Left Cardiac Sympathetic Denervation in Long QT Syndrome: Analysis of Therapeutic Non-Responders

Running title: Bos et al.; Analysis of LCSD breakthroughs

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Abstract:

**Background** - Long QT Syndrome (LQTS) is a potentially lethal but highly treatable cardiac channelopathy. Treatment options include pharmacotherapy, device therapy, and/or left cardiac sympathetic denervation (LCSD). Here, we sought to determine the characteristics of LQTS patients who have had $\geq 1$ LQTS-related breakthrough cardiac event (BCE) following LCSD.

**Methods and Results** - We performed retrospective chart review for 52 consecutive patients (24 male, mean age at diagnosis 10.0±10 years, mean QTc 528±74 ms) with LQTS who underwent LCSD between 2005 through 2010 (mean age at LCSD 14.1±10 years) and have been followed for 3.6 ± 1.3 years. A BCE was defined as either 1) an appropriate VF-terminating ICD shock or 2) arrhythmogenic syncope, seizures, or aborted cardiac arrest following LCSD. Thirty-three patients (61%) had LCSD as primary prevention because of either high risk assessment or beta blocker intolerance. So far, 12/52 (23%) patients (7 male) have experienced at least one BCE post-LCSD. The clinical phenotype of patients with BCE’s was significantly more severe than patients without a BCE. No BCEs were seen in patients undergoing LCSD for beta blocker intolerance (0/12 vs. 17/40; p < 0.001).

**Conclusions** - Although a marked reduction in number of cardiac events is usually seen following LCSD, nearly 50% of high risk LQTS patients have experienced at least one post-LCSD breakthrough. Therefore, LCSD must not be viewed as curative or as an ICD-alternative for high risk patients. Prophylactic LCSD may provide another option to counter a suboptimal quality of life resulting from medication-related side effects.

**Key words:** arrhythmia, long QT syndrome, sudden cardiac death, arrhythmia, syncope, LCSD, Left cardiac sympathetic denervation
Introduction

Congenital long QT syndrome (LQTS) affects approximately 1 in 2500 individuals, and is characterized by QT prolongation and susceptibility to syncope, seizures, or sudden cardiac death (SCD) secondary to its trademark arrhythmia, *torsades de pointes*.1, 2 LQTS is a heritable channelopathy, and 15 genes have been implicated in the pathogenesis of LQTS comprising an estimated 75% of all patients with LQTS.3 The mainstay treatments for LQTS range from daily medications (i.e. beta blockers) to the placement of an implantable cardioverter defibrillator (ICD). However, left cardiac sympathetic denervation (LCSD) has become an important additional option in the prevention of SCD in LQTS as well as catecholaminergic polymorphic ventricular tachycardia (CPVT).4-7 Thought to be due to the attenuation of localized neural/sympathetic chain release of norepinephrine and an increased ventricular fibrillation threshold, LCSD’s antifibrillatory effects in LQTS are well documented with an estimated 90% reduction of cardiac events post-denervation surgery overall.4, 6

Herein, we present our experiences with the first 52 LQTS patients referred for LCSD therapy at our institution with particular focus upon those patients experiencing at least one breakthrough cardiac event (BCE) post-denervation. The phenotype of those patients who did not respond to LCSD therapy (i.e. the “non-responders”) and the option of using LCSD for patients who are intolerant to beta blockers were examined closely.

Methods

Between 2000 and 2010, over 1200 patients were evaluated in Mayo Clinic’s Long QT Syndrome Clinic and 613 patients were diagnosed or confirmed to have LQTS. The first LCSD for LQTS at Mayo Clinic was performed in November 2005. During this time period, 54/613 LQTS patients (8.8%) have had a LCSD performed. In this study, approved by Mayo Clinic’s
Institutional Review Board (IRB), we retrospectively reviewed the electronic medical record (EMR) for 52 patients with LQTS who underwent LCSD at our institution from November 2005 through December 2010 and had at least 2 years follow-up post-LCSD. There were two additional patients who underwent LCSD during this time period but were lost to follow-up and therefore excluded from analysis. Clinical follow-up was censored at December 1, 2012 for analyses. All QTc’s were calculated using Bazett’s formula. Only patients who received denervation therapy at Mayo Clinic were included in this study.

