Videoscopic Left Cardiac Sympathetic Denervation for Patients with Recurrent Ventricular Fibrillation/Malignant Ventricular Arrhythmia Syndromes Besides Congenital Long QT Syndrome

Running title: Coleman et al.; LCSD in non-LQTS arrhythmia syndromes

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Abstract:

**Background** - Treatment options for patients with recurrent ventricular arrhythmias refractory to pharmacotherapy and/or ablation are minimal. While left cardiac sympathetic denervation (LCSD) is well established in long QT syndrome (LQTS), its role for non-LQTS arrhythmogenic channelopathies and cardiomyopathies is less clear. Here, we report our single-center experience in performing LCSD in this setting.

**Methods and Results** - In this IRB-approved study, we retrospectively reviewed the electronic medical records for all patients (N=91) who had videoscopic LCSD at our institution from 2005-2011. Data were analyzed for the subset (N=27) who were denervated for an underlying diagnosis other than autosomal dominant or sporadic LQTS. The spectrum of arrhythmogenic disease included catecholaminergic polymorphic ventricular tachycardia (N=13), Jervell and Lange-Nielsen syndrome (N=5), idiopathic ventricular fibrillation (N=4), left ventricular non-compaction (N=2), hypertrophic cardiomyopathy (N=1), ischemic cardiomyopathy (N=1), and arrhythmogenic right ventricular cardiomyopathy (N=1). Five patients had LCSD because of high risk assessment and/or beta blocker intolerance, none of which have had a sentinel breakthrough cardiac event (BCE) at early follow-up. Among the remaining 22 previously symptomatic patients who had LCSD as secondary prevention, all have had an attenuation in cardiac events with 18 having no BCEs so far and 4 patients having experienced ≥ 1 post-LCSD BCE.

**Conclusions** - LCSD may represent a substrate independent anti-fibrillatory treatment option for patients with life-threatening ventricular arrhythmia syndromes other than LQTS. The early follow-up looks promising with a marked reduction in the frequency of cardiac events post-denervation.

**Key words**: catecholaminergic polymorphic ventricular tachycardia; sudden cardiac arrest; ventricular fibrillation; LCSD; denervation
Introduction

Left cardiac sympathetic denervation (LCSD) is a safe and effective therapeutic option in patients with malignant ventricular arrhythmias stemming from both channelopathies and cardiomyopathies.\textsuperscript{1-5} Although beta-blocker pharmacotherapy is the mainstay of medical management for these patients, some are either intolerant or refractory to this therapy.\textsuperscript{6,7} For some patients, a more aggressive sudden cardiac death prevention strategy, such as implantable cardioverter defibrillators (ICDs), may be required. An ICD will arguably provide the most definitive protection against lethal ventricular arrhythmias; however, there are significant comorbidities, including device-related malfunction, inappropriate therapies, infections, and psychological stress, associated with their use.\textsuperscript{8}

With the therapeutic gap and side effects of pharmacotherapy and the comorbidity profile of ICDs, additional therapies may be necessary for those patients with severely arrhythmogenic disease. With the growing understanding of the anti-fibrillatory potential of LCSD, it has emerged as an additional and safe treatment option for patients with LQTS and CPVT.\textsuperscript{1,4} This procedure removes the lower half of the left stellate ganglion (T1) and thoracic ganglia T2 to T4 thereby diminishing the noradrenergic input to the left ventricular myocardium.\textsuperscript{9} In a study of 147 patients with LQTS,\textsuperscript{4} there was a $>90\%$ reduction in cardiac events post-denervation. LCSD raises the threshold for ventricular fibrillation without impairing myocardial contractility or reducing heart rate\textsuperscript{10,11} and reduces arrhythmias in post-myocardial infarction animal models.\textsuperscript{12,13} While LCSD has a well-established event attenuating effect in patients with LQTS,\textsuperscript{1,4} its efficacy for non-LQTS arrhythmogenic channelopathies and cardiomyopathies is less clear. Herein, we report our single-center experience in performing LCSD in these patients.
Methods

