Effects of Renal Sympathetic Denervation in Comparison to β-Blocker on Heart Rate Control in Hypertensive Patients with Permanent Atrial Fibrillation

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Abstract

Aim: We aim to compare the effects of renal sympathetic denervation (RSD) to β-blocker use in heart rate (HR), blood pressure (BP) and echocardiographic parameters in hypertensive patients with permanent atrial fibrillation (PAF).

Methods and results: Twenty hypertensive patients with PAF and elevated HR were submitted to β-blocker use (n=10) or underwent RSD (n=10) and completed 6 months of follow-up. The enrolled patients had 24-hour-Holter monitoring, 24-hour ABPM and echocardiogram at baseline and at 1st and 6th months of follow-up. Our results showed that in 20 controlled hypertensive patients with PAF there was decrease in maximum, average and minimum HR measured by 24-hour-Holter monitoring during the 6 months of follow-up, both for the group using bisoprolol (n=10) and the group that underwent RSD (n=10). However, we could observe that at the 6th month post RSD the decrease in HR was more intense in average HR (Δ=-12 ± 2 bpm, P<0.0001) and maximum HR (Δ=-21 ± 6 bpm, P=0.0050) in this group than β-blocker group. Furthermore, there was no significant change in mean 24-hour ABPM, and there was a reduction in left atrial diameter (Δ=-2.7 ± 1.2 mm, P=0.0391) in RSD group compared to β-blocker group at the 6th month of follow-up.

Conclusions: RSD appears to be safe in the treatment of PAF, as well as, improves some cardiac parameters assessed by echocardiogram. Average and maximum HR, besides LAD appear to be modifiable by the RSD in comparison to β-blocker, mainly at 6th month of follow-up.

Keywords: Permanent atrial fibrillation; Renal sympathetic denervation; Hypertension; Sympathetic hyperactivity; Structurally normal heart; Heart rate control

Introduction

Atrial fibrillation (AF) affects around 2% of the population worldwide, and probably this percentage will increase in the next 50 years [1,2]. The prevalence of AF is higher in elderly people, about 0 to 0.5% at 40–50 years, and 5–15% at 80 years [1-5]. Usually, men are more willing to develop AF than women. Therefore, rhythm control interventions are abandoned strategies in patients with PAF [7]. High ventricular rate and irregularity of the rhythm can lead to symptoms and severe haemodynamic distress in AF patients. Rate control has become one of the main goals in patients with AF. Uncontrolled rapid ventricular rates is associated with increased rates of death, stroke and other thrombo-embolic events [8,9], heart failure and re-hospitalizations, poor quality of life, limited exercise capacity, and left ventricular (LV) dysfunction [7].

Renal sympathetic denervation (RSD) is able to reduced heart rate (HR) and the PR interval in sinus rhythm [10], hypothetically, due to reduction in norepinephrine levels leading to a prolongation of the refractory period of de atrioventricular node, which would cause decreasing of heart rate (HR) in patients with PAF.

Methods

In this study, we conducted a prospective, longitudinal study in 20 hypertensive patients with PAF who underwent β-blocker use or percutaneous RSD. The study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee.

All patients gave written informed consent before inclusion. In the present study we aim to evaluate the effectiveness of the β-blocker (bisoprolol 10 mg/day) use compared to RSD in the HR measured by 24-hour-Holter, modifications in mean 24-hour ABPM, and cardiac parameters using echocardiography in all patients.
Study subjects

This study was conducted in the state of Rio de Janeiro, Brazil in the Hospital e Clínica São Gonçalo. Patients were recruited from January 2014 to January 2015 and were derived from Arrhythmias and Artificial Cardiac Pacing Service of the same hospital. Patients who had the combination of the following criteria were consecutively enrolled: (i) mean 24-hour systolic ambulatory blood pressure measurements (ABPM) ≥ 110 mmHg; (ii) age between 18 and 75 years; (iii) Structurally normal heart with an ejection fraction > 50%, measured by echocardiogram (Simpson's method); (iv) should be presenting with refractoriness to treatment with antiarrhythmic drugs; (v) underwent to at least 2 procedures of AF catheter ablation; (vi) should be present with symptomatic permanent AF; (vii) 24-hour Holter demonstrating with average HR > 100 bpm; (viii) left atrial diameter ≥ 45 mm; (ix) have essential hypertension for over one year; and (x) be able to read, understand and sign the informed consent form, besides to attend the clinic experiments.

