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6-Month Outcomes in Patients With Implantable Cardioverter-Defibrillators Undergoing Renal Sympathetic Denervation for the Treatment of Refractory Ventricular Arrhythmias

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ABSTRACT

OBJECTIVES This study aimed to assess 6-month outcomes in patients with implantable cardioverter-defibrillators (ICDs) undergoing renal sympathetic denervation (RSD) for refractory ventricular arrhythmias (VAs).

BACKGROUND ICDs are generally indicated for patients at high risk of malignant VAs. Sympathetic hyperactivity plays a critical role in the development, maintenance, and aggravation of VAs.

METHODS A total of 10 patients with refractory VA underwent RSD. Underlying conditions were Chagas disease (n = 6), nonischemic dilated cardiomyopathy (n = 2), and ischemic cardiomyopathy (n = 2). Information on the number of ventricular tachycardia (VT)/ventricular fibrillation (VF) episodes and device therapies (antitachycardia pacing/shocks) in the previous 6 months as well as 1 and 6 months post-treatment was obtained from ICD interrogation.

RESULTS The median number of VT/VF episodes/antitachycardia pacing/shocks 6 months before RSD was 28.5 (range 1 to 106)/20.5 (range 0 to 52)/8 (range 0 to 88), respectively, and was reduced to 1 (range 0 to 17)/0 (range 0 to 7)/0 (range 0 to 3) at 1 month and 0 (range 0 to 9)/0 (range 0 to 7)/0 (range 0 to 3) at 6 months afterward, respectively. There were no major procedure-related complications. Two patients experienced sustained VT within the first week; in both cases, no further episodes occurred during follow-up. Two patients were nonresponders: 1 with persistent idioventricular rhythm and 1 with multiple renal arteries and incomplete ablation. Three patients died during follow-up. None of the deaths was attributed to VA.

CONCLUSIONS In patients with ICDs and refractory VAs, RSD was associated with reduced arrhythmic burden with no procedure-related complications. Randomized controlled trials investigating RSD for treatment of refractory VAs in patients with increased sympathetic activity are needed. (J Am Coll Cardiol Intv 2015;8:984–90) © 2015 by the American College of Cardiology Foundation.

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Implantable cardioverter-defibrillators (ICDs) have shown effectiveness for primary and secondary prevention of sudden cardiac death and are generally indicated for patients considered at high risk of malignant arrhythmias (1). Treatment options for patients presenting with recurrent ICD shocks include pharmacologic treatment with antiarrhythmic drugs and beta-blockers (2–4) as well as catheter-based cardiac ablation (5,6). However, both approaches are associated with low long-term efficacy and, in the latter case, with potential complications (7). New treatment options in this high-risk patient population represent an unmet clinical need.

Sympathetic hyperactivity plays a critical role in the development, maintenance, and aggravation of ventricular arrhythmias (VAs) (8). Percutaneous renal

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sympathetic denervation (RSD) has been shown to decrease sympathetic activity (9) and thereby lower office and ambulatory blood pressure in certain patients with resistant hypertension for up to 3 years of follow-up (10,11). The effects of RSD on sympathetic nervous system activity suggest that this technique could potentially be used in other disease states associated with an increased sympathetic tone, such as chronic kidney disease, heart failure, and arrhythmias (12). Particularly for treatment of cardiac arrhythmias, RSD has a strong pathophysiological rationale (13). Recently, some case reports have suggested short-term benefits of RSD in patients with electrical storm (14,15). However, the data are scarce, and it is difficult to derive any conclusive analysis. The present study aimed to describe 6-month outcomes in patients with ICDs undergoing RSD for refractory VAs.

METHODS

The study was designed as a prospective, single-center trial conducted in a tertiary hospital in São Paulo, Brazil. Patients underwent RSD and were followed for 6 months. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards defined by local law. All patients provided written informed consent.

