Left Cardiac Sympathetic Denervation in the Therapy of Congenital Long QT Syndrome

A Worldwide Report

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Background. Long QT syndrome (LQTS) is a congenital disorder accompanied by a high incidence of sudden cardiac death. β-Adrenergic blockade is the therapy of choice, and it is successful in 75–80% of patients. For those in whom cardiac events (syncope or cardiac arrest) are not prevented by β-blockade, experimental studies suggest that left cardiac sympathetic denervation (LCSD) may be useful.

Methods and Results. We identified 85 LQTS patients worldwide who underwent LCSD, and we provide here the first large-scale evaluation of its efficacy. The time interval between the first cardiac event and LCSD and the follow-up period after LCSD were similar (5.6±6.1 versus 5.9±5.7 years). The mean age of the patients at surgery was 20±13 years. LCSD was followed by highly significant (p<0.0001) decreases in the number of patients with cardiac events (from 99% to 45%), in the number of cardiac events per patient (from 22±32 to 1±3), and in the number of patients with five or more cardiac events (from 71% to 10%). There were seven sudden deaths (8%), and the 5-year survival rate was 94%. The marked reduction in the incidence of tachyarrhythmic syncope suggests that LCSD has also reduced the risk for sudden death in this high-risk population.

Conclusions. The present findings demonstrate that for LQTS patients who continue with syncope or cardiac arrest despite the use of β-blockers, LCSD is a very effective therapy. (Circulation 1991;84:503–511)

The idiopathic long QT syndrome (LQTS) is an intriguing example of neurally mediated noncoronary sudden cardiac death.1–4 The young age of most affected patients and the high morbidity and mortality in untreated symptomatic patients highlight the need for effective therapies.

The current understanding of the pathogenetic mechanisms of LQTS involves the sympathetic nervous system either as the primary defect (sympathetic imbalance hypothesis)1,3,5 or as the trigger, acting in a setting of cardiac electrical instability likely to be secondary to an intracardiac abnormality possibly involving the potassium conductance.5–7 In either case, the malignant ventricular tachyarrhythmias associated with LQTS can be elicited by sudden increases in sympathetic activity, mostly mediated by the quantitatively dominant left stellate ganglion.1,3,9 β-Blockers have proven effective in preventing syncope in 75–80% of LQTS patients.3,4,9 However, despite full-dose β-blockade, 20–25% of patients continue to have syncopal episodes and remain at high risk for sudden cardiac death. It is for these patients that left cervicothoracic sympathectomy and high thoracic left sympathectomy (HTLS), the two equivalents in humans of left stellactomy in experimental preparations, have been considered.10

From our international prospective study of LQTS11–13 and our ongoing contact with physicians involved in the management of patients with this disorder, we have identified 85 patients worldwide who have been treated with left cardiac sympathetic denervation (LCSD); they are likely to constitute at least 90% of this specific population. The follow-up results of this surgical therapy in these 85 patients with LQTS are the subject of this report.
Methods

Study Population

To the best of our knowledge, LCSD has been performed worldwide in 85 LQTS patients between March 1969 and October 1990. Because of the difficult therapeutic management of LQTS patients who continue to have syncpe despite β-blockade and because of the limited specific surgical expertise, our group is often contacted for information before surgery. This clinical reality and the large participation in the International Prospective Registry suggest that this group of 85 patients is highly representative and probably includes the vast majority of patients who underwent this modality of treatment. The follow-up information has been gathered by us personally and through direct contact with the primary physicians. The most recent follow-up information was obtained in 1989–1990 for 56 patients (66%), in 1986–1988 for 20 patients (23%), and in 1985 or before in the remaining nine patients (11%), including five deceased patients. All 85 patients included in this study had been diagnosed as having LQTS by their primary physicians.

Thirty-nine patients were operated on in the United States, 29 in Italy, eight in the United Kingdom, and the remaining nine in the Federal Republic of Germany, France, Belgium, Switzerland, the Soviet Union, Israel, Australia, and Japan.

