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CLINICAL CASE REPORT

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Case Report: Renal Sympathetic Denervation as a Tool for the Treatment of Refractory Inappropriate Sinus Tachycardia

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Abstract: Inappropriate sinus tachycardia is defined as sinus tachycardia at rest (heart rate ≥100 bpm) in sitting position or/and as an average heart rate ≥90 bpm during 24-hour Holter monitoring. The most common symptoms are palpitation, dizziness, chest discomfort, orthostatic intolerance, and fatigue. Sometimes, the symptoms can be severe and debilitating, and its etiology is not well understood. Pharmacological approaches present limitation because of their relatively small effectiveness, intolerance, or side effects.

In this series of cases of inappropriate sinus tachycardia, the authors report 3 cases refractory to conventional pharmacological therapy, in which the authors were not tempted for ablation of the sinus node. The authors, however, use another therapeutic approach, which was renal sympathetic denervation, to reduce sympathetic activity in the sinus node, and consequently reduce tachycardia with improvement of symptoms.

Three months after renal sympathetic denervation, all patients were not using any type of medication, and reported no more symptoms. The authors know that this is the first report using the renal sympathetic denervation for the treatment of inappropriate sinus tachycardia. Studies with a larger number of patients, a longer time of follow-up, and a control group, however, should be performed.

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Abbreviations: ACT = activated coagulation time, AV = atrioventricular, HR = heart rate, IST = inappropriate sinus tachycardia, RF = radiofrequency, RSD = renal sympathetic denervation, VAS = ventricular arrhythmias.

INTRODUCTION

Inappropriate sinus tachycardia (IST) is defined as sinus tachycardia at rest [heart rate (HR) ≥100 bpm] in sitting position or/and as an average HR ≥ 90 bpm during 24-hour Holter monitoring.[1] The most common symptoms are palpitation, dizziness, chest discomfort, orthostatic intolerance, and fatigue.[1–4] Sometimes, the symptoms can be severe and debilitating, and its etiology is not well understood. Beta-blockers are the first-line therapy. Other potentially effective drugs, however, are nondihydropyridine calcium antagonists or amiodarone. The limitation of these pharmacological approaches is their relatively small effectiveness, intolerance, or side effects of the respective drugs.[2,4,5] Several studies with clinical follow-up[6–9] have suggested that ivabradine administration is a safe and effective second-line therapy in patient affected by IST. Other nonpharmacological interventions such as sinus node ablation are limited by their low efficiency or significant incidence of complications.[4,5,10–13]

Sympathetic hyperactivity plays a critical role in the development, maintenance, and aggravation of ventricular arrhythmias.[14] Recently, Armaganijan et al[15] reported the relevance of sympathetic activation in patients with VAs and suggest a potential role for catheter-based renal sympathetic denervation (RSD) in reducing arrhythmic burden. Pokushalov et al[16] reported that RSD reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces atrial fibrillation recurrences when combined with pulmonary vein isolation. We hypothesized that RSD could have a salutary effect on IST patterns in patients with poorly controlled of the heart rate by reduction in central sympathetic cardiac stimulation.

In this series of cases of IST, we report 3 cases refractory to conventional pharmacological therapy, in which we were not tempted for ablation of the sinus node. We, however, use another therapeutic approach, which was RSD, to reduce sympathetic activity in the sinus node. Individual baseline features and over time are shown in Table 1. The patients #1 and #2 complained daily of palpitations, tachycardic palpitations, and fatigue, for more than 1 year. The patient #3 reported daily palpitations and dizziness, also for more than a year. Three different pharmacological treatment strategies were tested in each patient (Table 1), without achieving an adequate response for symptoms.

All the 3 patients signed the informed consent and the ethics committee (composed by Paola Baars Gomes Moises, Luis Marcelo Rodrigues Paz, and Humberto Cesar Tinoco e Jonny Shogo Takahashi) approved the execution of the case. The procedures were performed in the catheterization laboratory with direct visualization using fluoroscopy and radiopaque contrast. We used three-dimensional mapping system EnSite Velocity (St. Jude Medical, St. Paul, MN) for construction of renal arteries and aorta anatomy, as well as for radiofrequency application in the selected sites. All patients remained under unconscious sedation. The patients #1 and #3 underwent to catheterization of the right femoral artery by the standard Seldinger technique was performed using a 7-Fr valved short sheath, after subcutaneous injection of local anesthetic.

