Safety and efficacy of thoracoscopic sympathectomy for control of recurrent ventricular tachycardia in patients mainly with Chagas disease.

Running Title: Sympathectomy for VT in Chagas Disease

Rodrigo M. Kulchetscki, MD[1]
Felipe K. B. Alexandre, MD[1]
Marina P. Mayrink, MD[1]
Carina A. Hardy, MD[1]
Sissy L. Melo, MD, PhD[1]
Muhieddine O. Chokr, MD[1]
Luis G. Abdalla, MD[3]
Martino Martinelli Filho, MD, PhD[2]
Francisco C. C. Darrieux, MD, PhD[1]
Cristiano F. Pisani, MD, PhD[1]
Mauricio I. Scanavacca, MD, PhD[1]
Paulo M. Pêgo-Fernandes, MD, PhD[3]

[1]Arrhythmia Unit, Heart Institute (InCor), Hospital das Clínicas, University of Sao Paulo Medical School, Sao Paulo, Brazil

[2]Pacemaker Unit, Heart Institute (InCor), Hospital das Clínicas, University of Sao Paulo Medical School, Sao Paulo, Brazil

[3]Thoracic Surgery Unit, Heart Institute (InCor), Hospital das Clínicas, University of Sao Paulo Medical School, Sao Paulo, Brazil

Address for correspondence:

Rodrigo Melo Kulchetscki

Avenida Dr Eneas de Carvalho Aguiar, 44, Instituto do Coração (InCor) - Secretaria da Eletrofisiologia, Laboratório de Hemodinâmica, 2º andar Bloco I

Tel: +55 11 2661-4144; +55 11 98246-8680

r.kulchetscki@hc.fm.usp.br

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Abstract

Introduction: The autonomous system plays an important role as a trigger of cardiac arrhythmias. Cardiac sympathetic denervation (CSD) achieved by stellate and proximal thoracic ganglia resection has been reported as an alternative approach for the management of ventricular arrhythmias (VA) in structural heart disease (SHD) patients. Insufficient data regarding Chagas Disease (ChD) is available.

Methods: Patients who underwent CSD for better management of ventricular arrhythmias (VA) in SHD, mainly ChD, in a single tertiary center in Brazil were evaluated for safety and efficacy outcomes.

Results: Between June 2014 and March 2020, fourteen patients (age 59±7.5, 85% male, mean ejection fraction 30.5±7.9%) were submitted to left or bilateral CSD. In a median follow-up time of 143 (Q1: 30; Q3: 374) days, eight patients (57,2%) presented VT recurrence. A significant reduction in the median burden of ventricular arrhythmias comparing six months before and after procedure (10 to 0; p=0.004). For the nine ChD patients, the median burden of appropriate therapies was also reduced (11 to 0; p=0.008). There were two cases of clinically relevant pneumothorax and three cases of transient hemodynamic instability, but no direct procedure-related deaths occurred. Additionally, there was no long-term adverse events,

Conclusion: CSD is safe and seems to be effective in reducing the burden of VT/VT storm in SHD patients, including ChD patients. Randomized trials are needed to clarify its role in the management of these patients.

Introduction

The genesis of ventricular arrhythmias is a complex subject, with multiple factors contributing as triggers and maintainers. The autonomous system plays an important role in this process (1, 2). Ventricular tachycardia (VT) and ventricular fibrillation (VF) are common pathological processes in patients with structural heart disease (SHD), and are usually managed with implantable cardiac defibrillators (ICD), antiarrhythmic drugs and catheter ablation (3).

Despite advances in the treatment of ventricular arrhythmias, recurrence is frequent, with a high incidence of appropriate ICD therapies during the follow-up (4, 5), especially in Chagas Disease (ChD), with up to 25% incidence per year after ICD implant (6-9). Besides, appropriate shocks are associated with decreased quality of life and survival (10, 11). Additional pharmacological and non-pharmacological therapies are essential to avoid ICD discharges in patients with SHD. Currently, the guidelines recommend catheter ablation in patients with ischemic (Class I) or non-ischemic (Class IIa) cardiomyopathy who presents multiples ICD therapies despite antiarrhythmic therapy. (12)