Ten consecutive patients with malignant VAs refractory to optimal medical therapy who had previous failed cardiac ablation or who were considered unsuitable for cardiac ablation due to polymorphic ventricular tachycardia (VT), ventricular fibrillation (VF), unstable/unmappable arrhythmias, or cardiac thrombus were eligible for the study. Those with active infection, significant hypotension (systolic blood pressure ≤80 mm Hg or demanding vasopressors), a known allergy to contrast agent, and main renal arteries unsuitable for intervention (<20 mm length or <4 mm diameter, stenosis >50%, fibrodysplasia, and previous stent) were excluded from the study.

Renal denervation was performed as previously described (16). After vascular line placement, unfractionated heparin was administered at a dose of 100 U/kg. Aortography at the level of the renal arteries was performed after administration of intravenous nitroglycerin (200 μg), followed by catheterization and selective renal arteriography for the evaluation of the anatomy. In 7 cases, the procedure was performed using the irrigate-tip cardiac ablation catheter (Therapy Cool Path, St. Jude Medical, Minneapolis, Minnesota). At least 4 radiofrequency lesions were delivered along both renal arteries, starting from the distal segments toward the ostia. The catheter was pulled 5 mm and was rotated after each radiofrequency delivery, thus producing a spiral configuration of the ablations. In 3 patients, the procedure was performed using the EnligHTN system (St. Jude Medical), with minimum catheter manipulation. In these cases, 8 lesions were applied to each renal artery. Due to the severe visceral pain generated by ablation, analgesia with fentanyl and morphine was performed in all cases. At the end of the procedure, a control renal arteriography was performed to assess the vascular integrity. The ICD monitoring zone was programmed between 120 and 130 beats/min in all patients.

STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD or median and range. Categorical variables were reported as frequencies and percentages. Because of the limited sample size, all analyses are descriptive in nature and no formal statistical tests are provided. All statistical analyses were performed using IBM SPSS Statistics software version 22.0 (IBM, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. Patient baseline characteristics are summarized in Table 1. In total, 10 patients (5 male, age 64.5 ± 6.3 years) with refractory VAs requiring recurrent antitachycardia pacing (ATP) or ICD shocks underwent RSD. One patient had persistent idioventricular rhythm below the ICD detection zone (and therefore received no ATP or shocks), which was refractory to medical therapy and cardiac ablation. Four patients had arterial hypertension, and 1 patient had diabetes. ICDs were

ABBREVIATIONS AND ACRONYMS

ATP = antitachycardia pacing
ICD = implantable cardioverter-defibrillator
RSD = renal sympathetic denervation
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

TABLE 1 Baseline Characteristics

Patient #	Age (yrs)	Sex	Etiology	Ejection Fraction (%)	Years of ICD	Previous Cardiac Ablation	Cardiac Thrombus	Medications
1	70	Male	CD	30	17	Yes	No	A, BB, ACEI, L
2	62	Male	NIDCMP	34	3	No	Yes	A, BB, ACEI
3	61	Female	CD	43	8	No	No	A, BB, P
4	62	Male	IDCMP	22	1	No	Yes	A, BB, ACEI
5	56	Female	CD	55	4	No	No	A, BB, ACEI
6	78	Male	NIDCMP	23	6	No	No	A, BB
7	69	Female	CD	29	5	No	No	A, ACEI
8	60	Female	CD	30	5	No	Yes	A, BB
9	64	Male	IDCMP	22	7	Yes	No	A, BB, ACEI
10	63	Female	CD	22	0.08 (1 month)	No	No	A, BB, ACEI, L

A = amiodarone; ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; CD = Chagas disease; IDCMP = ischemic dilated cardiomyopathy; L = lidocaine; NIDCMP = nonischemic dilated cardiomyopathy; P = propafenone.

implanted an average of 5.6 years before RSD (range 1 month to 17 years). Patients were taking a mean of 2 antiarrhythmic drugs (range 1 to 3). The mean dose of amiodarone was 510 mg daily. All patients but 1 were on long-term use of beta-blockers; 2 patients were taking lidocaine and 1 was taking propafenone. Mean ejection fraction was 31 ± 10.8%. The etiology of cardiomyopathy was Chagas disease in 6 patients, nonischemic cardiomyopathy in 2, and ischemic dilated cardiomyopathy in 2. Four patients had physical signs of amiodarone-induced hyperpigmentation. Two patients had undergone a previous unsuccessful cardiac ablation. In 3 patients, cardiac ablation was contraindicated due to the presence of cardiac thrombus. The remaining 5 patients presented with either polymorphic VT or VF and were deemed inappropriate candidates for cardiac catheter ablation.

