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Case Report Open Access

Case Report: Renal Sympathetic Denervation + Pulmonary Vein Re-isolation in Patients with Long-stand Persistent Atrial Fibrillation and Resistant Hypertension. Does it Work?

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Abstract

Introduction: A recent study reported that renal sympathetic denervation (RSD) reduces systolic and diastolic blood pressure (BP) in patients with drug-resistant hypertension and reduces atrial fibrillation (AF) recurrences when combined with pulmonary vein isolation (PVI), in a prospective randomized study that assessed the impact of renal artery denervation in patients with a history of refractory AF and drug-resistant hypertension who were referred for PVI.

Case presentation: In this series of cases of long-standing persistent atrial fibrillation (LSPAF) we report 5 cases refractory to treatment with antiarrhythmic drug that underwent to AF catheter ablation, at least one year. The five patients complained about tachycardic palpitations often, as well as, episodes of dyspnea and pre-syncope, were taking amiodarone 200 mg/day and returned to present LSPAF. Moreover, all of them had resistant hypertension besides to possessing other comorbidities. They had normal renal function, and were using the anti-hypertensive medications for at least 3 months, as well as all of them were using dabigatran 150 mg twice a day. All of them underwent to pulmonary vein re-isolation (PVRI) and RSD. All the patients submitted to RSD showed highly significant reduction in office BP and 24-hour APM, both systolic and diastolic at all times points after the procedure. No changes in the renal function were observed before and after the procedure. Even after prompt successful PVRI + RSD procedures, with the 5 patients recovering sinus rhythm, all of them had recurrence of persistent AF in less than one year. After controlling the BP, even all the individuals being in AF, we observed a reduction in left atrial volume at one year post procedure (P = 0.0008), measured by cardiac magnetic resonance. Due to the maintenance of AF we opted to maintain amiodarone and think a third ablation of this arrhythmia in the future with more aggressive strategies or even opt for the control of heart rate, depending on the symptoms of patients.

Conclusions: We can conclude that RSD was effective in controlling BP and associated to PVRI showed a reduction in volume of the left atrium, but in the control of LSPAF, we did not achieve the success.

Keywords: Atrial fibrillation; Blood pressure; Resistant hypertension; Long-stand persistent atrial fibrillation; Pulmonary vein re-isolation; Renal sympathetic denervation

Introduction

Catheter ablation is a common procedure used to treat patients with symptomatic paroxysmal atrial fibrillation (AF), refractory to at least one antiarrhythmic. Results from multiples studies comparing antiarrhythmic drug treatment with catheter ablation, showing a significantly better rhythm outcome after ablation, support this practice. Furthermore, meta-analyses of studies performed mostly in patients with paroxysmal AF, comparing antiarrhythmic drugs and catheter ablation, have also shown better rhythm outcome after ablation [1-6]. For patients with persistent AF or long-standing persistent AF (LSPAF), without or with minimal heart disease, the treatment strategies and the benefit–risk ratio of catheter ablation are less well established. In this kind of patient, extensive and frequently repeated ablation procedures may be necessary, and it seems reasonable to elucidate them about the refractoriness to antiarrhythmic drug treatment before ablation is considered. Once amiodarone may be associated with serious and frequent adverse effects, especially during long-term treatment, it is fair to consider catheter ablation, electrical pulmonary vein isolation (PVI), as an alternative to amiodarone treatment in younger patients [7].

In this series of case we aim to evaluate the effects of pulmonary vein re-isolation (PVRI) associated to renal sympathetic denervation (RSD) in hypertensive patients with LSPAF, once PVI failed in the past.

Case Presentation

In this series of cases of LSPAF we report 5 consecutive cases refractory to treatment with antiarrhythmic drug that underwent to AF catheter ablation, (PVI) in the past (at least one year). Baseline features of the five patients and their respective means and percentage are presented in Table 1. They had normal renal function (Table 2), and were using the anti-hypertensive medications for at least 3 months

(Table 3), as well as all of them were using dabigatran 150 mg twice a day.