After Thomas Jonnesco performed the first left cardiac sympathetic denervation (CSD) in a patient with uncontrollable angina and ventricular tachycardias in 1916 (13), and after Hughes performed the first endoscopic sympathectomy (14), the utility of thoracoscopic CSD for the management of ventricular arrhythmias has been established, but has been under-utilized in the SHD scenario (15). A reduction in the number of therapies in ICD patients with SHD was reported in a multicenter retrospective cohort (16) and there are also some reports in small series of Chagas disease patients (17, 18). Recent guidelines suggest cardiac sympathetic denervation as reasonable in patients with VT/VF storm in whom antiarrhythmic medications and catheter ablation are ineffective, not tolerated, or not possible. (3)

In this study, we aim to assess the safety and efficacy of CSD via a video-thoracoscopic approach in the control of ventricular arrhythmias and appropriate therapies in a series of patients with SHD, mainly in ChD cardiomyopathy.

Methods

Sample selection

We selected patients with structural heart disease who underwent CSD from June 2014 to March 2020 at Instituto do Coração (InCor), Hospital das Clinicas, University of Sao Paulo Medical School. Data were collected retrospectively, with the approval of the institution's review board. Patients defined as Chagas cardiomyopathy presented at least one positive serology for *Trypanossoma cruzi*. Electrical storm was defined as the presence of 3 or more appropriate therapies in the last 24h. Patients with normal heart and inherited arrhythmias, such as congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) who underwent CSD were excluded from the analysis.

Outcome definitions

Safety and efficacy endpoints were evaluated. Recurrence was defined based on device identification of appropriate therapies, or clinical VT that required evaluation in the emergency department. Adverse events included the need for an intercostal drainage system at the end of procedure, usually for better pulmonary expansion. Pneumothorax was defined as the presence of at least a mild visible layer in pleural cavity on imaging exams that resulted in clinical worsening or required any intervention. Bleeding was evaluated using the Bleeding Academic Research Consortium (BARC) graduation system, and if it was at least 3 would be considered major bleeding. Hemodynamic instability was considered if there was a need for vasopressors in the periprocedural period.

Study procedures

We reviewed all medical records regarding comorbidities, prescriptions, past catheter ablation procedures, imaging exams, procedure details and in-hospital stay, and follow-up outpatient records, including pre and post CSD arrhythmia burden and ICD interrogation parameters. Contact by telephone was performed in one specific case, for additional information.

The choice for left or bilateral CSD was defined according to the thoracic surgeon preference (PMPF). The procedure was performed via a video-assisted thoracoscopic approach according to a previously described (19, 20). Left CSD was preferentially performed in the first patients, before 2015, because of the available

evidence at the occasion favoring this approach. As previously described (14), stellate ganglia and T2-T4 thoracic sympathetic ganglia were removed. Procedures were performed under general anesthesia, and all the patients were sent to intensive care for 24 hours observation for identification of possible complications.

Reasons for CSD indication were mainly refractory ICD therapies due to monomorphic VT. Three patients performed CSD before a catheter ablation procedure. Reasons for that were: non inducibility of VT during electrophysiologic study with aggressive protocol, so case discussion led to indication of CSD; ventricular fibrillation in one case; and option for treatment in a frail patient in another case.

Data analysis

Continuous variables normally distributed are reported as mean ± standard deviation (SD), and median and interquartile range (IQR) for skewed distributions. Categorical data are reported as number and percentages. Normality of distribution was accessed via the Shapiro-Wilk test. The Fisher's exact test were used to compare differences across groups for categorical variables, and the paired Student *t* test or the Mann-Whitney *U* test were used when appropriate to compare continuous variables. Recurrence was reported with a time-to-event analysis and survival curves were created using the Kaplan-Meier method. Statistical significance was defined as a p value of ≤ 0.05. The statistical analysis was performed using IBM SPSS Statistics 26 software.

Results

Baseline

We identified 15 patients who underwent CSD between June 2014 to March 2020. One patient did not have adequate follow up data and was excluded from the analysis. Nine patients (64%) had Chagas cardiomyopathy. Baseline characteristics are presented on Table 1. Mean age was 58.9±7.5 years old. The mean left ventricle ejection fraction was 30.5±7.9%. Twenty nine percent of the sample was in NYHA functional class III or IV at hospital admission. Hypertension, Diabetes and Chronic Obstructive Pulmonary Disease (COPD) was present in 50%, 14% and 7%, respectively. Forty two percent had atrial fibrillation, and 29% had a history of

previous stroke or transient ischemic attack (TIA). The mean creatinine level was 1.05±0,28 mg/dL.