In this study, approved by Mayo Clinic’s Institutional Review Board (IRB) for protection of human subjects, we identified all patients (N = 27) with arrhythmogenic channelopathies and cardiomyopathies, other than autosomal dominant or sporadic LQTS, who had undergone LCSD at our institution between November 1, 2005, and December 1, 2011 as previously described. A detailed retrospective review of the electronic medical record was performed, specifically looking at demographic variables, genotype, indications for surgery, available follow-up, postoperative complications, presence of ICD or pharmacologic therapy, and incidence of aborted cardiac arrest (ACA) or appropriate VF-terminating ICD therapies before and after LCSD. The denervation surgery was considered secondary prevention if the patient had a history of either ACA or VF-terminating ICD therapy. Breakthrough cardiac events (BCEs) were defined as an appropriate VF-terminating ICD therapy, ACA, or syncope occurring after LCSD. Follow-up was censored as of January 1, 2012.

Procedure

Using a videoscopic transthoracic approach and single right bronchus intubation, the left-sided sympathetic ganglia were identified through the pleura, which was then divided to expose the sympathetic chain from T4 to T1. The ganglia were removed by dividing the major rami communicans and fully identifying the much smaller sympathetic nerve branches that ravel toward the heart. The lower half of the left stellate ganglion (T1) was then divided along the anatomic fusion between its upper and lower poles. The dissected materials were removed en bloc and sent to pathology for confirmation. A postoperative chest radiograph was performed to confirm the absence of significant pneumothorax and all patients were monitored postoperatively in the intensive care unit.
Statistical analysis

Statistical analysis was performed using JMP 8.0 statistical software (JMP 8.0®, SAS Institute Inc., Cary, NC, USA). All continuous variables were reported as the median (25th, 75th percentile) or were indicated as median (range). P-values <0.05 were considered statistically significant. Kaplan-Meier cumulative estimates were used to analyze cumulative postoperative event-free survival. Time to first event was characterized by time to first appropriate ICD therapy, ACA, or sudden cardiac death (SCD). For those without a BCE postoperatively, January 1, 2012 was considered the end-point for follow-up evaluation, and they were censored for Kaplan-Meier analysis. Event-free survival curves were calculated for the entire cohort and comparisons were made between asymptomatic patients (i.e., 0 CEs pre-LCSD) and previously symptomatic patients with 1-10 and >10 CEs pre-LCSD.

Results

Among the 91 patients who underwent videoscopic LCSD at our institution, 27 patients [14 female, median age at diagnosis 12 (4, 16) years, 19 genotype positive] had high risk malignant ventricular arrhythmia syndromes other than autosomal dominant/sporadic LQTS (Table 1 and Table 2). Their underlying etiologies included catecholaminergic polymorphic ventricular tachycardia (CPVT, n=13), Jervell and Lange-Nielsen syndrome (JLNS, n=5), idiopathic ventricular fibrillation (IVF, n=4), left ventricular non-compaction (LVNC, n=2), hypertrophic cardiomyopathy (HCM, n=1), ischemic cardiomyopathy (ICM, n=1), and arrhythmogenic right ventricular cardiomyopathy (ARVC, n=1) (Figure 1). Their median age at LCSD was 15 (9, 25) years (range 2 months – 56 years) and the median follow-up post-LSCD was 1.2 (0.5, 2.1) years (range 1 month - 6.2 years). In general, those patients with IVF, ARVC, and ICM were considerably older at age of diagnosis [36 (21, 38) years] and at LCSD [48 (30, 52) years] than
those with CPVT, JLNS, LVNC, and HCM [9 (3, 14) years at diagnosis and 14 (9, 18) years at
denervation]. In our cohort, 17 (63%) were pediatric patients.

The majority of patients were on beta blockers prior to LCSD (93%); 33% were being
treated with sodium channel blockers, 11% with potassium channel blockers, and 48% had an
ICD in place before LCSD. Post-LCSD, 59% of the total cohort and 73% of the secondary
prevention cohort had an ICD in place. For the 27% (n=6) of patients without ICDs in the
secondary prevention group, monitoring of BCEs was based on symptom reporting of syncope
and ACA and annual 24-hour ambulatory ECG monitoring.

