Is There a Title Role for Renal Sympathetic Denervation In Patients with Symptomatic Myocardial Bridging Refractory to Clinical Treatment and Ventricular Arrhythmias?

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Highlights
The connection concerning the autonomic nervous system and coronary spasm during the systole is multifaceted. An augmentation in sympathetic activity, due to pain caused by angina and the several transient ischemic episodes may cause an increase in noradrenaline, the neurotransmitter of efferent sympathetic fibers, triggering more vasoconstriction by stimulating vascular smooth muscle cells, cause cardiac hypertrophy. Based on these concepts we aim to find a role for renal sympathetic denervation in patients with symptomatic myocardial bridging refractory to standard clinical treatment and ventricular arrhythmias. In conclusion, our findings suggest that RSD can play a role in myocardial bridging treatment, augmenting the LVEF, diminishing the LV mass and the number of transient ischemic segments measured by CMRI, besides to reduce the number of individuals presenting symptoms, the mean of NSVT recorded by 24-hour-Holter monitoring, and the number of patients with SVT inducible by the EPS. Perhaps such benefits are due to the decrease in the LV mass and sympathetic cardiac activity, consequently, there being less constriction of the arteries with myocardial bridges and less ventricular arrhythmias.

We report preliminary data on 6 patients with controlled hypertension, with normal renal function, with symptomatic myocardial bridging refractory to clinical treatment and ventricular arrhythmias who underwent a pilot renal sympathetic denervation (RSD) procedure. At baseline, the 6 (100%) patients presented symptoms while 6 months after RSD only 1 (17%) subject still complained of the symptoms (P=0.0152). Our findings suggest that RSD can play a role in myocardial bridging treatment, augmenting LVEF, diminishing LV mass and the number of transient ischemic segments measured by CMRI.

Keywords: Myocardial Bridging; Renal Artery Denervation; Arrhythrias

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Introduction
The myocardial bridging was first described anatomically by Reyman in 1737 [1], as a congenital abnormal of a coronary artery in which a segment of an epicardial coronary artery (most commonly the middle potion of the left anterior descending artery) takes an intramuscular course [2]. The presence of a portion of the vessel under the “bridge” of contractile myocardium repeatedly results in arterial compression during each systole. While frequently asymptomatic, this condition in many cases may be guilty of adverse events including angina, myocardial...
ischemia [3], acute coronary syndromes [4–6], left ventricular dysfunction and stunning [7], arrhythmias [8,9], and even sudden cardiac death [10,11]. Described rates of myocardial bridging vary based on the mode of evaluation. Several autopsy series have been done, with rates reported from 5%–86% [12], with a mean of 25%. First-line treatment for individuals thought to be experiencing symptoms due to myocardial bridging comprises of beta-blockers [13,14] and non-dihydropyridine calcium channel blockers [15]. Nevertheless, the proof to support these interventions is limited, and justification is based on hypothetical improvement in coronary hemodynamics with decreased chronotropic and inotropic effects. For refractory symptoms, multiple interventional strategies have been attempted such as surgical myotomy, coronary artery bypass surgery, and stenting [16].

The connection concerning the autonomic nervous system and coronary spasm during the systole is multifaceted. An augmentation in sympathetic activity, due to pain caused by angina and the repeated transient ischemic episodes may augment noradrenaline, the neurotransmitter of the efferent sympathetic fibers, triggering more vasoconstriction by stimulating vascular smooth muscle cells, and contributing to cardiac hypertrophy. Based on these concepts we aim to find a role for renal sympathetic denervation in patients with symptomatic myocardial bridging refractory to standard clinical treatment and ventricular arrhythmias.

We selected 6 patients with controlled hypertension, with normal renal function, with symptomatic myocardial bridging refractory to clinical treatment and ventricular arrhythmias. The study was conducted in agreement with the Helsinki declaration and approved by the ethics committee of our institution. All patients signed the informed consent term before inclusion. This study was conducted at the Hospital e Clínica São Gonçalo in partnership with NitPace, Rio de Janeiro, Brazil. Patients were enrolled from January 2015 to January 2016 from the Cardiology Division of both Institutions. Patients with the grouping of the following criteria were successively enrolled: (i) mean 24-hour systolic ambulatory blood pressure measurements (ABPM) <130/80 mmHg; (ii) absence of significant obstructive coronary disease proven by computerized angiotomography and cardiac magnetic resonance images (CMRI); (iii) presence of myocardial bridging proven by computerized angiotomography; (iv) refractoriness of the symptoms (angina, dyspnea and syncope) to treatment with β blocker (Bisoprolol 10 mg) in maximum doses recommended or tolerated by the patients; (v) presence of transient ischemic segments diagnosed by the CMRI on the the areas irrigated by the myocardial bridging arterial segment associated with transient ST and ventricular tachycardia induced by the stress testing; (vi) age between 18 and 80 years; (vii) glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI equation), eGFR [17] >60mL/min/1.73 m2 (without microalbuminuria); and (viii) the capacity to read, comprehend, and sign the informed consent form and attend 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 within the 6 months before the procedure; (iv) renovascular abnormalities; (v) psychiatric disease; (vi) allergy to ionic contrast medium; (vii) the inability to be monitored clinically after the procedure; (viii) or a known addiction to drugs or alcohol that affects the intellect.