Surgical Procedures

The interventions were performed during a period of 21 years (1969–1990) in a number of institutions in the above-mentioned 11 countries, and important differences may exist in the surgical techniques used. Because this can create a terminology problem, the various techniques used and their characteristics will be briefly listed.

Left stellatectomy involves ablation of the left stellate ganglion, which in humans is the fusion of the eighth cervical and the first thoracic ganglion. This procedure produces Horner’s syndrome and provides only limited cardiac denervation in humans.

Left cervicothoracic sympathectomy involves total left stellatectomy and removal of the first four or five thoracic ganglia. This procedure produces an adequate cardiac sympathetic denervation with an associated Horner’s syndrome.

HTLS involves the lower part of the left stellate ganglion and removal of the first four or five thoracic ganglia. This procedure produces an adequate cardiac sympathetic denervation almost never associated with Horner’s syndrome. Of note, Horner’s syndrome results from interruption of the nerve fibers directed to the ocular region that cross the upper portion of the stellate ganglion unless there is significant anatomic variability. With HTLS, these ocular fibers are spared, and Horner’s syndrome is avoided or minimized.

Because of these anatomic and physiological considerations, we recommend HTLS as the most effective form of surgical cardiac sympathetic denervation. Henceforth, for simplicity, we use the acronym LCSD (left cardiac sympathetic denervation) here to indicate the overall group of surgical interventions, with the understanding that the actual surgeries performed and described here include all three types of denervation described above.

Statistical Analysis

Univariate analysis was performed with the use of a Yates’ corrected χ² test. Comparison among variables before and after LCSD were performed whenever appropriate by Student’s paired t tests.14 Because the number of cardiac events and their rates were apparently not normally distributed, the comparisons before and after LCSD were performed by Wilcoxon’s signed rank test.15 Clinical status and therapy before and after LCSD were analyzed by McNemar’s test for dichotomous outcome in matched samples. Nonmatched comparisons (Milan versus elsewhere, patients with and without symptoms after LCSD) were performed by unpaired Student’s t test whenever appropriate and by Mann-Whitney U test for the nonnormal variables. Dichotomous variables were compared by Yates’ corrected χ² test.14 Survivorship analyses were performed with the life-table method as modified by Cutler and Ederer.16 The significance of the differences among survival rates was tested by Mantel’s modified log-rank analysis.17,18 Data are presented throughout the text and tables as mean±SD.

Results

Table 1 includes data for the 85 patients who underwent LCSD. Most patients (73%) were female. Congenital deafness (Jervell and Lange-Nielsen syndrome) was present in nine patients, and 49 had family members with LQTS.

Surgery

The extent of LCSD could not be objectively assessed in all patients. The data reported here are provided by the referring physicians. In 10 patients, only left stellectomy was performed, and four of

| TABLE 1. Baseline Characteristics of Long QT Syndrome Patients With Left Cardiac Sympathetic Denervation |
|---------------------------------|-------------|
| Female gender (%)              | 73          |
| Familial history of LQTS (%)   | 62          |
| Congenital deafness (%)        | 11          |
| Participants in LQTS registry (%) | 71          |
| Age at first syncope (yr)      | 15±13       |
| Age at surgery (yr)            | 20±13       |
| Time between first syncope and LCSD (yr)* | 5.6±6.1 |
| Time of follow-up (yr)*        | 5.9±4.6     |
| LQTS, long QT syndrome; LCSD, left cardiac sympathetic denervation. |

*Time of exposure to events before (from first syncope to surgery) and after LCSD was not significantly different by Student’s paired t test analysis.
these patients subsequently underwent a second and more extensive surgery, that is, removal of three or four thoracic ganglia. Left cervicothoracic sympathectomy and HTLS were reported in 29 and 41 patients, respectively. In two patients, bilateral stellectomy was performed, and in three patients, the extent of surgery was unknown.

The surgical approach used is known for only 51 patients. The supraclavicular extrapleural approach was performed most frequently. No fatalities or significant complications were reported during the actual surgery. Ventricular tachyarrhythmias and long asystolic periods, not requiring specific interventions, occurred during the procedure in a few patients. In one patient, ventricular fibrillation followed the induction of anesthesia and was terminated by cardioversion without interfering with completion of surgery. One early postoperative death occurred in a 3-year-old female patient with suspected postanesthesia hypoxic distress (hypoglycemia, respiratory failure, complete heart block, and asystole).