All procedures were performed using the minimally invasive, video-assisted thoracoscopic technique that has been described previously. Briefly, using a videoscopic transthoracic approach, the left-sided sympathetic ganglia were identified. Subsequently, the sympathetic chain was exposed from T4 to T1 and the ganglia/sympathetic chain were removed en bloc including the lower half of the left stellate ganglion (C7/T1) which was divided along the anatomic fusion between its upper and lower poles. Postoperative chest X-ray was performed to confirm the absence of significant pneumothorax.

Each EMR was reviewed for initial diagnosis, sentinel and subsequent events, genotype, and indications for LCSD. After LCSD, the records were reviewed for follow-up data, complications (short and long-term) and events post-procedure. All patients were genotyped for mutations in the LQTS-associated genes by commercial genetic testing. Following their comprehensive clinical assessment by a single LQTS specialist (MJA), patients were classified clinically as being at ‘high’, ‘moderate’ or ‘low’ risk for subsequent cardiac events. In terms of this qualitative risk classification, ‘high’ risk patients included those with either i) a history of aborted cardiac arrest (ACA), ii) breakthrough cardiac events (BCEs) such as an appropriate VF-terminating ICD shock or arrhythmic syncope, seizures, or ACA., or iii) asymptomatic post-
pubertal LQT2 women with a QTc ≥ 500 ms. ‘Moderate’ risk patients included those with either i) history of arrhythmic (by documentation or by description) syncope/seizures, ii) asymptomatic with QTc ≥ 500 regardless of age and genotype besides postpubertal LQT2 women, and iii) asymptomatic prepubertal boys or postpubertal women with QTc ≥ 480 ms who are not LQT1. Comparatively ‘low’ risk status was assigned to asymptomatic prepubertal girls and postpubertal men with QTc < 480 ms regardless of genotype.8

Most patients were treated with nadolol or propranolol beta blockers. Nadolol was first line therapy in adults and adolescents while liquid propranolol was considered first line therapy in infants and young children. Patients were deemed “beta blocker intolerant” if they were unable to tolerate either of the preferred beta blockers at the prescribed dose due to side effects, including fatigue, hypotension, bradycardia, lightheadedness, and mood swings. Often, trials with both beta blockers at multiple doses were attempted before designating a patient ‘beta blocker intolerant’. Some patients deemed ‘beta blocker intolerant’ continued to use beta-blockers albeit at a potentially sub-therapeutic dose of < 0.5 mg/kg day (nadolol) or < 2 mg/kg/day (propranolol) being identified as their maximum, acceptably tolerated dose. Four of these patients, who chose denervation therapy because of drug-related side effects that were deemed unacceptable, have chosen LCSD monotherapy and are not on any LQTS-directed medications.

For this analysis, a BCE was defined as either 1) an appropriate VF-terminating ICD shock or 2) arrhythmic syncope, seizures, or aborted cardiac arrest following LCSD. Patients with either an increase in cardiac events post-procedure and those without a decrease in events were considered ‘therapeutic non-responders’, and their genotypes and phenotypes were scrutinized extensively for the purpose of this study.
Statistical analysis was performed using JMP 8.0 statistical software (JMP 8.0®, SAS Institute Inc., Cary, NC, USA) using Student’s t-test for continuous variables and Fisher’s exact test for nominal values in subgroup comparisons. Correction for multiple comparisons was performed using Bonferonni correction. Effect of genotype was calculated using ANOVA analysis of variance. Differences in incidence of cardiac events pre- and post-LCSD were tested using McNemar’s test for matched pairs. A p-value<.05 was considered statistically significant. Cumulative event-free survival was calculated using Kaplan-Meier curves and tested in subgroups by log-rank for trend. For this analysis, time was calculated to the first BCE post-LCSD and data are displayed as cumulative event-free survival.