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TABLE 1. Individual Baseline Features and Over Time

Baseline			
Patient	#1	#2	#3
Age	16	15	32
Sex	Female	Female	Male
Baseline mean office BP (mm Hg)	116/80	120/82	138/90
Baseline 24-hour Holter monitoring average HR (bpm)	122	124	119
First Month			
First attempt at treatment (mg/d) 1 month	Bisoprolol (10)	Bisoprolol (10)	Nebivolol (5)
Mean office BP after first attempt at treatment (mm Hg)	112/80	118/82	138/86
Twenty four-hour Holter monitoring average HR after first attempt at treatment (bpm)	118	116	113
Second Month			
Second attempt at treatment (mg/d) 1 month	Bisoprolol (10) + diltiazem SR (180)	Bisoprolol (10) + diltiazem SR (180)	Nebivolol (5) + diltiazem SR (180)
Mean office BP after second attempt at treatment (mm Hg)	108/76	112/78	130/82
Twenty four-hour Holter monitoring average HR after second attempt at treatment (bpm)	115	111	109
		Third month	
Third attempt at treatment (mg/d) 1 month	Bisoprolol (10) + diltiazem SR (180) + ivabradine (15)	Bisoprolol (10) + diltiazem SR (180) + ivabradine (15)	Nebivolol (5) + diltiazem SR (180) + ivabradine (15)
Mean office BP after third attempt at treatment (mm Hg)	107/76	113/79	133/81
Twenty four-hour Holter monitoring average HR after third attempt at treatment (bpm)	104	98	95
		Fourth month	
Mean office BP 1 month after RSD (mm Hg)	102/73	110/75	124/77
Twenty four-hour Holter monitoring average HR 1 month after RSD (bpm)	93	87	86
		Sixth month	
Mean office BP 3 months after RSD (mm Hg)	103/72	110/74	123/78
Twenty four-hour Holter monitoring average HR 3 months after RSD (bpm)	81	75	72

BP = blood pressure, HR = heart rate, RSD = renal sympathetic denervation.

Subsequently, it was replaced by the steerable long sheath (Agilis®, St. Jude Medical, St. Paul, MN) by the standard ''over the wire'' technique. Unfractionated heparin was administered intravenously, targeting an activated coagulation time between 250 and 350 seconds. This sheath was advanced to the level of the renal arteries and the ostia were located with nonselective aortography. The introducer was then carefully deflected to anchor at the ostium of each renal artery to introduce the ablation catheter with open irrigated tip (St. Jude Medical, St. Paul, MN), as shown in Figure 1A. And the patient #2 underwent to RSD using the system EnligHTN™ (St. Jude Medical, St. Paul, MN), as shown in Figure 1B. The number of ablation spots per artery in each patient, are shown in Table 2. All procedures were performed without any complications, and the patients remained clinically stable and awoke properly from sedation. Intravenous protamine was infused at the end of the procedure and manual compression of the femoral artery was performed with a mean time of 15 minutes in each patient, followed by compressive dressing. All procedures did not show any vascular complications. Patients were discharged after 24-hour hospitalization, clinically stable, walking without difficulty.

The results were expressed as mean and standard deviation (mean ± SD) of the mean in this case because of normal distribution. Statistical tests were all 2-sided. Comparisons between more than 2-paired values were performed by analysis of variance for repeated measures or with Kruskal–Wallis analysis of variance as appropriate complemented by a post hoc test. P-values <0.05 were considered significant. All statistical analysis was performed using the program GraphPad Prism v 6.0 (GraphPad Software, La Jolla, CA).