In two patients, chronic hyperemia of the left eye occurred and responded to topical vasoconstrictors. Horner's syndrome was present in most patients early after the surgery, but almost always it decreased or disappeared later.

Clinical History Before Surgery

Before surgery, all patients except one had a history of syncopal episodes or cardiac arrest (Tables 1 and 2). The incidence of these life-threatening cardiac events was very high, with a mean of 22 episodes per patient, and 71% had five or more cardiac events. Cardiac arrest (at least one) occurred in 60% of the patients (Table 2). The onset of symptoms (syncpe or cardiac arrest) occurred generally in childhood (median, 12 years), although the range was large (range, 1 month to 54 years).

The baseline electrocardiographic features were available in 74 of the 85 patients. The mean QTc was 548±81 msec. Eight patients did not have a prolonged QT interval (QTc<440 msec), whereas their clinical characteristics were similar to the remaining patients. The diagnosis of LQTS had been made by their primary physicians on the basis of stress-induced syncope and a family history of LQTS. These represent two of the major diagnostic criteria for LQTS.3 The actual importance of a precise value of QTc is reduced because of the inherent limitations of this quantitative measurement.19–21

As to the therapeutic management before surgery, 91% of patients were receiving β-blockers, alone or in combination with other drugs (most often diphenylhydantoin and phenobarbital). In four of the eight patients who were not treated with β-blockers, no pharmacological therapy before surgery was reported. Six patients had a pacemaker implanted before surgery, generally for marked sinus bradycardia.

<table>
<thead>
<tr>
<th>Table 2. Clinical Characteristics of Long QT Syndrome Patients Before and After Cardiac Sympathetic Denervation</th>
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<tr>
<td>Variable (n with available data)</td>
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<tr>
<td>Clinical history (%)*</td>
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<tr>
<td>Symptomatic (85, 82)</td>
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<td>Nonfatal cardiac arrest (77, 80)</td>
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<td>Sudden death (85, 82)</td>
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<td>Pharmacological therapy (85, 79) (%)</td>
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<td>None</td>
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<td>Miscellaneous (without β-blockers)</td>
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<td>β-Blockers only</td>
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<td>β-Blockers + other drugs</td>
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<td>Pacemaker (85, 82) (%)</td>
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<tr>
<td>Cardiac events (63, 81)‡</td>
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<td>Count (events/patient)</td>
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<tr>
<td>Rate (events/yr/patient)</td>
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<tr>
<td>Electrocardiographic parameters (74, 69)§</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<td>QT (msec)</td>
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<td>QTc (msec)</td>
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*Clinical status before and after left cardiac sympathetic denervation (LCSD) was analyzed by McNemar's test for dichotomous outcome in matched samples. Nonfatal cardiac arrest and sudden cardiac death were combined for the computation of the difference before and after LCSD.

†Proportions of pharmacological therapies and of pacemaker implantation before and after LCSD were analyzed by McNemar's test for matched samples. Treatment classes were dichotomized as with β-blockers (alone or with other drugs) and without β-blockers (no therapy or miscellaneous).

‡Number of events and event rates were analyzed by Wilcoxon's signed rank paired test among the 62 patients for whom complete information before and after LCSD was available. Numbers reported are the mean±SD of all the values available.

§Comparisons were performed by Student's paired t test.

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Clinical History After Surgery

The mean follow-up after surgery was 5.9±4.6 years (range, 2 months to 21 years). At the last follow-up, 86% of patients were alive, 11% were dead (death due to any cause), and 3% had been lost to follow-up. Among the nine deceased patients, seven died suddenly, one died from a noncardiac cause (neoplasia), and one died from perioperative complications.

