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Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up

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Abstract

BACKGROUND—Left and bilateral cardiac sympathetic denervation (CSD) have been shown to reduce burden of ventricular arrhythmias acutely in a small number of patients with ventricular tachyarrhythmia (VT) storm. The effects of this procedure beyond the acute setting are unknown.

OBJECTIVE—The purpose of this study was to evaluate the intermediate and long-term effects of left and bilateral CSD in patients with cardiomyopathy and refractory VT or VT storm.

METHODS—Retrospective analysis of medical records for patients who underwent either left or bilateral CSD for VT storm or refractory VT between April 2009 and December 2012 was performed.

RESULTS—Forty-one patients underwent CSD (14 left CSD, 27 bilateral CSD). There was a significant reduction in the burden of implantable cardioverter-defibrillator (ICD) shocks during follow-up compared to the 12 months before the procedure. The number of ICD shocks was reduced from a mean of 19.6 ± 19 preprocedure to 2.3 ± 2.9 postprocedure ($P < .001$), with 90% of patients experiencing a reduction in ICD shocks. At mean follow-up of 367 ± 251 days postprocedure, survival free of ICD shock was 30% in the left CSD group and 48% in the bilateral CSD group. Shock-free survival was greater in the bilateral group than in the left CSD group ($P = .04$).

CONCLUSION—In patients with VT storm, bilateral CSD is more beneficial than left CSD. The beneficial effects of bilateral CSD extend beyond the acute postsympathectomy period, with continued freedom from ICD shocks in 48% of patients and a significant reduction in ICD shocks in 90% of patients.

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Keywords

Sympathectomy; Cardiac denervation; Ventricular arrhythmias; Electrical storm

Introduction

The autonomic nervous system is known to play a role in the genesis and maintenance of ventricular arrhythmias.[1,2] Currently, antiarrhythmic therapies and catheter ablation represent the standard of care in patients with recurrent ventricular tachyarrhythmia (VT) and implantable cardioverter-defibrillator (ICD) shocks. Neuromodulation is increasingly emerging as an alternative therapy, with benefits of thoracic epidural anesthesia, cardiac sympathetic denervation (CSD), and spinal cord stimulation shown in animal models and case series of patients with and without cardiomyopathy.[3–9] Left CSD has also shown benefit in the setting of refractory VT and long QT syndrome or catecholaminergic polymorphic VT.[10–12] Left and bilateral sympathectomies, involving removal of the lower third to lower half of the stellate ganglion and T2–T4 sympathetic ganglia, have shown short-term benefit in the setting of VT storm and VT refractory to medical therapy in a small number of patients with cardiomyopathy. The benefits of left and bilateral CSD beyond the acute postprocedure period are unknown. The purpose of this study was to assess the intermediate and long-term effects of CSD in patients with cardiomyopathy and refractory VT.

Methods

Retrospective review of data was approved by the University of California, Los Angeles Institutional Review Board.

Patient population

Data from 41 patients with VT storm or refractory ventricular arrhythmias and ICD shocks who underwent CSD between April 2009 and December 2012 were reviewed. The type, cause, treatment of ventricular arrhythmias, type of CSD (left or bilateral), and procedural data and complications were reviewed in all patients. VT storm was defined as three or more episodes of sustained VT within a 24-hour period, each of which required termination by an intervention. Refractory VT was defined as recurrent ICD shocks that did not response to antiarrhythmic, medical, or catheter ablation therapy.