Twelve patients (85%) were in use of amiodarone at a mean daily dose of 311 ± 244. All patients were in use of beta-blockers, most commonly carvedilol and metoprolol, with a daily dose of 61±13mg and 187±103mg, respectively. All patients had an implantable electronic cardiac device before CSD, in which 11 (78%) were ICDs. Most (82%) were implanted for secondary prevention. Nine (64.3%) patients had one prior VT catheter ablation procedure and two (14.3%) had two prior ablations. Six patients (42.9%) fulfilled criteria for electrical storm at presentation.

CSD efficacy in preventing ICD therapies or VT recurrence

In a median follow-up time of 143 (Q1: 30.7; Q3: 374.75) days, six (42.9%) patients remained free from ICD therapies or sustained VT recurrence after CSD (Figure 2). All except one of the 11 patients with ICD had adequate pre-procedure therapies data. There was a reduction in ICD therapies from a median of 10.0 episodes (Q1: 4.75; Q3: 13.5) on the prior six months of CSD to 0 episodes (Q1: 0; Q3: 2.5) on the following 6 month (P=0.008) (Figure 1–A and Figure 3).

Four patients needed catheter ablation in the follow-up, in which two of them underwent left side only CSD. There were no differences regarding beta-blocker or amiodarone doses before and after the procedure.

Two patients (14%) underwent heart transplantation and five (35%) died in the follow-up. The median time for death was 50 (Q1: 6.5; Q3: 393.5) days (Figure 4). The main reason for death was cardiogenic shock in three patients, electrical storm associated with cardiogenic shock in one patient, and acute rejection of the transplanted organ in one patient. Kaplan-Meyer curve for survival time to death or ICD therapies is shown in Figure 4.

Each patient characteristic is presented in table 2.

ChD sub analysis

We performed a subgroup analysis with the nine (64%) CHD patients. There was a reduction in ICD therapies in the eight Chagas patients who had ICD, from a median of 11.0 episodes (Q1: 5.25; Q3: 16.5) on the prior six months of CSD to 0 episodes (Q1: 0; Q3: 2.5) on the following 6 months (P=0.012) (Figure 1-B). The patient who did not have ICD, underwent ICD implantation. Five of the nine Chagas

disease patients had VT recurrence after CSD. Ventricular tachycardia recurred in a median time of 6 (Q1: 3.5;15) days after CSD. There were no differences in safety outcomes in the subgroup.

Technical and safety data

All patients were submitted to a complete resection, except in one case where an azygos vein was coursing right next to the right sympathetic ganglia, and an incomplete right resection was performed. Technical aspects and CSD safety outcomes are shown on table 3.

Three patients needed an intercostal drainage system at the end of the procedure, for better pulmonary expansion. Two patients (14%) had a clinically relevant pneumothorax in the first post procedure day, in one case, a chest tube was already present, and it was repositioned at bedside for better draining, and in the other it required bedside drainage. In both cases, patients were in an electrical storm and already intubated with inotropic support - there was, however, some degree of hemodynamic instability partially attributed to the pneumothoraxes. At total, three patients (14%) had transitory hemodynamic instability, being two of them the same two patients previously mentioned. Two patients (14%) had subcutaneous emphysema, with no need for further interventions. There were no BARC 3-5 bleeding events. No long-term adverse events were reported in the follow up, including Horner syndrome or swelling issues that impaired quality of life. There were no direct procedure-related deaths.

Discussion

This series supports previous reports that CSD is a reasonable alternative for SHD patients with recurrent VT. This report is especially supportive for ChD patients since they comprised most patients (64%) of the sample.

The modulation of the autonomic system can be achieved with different strategies, including CSD. The use of this procedure for the management of VA was initially achieved with LQTS and CPVT patients and has gained more attention for SHD patients. Current evidences include retrospective observational studies, with no randomized controlled trials yet. The use of sympathectomy in ChD patient is of special interest since, in this pathology, there is a high incidence of VT, frequently

from epicardial and difficult-to-ablate foci, together with an interface with the cardiac autonomous system that is not yet fully comprehended (17, 21, 22).