After sympatheticectomy, 45 patients remained free of syncope or cardiac arrest, which was a significant change compared with only one patient asymptomatic before surgery. The details of the postsurgical incidence of cardiac events are presented in Tables 2 and 3. Figure 1 shows the effect of LCSD on the incidence of cardiac events. This figure includes the 62 patients for whom precise information was obtained on the number of cardiac events before and after surgery. This group is representative of the entire study population, as indicated by the similar incidence of symptomatic patients after surgery among the 23 for whom detailed information was not available.

Therapy with β-blockers, alone or associated with other drugs, was continued by 84% of patients; different medications not including β-blockers were used in two patients, whereas 13% patients were not prescribed any additional medication. Reasons for continuation of β-blocker therapy are unclear; our own experience suggests that this may simply reflect a “play safe” attitude and the assumption that β-blockade may still contribute to protection. In two patients, an automatic implantable defibrillator was implanted after nonfatal cardiac arrest, and in one of them, it discharged a couple of times. A pacemaker was implanted after surgery in 14 patients, in nine of them because of continuation of syncope. Among the

| TABLE 3. Clinical Characteristics of Long QT Syndrome Patients With Left Cardiac Sympathetic Denervation by Outcome* |
|--------------------------------------------------|--------------------------------------------------|-----------------|
| Baseline (%)                                      | No symptoms (n=45)                               | Symptoms (n=37) |
| Female gender                                    | 69                                               | 78              |
| Family history of LQTS                           | 67                                               | 59              |
| Congenital deafness                              | 11                                               | 11              |
| Left stellatectomy only                          | 9                                                | 16              |
| History before LCSD                              |                                                  |                 |
| Cardiac events (syncope or cardiac arrest) (%)  | 100                                              | 97.0            |
| Age at first syncope (yr)                        | 16±12                                             | 14±14           |
| Events/patient (mean+SD)†                        | 18±29                                             | 27±36           |
| Age at surgery (yr)                              | 22±13                                             | 19±13           |
| Time from first syncope to LCSD (yr)‡           | 5.8±6.4                                           | 5.5±5.8         |
| Events/patient/yr (mean+SD)†                     | 14±54                                             | 9.10            |
| Heart rate (beats/min) (mean+SD)                 | 61±11                                             | 70±22           |
| QT (msec) (mean+SD)                              | 523±77                                            | 538±79          |
| QTc (msec) (mean+SD)                             | 525±78                                            | 566±67          |
| History after LCSD                               |                                                  |                 |
| Cardiac events (syncope, cardiac arrest, or sudden death) (%) | 0                                              | 100             |
| Events/patient (mean+SD)‡                        | ...                                               | 3.6±4.4         |
| Time of follow-up (yr)‡                          | 5.2±4.5                                           | 7.2±4.5         |
| QT (msec) (mean+SD)§                             | 484±72                                            | 532±88          |
| QTc (msec) (mean+SD)§                            | 483±74                                            | 533±87          |

LQTS, long QT syndrome; LCSD, left cardiac sympathetic denervation.

*Follow-up information was not available for three patients. Patients with and without symptoms after LCSD were compared by unpaired Student's t test.

†Number of cardiac events and of event rates were significantly (p<0.0001) reduced after LCSD among asymptomatic and symptomatic patients, as compared by Wilcoxon's signed rank paired test. Number of events and the event rates before LCSD were not significantly different between the two groups, as compared by Mann-Whitney U test.

‡Time of exposure to events before (from first syncope to surgery) and after LCSD (from surgery to last follow-up) was not significantly different, as compared by paired t test analysis within both groups.

§QT interval was significantly reduced after LCSD in asymptomatic patients (p<0.001) but was unchanged among symptomatic patients, as analyzed by paired t test within each group.

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eight patients for whom information after pacemaker implantation is available, four patients were free of symptoms, one patient died suddenly, and three patients still had a few cardiac events. Reintervention for more extensive LCSD was performed in five patients because of recurrence of symptoms; after the second intervention, four of the five patients were asymptomatic.

The electrocardiographic features after surgery are shown in Table 2. QTc became normal after LCSD in seven patients (11.5%).

