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Letter to the Editor

When the first and the second renal sympathetic denervation in resistant hypertensive patients failure: What to do?

As reported in the SYMPLICITY HTN-3 trial [1], no significant differences in the 24-h ABPM were observed between 6 and 12 months in the denervation and crossover subjects. Ambulatory data were available for only 20 of 70 (29%) non-crossover subjects at 12 months, given that ABPM was not protocol-mandated for these subjects at this time point. However, in these 20 subjects, a pattern similar to that of office readings was observed, showing a larger 24-h ABPM reduction at 6 than 12 months (-11.0 ± 19.5 *vs.* -6.1 ± 14.4 mmHg at 6 and 12 months, respectively; $P = 0.272$) [1]. Moreover, we did not observe the change in 24-h ABPM as expected in our study even patients presenting resistant hypertension after antihypertensive staggered scheme and RSD and one predictor of success that is the baseline office systolic blood pressure of ≥180 mmHg [2]. Based on these results we performed a second RSD procedure, aiming to low the blood pressure in these resistant hypertensive patients.

This prospective, longitudinal study was conducted in 27 patients with resistant hypertension who underwent percutaneous RSD. The study was approved by the Hospital e Clínica São Gonçalo Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. All patients signed written informed consent prior to study inclusion. We evaluated the safety and effectiveness of RSD for improvement of clinical parameters and in reducing damage to the heart, through echocardiographic parameters, and kidneys, by assessing estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR), in patients with resistant hypertension. This study was conducted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil, where patients were recruited from January 2014 through to July 2015 from the Artificial Cardiac Pacing Department. Patients meeting all the following criteria were consecutively enrolled: (i) office systolic BP ≥140 mmHg despite using 3 antihypertensive drugs, being one of them a diuretic; (ii) aged between 18 and 80 years; (iii) undergoing antihypertensive staggered scheme with the following drugs for at least 6 months before being subjected to the first RSD procedure: β blocker followed by spironolactone, followed by α-1 adrenergic receptor blocker and after by α-2 adrenergic receptor blocker, in case of no reduction of blood pressure; (iv) left ventricular ejection fraction >50% measured by Simpson's method in the echocardiogram; (v) sinus rhythm; (vi) eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, eGFR [3] >60 mL/min/1.73 m^2 these patients without microalbuminuria); and (vii) able to read, understand and sign the informed consent form. Patients with any of the following criteria were excluded: (i) pregnancy; (ii) acute HF; (iii) acute coronary syndrome; (iv) valvular disease with significant hemodynamic repercussions; (v) myocardial infarction, unstable angina, stroke or transient ischemic attack within the previous 6 months; (vi) renovascular abnormalities (including severe renal artery stenosis, and renal angioplasty with or without stenting); (vii) psychiatric disease; (viii) allergy to ionic contrast; (ix) unable to be followed clinically after the procedure; (x) known to have drug or alcohol addiction, which can affect the ability to understand or follow medical instructions; (xi) a serious disease, which in the opinion of the investigator, may adversely affect the safety and/or efficacy of the participant or the study.

Transthoracic echocardiography was performed at baseline and at 6 months after RSD using a GE ultrasound system (Vivid I, General Electric, Frankfurt, Germany) equipped with a multi-frequency transducer and tissue Doppler imaging software according to the Guidelines of the American Society of Echocardiography [4]. Data were analyzed and interpreted by one experienced echocardiographer blinded to treatment status, HF stage, and the sequence of the images. Left ventricular (LV) mass was calculated from LV linear dimensions using the Devereux formula [4,5]. LV mass was indexed to body surface area [4,6], as indicated. The ABPM was performed for 24 h with a clinically validated device (CardioMapa; Cardios, São Paulo, Brazil) at baseline. The device was designed to measure every 15 min during daytime (from 6 to 22 h) and every 30 min during the night (from 22 to 6 h). The patients were instructed to continue their regular activities during recording and go to the bed not later than 23:00 h. The wakefulness ranged from 8 to 22 h and the sleep period from midnight till 6:00 am [7]. All subjects were trained to record in a diary the hours during which they took their meals, as well as periods of sleep and wakefulness, ingestion of drugs, in addition to symptoms and events that could influence blood pressure during this period. The measurements were transferred to a computer for analysis. The monitoring was repeated as necessary until ≥70% of day and night values measured were satisfactory [8].