Results
Between November 2005 and December 2010, 54 patients with LQTS underwent videoscopic LCSD at Mayo Clinic and were enrolled in our current study; however 2 patients were lost to follow-up and were excluded from further analyses. Demographics of this study cohort are summarized in Table 1 (first column) with a flow-chart showing the different subgroups in Figure 1. There were 24 males (46%), average age at diagnosis was 10.0 ± 10 years and mean baseline QTc before LCSD procedure was 528 ± 74 ms. Thirty-three patients (63%) underwent LCSD as primary prevention whereas the remaining 19 patients (37%) underwent LCSD as secondary prevention. Sixty-three percent of patients were considered at ‘high risk’ for a potentially lethal arrhythmia. The main clinical indications for LCSD were beta blocker intolerance (33%), assessment of severe/high risk LQTS (25%), a BCE while on medication (19%), or patients in whom additional protection was felt to be necessary (23%). The average age at surgery was 14.1 ± 10 years and the mean follow-up post-LCSD was 3.6 ± 1.3 years.
(range 2 – 6.3 years). Ninety-two percent of patients were genotype positive for 1 or more mutations in the 3 canonical LQTS-causing genes: \textit{KCNQ1} (LQT1), \textit{KCNH2} (LQT2), or \textit{SCN5A} (LQT3), with LQT1 as the most common genotype (43%).

Overall, out of 52 patients undergoing LCSD, 12 patients (23%) have experienced ≥1 BCE post-LCSD so far. Compared to 34 out of 52 patients who had cardiac events pre-LCSD, this shows a significant reduction of patients with cardiac events post-procedure (p<0.001). Of the 34 patients that had cardiac events pre-LCSD, 5 patients (15%) have not experienced any discernible reduction in cardiac events post-LCSD. Conversely, among the 29 previously symptomatic patients with a reduction of cardiac events post-LCSD, 79% of them have had no BCEs so far (Figure 2). The mean time to first BCE was 1.7 ± 1.6 years with the shortest interval from surgery to their first BCE being 4 days and the longest 4.4 years.

**Primary versus secondary prevention**

Looking at prevention strategies, all BCEs occurred in patients undergoing LCSD for secondary prevention (Table 1; middle columns). Ninety-five percent of these patients (18/19, 95%) were classified clinically as high risk, compared to 15 (45%) high risk patients in the primary prevention subgroup (p<0.001). Patients in the secondary prevention subgroup were also significantly younger at diagnosis, had a significantly higher baseline QTc, were more likely to have an ICD pre-procedure, and were more likely to experience a BCE while on pharmacotherapy prior to their LCSD (Table 1).

**LCSD surgical complications**

Of the 52 patients, there were no intraoperative or postoperative arrhythmias. A small, spontaneously resolving pneumothorax was observed in 3 patients and 4 patients had a transient left eyelid ptosis with resolution by 3 months post-LCSD.
Analysis of breakthrough cardiac events (BCEs)

Twelve patients (23%) experienced ≥ 1 BCE post-LCSD (Table 1). Overall, patients experiencing a BCE had a significantly higher baseline QTc (597 ± 106 vs. 507 ± 45 ms; p = 0.04), were more likely to have an ICD pre-procedure (83% vs. 15% respectively; p<0.001), and were more likely to have received ICD-shocks pre-procedure (100% vs. 22%; p<0.001).

There were no BCEs seen in patients with single mutation LQT1 whereas all 4 patients with neonatally expressed, malignant LQT3 experienced at least one post-LCSD BCE (Figure 3). Importantly, none of the LCSD patients who underwent LCSD for beta blocker intolerance have experienced a BCE so far. After correction for multiple comparisons, specific LQT diagnosis, risk classification and indication were still significantly different between patients with and without BCE post-LCSD (p<0.05).

Beta blocker intolerance

Overall, 17 patients (33%; 14 male) underwent LCSD for beta blocker intolerance as their primary indication. This included patients who either experienced too many side effects from their medication or were non-compliant with their prescriptions. Compared to the patients who underwent LCSD for another indication, patients designated as beta blocker intolerant were significantly older at diagnosis (15.6 ± 8 vs. 7.3 ± 9 years; p=0.001), older at LCSD (20.7 ± 8 vs. 11.1 ± 9 years; p<0.001), and had lower QTc pre-LCSD (492.5 ± 32 vs. 540.6 ± 13 ms; p=0.003, data not shown).

Only 4 of these 17 patients were classified clinically as high risk and the remainder (13/17) low risk, while for the other 35 patients, 29 were considered high risk (p<0.001). While 6 of these 17 beta blocker intolerant patients (36%) had experienced one or more cardiac events pre-LCSD, none have experienced a BCE so far (Figure 4). In contrast, of the other 35 patients,
28 had cardiac events pre-LCSD, and 12 have experienced a BCE (Figure 4; p<0.05).