The survival rate after surgery was 97% at 1 year, 94% at 5 years, and 85% at 10 years (Figure 2). Sudden cardiac death occurred in two patients within 1 year and in the remaining patients at 2, 4, 6, 7, and 8 years after surgery. Among the 10 patients who underwent the less extensive denervation produced by left stellactomy, sudden cardiac death tended to occur more frequently (20% versus 7%) compared with the patients who underwent either left cervicothoracic sympathectomy or HTLS.

When the patients without symptoms after LCSD (n=45) were compared with those with syncope, cardiac arrest, or sudden death after LCSD (n=37), no differences were found in several clinical characteristics (Table 3). On the other hand, one significant difference was found in the duration of ventricular repolarization of the two groups. The QT interval shortened only among the patients who became asymptomatic. Both symptomatic and asymptomatic patients had a significant shortening in QTc after surgery; however, the patients who became asymptomatic after LCSD had a shorter QTc at baseline and also after surgery.

Patients Operated on in Milan

Twenty-five patients (29%) were operated on in Milan, in the same institution, by the same surgeon.

Figure 1. Graphs of incidence of cardiac events before and after left cardiac sympathetic denervation (LCSD) in 62 long QT syndrome (LQTS) patients in whom the exact number of cardiac events (syncope or cardiac arrest) was available. Each line represents one patient and shows on the left of the vertical line (time of LCSD) events occurring from the onset of symptoms to LCSD and on the right of the vertical line events occurring between LCSD and last follow-up. Left panel: Absolute number of cardiac events per patient before and after LCSD. Right panel: Number of cardiac events per year. This represents the adjustment for the time of exposure to symptoms before (from first syncope to surgery) and after LCSD (from surgery to last follow-up). Of note, the incidence of symptoms after LCSD was not significantly different among the 23 patients excluded from this analysis because of the lack of exact information about the number of cardiac events before left cardiac sympathetic denervation.

Figure 2. Plot of effect of left cardiac sympathetic denervation (LCSD) on survival rate in 85 long QT syndrome (LQTS) patients. Mortality is 3% at 1 year, 6% at 5 years, 11% at 7 years, and 15% at 10 years.
number of patients operated on in Milan was 60% (p<0.05) by log-rank Mantel's modified analysis.

LQTS, long QT syndrome.

(U.R.), and by the same anesthesiologist (R.T.) in the years 1973–1990, after diagnosis of LQTS refractory to β-blockade by the same cardiologists (P.J.S. and E.L.). Thus, this represents a uniquely homogeneous group that warranted a specific analysis because, by the nature of this report, this is the only large group in which there is no question of variability in terms of diagnosis and of extent of denervation. With the exception of the first patient operated on in 1973, the first four left thoracic ganglia in all these patients were ablated by the supraclavicular approach, and the fifth ganglion was cauterized.

The clinical characteristics were similar to those of the patients operated on elsewhere. Two significant differences were that the patients operated on in Milan had the first syncopal episode at a younger age (10±9 versus 17±13 years, p<0.01) and were younger at the time of surgery (16±11 versus 23±14 years, p<0.05). No reintervention was necessary in this group, and in three, a pacemaker was implanted because of continuation of syncope.

The number and severity of cardiac events was significantly reduced in Milan and elsewhere. The 5-year survival rate for patients operated on in Milan was 100%, and it was 91% for patients operated on elsewhere (p<0.05) (Figure 3).

Discussion

This report provides the first comprehensive assessment of the therapeutic efficacy of LCSD in the management of the idiopathic long QT syndrome. The patient population includes most of the patients operated on worldwide. These data, collected in a relatively large population and with an adequate follow-up, demonstrate a dramatic reduction in the incidence of major cardiac events after surgery. Of note, 90% of these patients continued to have syncope or cardiac arrest before LCSD despite therapy with β-blockers.

