-3 Trial, no differences in efficacy were observed when operators who performed five or more procedures were compared with less-experienced operators. Although our patients did not undergo routine imaging of the renovascular system during follow-up, in a previous study, the rate of significant renal artery stenosis 6 months after renal sympathetic denervation was found to be zero in 76 patients undergoing radiological evaluation.[30] Thus, subjecting patients to additional examination and radiation would add unnecessary risk.

## Conclusions

Renal sympathetic denervation by radiofrequency catheter ablation using a saline-irrigated catheter is feasible and possibly safe and, at the same time, demonstrates lack of efficacy in reducing blood pressure as measured by 24-hour ambulatory blood pressure monitoring in highly selective patients with true resistant hypertension. The clinical use of renal ablation with saline-irrigated catheters to control blood pressure in patients with resistant hypertension should be tested in randomized, sham-controlled, clinical trials with well-selected resistant hypertensive patients.

## Funding sources

## Conflicts of interest

The authors declare no conflicts of interest.

## References

1. World Health Organization (WHO). Global Health Observatory. World Health Statistics 2012 [Internet]. Geneve: WHO, 2012 [cited 2017 Nov 11]. Available from: http://www.who.int/gho/publications/world_health_statistics/2012/en/
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23.
3. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011;57(6):1076-80.
4. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57(5):898-902.
5. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant patients hypertension in hypertensive patients. Circulation. 2012;125(13):1635-42.
6. Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true hypertension. Am J Hypertens. 2005;18(11):1422-8.
7. Oldham JB. Denervation of the kidney. Ann R Coll Surg Engl. 1950;7(3):222-45.
8. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol. 2014;64(7):635-43.
9. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275-81.
10. Symplicity HTN-2 investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial. Lancet. 2010;376(9671):1903-9.
11. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. New Engl J Med. 2014;370(15):1393-401.
12. Doumas M, Lazaridis A, Papademetriou V. Renal nerve ablation for resistant hypertension: the dust has not yet settled. J Clin Hypertens. 2014;16(6):399-400.
13. Nakagawa H, Yamanashi WS, Pitha JV, Arruda M, Wang X, Ohtomo K, et al. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with a saline-irrigated electrode versus temperature control in a canine thigh muscle preparation. Circulation. 1995;91(8):2264-73.
14. Vest JA, Seiler J, Stevenson WG. Clinical use of cooled radiofrequency ablation. J Cardiovasc Electrophysiol. 2008;19(7):769-73.

15. Bakris GL, Townsend RR, Flack JM, Brar S, Cohen SA, D'Agostino R, et al.; SYMPLICITY HTN-3 Investigators. 12-month blood pressure results of catheter-based renal artery denervation for resistant hypertension The SYMPLICITY HTN-3 Trial. J Am Coll Cardiol. 2015;65(13):1314-21.

16. Papademetriou V, Rashidi AA, Tsioufis C, Doumas M. Renal nerve ablation for resistant hypertension: how did we get here, present status, and future directions. Circulation. 2014;129(13):1440-51.

17. Olshansky B. Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. J Am Coll Cardiol 2007; 49(4):415-21.

18. Desch S, Okon T, Heinemann D, Kulle K, Röhnert K, Sonnabend M, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension. 2015;65(6):1202-8.

19. Mahfoud F, Bhatt DL. Catheter-based renal denervation: the black box procedure. JACC Cardiovasc Interv. 2013;6(10):1092-4.

20. Wang Z, Chen S, Zhou T, Su L, Ling Z, Fan J, et al. Comparison of Saline-Irrigated Catheter vs. Temperature-Controlled Catheter for Renal Denervation in a Canine Model. Am J Hypertens. 2015;28(12):1434-43.

21. Ahmed H, Neuzil P, Skoda J, Petru J, Sediva L, Schejbalova M, et al. Renal sympathetic denervation using an irrigated radiofrequency ablation catheter for the management of drug-resistant hypertension. J Am Coll Cardiol Intv 2012;5(7):758-65.

22. Armaganijan L, Staico R, Moraes A, Abizaid A, Moreira D, Amodeo C, et al. Renal Denervation Using an Irrigated Catheter in Patients with Resistant Hypertension: A Promising Strategy? Arq Bras Cardiol. 2014;102(4):355-63.

23. Kiuchi MG, Maia GL, de Queiroz Carreira MA, Kiuchi T, Chen S, Andrea BR, et al. Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood pressure and renal function in patients with chronic kidney disease and resistant hypertension. Eur Heart J. 2013;34(28):2114-21.

24. Mahfoud F, Ukena C, Schmieder RE, Cremers B, Rump LC, Vonend O, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. Circulation. 2013;128(2):132-40. Erratum in: Circulation. 2014;129(20):e502.

25. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension. 2013;61(2):457-64.

26. Esler M. Illusions of truths in the Symplicity HTN-3 trial: generic design strengths but neuroscience failings. J Am Soc Hypertens. 2014;8(8):593-8.

27. Hering D, Marusic P, Walton AS, Lambert EA, Krum H, Narkiewicz K, et al. Sustained sympathetic and blood pressure reduction 1 year after renal denervation in patients with resistant hypertension. Hypertension. 2014;64(1):118-24.

28. Sundlöf G, Wallin BG. Muscle-nerve sympathetic activity in man. Relationship to blood pressure in resting normo- and hyper-tensive subjects. Clin Sci Mol Med Suppl 1978;4:387s-389s.

29. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol. 2014;64(7):635-43.

30. Lambert T, Nahler A, Reiter C, Schwarz S, Gammer V, Blessberger H, et al. Frequency of renal artery stenosis after renal denervation in patients with resistant arterial hypertension. Am J Cardiol. 2015;115(11):1545-8.