Clinical Investigation and Reports

Left Cardiac Sympathetic Denervation in the Management of High-Risk Patients Affected by the Long-QT Syndrome

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Background—The management of long-QT syndrome (LQTS) patients who continue to have cardiac events (CEs) despite β-blockers is complex. We assessed the long-term efficacy of left cardiac sympathetic denervation (LCSD) in a group of high-risk patients.

Methods and Results—We identified 147 LQTS patients who underwent LCSD. Their QT interval was very prolonged (QTc, 543±65 ms); 99% were symptomatic; 48% had a cardiac arrest; and 75% of those treated with β-blockers remained symptomatic. The average follow-up periods between first CE and LCSD and post-LCSD were 4.6 and 7.8 years, respectively. After LCSD, 46% remained asymptomatic. Syncope occurred in 31%, aborted cardiac arrest in 16%, and sudden death in 7%. The mean yearly number of CEs per patient dropped by 91% (P<0.001). Among 74 patients with only syncope before LCSD, all types of CEs decreased significantly as in the entire group, and a post-LCSD QTc <500 ms predicted very low risk. The percentage of patients with >5 CEs declined from 55% to 8% (P<0.001). In 5 patients with preoperative implantable defibrillator and multiple discharges, the post-LCSD count of shocks decreased by 95% (P=0.02) from a median number of 25 to 0 per patient. Among 51 genotyped patients, LCSD appeared more effective in LQT1 and LQT3 patients.

Conclusions—LCSD is associated with a significant reduction in the incidence of aborted cardiac arrest and syncope in high-risk LQTS patients when compared with pre-LCSD events. However, LCSD is not entirely effective in preventing cardiac events including sudden cardiac death during long-term follow-up. LCSD should be considered in patients with recurrent syncope despite β-blockade and in patients who experience arrhythmia storms with an implanted defibrillator. (Circulation. 2004;109:1826-1833.)

Key Words: death, sudden ■ long-QT syndrome ■ nervous system, sympathetic ■ genetics

Whenever a life-threatening arrhythmogenic disorder manifests itself in the young, management is complex. This is the case for the long-QT syndrome (LQTS).1 Evidence for a major role of the sympathetic nervous system in triggering cardiac events in most LQTS patients2–4 provided the rationale for antiadrenergic interventions. β-Blockers are indeed very effective, but ~25% of LQTS patients continue to have arrhythmic recurrences despite therapy.3,5 Although an implantable cardioverter-defibrillator (ICD) is now indicated for patients who suffer an aborted cardiac arrest (ACA),1,5,6 more controversial is the management of those who continue to have syncope and the prevention of the tachyarrhythmias that trigger shocks in those with an ICD. The arrhythmogenic potential of the quantitatively dominant left stellate ganglion7 and the antifibrillatory effect of left stellactomy8 have contributed to the rationale for assessing the therapeutic value of left cardiac sympathetic denervation (LCSD) in high-risk LQTS patients. After the first intervention in 1970,9 LCSD was used in the United States and Europe. Worldwide experience with LCSD in 85 LQTS patients was reported in 1991.10 Now, 13 years later, we thought it appropriate to review the existing data on 162 patients who underwent left sympathectomy because this large population and the long follow-up permit a more definitive assessment of the role of LCSD in the management of high-risk LQTS patients.

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1826
**Surgical Procedures**

The interventions were performed over a 32-year period (1970 to 2002) in several institutions and countries. Differences in surgical techniques exist and have different implications for outcome. LCSD, also referred to as left cervicothoracic sympathectomy or high thoracic left sympathectomy, involves ablation of the lower half of the left stellate ganglion, together with the thoracic ganglia T2 to T4. It provides adequate cardiac denervation with no or minimal Horner’s syndrome because most of the sympathetic fibers directed to the ocular region usually cross the upper portion of the left stellate ganglion and thus are spared. A modest lowering of the left eyelid often appears transiently after surgery and seldom persists. The actual time for surgery is 35 to 40 minutes. This technique was first used in Rochester (NY) and subsequently by the Milan-Pavia group in Italy, and it involves a supraclavicular and retropleural approach without opening the chest. It is the preferred surgical approach. A technique that should be abandoned is left stellectomy. It ablates only the left stellate ganglion, providing only partial cardiac denervation, and produces Horner’s syndrome. In contrast, left stellectomy in animals provides complete cardiac sympathetic denervation; hence, experimental findings with left stellectomy predict the effects of LCSD in humans.7