Cardiac denervation procedure

All patients underwent either left or bilateral CSD. The first five patients in this series, between 2009 and 2010, only underwent left CSD, given the greater number of animal and human studies in support of left CSD compared to bilateral CSD at the time.[7,8] The decision to perform left or bilateral CSD also was partly driven by the patient's ability to tolerate the longer general anesthesia/procedure time required for bilateral CSD. Left CSD was often performed at the same time as right CSD. However, left CSD was always performed first. CSD was performed using video-assisted thoracic surgery in all patients. CSD consisted of resection and removal of the lower third to half of the stellate ganglia and T2–T4 thoracic ganglia as well as transection of the nerve of Kuntz, when present. The lower third to half of the stellate ganglia was removed to avoid Horner syndrome, as the ocular neural fibers generally cross at the upper half of the stellate ganglia. With the patient under general anesthesia, the ipsilateral lung was deflated and not ventilated, using a double-lumen endotracheal tube. Three 1.5-cm incisions were made in the ipsilateral subaxillary area. The left thoracic sympathetic chain was identified behind the parietal pleura, and the lower half of the stellate ganglion together with the thoracic ganglia at the T2–T4 level were dissected and removed. Histologic confirmation of neuronal cell bodies within the ganglia was obtained intraoperatively. The nerve of Kuntz (an intrathoracic nerve that connects the first and second thoracic nerves, bypassing the sympathetic chain between the T2 ganglion and stellate ganglion in some patients) was sought and divided in order to complete the sympathectomy.[13] Chest drains were placed and removed within 24 hours after confirmation of lung reexpansion and lack of a pleural effusion.

Follow-up

Hospitalization records, outpatient visits, and ICD interrogations were used to determine the outcome of CSD during follow-up. If the patient, next of kin, or referring physicians could not be contacted, the National Death Index was used to determine if the patient was deceased. Echocardiograms were used to assess follow-up left ventricular ejection fraction (EF) and pulmonary artery pressures (PAPs). For follow-up of ICD shock status, inpatient and outpatient notes and ICD interrogations were obtained and reviewed. In addition, phone calls to the primary physician, patient, or immediate relatives of deceased patients were made. Burden of ICD shocks was assessed from ICD interrogations and physician notes, and the data were included only if ICD interrogations or physician documentation of number of shocks before the procedure and during follow-up could be obtained.

Statistical analysis

Continuous variables are summarized as mean ± SD or median when appropriate. Comparison of outcomes between left and bilateral CSD was made using the Fisher exact test, and comparison of ICD burden, EF, and PAP pre- and postprocedure was made using the Wilcoxon signed rank test. All statistical analysis was performed using SAS software (version 9.1, SAS institute Inc, Cary, NC). $P < .05$ was considered significant. Cumulative shock-free survival and cardiovascular mortality were calculated using Kaplan-Meier curves and tested in subgroups by the log-rank test for trend. For these analyses, time to first shock or death post-CSD was calculated, and data are displayed as cumulative event-free survival. For Kaplan-Meier analysis of freedom from ICD shock only, the patients who were lost to long-term follow-up were censored at time of last follow-up.

Results

Patient characteristics

Forty-one patients (35 male; age 59 ± 13 years) who presented with either VT storm or recurrent ICD shocks refractory to medical therapy and catheter ablation underwent CSD. Fourteen patients (12 male; age 63 ± 11.3 years) underwent left CSD only and 27 patients (23 male; age 57 ± 14 years) underwent bilateral CSD (Table 1). Patients were taking a median of 2 (range 1–3) antiarrhythmic medications, usually amiodarone and lidocaine or mexiletine, and 73% were taking beta-blockers before the procedure. In the remaining 27% of patients, beta-blockers were not tolerated because of low blood pressure at presentation. Thirty-eight patients had undergone previous catheter ablation procedures. The median number of VT ablations before CSD was 2 (range 1–5). The three patients who had not undergone a VT ablation procedure had presented with polymorphic VT or idiopathic ventricular fibrillation and were deemed inappropriate candidates for catheter ablation.

Left CSD

Of the 14 patients who underwent left CSD, 7 (50%) had nonischemic cardiomyopathy, 5 (36%) had ischemic cardiomyopathy, and 2 patients had hypertrophic cardiomyopathy (Table 1).