The results over time, 6 months of follow-up (including 3 months after the procedure), are shown in Table 1. The 24-hour average HR at baseline was 121.7 ± 2.5 bpm, falling down to 76.0 ± 4.6 bpm 3 months after the ablation procedure ($P < 0.0001$), as shown in Figure 2. A reduction in the mean

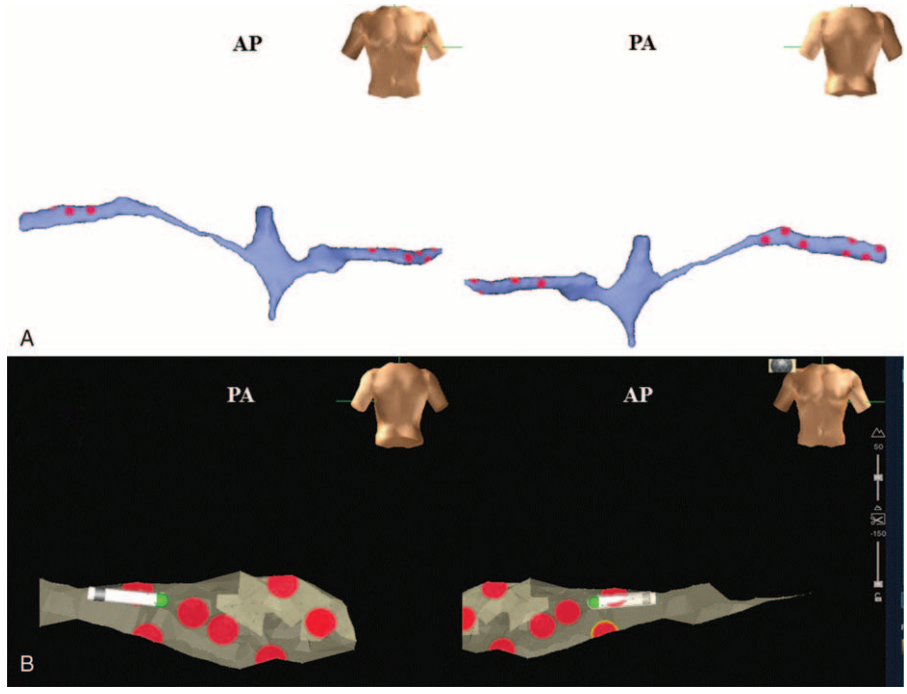

FIGURE 1. Anatomic reconstruction of renal arteries and abdominal aorta segment with the mapping system (EnSite Velocity®). Anteroposterior projection with patients' identification and posteroanterior projections are presented. In the upper panel (A), we used the standard ablation catheter with open irrigated tip and in the bottom panel (B) was used the EnligHTN™ catheter. Notice the red marks, tagged from each ablation spot.

office blood pressure was also observed, decreasing from $124.7 \pm 11.7/84.0 \pm 5.3$ to $112.0 \pm 10.2/74.7 \pm 3.1$ mm Hg ($P < 0.0001/P = 0.0480$), as shown in Figure 3. Three months after RSD, all patients were not using any type of medication, and no reported more symptoms. On the contrary, blockade of autonomic nervous system by ablation was defined previously in the other fields of cardiac diseases. For the first time, Pachon et al[17] in 2004 described in 21 patients, the increase in HR after ''Cardioneuroablation,'' considered a new treatment for vasovagal syncope, functional atrioventricular block, and sinus dysfunction, using radiofrequency (RF) ablation catheter. In 2011, Pachon et al demonstrated in a total of 43 patients with neurocardiogenic or vasovagal syncope with important cardioinhibition (pauses = 13.5 ± 13 seconds) at head-up tilt test, normal electrocardiogram, and normal atropine test that endocardial RF catheter ablation of severe neurally meditated reflex syncope prevented pacemaker implantation and showed excellent long-term results in well-selected patients. Despite no action in vasodepression, it seems to cause enough long-term vagal reflex attenuation, eliminating the cardioinhibition, and keeping most patients asymptomatic. The indication was based on clinical symptoms, reproduction of severe cardioinhibitory syncope, and normal atropine response.[18] More recently, Rivarola et al reported a case of a patient with frequent asymptomatic nocturnal ventricular pauses of 3 to 11 seconds, characteristic of a vagally mediated atrioventricular block,

TABLE 2. Number of Ablation Spots During Renal Sympathetic Denervation

Patient	Number of Ablation Spots Left Renal Artery	Number of Ablation Spots Right Renal Artery	Number of Ablation Spots Both Renal Arteries
#1	10	9	19
#2	8	8	16
#3	8	9	17
Average	9 ± 1	9 ± 1	17 ± 2

Average is presented as mean ± SD.