Parameters						**Mean**
Patient	**#1**	**#2**	**#3**	**#4**	**#5**	**N=5**
Age, years	34	48	56	60	63	52.2 ± 11.6[a]
Body mass index, kg/m^2	27.7	22.9	25.2	22.4	22	24.0 ± 2.4[a]
Male sex (%)	Male	Male	Male	Male	Male	5 (100%)
Ethnicity (white) (%)	White	Black	Black	White	White	3 (60%)
Previous AF ablation	Yes	Yes	Yes	Yes	Yes	5 (100%)
LSPAF	Yes	Yes	Yes	Yes	Yes	5 (100%)
Hypertension	Yes	Yes	Yes	Yes	Yes	5 (100%)
Type 2 diabetes mellitus	Yes	Yes	Yes	Yes	No	4 (80%)
Coronary artery disease	No	No	No	Yes	Yes	2 (40%)
All patients presented the following symptoms:	Tachycardic palpitations, episodes of dyspnea and pre-syncope					
CHA2DS2-VASc score	2	2	2	3	2	2.2 ± 0.4[a]
Left atrial volume, mL	101	79	90	81	72	85 ± 11[a]
eGFR, mL/min/1.73 m^2 (CKD-EPI)	141	129	116	93	95	114.8 ± 21.0[a]
Office blood pressure, mmHg	176/111	165/110	168/106	170/105	181/123	172 ± 6/111 ± 7[a]
24-hour ABPM, mmHg	155/110	148/112	152/100	159/98	167/120	156 ± 7/108 ± 9[a]
Amiodarone 200 mg/day	Yes	Yes	Yes	Yes	Yes	5 (100%)

[a]Mean ± SD; ABPM, ambulatory blood pressure measurements; CHA2DS2-VASc score, [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex category (female)] [8]; eGFR, estimated glomerular filtration rate; LSPAF, long-standing persistent AF; N, number of patients.

Table 1: General features of patients at baseline.

Variable	**Baseline**	**1st month**	**6th month**	**12thmonth**	**P-value**
Creatinine, mg/dL	0.7 ± 0.2[a]	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.4068
eGFR, mL/min/1.73m^2	104.8 ± 21.0[a]	112.8 ± 18.1	113.8 ± 17.0	115.8 ± 19.9	0.3934
ACR, mg/g	15.2[b] (11.1 – 20.8)	12.9 (12.5 – 21.7)	12.9 (11.7 – 19.8)	12.7 (11.7 – 18.9)	0.7476

[a]Mean ± SD; [b]Median (Inter-quartile range); ACR = Albumin: Creatinine Ratio; eGFR = Estimated Glomerular Filtration Rate; n = 5.

Table 2: Renal function parameters between baseline and 1st, 6th and 12th month after renal sympathetic denervation + pulmonary vein re-isolation.

The 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. JudeMedical, 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 anaesthetic 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 10min. 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. JudeMedical, St. Paul, Minnesota, USA) inside the renal artery, allowing the delivery of radiofrequency (RF) energy to the renal artery innervation. Because the application of RF is usually very painful, fentanyl was intravenously administered before the procedure. RF applications were performed

within the main stem of the renal arteries, bilaterally, with a series of applications with 8W power, 60 s duration each, with an irrigation flow rate of 17 mL/min, aiming >4 RF applications per renal artery, according to their length.

Patient	**# 1**		**# 2**		**# 3**		**# 4**		**# 5**	
Antihypertensive drugs (mg)	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
ACE-inhibitors										
Enalapril							40	40		
Angiotensin-receptor blocker										
Candesartan	16	16								
Losartan			100	50	100	50				
Valsartan									320	320
β-blocker										
Nebivolol	5	5	5	5	5	5	5	5	5	5
Aldosterone antagonist										
Spironolactone	25	25	25	25	25	25	25	25	25	25
Thiazide diuretics										
Chlorthalidone			25	25	25	25	25	25	25	25
Hydrochlorothiazide	25	25								
Calcium-channel blocker										
Amlodipine	10	10					10	10	10	10
Nifedipine prlolonged-release			60	60	60	60				
Nondihydropyridine α-2 adrenergic agonist										
Clonidine			0, 4	---	0, 4	---			0, 6	0, 6

Table 3: Pharmacological therapies before and 12 months after RSD + PVRI.

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 renal arteries was checked by angiography to assess whether there were any complications during the procedure. All procedures were performed without any complications, and the patients remained clinically stable. All procedures did not show any vascular complications. Patients were discharged after 48 hour hospitalization, clinically stable, walking without difficulty.

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).