**Study Population**

We identified 162 LQTS patients who underwent LCSD between 1970 and 2002. Among them, 15 underwent left stellectomy that we regarded as inadequate denervation and therefore insufficient therapy. Accordingly, while reporting outcome in this subgroup, we focused the analysis on the 147 patients who underwent LCSD. Most patients (101, 69%) were female. Congenital deafness was present in 13 patients (9%). The study population includes the vast majority of LQTS patients treated with LCSD worldwide. Most surgeries were performed by the Milan-Pavia group (n=66) and by the Rochester group (n=16), whereas variable numbers of patients were operated on elsewhere (United Kingdom, Finland, South Africa, China, Belgium, and other centers in the United States). Also included are the 10 patients previously reported by Bhandari et al.13 Follow-up data were obtained from the Pavia center, from the LQTS International Prospective Registry, and through other means, including direct contact with primary physicians. The diagnosis of LQTS was made clinically on the basis of symptoms, QTc interval, and family history.14

Follow-up information for the 137 patients who were still alive at last contact was updated in 2000 to 2003 for 104 patients (76%), in 1998 to 1999 for 9 (7%) patients, and before 1998 for the remaining 24 patients (17%).

**Statistical Analysis**

The 2 main objectives were the quantification of the effect of LCSD on the rate of cardiac events and on survival free of cardiac events. Data were computed as mean and SD for continuous variables; when the distribution was skewed, median and interquartile range (IQR) were reported. Number of events for a given patient >25 was counted as 25.

To assess the effect of LCSD on the rate of events, negative binomial regression was used while controlling for sex, age at surgery (<15 or ≥15 years), and pre-LCSD QTc. Huber White robust SEs were computed to account for intrapatient correlation over time. The incidence rate ratio was reported, together with its 95% CI, to measure the impact of LCSD on event counts over time. Rates of both any event (syncope, ACA, or sudden death (SD)) and ACA/SD were considered end points. Sensitivity analyses in which models were fitted on a matched period cohort and after the sentinel event was dropped gave similar results (data not shown).

Postoperative event-free survival was described by Kaplan-Meier cumulative estimates. Time to first event was considered for both any event and ACA/SD. The prognostic roles of preoperative QTc (<500 or ≥500 ms), change in QTc <40 or ≥40 ms, and QTc <500 or ≥500 ms within 6 months from LCSD were evaluated by a Cox model. Hazard ratio (HR) and its 95% CI were computed while controlling for age at surgery, sex, and the presence of preoperative ACA. Mean annual event rates (and 95% CI) before and after LCSD were determined. Association of selected risk factors and events over the post-LCSD follow-up was evaluated by negative binomial regression. Stata 7 (Stata Corp) was used for computation. Two-sided values of P<0.05 were considered statistically significant.

**Results**

Table 1 shows the baseline characteristics of the 147 patients who underwent LCSD. Their follow-up before and after surgery lasted 4.6 and 7.8 years, respectively.

**Clinical History Before LCSD**

Cardiac events (syncope and ACA) occurred before surgery in 145 patients (99%). Two patients, asymptomatic before surgery, refused β-blocker therapy despite multiple LQTS deaths in their family. A median of 6 events per patient (IQR, 3 to 11) was observed from onset of symptoms to surgery, corresponding to a mean yearly rate of 1.32 events per patient (95% CI, 1.25 to 1.40).

More than 5 cardiac events occurred in 77 of 141 patients (55%) with a known number of events, and at least 1 ACA occurred in 71 of 147 (48%). Syncope only occurred in 74 patients (50%), all with a known number of events. Onset of symptoms occurred in childhood (<8 years of age) in 50%. Age at surgery was <15 years in 61 patients (41%). Male patients became symptomatic earlier than female patients [5 years (IQR, 2 to 8 years) versus 12 years (IQR, 5 to 22 years); P<0.001] and underwent surgery earlier [age at LCSD, 10 years (IQR, 6 to 16 years) versus 22 years (IQR, 13 to 28 years); P<0.001].

Therapy before surgery was known in 142 patients (97%). β-Blockers were used in 121 patients (85%), 2 received different treatments, and 19 were still untreated. Of these, 12 (63%) could not tolerate β-blockers because of asthma or side effects. Among patients receiving β-blockers, 91 (75%) had suffered recurrences of cardiac events despite therapy.

In 21 patients, a pacemaker had been implanted before or at the time of surgery, usually for sinus bradycardia and to allow full-dose β-blockade. The 12 patients who received a pacemaker before LCSD continued with recurrences of cardiac events.