Of the 17 patients with beta blocker intolerance, 12 have been able to decrease their beta blocker dose post-LCSD to a more tolerable dosage (albeit likely insufficiently therapeutic by itself, < 0.5 mg/kg/day nadolol or < 2 mg/kg/day propranolol), and 4 have elected to rely on LCSD as monotherapy. One patient did not change the beta blocker dose, however it was already prescribed at a suboptimal dose as the full dose was tolerated poorly.

Event-free survival

Event-free survival from BCEs for the complete cohort is shown in Figure 5A. Overall, for those with ≥ 5 years of available follow-up, approximately 60% have experienced 1 BCE. Looking at the different indications, patients with a recent cardiac event pre-LCSD or severe/high risk LQTS are most likely to experience a breakthrough post-LCSD (Figure 5B; p=0.001). As discussed previously, patients with beta blocker intolerance did not experience any BCEs post-LCSD (Figure 5B). When grouping patients based on the number of cardiac events pre-LCSD (0, 1-5, 6-10 or >10 events), we see that patients with >10 events pre-LCSD do significantly worse post-LCSD compared to patients in the other subgroups (p<0.001; Figure 5C).

Phenotype of therapeutic non-responders/denervation failures

Of the 12 patients with ≥ 1 BCE post-LCSD, 5 patients had no measureable attenuation in LQTS-triggered cardiac events and were deemed ‘therapeutic non-responders’. The phenotypic characteristics of these patients are summarized in Table 2. Four of the five patients were male. Three of the cases had mutations in SCN5A (LQT3), while the other two had multiple mutations in KCNQ1 (without deafness). All 5 denervation non-responders had phenotypically extreme LQTS with a mean QTc of 691 ms (range 600 – 730 ms), and all five were diagnosed with LQTS as infants. Each of these patients underwent LCSD as secondary prevention and were classified
as high risk before the procedure. Two patients (Cases 2 and 5) have had an additional right cardiac sympathetic denervation (RCSD) performed in an attempt to provide sufficient protection to avoid/delay cardiac transplantation. A more detailed description of each patient categorized as ‘non-responder’ can be found in Supplemental File 1.

Discussion

The role of the autonomic nervous system, ventricular arrhythmogenesis, and concordantly LCSD’s antifibrillatory effect have been well described.\textsuperscript{9-11} Previous studies on groups of patients undergoing LCSD have shown it is a safe and effective treatment option to reduce life-threatening ventricular arrhythmias in patients with heritable channelopathies\textsuperscript{4,6,12} and possibly even hypertrophic cardiomyopathy.\textsuperscript{13,14} Furthermore, about 30% of denervated LQTS patients had a $\geq 30$ ms reduction in their QTc post-LCSD in one series.\textsuperscript{6}

In their first series of 85 patients (73 female), Schwartz \textit{et al.} reported a significant decrease in cardiac event rates from 99\% to 45\% ($p < 0.0001$) and 5-year survival rate of 94\%.\textsuperscript{12} In their follow-up study of 147 patients with LQTS, an approximate 90\% reduction in cardiac event rates was observed.\textsuperscript{6} In our initial experience in 20 patients with a heritable channelopathy (mostly LQTS), there was a reduction of cardiac events in 9/12 patients who received therapy because of secondary prevention, while none of the patients undergoing LCSD for primary prevention had an event post-procedure.\textsuperscript{4}

Overall, our current data showed similar post-LCSD success with 85\% of patients experiencing a reduction of cardiac events post-LCSD (Figure 2). However, while all these papers focus on the overall success of LCSD, the phenotype of patients who experience breakthrough cardiac events has not been examined. We therefore set out to evaluate the phenotype of those patients experiencing post-LCSD breakthroughs as well as evaluate LCSD as
an alternative treatment option for patients with beta blocker intolerance. Here, 12/52 patients have experienced at least one breakthrough cardiac event (BCE) post-LCSD and 5 patients (~15%) had no discernible attenuation in LQTS-triggered events following denervation (‘non-responders’).

Our analysis showed that patients who experienced a BCE had a significantly higher baseline QTc, were more likely to have an ICD pre-procedure, and were more likely to have received ICD-shocks pre-procedure compared to patients without a breakthrough event. As these comparisons already indicate, all of these patients were classified as “high risk” before the procedure whereas less than 60% of the heretofore non-breakthrough patients were considered “high risk”. Further, patients receiving denervation therapy as secondary prevention were more likely to have a BCE compared to patients having the procedure done for primary prevention (Table 1) demonstrating that the highly arrhythmogenic phenotype of patients with extreme cases of LQTS cannot be eliminated by LCSD alone.