Five asymptomatic patients (19%, 3 CPVT, 2 JLNS) had LCSD performed following
high risk assessment and/or beta blocker intolerance, and none have had a sentinel BCE at early
follow-up. Among the remaining 22 who had LCSD as secondary prevention, 18 have had no
recurrences so far while 4 (18%, 1 female, 1 with CPVT, 1 with JLNS, 1 with HCM, and 1 with
IVF) have experienced ≥ 1 BCE post-LCSD (Figure 2).

Of the 13 patients with CPVT, all were genotype positive for mutations in the CPVT-
associated RYR2-encoded cardiac ryanodine receptor or CASQ2-encoded calsequestrin protein,
10 had LCSD for secondary prevention, and 12 have had no recurrences post-LCSD. In the 5
JLNS patients, 4 were genotype positive with double KCNQ1 mutations (i.e. JLNS1), 3 had
LCSD as secondary prevention, and 4 have not experienced any events post-LCSD. All 4
patients with IVF had LCSD as secondary prevention and 3 have been event free since their
procedure, again at early follow-up. Both of the LVNC patients and the patients with ICM and
ARVC were symptomatic prior to LCSD and have been quiescent since the operation.

Analysis of BCEs

While 85% of patients remain event-free post-LCSD at early follow-up [1.5 (0.5, 2.1) years], 4
patients have had \( \geq 1 \) BCE post-LCSD. However, as shown in Figure 2, all have had a marked decrease in events compared to the number of disease-attributable cardiac events recorded pre-denervation. The individual characteristics of these 4 patients are illustrated in Table 2.

**Event-free survival**

A Kaplan-Meier analysis of cardiac event-free survival for the complete cohort demonstrated 76\% of patients to be event-free post-procedure (Figure 3). All asymptomatic patients pre-LCSD maintained a 100\% event-free survival at short follow-up. When comparing event-free survival based on number of events pre-procedure, the subset with >10 events prior to denervation had a 55\% chance of event-free survival compared to 80\% in the group with 1-10 events prior to surgery (data not shown). Although no statistically significant difference was reached, the data suggest that patients with heavier event burden preoperatively might be at higher risk of having BCEs post-LCSD.

**Postoperative Complications**

Short-term complications predominantly included transient symptoms of Horner’s syndrome (i.e., left eyelid ptosis and miosis in 3 and mild left-sided apical pneumothorax in 3 with spontaneous resolution in 2 and chest tube requirement in 1). These complications all resolved at follow-up. One patient had to be converted to an open thoracotomy due to a bleeding intercostal vessel. No long-term complications were present in our cohort, and technical success was 100\%.

**Discussion**

While LCSD is an increasingly recognized and well-established treatment option in LQTS, its role for other arrhythmogenic channelopathies and cardiomyopathies is less understood. Here, we report our single-center experience in performing LCSD for patients with malignant arrhythmias including those with CPVT, JLNS, IVF, LVNC, HCM, ICM, and ARVC. Overall,
we demonstrate a marked decrease in the number of cardiac events in the majority of these patients postoperatively. Since LCSD increases the fibrillatory threshold and decreases arrhythmogenicity in the myocardium after an acute ischemic event, LCSD may be a potential adjuvant treatment in patients with malignant ventricular arrhythmias stemming from substrates besides LQTS. In addition, LCSD should be considered in arrhythmogenic conditions which may be exacerbated specifically by sympathetic activation.

**Catecholaminergic polymorphic ventricular tachycardia (CPVT)**

CPVT is an autosomal-dominant arrhythmia syndrome caused by disruptions in calcium homeostasis, specifically by mutations in the RYR2-encoded cardiac ryanodine receptor (CPVT1) and more rarely in the CASQ2-encoded calsequestrin protein (CPVT2). Patients with CPVT usually have a normal resting ECG with ventricular ectopy on exercise or catecholamine stress testing, clinically presenting with exertional syncope or sudden death. Most CPVT patients are treated pharmacologically with beta blockers, calcium channel blockers, flecainide, or a combination thereof. However, some patients do not exhibit a sufficient response to beta blockade and remain symptomatic. In a meta-analysis of 11 studies including 354 CPVT patients treated with beta blockers, the estimated 8-year rates of arrhythmic events were 37.2% (95% confidence interval (CI): 16.6-57.7), near-fatal events was 15.3% (95% CI: 7.4-23.3), and fatal events was 6.4% (95% CI: 3.2-9.6).