Bilateral CSD

Of the 27 bilateral CSD patients, 15 (56%) had nonischemic cardiomyopathy, 4 (15%) had ischemic cardiomyopathy, and 2 had cardiac sarcoidosis. In addition, one hypertrophic, one chagasic, one arrhythmogenic right ventricular dysplasia, one valvular cardiomyopathy, and one idiopathic ventricular fibrillation patient also underwent bilateral CSD. Of these 27 patients, one had refractory VT in the setting of a history of transposition of the great arteries, status post arterial switch procedure complicated by a scar that occurred during coronary artery reimplantation (Table 1).

Patient outcomes

At mean follow-up of 367 ± 251 days (median 324 days), 17 patients died (10 in the left CSD and 7 in the bilateral CSD group). Of these patients, three were status post orthotopic heart transplantation and died of acute rejection/complications of transplantation. One died of cardiac perforation during a subsequent device lead extraction. One died of renal failure, and 13 died of heart failure/multiorgan failure. The cause of death was not clear in one patient.

Freedom from ICD shock

The information regarding ICD shocks postprocedure could not be obtained for four patients in the left CSD group and for one patient in the bilateral CSD group (Figure 1). The overall Kaplan-Meier curve for the incidence of shock for the entire cohort is shown in Figure 2. In the left CSD group, at 90 days, 8 of 14 patients (57%) were alive and ICD shock-free. At mean follow-up of 367 ± 251 days, 30% of the patients were ICD shock-free. In the bilateral CSD group, at 90 days, 21 patients (78%) were alive and completely ICD shock-free. At mean follow-up in this group, 13 of 27 patients (48%) continued to remain free of ICD shocks (Figure 2). Three patients had previously failed left CSD and subsequently underwent right CSD. Two of these patients were ICD shock-free at follow-up after right CSD was performed. The overall shock-free survival and incidence of death from a competitive risk analysis are shown in Figure 2 (lower panel). Given the high mortality rate in this cohort predominantly from heart or multiorgan failure, the survival from ICD shocks was also driven by the high death rate at follow-up. Of note, five patients (12%; one in the left CSD group and four in the bilateral CSD group) experienced one to two ICD shocks in the first 2 weeks after the procedure and were therefore deemed as "failures" in the freedom from ICD shock analysis. However, none of these patients had experienced a recurrent ICD shock after the initial 2-week period and during their mean follow-up of 431 ± 371 days (median 405 days). In subgroup analysis, the survival free from ICD shocks was significantly higher in the bilateral CSD than the left CSD group ($P = .04$; Figure 3), although this was partly driven by the higher mortality in the left CSD group ($P = .02$). The 50% median time to shock-free survival was 366 days in the bilateral CSD group and 128 days in the left CSD group ($P = .04$). Two patients in the left CSD group and one patient in the bilateral CSD group had no ICD shocks or VT storm before death.

Burden of ICD shocks

The burden of ICD shocks was assessed from ICD interrogations or physician documentation of number of shocks. ICD interrogations pre- and post-procedure were available for 28 of 41 patients (8 left CSD and 20 bilateral CSD). ICD shocks were reduced in 93% of patients, with 7 patients in the left CSD group and 19 patients in the bilateral CSD group demonstrating a decrease in ICD shocks. The mean number of ICD shocks preprocedure was 20 ± 19.8 (median 14) in the combined left and bilateral CSD groups. At mean follow-up of 367 ± 251 days, the number of ICD shocks in the combined left and bilateral CSD groups had been reduced to 2.3 ± 2.9 (median = 1) ($P < .001$). For the bilateral CSD group specifically, the mean number of ICD shocks was reduced from 19 ± 18 (median = 14) to 1.8 ± 2.5 (median = 1) ($P < .001$), whereas in the left CSD group, the mean number of ICD shocks was reduced from 15 ± 18 (median = 8) to 2.4 ± 3.4 (median = 1.5) ($P = .008$) compared to preprocedure for both groups (Figure 4).