All the patients submitted to RSD showed highly significant reduction in office BP, both systolic and diastolic at all times points after the procedure. Accordingly, BP diminished from 172 ± 6/111 ± 7 to 140 ± 4/89 ± 7, 138 ± 4/88 ± 6, and 136 ± 4/86 ± 4 mmHg, at the 1st, 6th, and 12th month, respectively (P<0.001 for systolic and diastolic values at every instance vs. baseline) (Figure 1A). Interestingly, a significant correlation was found between the decrease in office systolic BP at the 12th month and the total number of ablation spots (r = -0.9600, P = 0.0096). The reduction of the average values of systolic and diastolic blood pressure also was significant in 24-hour ambulatory blood pressure measurements (ABPM), after the 1st, 6th, and 12th month post procedure, with a reduction from 156 ± 7/108 ± 9 to 126 ± 6/87 ± 7, 125 ± 5/86 ± 7, and 125 ± 4/85 ± 7 mmHg (P < 0.001 for systolic and diastolic values at every instance vs. baseline), (Figure 1B). No changes in the renal function (Cr, eGFR and albumin:creatinine ratio) were observed before and after the procedure

(Table 2), and the individual changes in antihypertensive medications are minutely shown in Table 3.

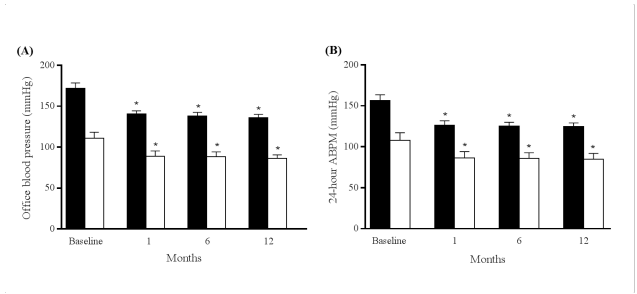

Figure 1: Systolic (closed bars) and diastolic (open bars) office (A) and 24-hour ambulatory blood pressure measurements (B) at baseline and months 1, 6, and 12, after renal sympathetic denervation + pulmonary vein re-isolation. *P<0.001 vs. correspondent baseline values (n = 5).

Even after prompt successful PVRI + RSD procedures, with the 5 patients recovering sinus rhythm, all of them had recurrence of persistent AF in less than one year, an average of 7.8 ± 2.2 months (Figure 2A). After controlling the BP, even all the individuals being in AF, we observed a reduction in left atrial volume, from 84.6 ± 112.2 mL at baseline to 76.8 ± 11.3 mL at one year post procedure (P = 0.0008), measured by cardiac magnetic resonance (Figure 2B). Due to the maintenance of AF we opted to maintain amiodarone and think a third ablation of this arrhythmia in the future with more aggressive strategies or even opt for the control of heart rate, depending on the symptoms of patients.

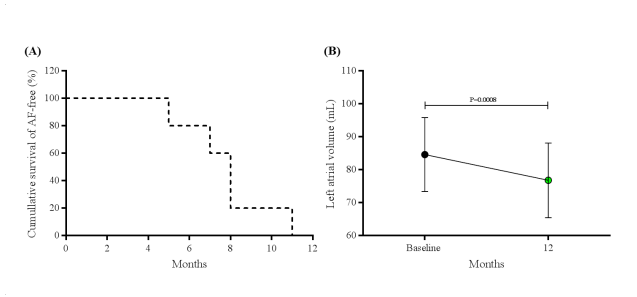

Figure 2: (A) Kaplan-Meier analysis for atrial fibrillation events during the follow-up period, and (B) Left atrial volume reduction at 12th month after renal sympathetic denervation + pulmonary vein re-isolation in comparison to baseline, measured by cardiac magnetic resonance (P = 0.0008), and (B); n = 5.

Discussion

In 2012, Pokushalov et al. [9] reported that RSD reduces systolic and diastolic blood pressure BP in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI, in a prospective randomized study that assessed the impact of renal artery denervation in patients with a history of refractory AF and drug-resistant hypertension who were referred for PVI. Recently, McLellan et al. [10] demonstrated that reduction in BP after RSD is associated with improved atrial electrophysiology, reduction in left ventricular (LV) mass, and reduction in LV diffuse fibrosis. These physiologic changes might explain, in part, the reduction in AF burden associated with improved BP control. Whether RSD may contribute to cause intrinsic effects beyond of BP decrease, on atrial electrophysiologic properties and structural parameters, it remains unclear.

Conclusion

So we can conclude that RSD was effective in controlling BP and associated to PVRI showed a reduction in volume of the left atrium, which were already increased at baseline, but in the control of LSPAF, we did not achieve the success.

Consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interests

The authors declare that they have no competing interests.

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