Patients with any of the following criteria were excluded: (i) pregnancy; (ii) valvular disease with significant adverse sequelae; (iii) myocardial infarction, unstable angina, stroke or transient ischemic attack within the previous 6 months; (iv) renovascular abnormalities (including severe renal artery stenosis, renal angioplasty with or without stenting); (v) psychiatric disease; (vi) allergy to ionic contrast; (vii) patient known to have drug addiction or alcohol, can affect the ability to understand or follow medical instructions; (ix) patient has a history and/or physical examination. We evaluated the effectiveness of the β-blocker and RSD in the changes of HR by 24-hour-Holter monitoring, in 24-hour ABPM, and echocardiographic parameters at baseline, 1st month and 6th month of follow-up. The Echo Doppler exams to evaluate the anatomy of the renal arteries of patients submitted to RSD were also performed at baseline and at the 6th month post-procedure.

24-hour ABPM

The BP monitoring was performed for 24 hours with a clinically validated device (CardioMapa, Cardios, Brazil) before the procedure. The devices were programmed to measure every 15 minutes for 6 to 22 hours, and every 30 minutes from 22 to 6 hours. Patients were instructed to continue their regular activities during the recording and go to bed no more than the 23 hours. The waking period was defined as the range of 8 to 22 hours, and the sleep period such as midnight interval to 6 hours [14]. All patients were instructed to record in a diary the hours of sleep and wake, meals, intake of medications, in addition to the symptoms and events that could influence BP during this period. Measurements were transferred to a computer and a series of analyzes could be performed. At least 70% of the measured values in the daytime and nighttime should be satisfactory or, monitoring should be repeated [15].

Study procedures and assessment

In this study, we treated 20 hypertensive patients with PAF, 10 of them were treated with β-blocker (bisoprolol 10 mg/day) use and the other 10 patients had RSD. Patients underwent a complete medical history and physical examination. We evaluated the effectiveness of the β-blocker and RSD in the changes of HR by 24-hour-Holter monitoring, in 24-hour ABPM, and echocardiographic parameters at baseline, 1st month and 6th month of follow-up. The Echo Doppler exams to evaluate the anatomy of the renal arteries of patients submitted to RSD were also performed at baseline and at the 6th month post-procedure.

The RSD procedures were performed in the catheterization laboratory with direct visualization using fluoroscopy and radiopaque contrast. In all cases, we also used three-dimensional mapping system EnSite Velocity (St. Jude Medical, St. Paul, Minnesota, USA) for the construction of renal arteries and aorta anatomy, as well as for radiofrequency application in the selected sites. Under the supervision of an anaesthesiologist, patients were pretreated with diazepam or midazolam. Catheterization of the femoral artery by the standard Seldinger technique was performed after s.c. injection of local anesthetic in the inguinal region. A 12-Fr valved sheath was introduced into this artery and unfractionated heparin was administered as i.v. bolus, targeting an activated coagulation time (ACT) > 250 s in the first 10 min. During the procedure the ACT targeted range was 250–350 s. Subsequently, using an 11-F steerable long sheath (Agilis™, St. Jude Medical, St. Paul, Minnesota, USA) by the standard “over the wire” technique, an angiogram of the aorta and renal arteries was performed, and the 7-Fr ablation catheter with open irrigated tip was inserted (Therapy™ Cool Path™, St. Jude Medical, St. Paul, Minnesota, USA) inside the renal artery, allowing the delivery of RF energy to the renal artery innervation. Because the application of RF is usually very painful, fentanyl was intravenously administered before the procedure. Radiofrequency applications were performed within the main stem of the renal arteries, bilaterally, with a series of applications with 10 W power, 60 s duration each, with an irrigation flow rate of 25 mL/min, aiming ~4 RF applications per renal artery, according to their length. These points ablated were made with at least 5 mm distance between them and moving the catheter from the distal to the proximal in circumferential manner. The number of lesions per artery was chosen based on the artery length measurement by baseline angiography. For arteries shorter than 20 mm, a minimum of four lesions was applied, and for every increase in 5 mm length one additional lesion was provided. After the procedure, the anatomy of the

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renal arteries was checked by angiography to assess whether there were any complications during the procedure.