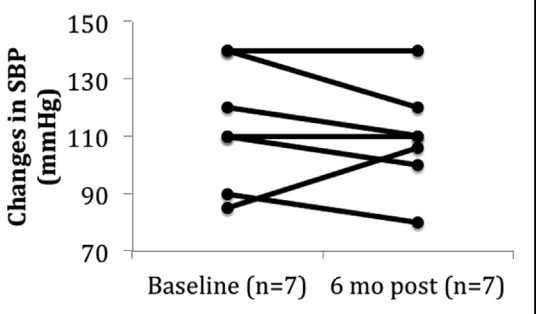
PROCEDURE CHARACTERISTICS. Mean right and left renal artery diameters were 4.9 ± 0.8 mm and 4.9 ± 0.6 mm, respectively. The mean lengths of the right and left renal arteries were 41.3 ± 8.5 mm and 31.4 ± 11.9 mm, respectively. In 1 patient, 3 accessory arteries were identified.

One patient had 2 accessory renal arteries, and 2 patients had 1 accessory renal artery. One patient had mild (<50%) bilateral renal artery stenosis. The average amount of dye used was 88.5 ml, and the mean total fluoroscopy time was 21.6 ± 14.9 min. The mean number of complete radiofrequency applications was 6.3 ± 1.5 in the right renal artery and 5.2 ± 1.7 in the left renal artery.

PROCEDURE-RELATED COMPLICATIONS. One patient developed severe bradycardia during the procedure, requiring adrenaline infusion. Mild renal artery irregularities were frequently detected immediately after the radiofrequency application and were attributed to vessel wall edema. None were considered blood-flow limiting at the end of the procedure. No puncture site complications were documented. Among all patients who completed the 6 months of follow-up, no changes in systolic blood pressure were observed during the entire follow-up (mean systolic blood pressure 113.57 ± 21.74 mm Hg at baseline and 109.42 ± 19.32 mm Hg at 6-month follow-up). No patients required reduction in heart failure medication due to significant reduction in blood pressure. Individual office blood pressure is represented in Figure 1. Kidney function measured by creatinine concentration remained unchanged during the study (mean creatinine 1.31 ± 0.53 mg/dl at baseline and 1.25 ± 0.42 mg/dl at 6-month follow-up).

FOLLOW-UP. Median follow-up was 180 days (range 18 days to 6 months). One patient died 18 days after the procedure due to heart failure and sepsis secondary to pneumonia, and 1 patient died after 45 days

FIGURE 1 Individual Changes in SBP Pre- and Post-Procedure



mo = months; SBP = systolic blood pressure.

due to decompensated heart failure. A third patient died 75 days after the procedure due to endocarditis. None of the death events were attributed to VAs. Among the survivors, all patients but 1 remained on beta-blockers during the 6 months of follow-up. Amiodarone was reduced in 5 patients and beta-blockers in 2 patients. No patients required an increase in antiarrhythmic medication. Table 2 illustrates individual changes in antiarrhythmic drugs at 6 months of follow-up.

All patients that completed 6 months of follow-up underwent renal artery ultrasound. No significant changes to the vessel lumen were observed.