An ICD was implanted in 4 patients at the time of surgery for additional protection and in 6 before LCSD. Of these 6 patients, 1 underwent surgery because of intolerance to β-blockers; the remaining 5 had surgery to prevent repetitive

<table>
<thead>
<tr>
<th>TABLE 1. Basal Characteristics of LQTS Patients With LCSD</th>
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<tbody>
<tr>
<td>Female gender, n (%)</td>
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<tr>
<td>Familial history of LQTS, n (%)</td>
</tr>
<tr>
<td>QTc, ms</td>
</tr>
<tr>
<td>Congenital deafness, n (%)</td>
</tr>
<tr>
<td>Median age at first syncope (IQR), y</td>
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<tr>
<td>Median age at surgery (IQR), y</td>
</tr>
<tr>
<td>Median time between first cardiac event and LCSD (IQR), mo</td>
</tr>
<tr>
<td>Median time of follow-up (IQR), mo</td>
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</tbody>
</table>
discharges from the device. In these 5 patients, a mean yearly rate of 29.3 shocks per patient (95% CI, 25.4 to 33.6) had occurred with a median of 25 shocks per patient (IQR, 3 to 50).

Clinical History After LCSD

Morbidity/Mortality

After LCSD, 67 patients (46%) remained totally asymptomatic. Symptoms continued in 80 patients (54%). Syncope only occurred in 46 (31%), ACA occurred in 24 (16%), and 10 (6.8%) died suddenly. Of the 46 patients whose recurrences were limited to syncope, 26 (56%) had only 1 event during follow-up; thus, 93 patients (63%) during the entire follow-up period either remained asymptomatic or suffered a single syncope. Among the 34 patients (23%) with ACA/SD after surgery, 22 (65%) had experienced ACA before LCSD.

The first post-LCSD event was syncope in 64 patients, ACA in 13, and SD in 3 (2%). These 80 patients experienced the first event at a median of 16 months (IQR, 6 to 48 months) after LCSD; 34 patients had an ACA/SD 25 months (IQR, 6 to 82 months) after surgery; and 10 patients died suddenly after 54 months (IQR, 24 to 82 months).

Five-year cumulative event-free survival was 45% (95% CI, 36 to 53), 82% (95% CI, 74 to 87), and 95% (95% CI, 89 to 98) for any event, ACA/SD, and SD, respectively. Figure 1A highlights the 2-, 5-, and 10-year cumulative survival.

Among the 74 patients with preoperative syncope only, 41 experienced an event during follow-up, 12 had an ACA/SD, and 5 died suddenly, with a 5-year cumulative event-free survival of 43% (95% CI, 30 to 55), 89% (95% CI, 77 to 94), and 97% (95% CI, 89 to 99), respectively. Figure 1B highlights their 2-, 5-, and 10-year cumulative event-free survival and that of patients with preoperative ACA and shows a lower probability of ACA in patients with preoperative syncope (P=0.06).

Number of Events

Table 2 summarizes the effect of LCSD in reducing the count of events during follow-up when age at surgery, sex, and pre-LCSD QTc are accounted for. The mean yearly rate of events per patient dropped by 91%, from 1.32 to 0.19. Similarly, the rate of life-threatening cardiac events declined by 56%, from 0.13 (ACA before LCSD) to 0.06 (ACA/SD after LCSD) events. Among the 74 patients with only syncope before surgery, the rate of any event decreased by 91%; however, ACA/SD still occurred after surgery, with a mean yearly rate of 0.05% per patient (95% CI, 0.03 to 0.07).
The number of patients with >5 events decreased from 77 (55%) to 11 (8%, P<0.001).

In the 5 patients with preoperative ICD and multiple discharges, the post-LCSD rate of shocks dropped by 95% (P=0.02) to a rate of 3.3 shocks per person per year (95% CI, 2.6 to 4.2) with a median rate of 0 shocks per patient (IQR, 0 to 10).

Of the 17 patients who did not take β-blockers after surgery, 14 (82%) remained completely asymptomatic. Their QTc shortened by 75 ms, from 551 ± 65 to 476 ± 41 ms.

The potential confounding role of β-blockers was assessed in 78 patients from the LQTS Registry who were on β-blocker therapy for matched periods of time before and after LCSD (Figure 2). Their mean cardiac event rate per month decreased after LCSD by 78%, from 0.32 to 0.07 (P<0.001). Their number of ACAs decreased by 59%, from 22 to 8 ACA plus 1 SD (P<0.004).

### QT interval and LCSD

For 132 patients (90%), baseline ECG before surgery was available. The mean QTc in lead II was 543 ± 65 ms. Surprisingly for this highly symptomatic group, 5 patients (4%) had a normal QTc (≤ 440 ms).