After the procedure, patients remained hospitalized for a period of 24 h in a ward. The follow-up was performed weekly for the first month and monthly from the second to the sixth month after the onset of β-blocker or post RSD. The following variables were monitored during the follow-up period: doses of medications, cardiac parameters by the echocardiogram, HR by the 24-hour-Holter monitoring, and blood pressure by the 24-hour ABPM.

Statistical analysis

The results were expressed as mean and standard deviation (mean ± SD) of the mean in case of normal distribution and as the median with inter-quartile range otherwise. Statistical tests were all two sided. Comparisons between two-paired values were performed by the paired t-test in 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 x² test. P-values<0.05 were considered significant. Correlations between two variables were performed by Pearson in case of Gaussian distribution or, alternatively, with the Spearman correlation test. All statistical analysis was performed using the program Graphpad Prism v 6.0 (Graphpad software, La Jolla, CA, USA).

Results

Baseline characteristics of patients

General features of the patients are listed in Table 1, for overall (n=20), for β-blocker group (n=10) and for RSD group (n=10).

Table 1: General features of patients at baseline.

| Parameters                                      | Overall | β-blocker | RSD      | P-value |
|-------------------------------------------------|---------|-----------|----------|---------|
| N                                               | 20      | 10        | 10       | ---     |
| Age (years)                                     | 61 ± 7a | 58 ± 7    | 63 ± 8   | 0.1846  |
| Body mass index, kg/m²                          | 27 ± 4a | 26 ± 3    | 28 ± 4   | 0.4695  |
| Male sex (%)                                    | 13 (65%)| 6 (60%)   | 7 (70%)  | 1       |
| Ethnicity (white) (%)                           | 13 (65%)| 7 (70%)   | 6 (60%)  | 1       |
| Hypertension                                    | 20 (100%)| 10 (100%)| 10 (100%)| 1       |
| Type 2 Diabetes Mellitus                        | 13 (65%)| 6 (60%)   | 7 (70%)  | 1       |
| Coronary artery disease                         | 12 (60%)| 6 (60%)   | 6 (60%)  | 1       |
| Stroke/Transient ischemic attack                | 4 (20%) | 2 (20%)   | 2 (20%)  | 1       |
| Atrial fibrillation duration, months            | 47 ± 8a | 48 ± 8    | 48 ± 9   | 0.4908  |
| CHA2DS2-VASc                                     | 3.2 ± 1.3a | 3.0 ± 1.4| 3.3 ± 1.3| 0.6319  |
| Antihypertensive                                | 2.3 ± 0.5a| 2.4 ± 0.5| 2.2 ± 0.4| 0.3553  |
| ACE-inhibitors/ARB                              | 20 (100%)| 10 (100%)| 10 (100%)| 1       |
| Diuretics                                       | 17 (85%)| 9 (90%)   | 8 (80%)  | 1       |
| DHP calcium channel blockers                    | 9 (45%) | 5 (50%)   | 4 (40%)  | 1       |
| 24-hour ABPM, mmHg                              | 126 ± 6/79 ± 4a| 127 ± 7/79 ± 4| 125 ± 6/78 ± 3| 0.6252/0.9151 |

24-hour Holter monitoring

| Parameters                                      | Overall | β-blocker | RSD      |
|-------------------------------------------------|---------|-----------|----------|
| Heart rate minimum, bpm                         | 52 ± 7  | 53 ± 8    | 52 ± 7   | 0.7904  |
| Heart rate average, bpm                         | 110 ± 5 | 109 ± 5   | 111 ± 6  | 0.4895  |
| Heart rate maximum, bpm                         | 174 ± 11| 173 ± 10  | 175 ± 12 | 0.7197  |

*Mean ± SD; ABPM, ambulatory blood pressure measurements; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DHP, dihydropyridine; N, number of patients; RSD, renal sympathetic denervation.

Table 1: General features of patients at baseline.