In total, 27 hypertensive resistant patients were treated in this study. All patients underwent a complete medical history and physical examination, and their HF medication was reviewed. Blood pressure was measured in the standing, sitting, and supine positions on at least two subsequent visits in both arms. Blood samples were collected to determine a complete blood count, and biochemistry (including serum creatinine to estimate GFR). Urine samples were obtained to determine albuminuria, protein, and creatinine levels. Twenty-four hour ambulatory BP monitoring (ABPM), echocardiogram, and Echo Doppler evaluation of the anatomy of the renal arteries of patients were also assessed. To evaluate the true effects of RSD on resistant hypertension, baseline antihypertensive staggered scheme was unchanged for at least 6 months before 1st RSD procedure and treatment were maintained at follow-up. Patients were instructed not to change their medication and dosages after the procedure unless clinically indicated. For all patients, drug records and adherence were comprehensively reviewed and documented at each visit. The RSD procedure has been described in detail previously [9]. Samples were collected for blood and urine tests to monitor variables. In addition, 24-hour ABPM, and echocardiogram were performed at 6 (2nd RSD procedure) and 12 months after the 1st RSD. Echo Doppler was also performed to evaluate the anatomy of the renal arteries of patients at 6 months after RSD. The following variables were monitored during the follow-up period: echocardiographic

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Table 1
General features of patients at baseline.

N	27
Age, years	58 ± 9
Body mass index, kg/m^2	29.5 ± 4.0
Male sex, %	20 (74%)
White ethnicity, %	16 (59%)
Hypertension, %	27 (100%)
Type 2 Diabetes *Mellitus*, %	13 (48%)
Coronary artery disease, %	8 (30%)
eGFR, mL/min/1.73 m^2 (CKD-EPI)	83.0 ± 26.5
LVEF (Simpson),%	57.8 ± 6.4
Office blood pressure, mmHg	187 ± 18/133 ± 10
24-hour ABPM, mmHg	156 ± 13/123 ± 15
Antihypertensive agents	
ACE-inhibitor/ARB	27 (100%)
Diuretic	27 (100%)
DHP Ca^{++} channel blocker	27 (100%)
β blocker	27 (100%)
Spironolactone	27 (100%)
α-1 Adrenergic receptor blocker	27 (100%)
α-2 Adrenergic agonist	27 (100%)

Values are presented as mean ± SD or %; ABPM, ambulatory blood pressure measurements; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; N, number of patients.

parameters, systolic and diastolic blood pressure, eGFR, and albuminuria.

Results are expressed as the mean and standard deviation (mean ± SD), in the case of normal distribution, or as the median with interquartile range. Statistical tests were all two sided. Comparisons between two-paired values were performed by the paired t-test in the case of Gaussian distribution or, alternatively, by the Wilcoxon test. Comparisons between more than two-paired values were performed by ANOVA for repeated measures or with Kruskal–Wallis ANOVA as appropriate, complemented by a *post hoc* test. Frequencies were compared with Fisher's exact test. P-values <0.05 were considered statistically significant. Correlations between two variables were performed by the Pearson method in the case of Gaussian distribution or, alternatively, with the Spearman correlation test. All statistical analyses were performed using Graphpad Prism version 7.0 (Graphpad software, La Jolla, CA, USA).