Vaseghi et al [15] in the large multicenter retrospective study evaluated 121 patients with SHD, at a mean follow-up of 1.5±1.4 years and found a 49% incidence of freedom from ICD shocks or sustained VT post CSD. Patient population consisted mostly in NICM (71%), being 12 (9.9%) ChD patients. The mean number of ICD shocks or sustained VT in the year pre-procedure was 18±20, compared to 2,0±4,3 post procedure, until the end of the follow-up, this was a reduction in 88% of events.

In a case series by Richardson et al (23) with a mixed population of seven patients who have had a failed prior catheter ablation, no patient had recurrence of ventricular arrhythmias in a seven-month follow-up period after the procedure. Bilateral CSD was performed in all but one patient.

The use of bilateral CSD has been shown to be superior to left only procedures in canine (24, 25). In a retrospective analysis, 41 patients with VT storm, refractory VA or ICD shocks, Vaseghi et al (26) found a higher survival rate free from ICD shocks among the bilateral CSD group against the left only procedure. The median time to shock-free survival was 366 days in the bilateral CSD group and 128 days in the left CSD group (p 0.04).

After 2014, the CSDs performed at our institution\ were all bilateral. In our population, only two patients performed left only procedures, and they were also among those who had arrhythmia recurrence and underwent to a catheter ablation in the follow-up. This finding could also be explained by learning curve and time-related bias, since they were also the first ones who underwent CSD in this series.

Our study found similar results compared to these previous trials. We found a statistically significant reduction in arrhythmia burden after CSD and a freedom from any event of 43%, similar to the 49% reported by Vaseghi et al (16). However, we had a lower follow-up time (about five months, against 1.1 years in the aforementioned trial), as well as a much lower time for first ICD therapy (6 days versus 1.2 years). Two possible reasons for this difference, apart from small sample bias, are that we considered all events as recurrence (either shocks and anti-tachycardia pacing, as well as a slow VT that was detected in an emergency department setting). Additionally, we had a higher proportion of ChD patients (64%), that are known to have a higher arrhythmia recurrence rate.

A Latin American report on CSD for ChD was published in 2015 by Saenz et al (17). A total of seven ChD patients, all of them with past history of monomorphic VT who were not candidates or have a prior failed catheter ablation, underwent bilateral CSD, with a median follow-up period of seven months. There was a decrease of 4 (Q1:2; Q3: 30 ICD shocks in the prior month of the procedure to 0 (Q1: 0; Q3: 2) to after CSD. The Survival free of ICD shocks rate was 48% at mean follow-up of 367 days. However, 90% of patients demonstrated a decrease in number ICD therapies.

NYHA functional class III or IV was an important independent predictor of VT recurrence and survival found in other studies (27-29). Vaseghi et al (16) found a significant association of NYHA class III (HR 4.1, 95% CI: 1.36 to 12.2; $p = 0.012$) and NYHA class I (HR 8.8, 95% CI: 2.5 to 30.9; $p < 0.001$) with reduced CSD effectiveness. In our sample, the small proportion of patients with NYHA III and IV before CSD prevented us from performing accurate analysis. Like Vaseghi et al (16), we did not find any difference in pre and post procedure amiodarone dose.

Bilateral CSD is an invasive procedure that requires general anesthesia and, despite being considered an overall safe procedure, the decision to expose hemodynamically vulnerable patients to general anesthesia must outweigh the risks. In this study, our population had low mean left ventricle ejection fraction (30%) and a relevant proportion of electrical storm at presentation (42.8%). We found CSD as a low morbidity procedure, but in patients with critical conditions before the procedure, the incidence of complications such as pneumothorax and hemodynamic instability were not irrelevant. These findings are consistent with previous reports (16, 24).

Limitations

Our study has several limitations. The retrospective analyses and its small sample size preclude from achieving broader conclusions regarding the applicability of the results. However, the same limitation is encountered on previous reports. Furthermore, because of lack of randomization and the retrospective analysis mainly based on medical reports, biases that may have been involved in the decision-making process cannot be excluded. Finally, ICD programming was not uniform across patients but there were no major changes comparing pre and post CSD procedures.