In our study, none of the type 1 LQTS patients (i.e. patients with single mutations in KCNQ1) had a BCE while all 4 of the type 3 LQTS patients had a post-denervation BCE (Figure 3). Although small in numbers, these results might be explained by the different pathogenic processes in patients with LQT1 and LQT3 and mirror the clinical results observed regarding the differential efficacy of beta blockers. Physiologically, the β-adrenergic effect of the sympathetic nervous system on the heart is propagated primarily through activation of the delayed rectifier potassium channels (IKs-channels). Mutations in IKs channels, such as the Kv7.1 potassium channel in patients with LQT1, impair QT shortening in response to a heart rate increase with increased sympathetic activity leading to a propensity of cardiac events during for example exercise.
LQT3 is characterized by mutations in the SCN5A-encoded alpha subunit of the cardiac Nav1.5 sodium channel, and these patients do not typically have events during exercise, but during rest. Furthermore, the poorer results in LQT3 patients might be explained partially by the studies into the efficacy of beta blockers in LQTS. Exerting their activity on blocking beta-receptors, potassium currents and sympathetic activity, various clinical studies have shown beta blockers to be far more effective in patients with LQT1 compared to LQT3, suggesting that pro-arrhythmic triggers in LQT3 might lie outside the sympathetic chain. However, in contrast to our observations, all non-responders had their cardiac event in the first year of life emphasizing the severity of their disease and propensity to be a non-responder to any therapy.

Interestingly, of the 17 patients who underwent LCSD for beta blocker intolerance, none have thus far experienced a BCE. Furthermore, most of these patients have decreased their beta blocker dosage or even discontinued its use. This data shows prophylactic LCSD may provide an acceptable, quality of life improving alternative to an ICD in these patients thereby providing sufficient LQTS protection without the intolerable side-effects from their beta blockers. However, one must be very prudent in patient selection and LCSD should certainly not be viewed as curative or an ICD-alternative in high risk patients. More data and longer follow-up is needed before LCSD could be considered as an alternative to beta blocker therapy in the appropriately selected low-to-moderate risk patient.

Underscoring the evidence that LCSD cannot and must not be viewed as curative, five patients (10%) were ‘therapeutic non-responders’ or ‘denervation failures’. However, their
expressed LQTS phenotypes were clearly extreme. Four of the 5 were diagnosed during the first week of life and all exhibited extreme QT prolongation. Whether or not the addition of right sided cardiac denervation will help achieve adequate arrhythmia suppression in those patients with extreme LQTS expressivity refractory to pharmacotherapy and LCSD will require further investigation.

Limitations

Inherent to the nature of retrospective study, our current study has some limitations. First of all, due to the nature of Mayo Clinic as a tertiary referral center, ICD interrogations are not universally available. Therefore, data on the effect of beta-blockers (pre- and post procedure) or effect of LCSD on mitigation of adrenergic surges or efficacy of sympathetic blockade using the ICD-data was not available. A temporary ganglion block pre-LCSD to test these effects was not performed in our patients. Lastly, while in our study all 4 patients with LQT3 showed poor response to LCSD, the small number of patients in this subset does not provide sufficient evidence to suggest that there is no role for denervation therapy in LQT3. Future studies on a larger cohort of patients with LQT3 patients with additional follow-up should be able to demonstrate whether there is LQT3-specific inferiority to denervation’s antifibrillatory effect.

Conclusions

LCSD is an important therapeutic option for patients with LQTS. In our cohort akin to previous observations, a reduction in cardiac events was achieved in 85% of patients. Analysis of patients who have had breakthrough cardiac events suggests that LCSD must not be viewed as curative or as an ICD-alternative for high risk patients. Although a marked reduction in cardiac events is usually seen following LCSD from an overall perspective, nearly 50% of high-risk LQTS patients have experienced at least one post-LCSD breakthrough cardiac event and patients
with extremely malignant LQTS might not be responsive to left sided denervation therapy. Among appropriately risk stratified patients, a prophylactic LCSD, rather than a prophylactic ICD, may represent a robust therapeutic option for patients with unacceptable beta blocker-related side effects.