General baseline characteristics of the 27 resistant hypertensive patients are listed in Table 1. Mean office systolic/diastolic BP was 187 ± 18/133 ± 10 mmHg. Mean Left ventricular ejection fraction (LVEF) was 57.8 ± 6.4%. No patient was re-admitted for procedural complications during follow-up. No hypotensive (systolic BP <90 mmHg) [10] or syncopal episodes were reported. Real-time renal artery imaging was performed to assess potential structural changes related to the procedure. Some small focal irregularities of the renal arteries that were present during the procedure (possibly due to minor spasm or edema) were no longer seen postoperatively. At 6 months post-procedure, all patients underwent a Doppler scan of renal arteries, and there was no evidence of stenosis or flow limitation. Effects of RSD on creatinine values, eGFR, and albumin:creatinine ratio is also shown in Table 2. At baseline after the 1st RSD procedure the systolic/diastolic office blood pressure were 187 ± 18/133 ± 10 mmHg, at 6 months of follow-up the office blood pressure was 185 ± 13/129 ± 16 mmHg and the 2nd RSD was performed, and at 12 months of follow-up the office blood pressure was 188 ± 16/132 ± 13 mmHg (P = 0.8878/0.3169 for baseline *vs.* 6th month, P = 0.9706/0.9295for baseline *vs.* 12th month, and P = 0.7656/0.5211 for 6th *vs.* 12th month), as shown in Fig. 1A. The same occurred with the 24-hour ABPM, at baseline after the 1st RSD procedure the systolic/diastolic 24-hour ABPM were 156 ± 13/123 ± 15 mmHg, at 6 months of follow-up the 24-hour ABPM was 158 ± 20/128 ± 12 mmHg and the 2nd RSD was performed, and at 12 months of follow-up the 24-hour ABPM was 155 ± 17/124 ± 16 mmHg (P = 0.9013/0.4147 for baseline *vs.* 6th month, P = 0.9743/0.9649 for baseline *vs.* 12th month, and P = 0.7919/0.5677 for 6th *vs.* 12th month), as shown in Fig. 1B. Table 3 shows the effects of RSD at baseline, 6, and 12 months of follow-up on echocardiographic parameters: LVEF, end diastolic left ventricular diameter (EDLVD), end diastolic left ventricular volume (EDLVV), end systolic left ventricular diameter (ESLVD), end systolic left ventricular volume (ESLVV), left ventricular

Table 2
Renal function at baseline *vs.* 6th and 12th month of follow-up.

Variable	Baseline (n = 27) 1st RSD	6th month (n = 27) 2nd RSD	P value 6th month *vs.* baseline	12th month (n = 27) End of follow-up	P value 12th month *vs.* baseline	P value 6th *vs.* 12th month
Creatinine, mg/dL	1.00 ± 0.65	1.10 ± 0.36	0.6875	1.12 ± 0.20	0.5838	0.9850
eGFR, mL/min/1.73m^2	83.0 ± 26.5	73.7 ± 21.4	0.2772	72.3 ± 17.7	0.1851	0.9708
ACR, mg/g	13.4 ± 8.0	16.9 ± 6.5	0.2337	14.6 ± 8.8	0.8399	0.5293

Values are presented as mean ± SD; ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; RSD, renal sympathetic denervation.

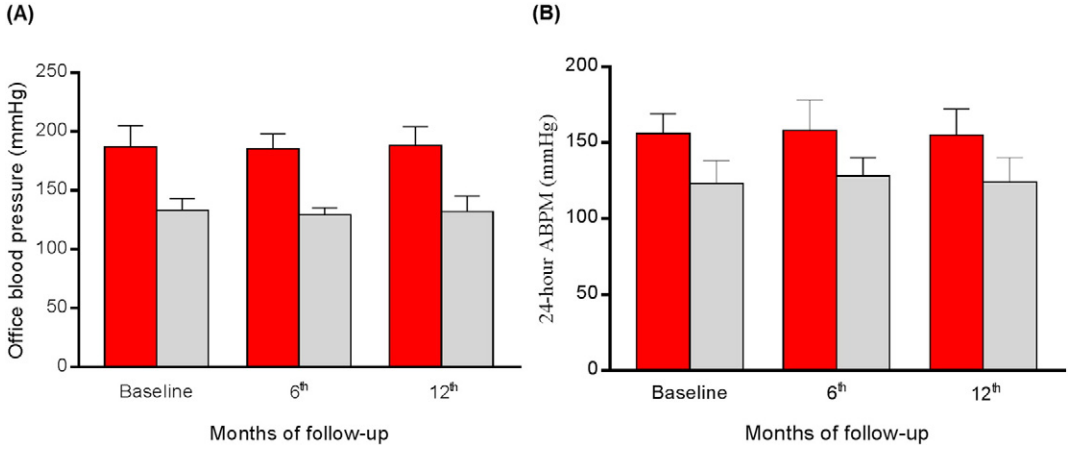

Fig. 1. No changes happened in office (A) and 24-h ABPM (B) systolic (red bars)/diastolic (gray bars) blood pressure during the 12 months of follow-up. Values are presented as mean ± SD; ABPM, ambulatory blood pressure measurements.