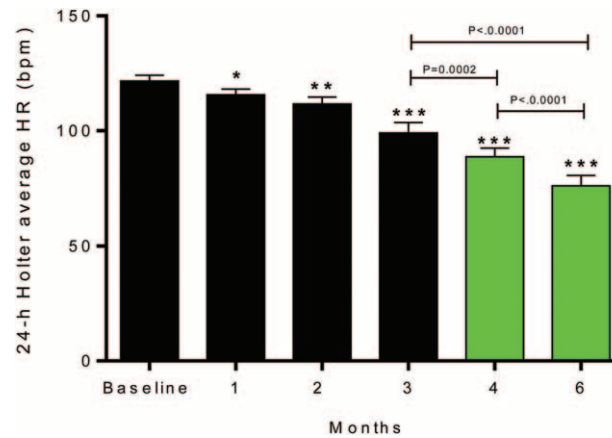

FIGURE 2. Average heart rate (bpm) during 24-hour Holter monitoring at baseline, at months 1, 2, and 3 using standard pharmacologic therapy, and postprocedure at the fourth and sixth months of follow-up (1 and 3 months after renal sympathetic denervation, respectively). $^{*}P < 0.01$, $^{**}P < 0.001$, $^{***}P < 0.0001$ versus baseline values. HR = heart rate. Values are presented as mean ± SD (n = 3).

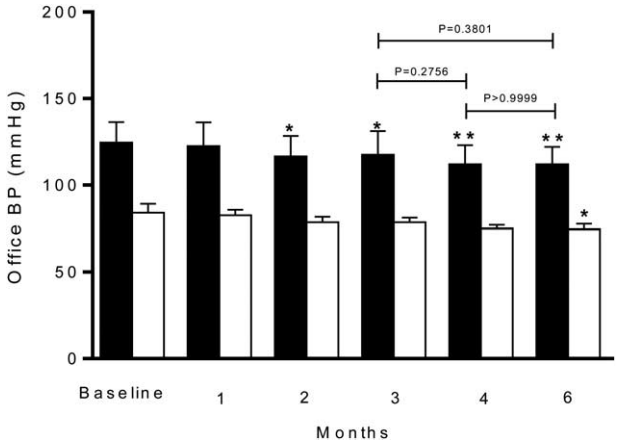

FIGURE 3. Mean office systolic (closed bars) and diastolic (open bars) blood pressure (mm Hg) at baseline, at months 1, 2, and 3 using standard pharmacologic therapy, and postprocedure at the fourth and sixth months of follow-up (1 and 3 months after renal sympathetic denervation, respectively). $^{*}P < 0.001$, $^{**}P < 0.0001$ versus baseline values. BP = blood pressure. Values are presented as mean ± SD (n = 3).

underwent to spectral mapping, used to localize endocardial vagal innervation in the right and left aspects of the interatrial septum, responsible for the sinus node and atrioventricular node modulation, and RF pulses were applied in those sites only. Ablation of the endocardial vagal innervation sites seems to be safe and efficient in reducing the frequency and the length of the ventricular pauses. It was possible by identifying certain spectral components of the atrial electrogram, resulting in a conservative approach.[19]

Even trying to map the renal arteries in all their extension, in search of some electric potential of the autonomic nervous system, we were not able to find any electrical signal. The sympathetic nerves, however, are largely located in the adventitia layer, 1.5 to 2 mm from the lumen of the renal artery,[20] and a greater number of ablated spots already mentioned as a predictor of success, according to the analysis of Symplycity HTN-3 trial results,[21] may cause more destruction of sympathetic arterial nerves. We know that this is the first report using the RSD for the treatment of IST. Studies with a larger number of patients, a longer time of follow-up, and a control group, however, should be performed. The success of these 3 consecutive cases makes us think that this may be a promising strategy for treating this disease.