Effect of CSD on left ventricular function and PAPs

Of the 41 patients who underwent CSD, echocardiographic reports were available for 22 patients preprocedure and at follow-up. Preprocedure, left ventricular EF was 31 ± 13% (mean ± SD) in the combined group. At follow-up, mean left ventricular EF was 36% ± 13% ($P = .13$). There was no statistically significant difference in PAPs as estimated by echocardiography preprocedure and at follow-up. Mean PAP before the procedure was 39 ± 11.5 mm Hg. At follow-up, mean PAP was 36 ± 14 mm Hg ($P = 0.4$) compared to preprocedure.

Complications

Acute complications—Two patients (4.8%; one in the bilateral CSD group and one in the left CSD group) developed hemothorax postoperatively, requiring repeat thoracoscopy, and one of these patients (in the left CSD group) also had a pneumothorax. These patients demonstrated significant scarring/adhesions in the posterior thorax at the time of sympathectomy. Three episodes of mild ptosis were noted (two in the bilateral CSD group and one in the left CSD group), one of which persisted at follow-up but did not prove bothersome to the patient or require intervention. The other two were temporary and resolved by 3 months of follow-up. One patient in the bilateral CSD group required vasopressors postoperatively because of persistently low blood pressures that were then successfully weaned, but the duration of hospitalization was increased (Table 2).

Chronic complications—Four patients (9.7%; three in the bilateral CSD group and one in the left CSD group) noted a significant change in their sweating pattern, with the expected decreased sweating of upper extremities, but now noted increased sweating of their lower extremities. Five patients (12%; 3 in the bilateral CSD group and one in the left CSD group) complained of significant skin sensitivity on parts of their chest, back, and portions of their shoulders or arms, which included numbness, tingling, or neuropathic pain, or increased sensitivity to touch in certain regions. These changes persisted beyond the 3-month follow-up period in three patients (Table 2).

Discussion

Major findings

This study reports the largest series of patients who underwent left or bilateral CSD for VT storm or recurrent VT refractory to medical therapy and catheter ablation. It shows that bilateral more than left CSD has beneficial effects that extend beyond the acute hospitalization period. Almost 50% of the patients were completely free of ICD shocks at 1-year follow-up. Furthermore, the burden of ICD shocks was significantly reduced after CSD by 90% in 90% of patients.

Neuromodulation in the management of ventricular arrhythmias

Neuromodulation in the form of spinal cord stimulation, thoracic epidural anesthesia, CSD, and renal denervation is emerging as a treatment option for both atrial and ventricular arrhythmias.[3,4,6–9,14–23] In particular, left and bilateral CSD had been shown to reduce the burden of ICD shocks and VT storm in a small number of patients acutely.[3,4] Left CSD was shown to reduce the risk of ventricular arrhythmias in patients with sustained or nonsustained VT postmyocardial infarction, an effect that was equivalent to the use of beta-blockers.[17] Furthermore, in a canine model of myocardial infarction, left stellate gangliectomy was shown to decrease ventricular arrhythmias during ischemia.[16] Case reports of bilateral CSD in the management of ventricular arrhythmias date back to 1961 when Estes and Izlar[24] first described the case of a patient with recurrent VT treated with bilateral CSD. Since then, the benefits of this procedure have been described in other case reports.[3,25–28] The current study contains the largest series of patients in whom the intermediate and long-term benefits of CSD in the treatment of refractory ventricular arrhythmias or VT storm was evaluated. This is the first study to show that in this high-risk population, CSD demonstrated benefits that extend beyond the acute postoperative period, with a reduction in ICD shock burden of close to 90%. This result was evident despite the fact that the majority of these patients had nonischemic cardiomyopathy, had undergone a median of 2 previous catheter ablation procedures, and were already on maximal medical therapy. Given that the sympathetic nerves that innervate the heart also innervate the upper extremities and chest, approximately 10% of our patients noted a change in their sweating pattern with increased sweating of the lower extremities to “compensate” for the lack of sweating in the upper extremities and chest. Furthermore, five patients noted a change in their skin sensation, with three noting a persistent change beyond the 3-month follow-up period. Given that only the lower half of the stellate ganglia were removed, the risk of ptosis in this patient population was small, with two patients developing mild ptosis that resolved at follow-up and only one patient experiencing mild persistent ptosis. None of these patients sought or required medical intervention for ptosis at follow-up.