BURDEN OF VAS AND ICD THERAPIES

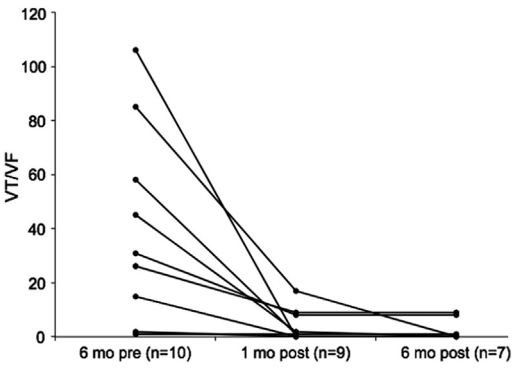
ICD interrogation pre- and post-procedure was available in 9 patients at 30 days and in 7 patients at 6 months of follow-up. The median number of VT/VF episodes 6 months before the procedure was 28.5 (range 1 to 106) and reduced to 1 (range 0 to 17) and 0 (range 0 to 9) at 1 and 6 months, respectively (Figure 2). The median number of ATPs 6 months before the procedure was 20.5 (range 0 to 52) and reduced to 0 (range 0 to 7) and 0 (range 0 to 7) at 1 and 6 months, respectively (Figure 3). The median number of shocks 6 months prior to RSD was 8 (range 0 to 88) and reduced to 0 (range 0 to 3) and 0 (range 0 to 3) at 1 and 6 months, respectively (Figure 4). Two patients experienced episodes of sustained VT within the first week after the procedure, and 1 of these patients required a shock on 1 occasion. In both cases, no more episodes occurred during the entire follow-up. A total of 2 of the 10 patients were considered to be nonresponders to RSD: 1 patient with ischemic cardiomyopathy and persistent idioventricular rhythm, and 1 patient with multiple renal arteries in whom incomplete RSD was performed (3 of the 5 renal arteries were treated). One of the patients remained arrhythmia-free for 2 months after the procedure and developed VT requiring external shock after this period in the context of septic shock of urinary origin. No differences in response were observed with regard to type of catheter used.

TABLE 2 Antiarrhythmic Medications at Baseline and at 6 Months of Follow-Up

Patient #	Medications	Dose at Baseline (mg)	Dose at 6 Months of Follow-Up (mg)
1	A, BB, L	600, 200, 300	400 (↓), 150 (↓), 0 (↓)
2	A, BB	900, 100	200 (↓), 100
3	A, BB, P	200, 50, 900	0 (↓), 50, 900
4	A, BB	600, 200	300 (↓), 100 (↓)
5	A	200	200
6	A, BB	600, 25	Death
7	A, BB	600, 25	200 (↓), 25
8	A, BB	600, 50	Death
9	A, BB	200, 100	200, 100
10	A, BB, L	600, 6.25, 300	Death

A = amiodarone; BB = beta-blocker; L = lidocaine; P = propafenone.

FIGURE 2 Burden of Ventricular Arrhythmias Before and After Renal Denervation

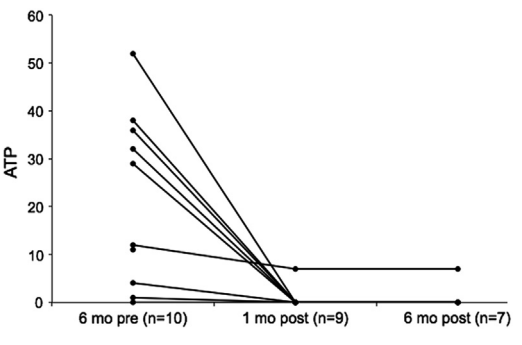


mo = months; VF = ventricular fibrillation; VT = ventricular tachycardia.

DISCUSSION

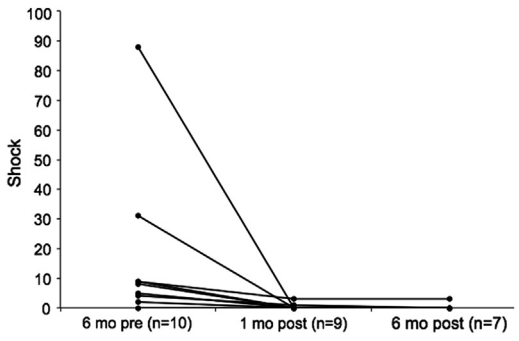
This is the largest prospective, nonrandomized study to demonstrate that, in patients with ICDs and refractory ventricular arrhythmias, RSD is associated with reduced arrhythmic burden and no procedure-related complications. Importantly, our

FIGURE 3 Number of ATP Therapies Before and After Renal Denervation



ATP = antitachycardia pacing; mo = months.