Conclusion

Our study suggests that bilateral cardiac sympathetic denervation is a reasonable and safe treatment strategy to control VA in a sample of patients with structural heart disease, especially Chagas disease cardiomyopathy. Two RCT, one for ChD (NCT04239144) and other for other cardiomyopathies (NCT01013714) are ongoing and may provide stronger evidence for CSD role in VA treatment.

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Table 1 – Baseline Characteristics of the Patients

	N = 14
Age, mean±SD	59±7.5
Male, n (%)	12 (85%)
Type of Cardiomyopathy, n (%)	
Ischemic	2 (14%)
Idiopathic Dilated	2 (14%)
Valvular	1 (7%)
Chagas	9 (64%)
NYHA Functional Class, n (%)	
I-II	10 (71%)
III-IV	4 (29%)
LV Ejection Fraction, %	30±7.9
Creatinine, mg/dL	1.0±0.28
Hemoglobin, g/dL	12,7±2
Atrial Fibrillation, n (%)	6 (42.8%)
Hypertension, n (%)	7 (50%)
COPD, n (%)	1 (7%)
Diabetes, n (%)	2 (14%)
Stroke or TIA, n (%)	4 (29%)
Prior Catheter Ablation, n (%)	11 (78%)
Number of Prior Catheter Ablation Procedures, mean±SD	1.26±0.99
Electrical Storm at presentation, n (%)	6 (42.8%)
Medications	
Amiodarone, n (mg/day ± SD)	12 (311 ± 244)
Carvedilol, n (mg/day ± SD)	9 (61 ± 13)
Metoprolol, n (mg/day ± SD)	4 (187 ± 103)
Bisoprolol, n (mg/day ± SD)	1 (3 ± 0)
Pre procedure ICD, n (%)	11 (78%)
Primary prevention, n (%)	2 (18%)
Secondary prevention, n (%)	9 (64%)

NYHA: New York Heart Association; LV: Left Ventricle; COPD: Chronic Obstructive Pulmonary Disease; TIA: Transient Ischemic Attack; ICD: Implantable Cardiac Defibrillator

Table 2 – Each Patient Characteristics.

Case	Sex	Age	Type of CMP	EF (%)	Nr of Events (6 months)	Electrical Storm	Amiodarone, mg/day	Prior catheter ablation, n	Type of Procedure	In-hospital days	Days to recurrence	Post CSD CA	Days to Death	Days to Transplant
1	M	51	Chagasic	38	35	Yes	600	2	Bilateral	31	6	No	No	137
2	M	58	Idiopathic	35	3	No	600	1	Bilateral	66	No	No	No	No
3	M	59	Chagasic	30	10	No	400	1	Bilateral	6	No	No	No	No
4	M	48	Chagasic	25	12	Yes	600	1	Bilateral	14	1	No	3	No
5	M	72	Ischemic	30	Incessant	Yes	900	2	Bilateral	46	3	No	10	No
6	M	66	Chagasic	21	18	Yes	No	0	Bilateral	26	No	No	No	No
7	F	43	Chagasic	24	5	No	200	1	Bilateral	3	30	No	No	In evaluation
8	M	64	Chagasic	24	18	Yes	No (Amiodarone related pneumonitis)	3	Bilateral	12	No	No	No	No

9	M	57	Chagasic	31	12	Yes	600	1	Left	23	6	Yes	179	No
10	M	60	Idiopathic	29	3	No	400	0	Left	3	457	Yes	608	No
11	M	59	Valvopathy	45	10	No	400	2	Bilateral	12	5	No	No	No
12	F	53	Ischemic	20	3	Yes	400	3	Bilateral	18	No	No	No	No
13	M	64	Chagasic	30	6	No	200	0	Bilateral	19	No	No	No	No
14	M	61	Chagasic	45	4	No	600	3	Left	126	0	No	143	49

Table 3 - Cardiac Sympathetic Denervation Technical and Safety Data

Type of Procedure	Number (%)
Left Only, n (%)	2 (16%)
Bilateral, n (%)	12 (84%)
Complete Proposed Resection, n (%)	
Yes	13 (93%)
No	1 (7%)
Intercostal drain at the end of the procedure, n (%)	3 (21%)
Pneumothorax, n (%)	2 (14%)
Subcutaneous Emphysema, n (%)	2 (14%)
Transitory Hemodynamic Instability, n (%)	3 (21%)