Left vs bilateral CSD

Although the retrospective nature and small number of patients in each group are limitations, in this study, the bilateral CSD group had a greater survival from ICD shocks at follow-up. Although this was partially driven by the higher death rate in the left CSD group, the greater reduction in the long-term benefit of left CSD may also result because the right stellate ganglion provides significant innervation to the ventricles, particularly the anterior ventricular wall and base of the heart.[29–32] Furthermore, neural remodeling including neuron cell body hypertrophy, increased fibrosis, and increased synaptic density have been shown to occur, not just in the left[33] but in both stellate ganglia in patients with cardiomyopathy and in a canine model of myocardial infarction.[34,35] Finally, it has been shown that resection of the ipsilateral superior cervical ganglion leads to hypertrophy of neurons and structural changes in the contralateral superior cervical ganglion in sheep.[36] The same type of nerve plasticity likely exists for the stellate ganglia and could occur after left CSD.

Possible mechanisms of failure

Although the burden of ICD shocks was significantly reduced in this patient population, the fact that approximately half of the patients continued to experience at least one ICD shock may be explained by the progressive nature of their heart failure, lack of a sympathetic trigger for the initiation or perpetuation of their arrhythmias, as well as an increase in circulating catecholamines in the initial postoperative period. In fact, in this study, 12% of patients experienced an ICD shock in the first 2 weeks after the procedure but then were completely ICD shock-free at follow-up. This may also point to the fact that, in addition to the earlier discussion, reverse neural remodeling in patients with cardiomyopathy may take time, as observed in reverse myocardial structural remodeling with biventricular pacemakers.[37,38]

Study limitations

This is a retrospective observational study, so patients were not randomized. Therefore, the true effects of CSD in this patient population may have been under- or overestimated. Furthermore, although these patients continued to experience recurrent VT and ICD shocks despite catheter ablation and maximum medical therapy, VT storm can spontaneously subside, and the effect of this on the results of this study vs the natural history of storm cannot be clearly delineated. However, in this cohort, CSD was often offered when death was imminent as a lifesaving therapy. Furthermore, the retrospective nature of this study does not allow for assessment of other potential confounding factors on the outcome of CSD, such comorbidities, pathogenesis of cardiomyopathy, and previous VT storm. Finally, although the overall data in addition to the subgroup data for left and bilateral CSD are reported, a comparison of left vs bilateral CSD is limited by the small number of patients (particularly in the left CSD group), the greater number of patients who were lost to follow-up with regard to ICD shocks in the left CSD group, and the fact that not all left CSD patients could tolerate the bilateral procedure and may have represented a sicker patient population.

Conclusion

This study demonstrates that in patients with VT storm or recurrent VT refractory to medical therapy and catheter ablation, CSD demonstrates beneficial effects at both intermediate and long-term follow-up. Bilateral CSD appears to have a greater shock-free survival compared to left CSD alone. Not only is there continued freedom from ICD shocks in many patients, but the burden of ICD shocks is also significantly reduced in both groups. An assessment of the exact benefit of bilateral CSD on ICD shocks, however, requires randomized controlled clinical trials.