For those patients who are not fully protected with beta blockade, ICDs are generally recommended as additional therapy. However, given the nature of CPVT, both the fear and pain elicited from an ICD discharge can result in further catecholamine release and cardiac events, ultimately resulting in the administration of multiple shocks in what is called an “ICD storm”. In this vicious cycle, the patient may not always be rescued. Additionally, inappropriate ICD
shocks may trigger an ICD storm. If the patient has sympathetic denervation, this cycle theoretically is short-circuited, making LCSD a useful adjunctive therapy for CPVT patients.

For CPVT patients who continue to be symptomatic despite beta blocker usage, LCSD has been shown to be a safe and effective anti-fibrillatory therapy in two previous case series \(^1,5,18\) and one case report \(^19\) in addition to our success with 13 patients. Wilde \(et\ al.\) \(^5\) had a highly successful outcome with 3 CPVT patients; Atallah \(et\ al.\) \(^18\) demonstrated complete resolution of cardiac events in \(3/4\) patients and partial resolution in one; and Scott \(et\ al.\) \(^19\) described a successful treatment of 1 CPVT patient with bilateral sympathetic denervation. Here, we present 13 CPVT patients with thus far, no post-LCSD BCEs in 12 of the 13 patients, and a reduction in events shown in the other patient. Although the average follow-up for these patients is only 1.3 years (range, 0.1-4.1 years), these early results are encouraging.

Since LCSD involves postganglionic and preganglionic denervation, postoperative supersensitivity and reinnervation are highly unlikely, and thus the anti-fibrillatory effects of this procedure should be durable. Although there is no long term follow-up for CPVT patients who have had LCSD, there is 30-year data in LQTS patients that demonstrates the successful longevity of this procedure. \(^4\) Denervation may be of additional benefit to those who are poorly compliant with pharmacotherapy. LCSD does not, however, eliminate the need for ICDs for sudden cardiac death prevention in the highest risk subjects and must not be misconstrued as a therapeutic cure. Indeed, they should be used together along with beta blockers to ensure the highest level of protection in CPVT patients deemed at greatest risk. Without treatment altogether, there is a 30 to 50% lethality rate by age 40 in patients with CPVT. \(^7\)

**Jervell and Lange-Nielsen syndrome (JLNS)**

JLNS is an autosomal recessive variant of congenital long QT syndrome associated with
deafness and a more malignant arrhythmia phenotype. In a study of 186 JLNS patients, the QTc was markedly prolonged (>550 ms), 86% of the cohort had a cardiac event, and of those, 95% were triggered by emotional or physical stress. Greater than 25% of these patients experienced sudden cardiac death. Due to the severity of this phenotype, pharmacologic therapy alone is often inadequate and more aggressive measures need to be pursued. Since cardiac events in JLNS can be triggered by stress, LCSD could be hypothesized to be highly efficacious. Additionally, with >90% efficacy in LQTS, it can be expected that LCSD would be highly successful in JLNS.

In our study, we performed LCSD on 5 patients with JLNS, of which only one suffered breakthrough events post-LCDS [follow-up, 1.8 (range 0.5 – 4.8 years) years]. In the study by Atellah et al., two patients with JLNS were identified; one had resolution of symptoms post-LCSD while the other experienced one event in the 26-month follow-up. Two other case reports have demonstrated a reduction in symptoms in JLNS patients post-LCSD, one with no post-operative symptoms and the other demonstrating ventricular ectopy immediately following surgery but not since in the 18 month follow-up. Again, LCSD should not preclude ICD placement in a patient with JLNS who has been assessed to be at high risk.