Table 3
Echocardiographic parameters at baseline *vs.* 6th and 12th month of follow-up.

Variable	Baseline (n = 27) 1st RSD	6th month (n = 27) 2nd RSD	P value 6th month *vs.* baseline	12th month (n = 27) End of follow-up	P value 12th month *vs.* baseline	P value 6th *vs.* 12th month
LVEF (Simpson), %	57.8 ± 6.4	60.0 ± 8.8	0.5364	59.3 ± 7.3	0.7474	0.9383
EDLVD, mm	54.4 ± 4.0	51.4 ± 2.9	0.0020	50.0 ± 2.2	<0.0001	0.2322
EDLVV, mL	190.2 ± 11.3	177.8 ± 8.4	<0.0001	173.6 ± 9.0	<0.0001	0.2519
ESLVD, mm	45.8 ± 3.3	42.6 ± 2.0	<0.0001	41.4 ± 2.1	<0.0001	0.1976
ESLVV, mL	76.5 ± 8.8	71.2 ± 7.3	0.0295	69.6 ± 6.1	0.0031	0.7129
LV mass, g/m^2	135.8 ± 14.2	116.8 ± 13.7	<0.0001	110.4 ± 15.1	<0.0001	0.2354
EDPWT, mm	12.3 ± 1.0	11.0 ± 0.8	<0.0001	10.6 ± 0.6	<0.0001	0.1763
EDIVST, mm	10.8 ± 0.8	10.1 ± 0.7	0.0012	10.0 ± 0.7	0.0002	0.8587

Values are presented as mean ± SD. LVEF, left ventricular ejection fraction; EDLVD, end diastolic left ventricular diameter; EDLVV, end diastolic left ventricular volume; ESLVD, end systolic left ventricular diameter; ESLVV, end systolic left ventricular volume; LV, left ventricular; EDPWT, end diastolic posterior wall thickness; EDIVST, end diastolic inter ventricular septum thickness; RSD, renal sympathetic denervation.

mass, end diastolic posterior wall thickness (EDPWT), and end diastolic inter ventricular septum thickness (EDIVST). Compared with baseline, some parameters were statistically significantly changed at both 6 and 12 months of follow-up.

This study was a safety evaluation and was therefore neither blinded nor powered to assess clinical efficacy. The use of echo Doppler to assess damage in the renal arteries is in some way a limitation. However, early complications caused by the RF applications were excluded by angiography performed at the end of the procedure. Any other method, such as computed tomography angiography or a new angiography of the renal arteries, could expose patients to additional undesirable toxic insults. Angiography using CO_2 is not available at our center. In addition, more precise methods for the assessment of GFR, such as cystatin C or iothalamate, should be used in future studies to confirm our findings regarding the effects of RSD upon eGFR, especially considering that only one measurement of serum creatinine was performed at each time point in our study.

Many of the echocardiographic parameters reported above improved even without a reduction in blood pressure after two RSD procedures. However, we did not have successful in renal function improvement or in decrease blood pressure, even after patients undergoing antihypertensive staggered scheme at least 6 months and two RSD procedures. What to do in these cases?

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Conflict of interest

None declared.

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Márcio Galindo Kiuchi, MD, PhD
Divisão de Cirurgia Cardíaca, Departamento deMedicina, Hospital e Clínica São Gonçalo, São Gonçalo, RJ, Brazil
Department of Cardiology, Elisabethinen University Teaching Hospital Linz, Linz, Austria
Corresponding author at: Rua Cel. Moreira César, 138 - Centro, São Gonçalo, Rio de Janeiro 24440-400, Brazil.
E-mail address: marciokiuchi@gmail.com.

Shaojie Chen, MD, PhD, Prof.
Department of Cardiology, Shanghai First People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
Department of Cardiology, Elisabethinen University Teaching Hospital Linz, Linz, Austria

Helmut Pürerfellner MD, PhD
Department of Cardiology, Elisabethinen University Teaching Hospital Linz, Linz, Austria

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