FIGURE 4 Number of Shocks Before and After Renal Denervation



mo = months.

study included patients with Chagas disease, nonischemic dilated cardiomyopathy, and ischemic cardiomyopathy. Randomization to cardiac ablation was not feasible once 50% of patients had either previous failed cardiac ablation (2 of 10) or cardiac thrombus (3 of 10). A sham procedure was not considered due to patients' condition (refractoriness to optimal medical therapy).

The heart is highly innervated by sympathetic nerve fibers, and it is well established that sympathetic activation increases heart rate and facilitates atrioventricular conduction (17). In the ventricles, increased sympathetic tone reduces ventricular effective refractory period, increases automaticity, and reduces the threshold for VAs (18). Indeed, a growing body of clinical and pre-clinical evidence indicates that sympatho-modulation by either surgical cardiac ablation or catheter-based RSD might represent new treatment options (19). Vaseghi et al. (20) recently demonstrated that surgical cardiac sympathetic denervation reduces ICD shock burden by up to 90%. Despite the promising results, the nonselective effects of surgical denervation may result in autonomic dysfunction, as demonstrated in a small number of patients in that study (changes in sweating pattern in 10%, skin sensitivity in 12%, and persistent ptosis in 1 patient). Ukena et al. (14) reported the first-in-man experience of percutaneous RSD in 2 patients with heart failure and electrical storm: 1 patient with hypertrophic cardiomyopathy, monomorphic VT despite the use of multiple antiarrhythmics, and unsuccessful endocardial and epicardial cardiac ablation; and 1 patient with dilated cardiomyopathy, frequent episodes of VF, and polymorphic VT who declined to receive cardiac ablation therapy. In both cases, a significant reduction of VAs was documented.

Our group reported substantial reduction of VT and appropriate therapies from ICD in a patient with dilated cardiomyopathy and with contraindication for cardiac ablation (left ventricular thrombus) undergoing percutaneous RSD (15). Remo et al. (21) recently showed the benefits of RSD as adjunctive therapy for refractory VT in 4 patients with underlying cardiomyopathy, with similar results for ischemic and nonischemic patients. In an experimental model, Linz et al. (22) were able to show that RSD by use of radiofrequency energy significantly reduced the occurrence of spontaneous VAs and attenuated the rise in left ventricular end-diastolic pressure during left ischemic events. Interestingly, 6 of the 10 patients in the current study suffered from Chagas disease. Despite the implementation of socioeconomic measures and the development of drugs that allow treatment of the acute phase of the disease, chronic Chagas cardiomyopathy remains a major public health problem in many Latin American countries, affecting approximately 15 to 16 million people and accounting for a mortality of 20,000 individuals/year (23). About two-thirds of people with chronic symptoms develop cardiac damage, including dilation and severe ventricular dysfunction, tachyarrhythmias, bradyarrhythmias and, not uncommonly, sudden and unexpected death (24). Sudden death accounts for approximately 55% to 65% of overall death in patients with Chagas disease, surpassing deaths from heart failure (25). The arrhythmogenic nature of Chagas disease is related to the presence of fibrotic tissue intermingled with preserved myocardial areas and dyskinetic regions generating an area of high propensity of complex VAs (26). Treatment of VAs includes antiarrhythmic drugs, correction of reversible causes such as electrolyte disturbances, and cardiac ablation (27–29). Although amiodarone has been shown to reduce the risk of sudden death and cardiovascular death in this population by 29% and 18%, respectively, the antiarrhythmic therapy is neutral with respect to all-cause mortality and is associated with a 2- and 5-fold increased risk of pulmonary and thyroid toxicity, respectively (29). Approximately 50% of patients undergoing conventional endocardial ablation have recurrence of their arrhythmia (30). Not uncommonly, VTs in Chagasic patients have multiple sites of origin, including the subepicardium, and are hemodynamically unstable/unmappable (31). The epicardial approach in these cases is often challenging, especially in those with severe ventricular dysfunction and impaired clinical condition. RSD might represent an alternative treatment option for patients with Chagas disease presenting with refractory VAs.