Rationale for LCSD

The first surgical denervations for LQTS in the United States and Europe were performed by Moss's group in 1969-1970 and by Schwartz's group in 1973. The concept behind these interventions was that left sympathecotmy would normalize the prolonged QT interval, thereby reducing the probability of malignant arrhythmias. The actual failure of LCSD to consistently normalize the QT interval decreased interest for this surgical approach. In 1976 and 1977, Schwartz and colleagues demonstrated that left stellateganglion markedly increases ventricular fibrillation threshold and prolongs ventricular refractoriness. In those years, another electrocardiographic characteristic of LQTS, T wave alternans, was reproduced by stimulation of the left stellate ganlion in experimental animals and in humans. These and other findings constituted a strong rationale for the use of LCSD in high-risk states for ventricular fibrillation triggered by sympathetic activation, including LQTS. The antifibrillatory effect of left stellactomy and a widespread acceptance of the "sympathetic imbalance" hypothesis contributed to a resumption of the surgical therapy for LQTS. Nonetheless, it is fair to say that the efficacy of LCSD fits equally well with the sympathetic imbalance hypothesis as with the intracardiac abnormality hypothesis and, therefore, proves only the importance of the sympathetic nervous system in triggering lethal arrhythmias.

Mechanisms of Action

The most likely mechanisms for the protective effect of LCSD are the electrophysiological consequences of a markedly reduced release of norepinephrine in localized areas of the ventricles. Among these actions, LCSD may reduce the occurrence of both early and delayed afterdepolarizations, which are thought to play a potentially important role in LQTS. Indeed, left stellate ganglion stimulation has been reported to induce delayed afterdepolarizations and to increase the amplitude of early afterdepolarizations, possibly because of an α-adrenergic-mediated mechanism. The efficacy of sympathetic denervation in patients who continue to have syncope or cardiac arrest despite full-dose β-blockade points strongly to the importance of an α-adrenergic mechanism in the arrhythmias of LQTS.

The finding of a less prolonged QT interval and QTc after LCSD among the patients who became asymptomatic (Table 3) raises the possibility that both QT and QTc shortening may contribute to the antiarrhythmic efficacy of LCSD. Given the initial difference, the QTc of the asymptomatic patients became definitively closer to the normal values. Thus, this shortening of even moderate magnitude may have favorably modified the electrophysiological parameter involved in arrhythmogenesis. Altogether, these data suggest that LCSD acts both by modifying the substrate and by removing the trigger.
Misconceptions About LCSD

It is often thought that the results of sympathectomy can be predicted by the results of pharmacological blockade of the left stellate ganglion. This reflects the erroneous concept that the appearance of Horner’s syndrome is a marker of an effective stellate ganglion blockade and, therefore, of the cardiac nerves. On the contrary, Horner’s syndrome indicates only the blockade of the fibers that cross the upper part of the stellate ganglion, and it may or may not be accompanied by effective blockade of the fibers innervating the heart.1

The efficacy of LCSD has been questioned on the basis of the lack of normalization of the prolonged QT interval. The data presented here indicate that this normalization occurs in 11.5% of the patients and that complete suppression of the syncopal episodes occurs despite persistence of an abnormal repolarization. The efficacy of sympathectomy must be judged only on the basis of the suppression or continuation of the syncopal episodes.

The same lack of uniform normalization of the QT interval duration has been interpreted as an indication of the nonvalidity of the sympathetic imbalance hypothesis. This interpretation is weakened by the recent finding that delayed sympathetic innervation of the heart induces QT interval prolongation and causes changes in G proteins, involved in the ionic control of channels affecting ventricular repolarization, likely to be irreversible.35 If this occurs as a developmental abnormality in patients affected by LQTS, one would not expect the QT interval to return to normal values after LCSD. Besides, if the prolongation of the QT interval is secondary to insufficient right-sided innervation of the heart, then left sympathectomy would not correct this alteration.

Therapeutic Efficacy

The analysis of the incidence of cardiac events before and after surgery, within the same patients, provides the first large-scale documented evidence that LCSD prevents or reduces the occurrence of life-threatening arrhythmias in patients affected by LQTS. This result is particularly impressive because it was obtained in a group of patients with arrhythmias largely resistant to β-blockade.

The time interval between the first syncope and LCSD is almost identical to that of the follow-up interval after LCSD, a critical factor for a meaningful comparison. The number of patients without symptoms increased from 1% to 55%. The mean number of cardiac events per patient decreased from 22 to one. The number of patients with five or more episodes of syncope or cardiac arrest decreased from 71% to 10%. These figures provide evidence for a dramatic improvement in the quality of life of the patients after LCSD.