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ABBREVIATIONS

CSD	cardiac sympathetic denervation
EF	ejection fraction
ICD	implantable cardioverter-defibrillator
PAP	pulmonary artery pressure
VT	ventricular tachyarrhythmia

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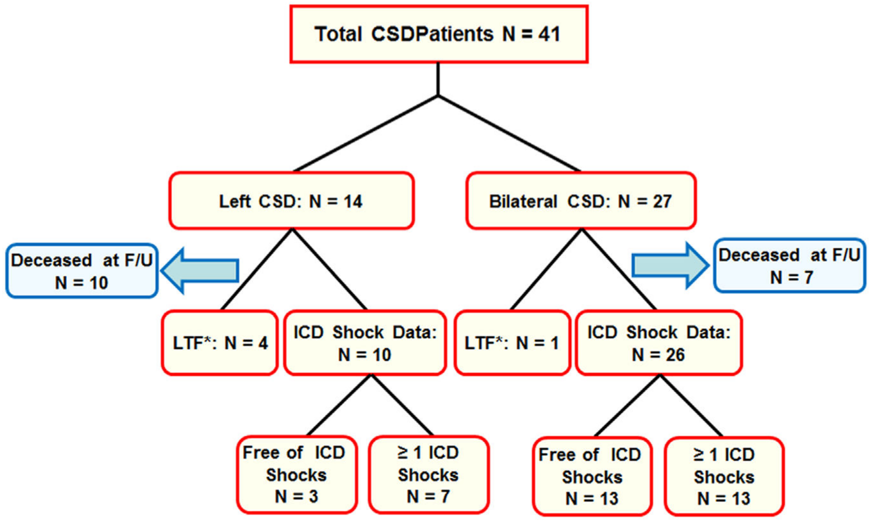

Figure 1.

Flow chart of the study cohort. Of the 41 patients, 27 underwent bilateral and 14 underwent left cardiac sympathetic denervation (CSD). LTF = patients lost to long-term follow-up (F/U) with regard to implantable cardioverter-defibrillator (ICD) shock status.