Two patients in our study showed no reduction in the burden of arrhythmias during follow-up. One patient had persistent idioventricular rhythm at a mean heart rate of 90 beats/min. It is possible that there was a lack of sympathetic trigger for the initiation and maintenance of the VAs in this particular case. The other patient remained asymptomatic for 2 months after the procedure but experienced a new episode of VAs thereafter. In the latter case, significant renal artery anatomy variation was observed (3 small renal arteries on the right side and a small trunk on the left side with early bifurcation), and incomplete ablation of renal sympathetic nerves might at least partially account for the observed response. Three patients died of nonarrhythmic causes during follow-up, which reflects the high-risk population with advanced heart disease included in the study. Although concomitant pharmacological therapy could interfere with the results, no patients required an increase in the number or dose of antiarrhythmic medications.

The negative results observed in the Symplicity HTN-3 study (A Controlled Trial of Renal Denervation for Resistant Hypertension) raises the question of how this procedure could be more effective in selected patients. The causes of nonresponse are not yet fully understood; however, assumptions can be made on the basis of knowledge of the pathophysiology of hypertension and RSD procedure. Among them, we emphasize: 1) the actual relevance of sympathetic hyperactivity in the physiopathology of resistant hypertension; 2) the inappropriate selection of patients, including those with pseudoresistance and secondary hypertension; and 3) conditions related to the patient, such as nonadherence to drug treatment and lifestyle changes. The standard deviation in systolic blood pressure measured in the RSD and control groups in both Symplicity HTN-1 and -2 were large and similar, indicating large variations in the response. Another possible explanation for the unexpected results of the Symplicity HTN-3 trial includes the large number of participating centers and, therefore, the small number of cases/center and the high percentage of nonexpert operators with the technique. Finally, it is well established that the reduction in blood pressure is directly proportional to the number of radiofrequency applications in the renal arteries. Unlike the Symplicity HTN-3 study, in which the mean number of radiofrequency applications was 3.9, in this study an average of 6.3 and 5.2 lesions were delivered to the right and left renal arteries, respectively.

STUDY LIMITATIONS. The nonrandomized design, relatively small sample size, and absence of a control arm represent potential limitations of the present study. Although sympathetic activity was not directly measured, a significant association between RSD and a reduction in the burden of VAs was notable. More than one-half of the patients had Chagasic cardiomyopathy, and the response to RSD could be different in this population. It is possible that, besides the effects on autonomic tone, RSD could result in beneficial effects secondary to the reduction in volume excess and hormonal activation seen in heart failure. However, all patients but 1 had no signs of congestion, suggesting that the reduction of arrhythmias may not be primarily related to improvements in heart failure.

CONCLUSIONS

Our findings illustrate the relevance of sympathetic activation in patients with VAs and suggest a potential role for catheter-based RSD in reducing arrhythmic burden. Larger studies on the effect of RSD on VAs are needed and ongoing. If proven to be safe and effective in randomized and well-controlled trials, RSD might become an attractive strategy for the treatment of refractory VAs in patients with increased sympathetic activity.

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PERSPECTIVES

WHAT IS KNOWN? Sympathetic hyperactivity plays a critical role in the development and maintenance of ventricular arrhythmias. Some case reports have suggested short-term benefits of catheter-based renal sympathetic denervation (RSD) in patients with electrical storm.

WHAT IS NEW? This is the largest prospective, nonrandomized study to demonstrate the feasibility and potential efficacy of renal sympathetic denervation to reduce ventricular arrhythmia burden.

WHAT IS NEXT? If proven to be safe and effective in randomized and well-controlled trials, renal sympathetic denervation might become an attractive strategy for the treatment of refractory ventricular arrhythmias in patients with increased sympathetic activity.

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KEY WORDS implantable cardiac defibrillators, renal denervation, sympathetic activity, ventricular arrhythmias