**Idiopathic ventricular fibrillation**

IVF is a diagnosis of exclusion identified in patients with structurally normal hearts. These patients generally present later in life at a mean age of 36 years old, and have an excellent prognosis as long as the VF is controlled. Therefore, an ICD along with beta blockade is often advised. Additionally, radiofrequency ablation can be used in IVF, and LCSD may also be of benefit. In our 4 IVF patients, 3 have remained symptom free and 1 has had a single BCE but has an apparently attenuated arrhythmogenic substrate (>200 events over 12 years pre-LCSD [17
events/year] to 1 event post-LCSD in 2.5 year follow-up [0.4 events/year]).

**Cardiomyopathies**

All of the other diseases in our LCSD cohort were cardiomyopathies with severely arrhythmogenic presentations: LVNC, HCM, ICM, and ARVC. In a study conducted by Bourke et al., LCSD was performed on 9 patients who had recalcitrant ventricular arrhythmias with a decrease in arrhythmia burden in 5 patients. In their study, 2 patients had ICM with partial improvement in one and no measureable reduction in the other. Similarly, two patients had HCM with one exhibiting no response to LCSD and the other having a full response with no further VT at early follow-up. There was also a patient with ARVC who demonstrated complete resolution of symptoms post-LCSD. The other 4 LCSD patients in this cohort included two with nonischemic cardiomyopathy (one with complete response and one with no response) and two with sarcoid cardiomyopathy (one with partial response and one with no response). Considering that LCSD’s antifibrillatory effect may be somewhat substrate independent, it seems reasonable to consider denervation therapy for some of these malignant cardiomyopathies where life-threatening ventricular arrhythmias persist despite conventional therapy.

**Limitations**

Due to the nature of tertiary referral to Mayo Clinic’s Congenital Heart Center and the retrospective nature of this study, an time-indexed arrhythmia burden was nearly impossible to obtain from our cohort as a significant number of patients was not able to recollect the exact date of first arrhythmic event or number of events occurred prior to LCSD. Since uniform data was not available for all patients, quantifying this in a time-indexed manner would certainly lead to misinterpretation and be subject to investigator bias.
Conclusions

The early follow-up of LCSD looks promising with a marked reduction in the frequency of cardiac events observed post-denervation. LCSD should be considered as part of an expanded treatment armamentarium for patients with highly arrhythmogenic non-LQTS channelopathies and cardiomyopathies who remain symptomatic despite standard therapy. However, larger studies for each disease are required prior to making any definitive recommendations. In addition, a randomized trial or comparison between patients after LCSD and patients without would contribute significantly to our understanding of LCSD efficacy.

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**Conflict of Interest Disclosures:** Michael J. Ackerman MD, PhD is a consultant for Transgenomic and chairs their FAMILION Medical/Scientific Advisory Board (approved by Mayo Clinic’s Medical-Industry Relations Office and Conflict of Interests Review Board). In addition, “cardiac channel gene screen” and “know-how relating to long QT genetic testing” license agreements, resulting in consideration and royalty payments, were established between Genaissance Pharmaceuticals (then PGxHealth, and now Transgenomic) and Mayo Medical Ventures (now Mayo Clinic Health Solutions) in 2004. Michael J. Ackerman MD, PhD is also a consultant for Biotronik, Boston Scientific Corporation, Medtronic, and St. Jude Medical Inc. However, none of these entities provided financial support for this study.