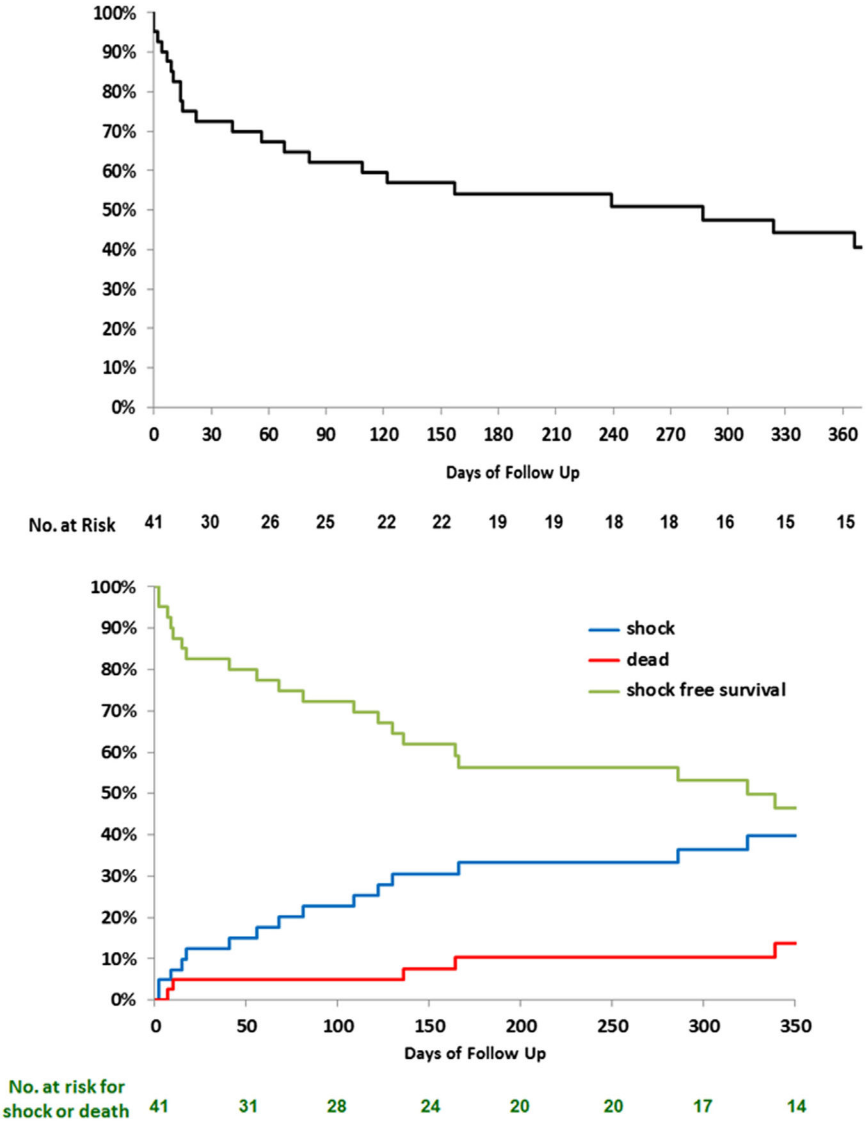

Figure 2.

Top: Freedom from implantable cardioverter-defibrillator (ICD) shock. Kaplan-Meier curve for freedom from ICD shock only is shown. For this analysis, death was censored and the patients who were lost to long-term follow were censored at the last follow-up, which was approximately 2 weeks post-procedure. **Bottom:** Survival free from ICD shock. Kaplan-Meier curves for survival free from ICD shock as well as risk of death and shock for this cohort are shown. Because of the higher incidence of death in this cohort, the survival free from ICD shocks was also driven by the high risk of mortality in this patient population.

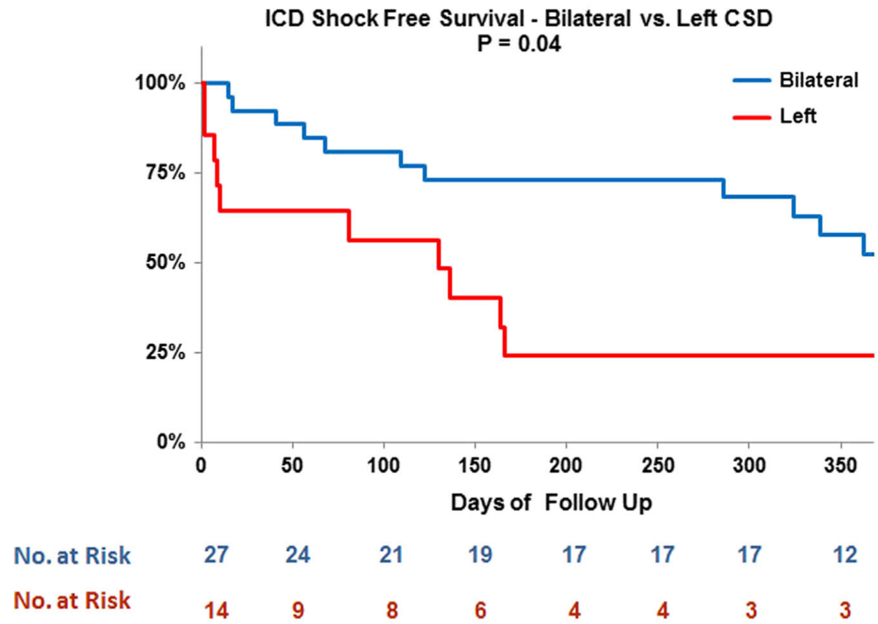

Figure 3.

Analysis of shock-free survival in the bilateral vs left cardiac sympathetic denervation (CSD) groups. Kaplan-Meier curves for survival free from implantable cardioverter-defibrillator (ICD) shocks are shown for both the bilateral and left CSD subgroups. The 50% median time to shock-free survival was 366 days in the bilateral CSD group and 128 days in the left CSD group (*P* = .04). The greater survival free of ICD shocks in the bilateral CSD group was partly driven by the higher mortality rate in the left CSD group.