Safety evaluation of RSD

No patient had or presented with procedural complications. No hypotensive or syncopal episodes were reported after β-blocker onset or RSD. Real-time renal artery imaging was performed to assess eventual 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 oedema) were no longer seen postoperatively. At the 6th after the procedure all the patients from RSD group underwent a Doppler scan of renal arteries without any evidence of stenosis or flow limitation.

**Ablation procedure**

In this patient cohort, 200 ablation spots were performed. The average of the number of lesions delivered was 10 ± 2 (range 7–13) in the right renal artery and 10 ± 2 (range 7–13) in the left renal artery. The mean duration of ablation was 1200 ± 251 s of RF per patient (range 900–1560 s), the duration of the procedure ranged from 30 to 60 min, and the mean exposure time to fluoroscopy was 15 ± 8 min.

**Effects on blood pressure**

During the 6 months of follow-up, there was nonsignificant change on mean 24-hour ABPM from baseline (127 ± 7/79 ± 4 mmHg) to 1st (125 ± 6/79 ± 4 mmHg) and 6th month (120 ± 6/75 ± 4 mmHg) after onset of β-blocker neither from baseline (121 ± 6/75 ± 4 mmHg) to 1st (122 ± 7/76 ± 4 mmHg) and 6th month (120 ± 6/76 ± 4 mmHg) post RSD. There was no difference in the comparison between groups at the same time points.

**Effects on heart rate**

The minimum HR for β-blocker and RSD groups, respectively, was 53 ± 8 and 52 ± 7 bpm at baseline, 51 ± 7 and 50 ± 6 bpm at the 1st month, and 49 ± 7 and 48 ± 6 bpm at the 6th month of follow-up (P>0.05 for comparisons between 1 and 6 months vs. baseline values in each group; P>0.05 for comparisons at the same time point between groups), as shown in Figure 1A. The average HR for β-blocker and RSD groups, respectively, was 109 ± 5 and 111 ± 6 bpm at baseline, 87 ± 3 and 86 ± 3 bpm at the 1st month, and 85 ± 3 and 74 ± 6 bpm at the 6th month of follow-up (P<0.0001 for comparisons between 1 and 6 months vs. baseline values in each group; P<0.0001 only for comparison at 6th month between groups), as shown in Figure 1B. The maximum HR for β-blocker and RSD groups, respectively, was 173 ± 10 and 175 ± 12 bpm at baseline, 140 ± 14 and 141 ± 12 bpm at the 1st month, and 139 ± 18 and 118 ± 9 bpm at the 6th month of follow-up (P<0.0001 for comparisons between 1 and 6 months vs. baseline values in each group; P=0.0050 only for comparison at 6th month between groups), as shown in Figure 1C.

![Figure 1](image_url)

**Effects on echocardiographic parameters**

Changes in left ventricular ejection fraction (LVEF), left atrial diameter (LAD), end diastolic left ventricular internal dimension (LVIDd), and LV mass index at 6th month after onset of β-blocker and post RSD vs. respective baseline values, besides comparisons at the same time point between groups are shown in Table 2.

| Echocardiographic parameters | β-blocker (n=10) | RSD (n=10) |
|----------------------------|----------------|------------|
| LVEF (Simpson %) | Baseline: 62.1 ± 8.0 | 62.4 ± 7.8 | 0.9335 | 59.6 ± 7.9 | 60.7 ± 7.3 | 0.7503 |
| LAD (mm) | 48.3 ± 2.7 | 48.4 ± 2.5 | 0.9326 | 48.5 ± 2.8 | 45.7 ± 2.9* | 0.0404 |
| LVIDd (mm) | 52.9 ± 2.3 | 52.6 ± 2.5 | 0.7847 | 52.5 ± 2.6 | 51.3 ± 2.3 | 0.2847 |
| LV mass index (g/m²) | 102.1 ± 11.3 | 99.0 ± 11.6 | 0.5514 | 108.3 ± 11.0 | 97.8 ± 9.3 | 0.0326 |

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Several randomized trials compared outcomes of rhythm vs. rate control strategies in patients with AF [16-22]. Among these, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) found no difference in all-cause mortality (primary outcome) or stroke rate between patients assigned to one strategy or the other [16]. The Rate Control versus Electrical Cardioversion for persistent atrial fibrillation (RACE) trial found rate control not inferior to rhythm control for prevention of cardiovascular mortality and morbidity (composite endpoint) [17]. The optimal level of HR control with respect to morbidity, mortality, quality of life, and symptoms remains unknown. Previous guidelines recommended strict rate control aiming at a resting heart rate between 60–80 bpm and 90–115 bpm during moderate exercise, based on the type of therapy applied in the AFFIRM trial [16].