**References:**


### Table 1: Demographics of our LCSD Cohort

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<tr>
<th></th>
<th>Total Cohort</th>
<th>CPVT</th>
<th>JLNS</th>
<th>IVF</th>
<th>LVNC</th>
<th>ARVC</th>
<th>HCM</th>
<th>ICM</th>
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<tr>
<td>N</td>
<td>27</td>
<td>13</td>
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<td>4</td>
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<td>1</td>
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<td>1</td>
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<tr>
<td>Male/female</td>
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<td>1/0</td>
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<td>Age at diagnosis (yrs)</td>
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<td>12 (9, 15)</td>
<td>3 (0, 14)*</td>
<td>26 (0, 34)*</td>
<td>7 (0, 13)*</td>
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<td>37</td>
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<td>Pediatric n(%)</td>
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<td>10 (77)</td>
<td>4 (80)</td>
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<td>0 (0)</td>
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<td>β-blocker n(%)</td>
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<td>1 (100)</td>
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<td>4 (31)</td>
<td>1 (20)</td>
<td>1 (25)</td>
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<td>β-blocker intolerance n(%)</td>
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<td>3 (23)</td>
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<td>Break-through event n(%)</td>
<td>7 (26)</td>
<td>1 (8)</td>
<td>2 (40)</td>
<td>2 (50)</td>
<td>1 (100)</td>
<td>0 (0)</td>
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<td>Additional protection n(%)</td>
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<td>9 (69)</td>
<td>3 (60)</td>
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<td>15 (9, 25)</td>
<td>15 (10, 18)</td>
<td>14 (1, 25)*</td>
<td>35 (1, 53)*</td>
<td>11 (0, 22)*</td>
<td>56</td>
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<td>50</td>
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<td>Follow-up time (yrs)</td>
<td>1.2 (0.5, 2.1)</td>
<td>0.8 (0.4, 1.4)</td>
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<td>1 (20)</td>
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*Medians with range instead of 25th and 75th percentiles

ICD = Implantable cardioverter defibrillator; LCSD = Left cardiac sympathetic denervation; CPVT = Catecholaminergic polymorphic ventricular tachycardia; JLNS = Jervell and Lange-Nielsen syndrome; IVF = Idiopathic ventricular fibrillation; LVNC = Left ventricular non-compaction; HCM = Hypertrophic cardiomyopathy; ICM = Ischemic cardiomyopathy; ARVC = Arrhythmogenic right ventricular cardiomyopathy
Table 2: Individual Characteristics of All Patients

<table>
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<th>Case #</th>
<th>Age at Diagnosis (years)</th>
<th>Male/Female</th>
<th>Follow up time (years)</th>
<th># Cardiac Events Pre-LCSD</th>
<th># Cardiac Events Post-LCSD</th>
<th>Surgical Complications*</th>
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<td></td>
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<td>1</td>
<td>2.4</td>
<td>M</td>
<td>1.3</td>
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<td>0</td>
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<td>2</td>
<td>9.2</td>
<td>F</td>
<td>4.1</td>
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<td>0</td>
<td>Transient pneumothorax</td>
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<td>4</td>
<td>9.6</td>
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<td>1.4</td>
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<td>Converted to open thoracotomy secondary to bleeding intercostal vessel</td>
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<td>M</td>
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<td>Transient pneumothorax</td>
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<td>10</td>
<td>18</td>
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<td>1.8</td>
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*No long-term complications in any of the 27 patients.

LCSD = Left cardiac sympathetic denervation; CPVT = Catecholaminergic polymorphic ventricular tachycardia; JLNS = Jervell and Lange-Nielsen syndrome; IVF = Idiopathic ventricular fibrillation; LVNC = Left ventricular non-compaction; HCM = Hypertrophic cardiomyopathy; ICM = Ischemic cardiomyopathy; ARVC = Arrhythmogenic right ventricular cardiomyopathy
Figure Legends:

**Figure 1:** Spectrum of underlying etiologies of patients undergoing left cardiac sympathetic denervation.

**Figure 2:** Cardiac event rate pre- and post-LCSD. This bar graph illustrates the cardiac event burden before and after LCSD for three groups: those with 0 events prior to surgery (asymptomatic), those with 1-10 events, and those with >10 events. Overall, the graph shows a substantial left shift in events post-LCSD. LCSD = Left cardiac sympathetic denervation.

**Figure 3:** Kaplan-Meier of overall and cumulative event-free survival. Kaplan-Meier curve demonstrating overall survival (no deaths occurred in our cohort) and cumulative event-free survival in our study cohort.
CPVT, 13

JLNS, 5

IVF, 4

LVNC, 2

HCM, 1

ICM, 1

ARVC, 1
Videoscopic Left Cardiac Sympathetic Denervation for Patients with Recurrent Ventricular Fibrillation/Malignant Ventricular Arrhythmia Syndromes Besides Congenital Long QT Syndrome
Mira A. Coleman, J. Martijn Bos, Jonathan N. Johnson, Heidi J. Owen, Claude Deschamps, Christopher Moir and Michael J. Ackerman

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