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Acute epinephrine test after renal sympathetic denervation in uncontrolled hypertensive patients

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Studies employing percutaneous renal sympathetic denervation (RSD) [1-4] showed a reduction in both systolic and diastolic blood pressure (BP) among refractory hypertensive patients. As we described previously [5,6], the reduction in office BP was evident from the 1st month until one year after RSD in refractory hypertensive patients. A recent study in animals showed the pathology of radiofrequency-derived RSD during the time and provided important knowledge of the mechanisms resulting in sustained BP reduction, and reported that the nerve damage post radiofrequency ablation was greatest at 7 days, with maximum functional nerve damage sustained ≤30 days. Focal terminal nerve regeneration was observed only at the sites of ablation as early as 2 months and continued to 6 months [7]. Another study reported a substantial decrease in office systolic BP in relation to the number of ablation points at 6 months [8]. To date, there is no test to prove the acute efficacy of RSD.

As a hormone, epinephrine plays on closely all body tissues. Its actions vary by tissue kind and tissue manifestation of adrenergic receptors. Epinephrine acts by binding to a diversity of adrenergic receptors. Epinephrine is a nonselective agonist of altogether adrenergic receptors, comprising the major subtype's α_1, α_2, β_1, β_2, and β_3. Its activities are to increase peripheral resistance via α1 receptor-dependent vasoconstriction and to growth cardiac output via its binding to β1 receptors. Based on this information, we believe that epinephrine can be used to evaluate the acute response of BP and heart rate (HR) to RSD in uncontrolled hypertensive patients.

This transversal study involved 25 uncontrolled hypertensive subjects, was conducted in agreement with the Helsinki declaration and approved by the ethics committee of our institution. All subects sign up the informed consent term before inclusion. This study was piloted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil. Patients were recruited from January 2015 to December 2016 from the Arrhythmias and Artificial Cardiac Pacing Service of the same hospital. Patients with the mixture of the subsequent criteria were successively enrolled: (i) mean 24-hour systolic ambulatory BP measurements (ABPM) of >130 mmHg and mean 24-hour diastolic ambulatory BP >80 mmHg, in use of at least 3 antihypertensive agents in the maximum doses prescribed or tolerated, being one of them a diuretic; (ii) a physically normal heart with an ejection fraction of >50% (Simpson's method) to CRM, without ischemia, fibrosis area, or any other disease; (iii) age of 18 to 80 years, (iv) estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [9] (without microalbuminuria), and (vi) the capacity to read, understand, and sign the informed consent form and go to the clinical tests. The patients that presented any of the subsequent criteria were excluded: (i) pregnancy; (ii) valvular disease with significant adverse sequelae; (iii) unstable angina, myocardial infarction, transient ischemic attack or stroke previosly; (iv) renovascular abnormalities; (v) psychiatric disease; (vi) allergy to ionic contrast medium; (vii) the inability to be monitored clinically after the procedure; (viii) a known addiction to drugs or alcohol that disturbs the intellect; (ix) congestive heart failure presenting functional class II to IV symptoms according to New York Heart Association.

The general features of the the 25 uncontrolled hypertensive subjects at baseline are displayed in Table 1. The main goal of this study evaluated if RSD can reduce hypertensive response acutely even in the presence of a sympathomimetic agent. The RSD procedure has been defined in detail previously [10]. Before and after RSD the 2 mg of epinephrine intravenous were administered and we observed the variations in invasive BP and HR. The patients continued hospitalized in the ward for 24 h after the RSD.

The results are expressed as a mean and standard deviation for normally distributed data and as median with interquartile range otherwise. All statistical tests were two-sided. Comparisons between two-paired values were performed with the paired t-test in cases of a Gaussian distribution and by the Wilcoxon test otherwise. Comparisons between more than two-paired values were made by repeated-measures analysis of variance or by Kruskal–Wallis analysis of variance as appropriate, complemented by a post-hoc test. A P-value <0.05 was considered significant. All statistical analyses were performed using the program Graphpad Prism v 7.0 (Graphpad Software, La Jolla, CA, USA).

At baseline, the mean invasive systolic/diastolic BP were 128.0 ± 6.9/87.1 ± 4.1 mmHg and the mean HR was 71.0 ± 8.3 bpm. After 2 mg of ephedrine intravenous and before RSD, the mean invasive systolic/diastolic BP were 189.4 ± 10.9/134.5 ± 6.9 mmHg and the mean HR was 131.4 ± 9.6 bpm. Acutely post RSD procedure the mean invasive systolic/diastolic BP were 110.3 ± 8.5/73.3 ± 2.4 mmHg and the mean HR was 61.3 ± 7.7 bpm. The same infusion of 2 mg of ephedrine intravenous after RSD, the mean invasive systolic/diastolic BP were

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Table 1. General features of patients at baseline.