The control of high HR has been shown to be an important and became a target to be achieved, because this is an important predictor of augmented cardiovascular morbidity and mortality in healthy populations and in patients with cardiovascular disorders such as hypertension, coronary artery disease, chronic heart failure and myocardial infarction [23,24]. The β-blockers may be especially useful in the presence of high adrenergic tone or symptomatic myocardial ischemia occurring in association with AF. During chronic treatment β-blockers have been shown to be effective and safe in several studies compared with placebo and digoxin. In AFFIRM [16], β-blockers were commonly used to achieve strict rate control. Small and preliminary studies suggested that catheter-based radiofrequency modification of atrioventricular nodal conduction properties may reduce ventricular rate and AF-related symptoms. However, the procedure has no defined endpoint, and atrioventricular node ablation and pacemaker implantation appear superior. Therefore, atrioventricular node modification without permanent pacemaker insertion is rarely used.

Our results showed that in 20 controlled hypertensive patients with PAF there was a reduction in the minimum, average and maximum HR measured by 24-hour-Holter monitoring during the 6 months of follow-up, both for the group using bisoprolol (n=10) and the group that underwent RSD (n=10). However, we observed that at the 6th month post RSD the decreased HR seen was more intense in average HR (Δ=-12 ± 2 bpm, P<0.0001) and maximum HR (Δ=-21 ± 6 bpm, P=0.0050) in this group than β-blocker group. RSD probably can reduce HR due to electrophysiological chronotropic and dromotropic properties of the atrioventricular node that is subjected to a higher influence of autonomic nervous system. The depolarization rate of atrioventricular conduction is largely mediated by sympathetic and vagal activity. Lower HR provoked by RSD in these patients may be possibly caused by a reduction in overall sympathetic activity, which is mediated by a decrease of renal nerves activity.

In agreement with other studies [25,26], the LV mass index decreased at the 6th month after RSD in comparison to baseline (Δ=-10.5 ± 4.5 g/m², P=0.0326), and in the β-blocker group there was no difference between baseline and bisoprolol use at the 6th month of follow-up (Δ=-3.1 ± 5.1 g/m², P=0.5514). However, there was no difference in reduction between groups (Δ=-1.2 ± 4.7 g/m², P=0.8013).

Furthermore, there was no significant change in mean 24-hour ABPM, and there was an expressive reduction in LAD (Δ=-2.7 ± 1.2 mm, P=0.0391) in RSD group compared to β-blocker group at the 6th month of follow-up, in agreement with other studies [25,26]. The myocardial improvement and end-diastolic pressures after RSD as measured by LAD reduction, which have been linked to improved prognosis in pharmaceutical interventional trials. An interesting finding was the significant correlation between the Δ reduction average HR at the 6th month (r=-0.8639, P=0.0022) after the RSD and the total number of ablation spots.

In hypertensive patients with PAF, the pharmacological and non-pharmacological therapy for control HR in several ones with high ventricular rate remains unsatisfactory. Recently, Ukena et al. [27] reported that RSD reduces BP during exercise without compromising chronotropic competence in resistant hypertensive patients. Post RSD, HR at rest decreased (4 ± 11 bpm; P=0.028), maximum HR and HR increase during exercise were not different. HR recovery improved significantly by 4 ± 7 bpm (P=0.009). Afterwards, Ukena et al. [10] also reported that 136 resistant hypertensive patients in sinus rhythm had a mean HR at baseline of 66.1 ± 1 bpm. At the 3rd and 6th months after RSD, HR was reduced by 2.6 ± 0.8 bpm (P=0.001), and 2.1 ± 1.1 bpm (P=0.046), respectively. In addition, they related that the PR interval

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**Table 2:** Echocardiographic parameters during the follow-up period.

**Correlation**

A significant correlation was found between the Δ average HR reduction at the 6th month (r=-0.8639, P=0.0022) after the RSD and the total number of ablation spots, as shown in Figure 2.