One year after the onset of the standard treatment (n=6) using β blockers in maximum doses recommended or tolerated by the patients, and the refractoriness to this treatment, the subjects underwent a pilot renal sympathetic denervation (RSD) procedure. All of them were followed during six months to assess the records of the symptoms, renal function, cardiac MRI parameters, 24-hour Holter monitoring, 24-hour ambulatory blood pressure measurements (ABPM) and sustained ventricular tachycardia induced by the electrophysiological study (EPS). RSD, Renal function, 24-hour ABPM and cardiac MRI were previously described [18,19].

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. Categorical variables were compared with Fisher’s exact test. A P-value <0.05 was considered significant. Correlations between two variables were performed by Pearson’s chi-square test in case of a Gaussian distribution and with the Spearman correlation test otherwise. All statistical analyses were performed using the program GraphPad Prism v 7.0 (GraphPad Software, La Jolla, CA, USA).

The general features of the 6 patients are listed in Table 1. The CMRI showed some particularities comparing the baseline and the 6 months of follow-up values of the left ventricular (LV) mass/BSA, g/m2, LV ejection fraction (LVEF, measured by Simpson’s method), LV end-diastolic volume index (LVEDVI, mL/m2), LV end-systolic volume index (LVESVI, mL/m2), myocardial scar score (%), and transient ischemic segments (%): 118.5±17.9 vs. 88.5±9.6 g/m2 (P=0.0007) as shown in Figure 1A, 57.5±4.0 vs. 59.3±3.7 % (P=0.0019) as shown in Figure 1B, 89.2±8.0 vs. 87.8 5.1 mL/m2 (P=0.3276), 35.5±3.1 vs. 34.5±1.5 mL/m2 (P=0.4921), 0 vs. 0 % (P=1.0000), and 4.8±0.8 vs. 2.2±0.4 (P<0.0001) as displayed in Figure 1C, respectively.

At baseline, the 6 (100%) patients presented symptoms while 6 months after RSD only 1 (17%) subject still complained of the symptoms (P=0.0152). The mean 24-hour ABPM did not differ before and after the procedure, 119.7±8.8/ 76.5±4.2 mmHg vs. 119.0±8.0/ 75.2±3.5 mmHg (P=0.5301/ 0.2617), respectively. AT baseline, the 24-hour Holter monitoring showed minimum, average and maximum heart rate of 49.8±3.2, 63.3±2.9, and 100.8±6.0 bpm, respectively, in comparison with the same variables at the 6th month post RSD, 46.5±2.3, 58.8±2.2, and 81.7±4.1 bpm (P=0.0055, P=0.0004, and P<0.0001 for comparisons between the same variable), respectively. The mean of non-sustained ventricular tachycardia (NSVT) episodes recorded during the 24 hour period was 30.3±9.6 at baseline vs. 6.7±2.0 at the 6th month of follow-up (P=0.0002), as depicted in Figure 1D. From the 6 (100%) patients at baseline, all of them had sustained ventricular tachycardia (SVT) during the electrophysiological study (EPS), while just 1 (17%) individual
still presented SVT 6 months after the RSD. Evaluating the renal function, we observed that the plasmatic creatinine at baseline was 0.89±0.10 mg/dL and did not show at the 6th month post RSD 0.86±0.10 mg/dL (P=0.3760), consequently the same occurred with eGFR at baseline 98.0±6.5 vs. 103.3±8.0 mL/min/1.73 m2 at 6th month of follow-up (P=0.2365), and the albumin:creatinine ratio (ACR) also did not change from baseline to 6 months after the procedure 13.7±5.3 vs. 15.0±4.2 mg/g (P=0.6478).

In conclusion, our findings suggest that RSD can play a role in myocardial bridging treatment, augmenting the LVEF, diminishing the LV mass and the number of transient ischemic segments measured by CMRI, besides to reduce the number of individuals presenting symptoms, the mean of NSVT recorded by 24-hour-Holter monitoring, and the number of patients with SVT inducible by the EPS. Perhaps such benefits are due to the decrease in the LV mass and sympathetic cardiac activity, consequently, there being less constriction of the arteries with myocardial bridges and less ventricular arrhythmias.

Declarations of Interest
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REFERENCES