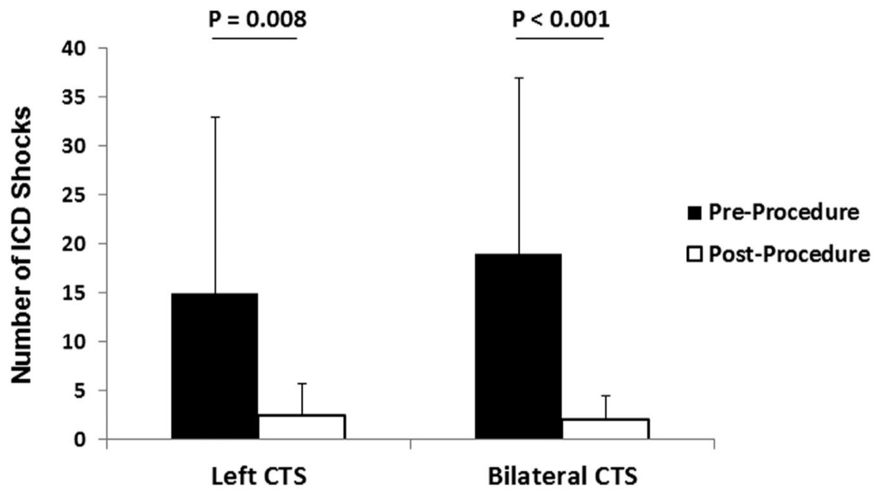

Figure 4.

Burden of implantable cardioverter-defibrillator (ICD) shocks pre- and postprocedure. At mean follow-up, the total number of ICD shocks was significantly reduced in both the left and bilateral cardiac sympathetic denervation (CSD) groups after the CSD procedure compared to preprocedure (mean ± SD).

Table 1

Patient characteristics

Patient Characteristics	Bilateral CSD (N = 27)	Left CSD (N = 14)
Male	23 (85%)	12 (86%)
Age (years)	57 ± 14	63 ± 11
Cardiomyopathy		
ICM	4 (15%)	5 (36%)
NICM	15 (56%)	7 (50%)
HCM	1 (3.7%)	2 (14%)
Sarcoid	2 (7.4%)	
Chagasic	1 (3.7%)	
ARVC	1 (3.7%)	
Valvular	1 (3.7%)	
TGA (+infarct)	1 (3.7%)	
None (idiopathic VF)	1 (3.7%)	
Type of VT		
PMVT/VF	6 (22%)	2 (14%)
MMVTS	21 (78%)	12 (86%)
Left ventricular ejection fraction (%)	32 ± 13	29 ± 13
Pulmonary artery pressure (mm Hg)	38 ± 12.5	39 ± 9.8
Median no. of VT ablations	2 (0–5)	2 (0–4)

ARVC = arrhythmogenic right ventricular cardiomyopathy/dysplasia, CSD = cardiac sympathetic denervation, HCM = hypertrophic cardiomyopathy, ICM = ischemic cardiomyopathy, MMVTS = monmorphic VTs, NICM = non-ischemic cardiomyopathy, PMVT = polymorphic VT, TGA = transposition of the great arteries, VF = ventricular fibrillation, VT = ventricular tachycardia.

Table 2

Complications Related to CSD procedure.

Procedural Complications	Total (N = 41)	Bilateral CSD (N = 27)	Left CSD (N = 14)
Acute			
Hemothorax	2 (5%)	1 (4%)	1 (7%)
Pneumothorax	1 (2%)	0	1 (7%)
Ptosis (mild)	3 (7%)	2 (7%)	1 (7%)
Chronic (>3 months)			
Skin sensitivity	5 (12%)	3 (11%)	2 (14%)
Change in sweating pattern	4 (10%)	3 (11%)	1 (7%)
Ptosis (mild)	1 (2%)	0	1 (7%)

CSD = Cardiac Sympathetic Denervation.