![Figure 2](image-url)  
**Figure 2:** A significant correlation was found between the Δ reduction average HR at the 6th month (r=-0.8639, P=0.0022) after the RSD and the total number of ablation spots. HR, heart rate; n=10.

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**Discussion**

In hypertensive patients with PAF, the pharmacological and non-pharmacological therapy for control HR in several ones with high ventricular rate remains unsatisfactory. Recently, Ukena et al. [27] reported that RSD reduces BP during exercise without compromising chronotropic competence in resistant hypertensive patients. Post RSD, HR at rest decreased (4 ± 11 bpm; P=0.028), maximum HR and HR increase during exercise were not different. HR recovery improved significantly by 4 ± 7 bpm (P=0.009). Afterwards, Ukena et al. [10] also reported that 136 resistant hypertensive patients in sinus rhythm had a mean HR at baseline of 66.1 ± 1 bpm. At the 3rd and 6th months after RSD, HR was reduced by 2.6 ± 0.8 bpm (P=0.001), and 2.1 ± 1.1 bpm (P=0.046), respectively. In addition, they related that the PR interval
was prolonged by 11.3 ± 2.5 ms (P=0.0001) and 10.3 ± 2.5 ms (P=0.0001) at 3 and 6 months post RSD, respectively. In 2015, McLellan et al. [28] studied 14 resistant hypertensive patients in treatment, presenting sinus rhythm that underwent baseline 24-hour ambulatory BP monitoring, echocardiography, cardiac magnetic resonance imaging, and electrophysiologic study. Electrophysiologic study included measurements of P-wave duration, effective refractory periods, and conduction times. Electroanatomic mapping of the right atrium was completed using CARTO3 to determine local and regional conduction velocity and tissue voltage. Bilateral renal denervation was performed, and all measurements repeated after 6 months. After renal denervation, mean 24-hour BP reduced from 152/84 mmHg to 141/80 mmHg at 6-month follow-up (P<0.01). Global conduction velocity increased significantly (0.98 ± 0.13 m/s to 1.2 ± 0.16 m/s at 6 months, P<0.01), conduction time shortened (32 ± 5 ms to 27 ± 6 ms, P<0.01), and complex fractionated activity was reduced (37 ± 14% to 19 ± 12%, P=0.02). Changes in conduction velocity correlated positively with changes in 24-hour mean systolic BP (R²=0.55, P=0.01). There was a significant reduction in left ventricular mass (139 ± 37 g to 120 ± 29 g, P<0.01) and diffuse ventricular fibrosis (T1 partition coefficient 0.39 ± 0.07 to 0.31 ± 0.09, P<0.01) on cardiac magnetic resonance imaging. In 2016, Qiu et al. [29] reported the improvement in ventricular HR control in 21 patients persistent AF, slowing atrioventricular node conduction in baseline HR-dependent manner.

All these data aforementioned support our results, showing that RSD is able to modify the properties of atrioventricular node, probably, due to the atrioventricular conduction to be largely mediated by sympathetic and vagal activity. RSD can become an alternative in cases of PAF that β-blockers, calcium channel blockers and other drugs failed to control the HR, before to implant a pacemaker and perform atrioventricular junction ablation.

Study Limitations

This study was a safety evaluation therefore was neither blinded nor powered to assess clinical efficacy. Whilst there was self-reported improvement in symptoms, average and maximum HR, and some cardiac parameters observed by echocardiogram in both groups, these findings should be interpreted with caution given the unblinded non-randomised nature of the study. A randomised trial with appropriate concealment of treatment, more patients and for a long follow-up period is required to address the potential benefits of RSD in PAF.

In future studies the neuromuscular sympathetic activity (MSN) can be measured, which can contribute greatly to assess the degree of sympathetic blockade.

Conclusion

In conclusion RSD appears to be safe in the treatment of PAF, as well as, improves some cardiac parameters assessed by echocardiogram. Average and maximum HR, besides LAD appear to be modified by the RSD according to the aforementioned results, in comparison to β-blocker, mainly at 6th month of follow-up. Although encouraging, our data are preliminary and need to be validated in a large population and in long term. If this will be affirmed, this can become a potential tool to be incorporated in clinical practice in the future.

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Conflict of Interest

None declared.

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