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REFERENCES

1. Still A-M, Raatikainen P, Ylitalo A, et al. Prevalence, characteristics and natural course of inappropriate sinus tachycardia. *Europace.* 2005;7:104–112.
2. Cossu SF, Steinberg JS. Supraventricular tachyarrhythmias involving the sinus node: clinical and electrophysiologic characteristics. *Prog Cardiovasc Dis.* 1998;41:51–63.
3. Kalman JM. Inappropriate sinus tachycardia: an update. *Cardiac Electrophysiol Rev.* 1999;3:115–116.
4. Femenia F, Baranchuk A, Morillo CA. Inappropriate sinus tachycardia: current therapeutic options. *Cardiol Rev.* 2012;20:8–14.
5. Lee RJ, Shinbane JS. Inappropriate sinus tachycardia. Diagnosis and treatment. *Cardiol Clin.* 1997;15:599–605.
6. Rakovec P. Treatment of inappropriate sinus tachycardia with ivabradine. *Wien Klin Wochenschr.* 2009;121:716–718.
7. Calò L, Rebecchi M, Sette A, et al. Efficacy of ivabradine administration in patients affected by inappropriate sinus tachycardia. *Heart Rhythm.* 2010;7:1318–1323.
8. Kaplinsky E, Comes FP, Urondo LS, et al. Efficacy of ivabradine in four patients with inappropriate sinus tachycardia: a three month-long experience based on electrocardiographic, Holter monitoring, exercise tolerance and quality of life assessment. *Cardiol J.* 2010;17:166–171.
9. Zellerhoff S, Hinterseer M, Felix Krull B, et al. Ivabradine in patients with inappropriate sinus tachycardia. *Naunyn Schmiedebergs Arch Pharmacol.* 2010;382:483–486.
10. Shen W-K. Modification and ablation for inappropriate sinus tachycardia: current status. *Card Electrophysiol Rev.* 2002;6:349–355.
11. Lee RJ, Kalman JM, Fitzpatrick AP, et al. Radiofrequency catheter modification of the sinus node for ''inappropriate'' sinus tachycardia. *Circulation.* 1995;92:2919–2928.
12. Man K, Knight B, Tse H, et al. Radiofrequency catheter ablation of inappropriate sinus tachycardia guided by activation mapping. *J Am Coll Cardiol.* 2000;35:451–457.
13. Marrouche N, Beheiry S, Tomassoni G, et al. Three-dimensional nonfluoroscopic mapping and ablation of inappropriate sinus tachycardia. Procedural strategies and long-term outcome. *J Am Coll Cardiol.* 2002;39:1046–1054.
14. Leenen FH. Cardiovascular consequences of sympathetic hyperactivity. *Can J Cardiol.* 1999;15:2A–7A.
15. Armaganijan LV, Staico R, Moreira DA, et al. 6-month outcomes in patients with implantable cardioverter-defibrillators undergoing renal sympathetic denervation for the treatment of refractory ventricular arrhythmias. *JACC Cardiovasc Interv.* 2015;8:984–990.
16. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol.* 2012;60:1163–1170.
17. Pachon JC, Pachon EI, Pachon JC, et al. Cardioneuroablation'': new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. *Europace.* 2005;7:1–13.
18. Pachon JC, Pachon EI, Cunha Pachon MZ, et al. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. *Europace.* 2011;13:1231–1242.
19. Rivarola E, Hardy C, Sosa E, et al. Selective atrial vagal denervation guided by spectral mapping to treat advanced atrioventricular block. *Europace.* 2015. pii: euv142. [Epub ahead of print].
20. Atherton DS, Deep NL, Mendelsohn FO. Micro-anatomy of the renal sympathetic nervous system: a human postmortem histologic study. *Clin Anat.* 2012;25:628–633.
21. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J.* 2015;36:219–227.