In theory, a reduction of events after a given intervention may simply depend on the time factor. Two facts argue strongly against this possibility. The duration of exposure to events before LCSD (from first syncope to surgery) and after LCSD (from surgery to last follow-up contact) was similar between patients symptomatic and asymptomatic after surgery. The age at first syncope and the age at surgery were not significantly different among the two groups, which rules out the possibility of a natural decline in the incidence related to the aging of the patients.

The internal control design of this study does not allow us to evaluate whether LCSD reduces mortality in LQTS. However, because ample evidence indicates that the fatal episodes in these patients depend on the same electrophysiological mechanisms as the nonfatal ones, it is logical to surmise that a reduction in the incidence of syncope or cardiac arrest implies also a reduction in the risk for fatal events. Indeed, the 5-year mortality rate of 6% seems very low for this high-risk population that was largely not protected by β-blockade alone. The only logical comparison, albeit indirect and retrospective, would be with the 5-year mortality rate, from the time of the first syncope, of 35% observed in 126 patients not treated with antiadrenergic interventions.9 That population included a large proportion of patients who would have been protected by β-blockade, which makes it, if anything, at lower risk compared with the population of this study.

To specifically address the question of mortality would require the availability of an adequate number of LQTS patients who continue to have syncope or cardiac arrest despite β-blockade and then to randomize them to either LCSD or to a therapy already found ineffective for them (that is, β-blockers) perhaps in conjunction with cardiac pacing or drugs of unproven efficacy in LQTS. Dealing with the subgroup of patients at highest risk among those affected by an uncommon and often lethal disease, the availability of an effective treatment (that is, LCSD) makes a randomized clinical trial unethical and hardly feasible.

The overall similarity of results obtained with a rigorously controlled and standardized procedure (Milan) and with a more variable technique (elsewhere) indicates that this surgical intervention produces consistent outcomes in a variety of institutions and countries.

The trend toward a greater risk for sudden cardiac death after the incomplete denervation produced by left stellectomy indicates that if sympathectomy is to be maximally effective it must be as complete as possible and involve the first four thoracic ganglia.

Role of Additional Therapies

Most patients continued to receive β-blockers after surgery. Whether the patients should be continued on the regimens despite their incomplete efficacy or slowly withdrawn from such regimens after LCSD is unclear at this time. Despite the encouraging reports on cardiac pacing,36,37 it is not yet known whether this modality of treatment can provide protection in the
absence of adequate antiadrenergic therapy or whether it becomes useful only when \( \beta \)-blockers and LCSD have failed.

**Previous Reports**

Following the description of the first left sympathectomy,\(^{10}\) several reports with a limited follow-up on single patients or on small series\(^{38–54}\) have appeared. None of them had sufficient power to allow meaningful conclusions on the efficacy of LCSD. The largest report involved 10 patients with a mean follow-up of 3 years. In this group, one patient had recurrent cardiac arrest and died; repeated surgery was necessary in three patients; a pacemaker was implanted in three, and an automatic defibrillator in one. After the more extensive surgery, eight patients remained free of symptoms. These 10 patients are, of course, part of the present report, and they constitute 12% of the entire study population.

Our group has observed patients during a 15-year period to accumulate adequate numbers with a sufficiently long follow-up to allow drawing reasonably definite conclusions about the clinical value of LCSD in the management of LQTS. We believe that these data are now available and that they demonstrate that LCSD is highly effective.

**Implications for Management**

The present report has important practical implications because it stresses antiadrenergic interventions as the cornerstone of the therapy for LQTS. \( \beta \)-Adrenergic blockade, with efficacy in approximately 75–80% of LQTS patients, is not questioned, and it remains the therapy of first choice.\(^{1–3,6,9,12,37}\) For the patients who continue to have syncope or cardiac arrest despite \( \beta \)-blockade, this study provides firm evidence that LCSD represents a very effective treatment.

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**References**


KEY WORDS • sudden cardiac death • sympathetic nervous system • QT interval

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