The QTc shortened after LCSD (39 ± 54 ms; P<0.001) in the 85 patients with both measures available. However, neither a preoperative value ≥ 500 ms nor a change <40 ms appeared to significantly worsen prognosis in terms of both event-free survival and rate of events. In contrast, the persistence of a QTc ≥ 500 ms within 6 months from surgery was associated with significantly lower cumulative event-free survival rates (Figure 3 and Table 3) and resulted in an unadjusted increase of risk (HR, 2.13; 95% CI, 1.17 to 3.90; P=0.013; and HR, 3.04; 95% CI, 1.16 to 7.93; P=0.023 for any event and for ACA/SD, respectively). After age at surgery, sex, and preoperative ACA are accounted for, this increase in risk was still present (P=0.037) for any event. Similarly, the mean yearly rate of any event or ACA/SD was significantly higher for patients with QTc ≥ 500 ms after LCSD (incidence rate ratio, 3.8 and 13, respectively). Importantly, among patients with syncope only, a post-LCSD QTc <500 ms predicted very low risk (Figure 3).

### Effect of Left Stellectomy

Left stellectomy alone did not appear protective. Among 15 patients with left stellectomy, there were 5 ACA/SD events (33%), including 4 SDs (27%). QTc was not significantly modified by left stellectomy (from 559 ms to 549 ms; P=0.65).

### Genotype and LCSD

Fifty-one patients (35%) were genotyped. There were 18 LQT1, 15 LQT2, 8 LQT3, and 9 JLN patients. One patient had a double-mutation KCNJQ1/HERG.15 Within the limitations of small numbers, the data suggest some differential effect of LCSD within the 4 genotypes (P=0.08). The combined incidence of ACA/SD, presented as events per 100 person-years, appeared higher in JLN (3.3) and LQT2 (2.8) patients compared with LQT1 (1.0) and LQT3 (0.0) patients (Figure 4).

### Discussion

This report provides the largest data set available on LCSD, 1 of the 3 modalities of treatment for LQTS. Although
adequate data exist on the efficacy of β-blockers \(^5\) and 1 recent report is available on the value of the ICD, 16 the only nonanecdotal information on the efficacy of LCSD was presented in 1991. 10

Importantly for the assessment of the present results, the population under study was at particularly high risk for arrhythmic death, as indicated by the number of symptomatic patients (99%), the high percentage (75%) of those with cardiac events despite β-blockers, and the extreme average prolongation of the QT interval (QTc, 543 ± 65 ms). The last value, which reflects a major arrhythmogenic substrate, 17 should be compared with the mean QTc (QTc, 510 ± 60 ms) of the largest population in which the effect of β-blockers was analyzed. 5

The main findings were that LCSD significantly reduced the frequency and occurrence of both syncope and cardiac arrest; that among patients with only syncope before surgery, the 5-year postoperative cumulative probability of ACA or SD was 11% and actual survival at 5 years was 97%; and that the 5-year survival for the entire group, including preoperative ACA, was 95%. In addition, LCSD was associated with significant shortening of the QTc.

These findings, with the long follow-up in this large high-risk population, provide useful information for management of LQTS patients. They are especially relevant for young patients, for those who continue to have syncope despite β-blocker therapy, and for those who have indications for an ICD implant.

**Rationale and Mechanism of Action of LCSD**

The rationale for the use of LCSD in LQTS has multiple origins. The pioneering studies by Yanowitz et al 18 called attention to the differential effects of right and left stellectomy on ventricular repolarization. This was followed by the early recognition 2, 9 of a ‘triggering role’ for the sympathetic nervous system 4 and by evidence for multiple mechanisms underlying the antiarrhythmic and antifibrillatory action of LCSD. 7 This is due largely to the electrophysiological consequences of reduced release of norepinephrine at the ventricular level and includes prevention/suppression of early afterdepolarizations and of reentrant mechanisms. 19 Recent experimental studies confirmed the highly specific arrhythmogenic potential of left-sided cardiac sympathetic...
TABLE 3. Prognostic Factors for Event-Free Survival After LCSD