**Conflict of Interest Disclosures:** MJA is a consultant for Transgenomic (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. MJA is also a consultant for Boston Scientific Corporation, Medtronic, and St. Jude Medical Inc. However, none of these entities provided financial support for this study. The other authors have no conflicts of interest to disclose.

**References:**


Table 1: Demographics of study cohort and subgroup comparisons

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<td>Male/female</td>
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<td>505 ± 44</td>
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<td>507 ± 45</td>
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<td>3 (9)</td>
<td>13 (68)</td>
<td>&lt;0.001</td>
<td>6 (15)</td>
<td>10 (83)</td>
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<td>20 (61)</td>
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<td>16 (48)</td>
<td>9 (47)</td>
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<td>High risk n(%)</td>
<td>33 (63)</td>
<td>15 (45)</td>
<td>18 (95)</td>
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<td>21 (52.5)</td>
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<td>13 (40)</td>
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<td>Age at surgery (yrs)</td>
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<td>15.6 ± 9</td>
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<td>12 (23)</td>
<td>0 (0)</td>
<td>12 (63)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

BCE – breakthrough cardiac event
**Table 2: Phenotype of LCSD ‘Non-Responders’**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Genotype</th>
<th>Mutation(s)</th>
<th>Age at Dx (yrs)</th>
<th>Family History</th>
<th>QTc (ms)</th>
<th>Age at LCSD (yrs)</th>
<th>Indication for LCSD</th>
<th>Type of Prevention</th>
<th>Risk Class</th>
<th># Events before LCSD</th>
<th># Events after LCSD</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Multiple LQT1</td>
<td>KCNQ1 R174C, KCNQ1 R174C*</td>
<td>Birth</td>
<td>None</td>
<td>730</td>
<td>2.1</td>
<td>Severe LQTS</td>
<td>Secondary</td>
<td>High</td>
<td>&gt;10</td>
<td>10</td>
<td>Homozygous KCNQ1 but without deafness. RCSD advised but family declined. Patient died after multiple episodes of VF and asystole</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Multiple LQT1</td>
<td>KCNQ1 L191fs90, KCNQ1 V524G</td>
<td>1 LQTS/SCD</td>
<td>600</td>
<td>14.1</td>
<td>Severe LQTS with recent BCE</td>
<td>Secondary</td>
<td>High</td>
<td>5</td>
<td>2</td>
<td>RCSD performed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>LQT3</td>
<td>SCN5A F1473C</td>
<td>Birth</td>
<td>None</td>
<td>687</td>
<td>0.3</td>
<td>Severe LQTS</td>
<td>Secondary</td>
<td>High</td>
<td>2</td>
<td>&gt;10</td>
<td>Extremely malignant arrhythmias; ~ 90 ICD shocks since LCSD; RCSD offered, family declined</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>LQT3</td>
<td>SCN5A I397F</td>
<td>Birth</td>
<td>Unknown</td>
<td>600</td>
<td>3.2</td>
<td>Severe LQTS with recent BCE (cardiac arrest)</td>
<td>Secondary</td>
<td>High</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>RCSD advised, family declined</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>LQT3</td>
<td>SCN5A R1623Q</td>
<td>Birth</td>
<td>None</td>
<td>700</td>
<td>16.2</td>
<td>Severe LQTS</td>
<td>Secondary</td>
<td>High</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>RCSD performed, patient later transplanted elsewhere</td>
</tr>
</tbody>
</table>
Figure Legends:

Figure 1: Flow-chart of study cohort. Flow-chart showing the study cohort and the breakdown of different subgroups analyzed. Of 54 patients undergoing LCSD during the study period, 2 were lost two follow up. The subsets were analyzed by indication (primary versus secondary prevention), beta-blocker intolerance, or occurrence of ≥ 1 BCE post-LCSD.

Figure 2: Number of events pre- and post-LCSD. Diagram showing patients grouped by number of cardiac events pre- and post LCSD. Shading assigned to each of the three groups before LCSD for number events demonstrates the direction shift of number of events post LCSD.

Figure 3: Number of patients with breakthrough events by genotype. Graph demonstrating the breakthrough events by genotype. No breakthroughs were observed in patients with LQT1 while the four patients with LQT3 have each experienced at least one breakthrough event. G-/P+: genotype negative, phenotype positive

Figure 4: Number of patients with breakthrough events by indication of beta blocker intolerance. Graph demonstrating the breakthrough events for patients with or without beta blocker intolerance.