General features of patients at baseline	
N	25
Age, years	53.0 ± 8.0
Body mass index, kg/m²	27.8 ± 3.0
Male sex (%)	17 (68%)
White ethnicity (%)	15 (60%)
Type 2 Diabetes *Mellitus* (%)	6 (24%)
Coronary artery disease	5 (20%)
Uncontrolled hypertension	25 (100%)
Creatinine, mg/dL	0.90 ± 0.11
eGFR, mL/min/1.73 m² (CKD-EPI)	99.0 ± 7.5
ACR, mg/g	13.8 ± 5.5
Mean 24-hour ABPM, mmHg	141.0 ± 6.0/90.4 ± 4.5
Antihypertensive agents	
ACEI/ARB	25 (100%)
Diuretics	25 (100%)
DHP Ca++ channel blockers	25 (100%)
β-blockers	15 (60%)
Spironolactone	13 (52%)
Clonidine	12 (48%)
Cardiac magnetic resonance	
Indexed LV mass/BSA, g/m2	128.3 ± 13.5
LVEF, % (Simpson)	67.0 ± 6.8
LVEDD, mm	45.0 ± 2.3
LVESD, mm	36.2 ± 3.0
Indexed LA volume, mL/m2	27.0 ± 1.3

Values are presented as Mean ± SD or %; ABPM: ambulatory blood pressure measurements; ACEI: receptor inhibitor of angiotensin converting enzyme; ACR: albumin creatinine ratio; ARB: angiotensin receptor blocker; BSA: body surface area; DHP: dihydropyridyne; EF: ejection fraction; eGFR: estimated glomerular filtration rate; LA: left atrium; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; N: number of patients.

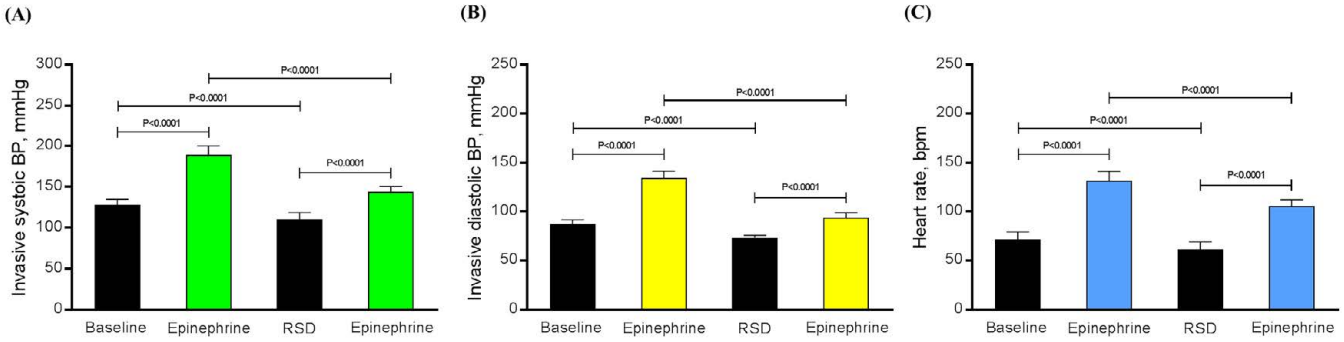

Figure 1. The variation in mean invasive systolic/diastolic BP (A) and (B), respectively, as well as, in the mean heart rate (C) at baseline, after 2 mg of ephedrine intravenous and before RSD, immediately after RSD, and post 2 mg of ephedrine intravenous post RSD. N = 25 uncontrolled hypertensive patients.

144.3 ± 6.2/93.6 ± 5.2 mmHg and the mean HR was 105.2 ± 6.7 bpm. All the comparisons between the same parameter were significant (P<0.0001), as shown in Figure 1.

In conclusion, our study shows that the RSD reduces the hyperactive response in mean invasive systolic/diastolic BP and the rise in the acutely HR even in the presence of epinephrine intravenous. These findings suggest that this fast and acute test in the future may be used, but other studies with a large number of patients should be performed.

Conflict of interest

None declared.

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