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Any event</th>
<th>ACA/SCD</th>
<th>Post-LCSD QTc</th>
<th>Post-LCSD QTc</th>
<th>Post-LCSD QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>n</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>19.7</td>
<td>0.75</td>
<td>0.47</td>
<td>0.046</td>
<td>2.92</td>
<td>0.45</td>
</tr>
<tr>
<td>10.2</td>
<td>0.47</td>
<td>0.34</td>
<td>0.027</td>
<td>2.92</td>
<td>0.34</td>
</tr>
<tr>
<td>8.6</td>
<td>0.26</td>
<td>0.18</td>
<td>0.001</td>
<td>2.59</td>
<td>0.46</td>
</tr>
<tr>
<td>7.4</td>
<td>0.36</td>
<td>0.23</td>
<td>0.006</td>
<td>2.71</td>
<td>0.37</td>
</tr>
<tr>
<td>6.3</td>
<td>0.34</td>
<td>0.21</td>
<td>0.017</td>
<td>2.57</td>
<td>0.34</td>
</tr>
<tr>
<td>5.0</td>
<td>0.30</td>
<td>0.17</td>
<td>0.003</td>
<td>2.71</td>
<td>0.37</td>
</tr>
<tr>
<td>4.3</td>
<td>0.30</td>
<td>0.16</td>
<td>0.002</td>
<td>2.59</td>
<td>0.46</td>
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<tr>
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<tr>
<td>0.9</td>
<td>0.30</td>
<td>0.17</td>
<td>0.003</td>
<td>2.59</td>
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<td>0.16</td>
<td>0.002</td>
<td>2.59</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Incidence rate ratio (IRR) is estimate controlled for age (<15 or ≥15 years), sex, and preoperative ACA.

* Cox model estimate controlled for age at surgery (<15 or ≥15 years), sex, and preoperative ACA.

† Computed over a median follow-up time of 94 months (IQR, 48 to 144 months) after LCSD.

‡ Because of small numbers, HR and incidence rate ratio are not shown.

nerves. Clinically, the only randomized study with LCSD has demonstrated a significant reduction (from 22% to 3.5%) during a 21-month follow-up of SD among high-risk post-myocardial infarction patients. Thus, there is a strong experimental and clinical rationale fostering the expectation that, especially in the setting of augmented sympathetic activity, life-threatening arrhythmias might be prevented or reduced by LCSD.

LCSD and Cardiac Events

LCSD significantly (by 91%) reduced serious cardiac events after we controlled for β-blockers therapy as well as possible. Because patients who suffered cardiac arrest already have an indication for an ICD implant, the most practical implications concern the efficacy of LCSD among those with only syncope before surgery. After LCSD, their 5-year risk was 8% for ACA and 3% for SD; thus, prevention of SD is not complete. The fact that their median count of cardiac events declined from 5 to 1 carries implications in terms of quality of life.

LCSD and the QT Interval

LCSD shortened QTc duration by an average of 39 ms. The patients who continue to have a QTc ≥500 ms 6 months after surgery remain at higher risk for subsequent events, and an ICD implant might be considered. Thus, LCSD seems to act in some patients not only by interfering with the "trigger," represented by sympathetic activation, but also by favorably changing the arrhythmogenic substrate, represented by QT interval duration.

LQTS patients. Thus, there is a strong clinical rationale for LCSD among those with only syncope before surgery. After LCSD, their 5-year risk was 8% for ACA and 3% for SD; thus, prevention of SD is not complete. The fact that their median count of cardiac events declined from 5 to 1 carries implications in terms of quality of life.

Effect of LCSD Across Genotypes

The limited number of genotyped patients allows only a few guarded considerations. In LQT1, the low incidence of lethal events fits with the established relationship between sympathetic activation and arrhythmias. LCSD might be less effective in LQT2. It would be unwise to comment on the absence of cardiac events among the 8 LQT3 patients. Mechanistically, however, it is interesting that 1 feature of LCSD—the antiadrenergic effect obtained without reducing heart rate—might be especially valuable among the LQT3 patients who have disproportionate QT prolongations at low heart rates and appear insufficiently protected by β-blockers.

Study Limitations

This observational study involves retrospective analysis of prospectively accumulated data with variable follow-up. As
with any nonrandomized therapeutic study, potential bias exists in the selection of patients for LCSD therapy. The results of LCSD also depend on the experience of the surgeon who performs the operation.

Clinical Implications
The present data offer a useful tool for the management of high-risk LQTS patients. The long-term protection provided by LCSD is important when dealing with teenagers who are frequently less than optimally compliant with drug therapy. For those with ICDs, LCSD may be useful in reducing the frequency of appropriate ICD shocks. In small infants, LCSD may be a bridge to the ICD.

An important implication of the present findings relates to those who continue to have syncope despite β-blockers. LCSD, even without affording 100% protection from SD, clearly reduces cardiac events. Before a decision is made on the next therapeutic step, these patients and their parents should be informed about the long-term benefits and limitations of both ICDs and LCSD.

Acknowledgments
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References


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