Figure 5: Kaplan-Meier survival curves. Kaplan-Meier survival curves showing cumulative event-free survival for (A) the complete cohort, (B) grouped by indication and (C) grouped by number of events pre-procedure. Overall, about 40% of patients experienced at least one BCE
and previously symptomatic patients, especially those with multiple events pre-procedure, are more likely to experience a BCE following denervation therapy. Each subgroup has the number of patients at risk listed in order of appearance in the figure.
Left Cardiac Sympathetic Denervation in Long QT Syndrome: Analysis of Therapeutic Non-Responders

J. Martijn Bos, Katy M. Bos, Jonathan N. Johnson, Christopher Moir and Michael J. Ackerman

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SUPPLEMENTAL MATERIAL

Description of patients classified as ‘non-responders’

There were two cases with double mutations in KCNQ1 (Case 1 and 2). One patient (Case 1) was homozygous for R174C-KCNQ1 but did not have concomitant deafness. His family history was negative for LQTS or SCD and the family history was negative for consanguinity. Although a dramatic decrease in ICD-shocks was observed initially, he had several VF-storms several months later. A right sided cardiac sympathetic denervation (RCSD), to complete a bilateral sympathectomy, was advised but the family declined. About 14 months after LCSD, he was admitted to the emergency department after having several episodes of symptomatic VT and after 2 periods of asystole, the child expired at age 3 of multiple organ failure. The second patient (Case 2) was a boy diagnosed with compound LQT1 at 1 month of age with an L191fs/90 (maternal) and V524G (paternal) KCNQ1-mutation without concomitant deafness. Both parents are asymptomatic with borderline QTc and he has two brothers that are asymptomatic, one heterozygous for the frameshift mutation and the other heterozygous for the missense mutation. He has one sister who is compound heterozygous for both variants with symptomatic LQTS albeit not as severe as this patient. Our patient received his ICD in 2007 after a breakthrough cardiac event while on nadolol. Following an event-free period of 3 years, he received 5 VF-terminating therapies after which LCSD was performed. Within 6 months however, he received two additional VF-terminating shocks, which led to the decision to perform a RSCD. After 1 event-free year, he recently received a VF-terminating shock while status post both LCSD and RCSD and compliant on high dose nadolol.

The arrhythmic phenotype of Case 3, a now 4 year-old boy, has shown to be extremely malignant. Diagnosed with LQT3 (F1473C-SCN5A; QTc 687 ms) after hospitalization for necrotizing enterocolitis, he underwent LCSD at three months of age after 2 previous ICD shocks. Since his
procedure, he has had hundreds of recorded arrhythmias and over 90 appropriate VF/VT-terminating ICD shocks while on high dose mexiletine and propranolol.

**Case 4**, a now 5 year-old boy, presented at birth with 2:1 AV-block with extreme QT-prolongation. He was genotype positive for a I397F mutation in SCN5A (LQT3). He was implanted with a pacemaker and treated with propranolol until he experienced an out-of-hospital cardiac arrest (OHCA) while sleeping at age 7 months. He was defibrillated externally and an ICD was implanted. As the patient is adopted, his family history is largely unknown. After his ICD implantation, he had multiple VF-terminating shocks, after which LCSD was performed. Despite LCSD and beta blocker therapy, he has had multiple breakthrough events, and either RCSD or cardiac transplant are being considered currently.

Lastly, **case 5** is now a 17-year-old woman, diagnosed at birth with LQT3 (R1623Q-SCN5A) and 2:1 AV-block with QTc values ranging between 600 – 700 ms for which she received a pacemaker and treatment with a beta blocker. Shortly after dismissal home, she had an OHCA at 6 weeks of age. At age 4, she received an ICD and between age 4 and 16, she had approximately 20 VF-terminating ICD shocks. Because of these breakthrough events and mexiletine-CNS-toxicity (including hallucinations) affecting her quality of life, LCSD was performed. She, however, continued having arrhythmias and drug-induced hallucinations after which RCSD and VF-ablation were performed leading to a decrease in arrhythmia burden. However, because of persistent unwanted side effects from her LQT3-directed pharmacotherapies and concerns of possible recurrences, she received a cardiac transplant elsewhere.