Efficacy of left cardiac sympathectomy in the treatment of patients with the long QT syndrome

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ABSTRACT Ten patients with the long QT syndrome and recurrent syncope and/or cardiac arrest caused by ventricular arrhythmias underwent left stellate (one patient) or left cervicothoracic sympathectomy (nine patients) after failing to respond to high-dose β-blocker therapy. The syndrome was familial in four and idiopathic in six. All patients had a prolonged resting QT interval (548 ± 51 msec, mean ± SD) and corrected QT interval (QTc) (556 ± 43 msec). After sympathectomy the mean QTc shortened significantly from 556 ± 43 to 508 ± 65 msec (p < .05) but the QTc remained abnormal in all but one patient. Over a mean follow-up period of 38.6 ± 19 months, eight patients developed recurrent symptoms that included cardiac arrest in three (one fatal, two nonfatal), syncope in four, and presyncope in six. The addition of β-blockers was ineffective in suppressing the recurrent symptoms. The control of symptoms required more extensive sympathectomy (three patients), chronic atrial pacing (three patients), and implantation of an automatic internal defibrillator (one patient). Only one patient has remained asymptomatic without drug or pacemaker therapy. In conclusion, left cervicothoracic sympathectomy proved inadequate for long-term control of symptoms in most patients with the long QT syndrome. These patients usually required concomitant drugs, more extensive surgery, or long-term cardiac pacing for symptomatic relief.

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THE ASSOCIATION of idiopathic prolongation of the QT interval with recurrent attacks of syncope and cardiac arrest is known as the long QT syndrome.1–6 The mortality rate in untreated patients is thought to be as high as 78%.3,5 Although β-blockers have proved valuable in the long-term management of patients with this syndrome, at least 6% of patients fail to respond to β-blockade.2,3,5

Left cervicothoracic sympathectomy has been reported to be the treatment of choice for patients with this syndrome who do not respond to pharmacologic treatment.7–11 Although the available data suggest that sympathectomy is highly effective in suppressing episodes of syncope and cardiac arrest caused by ventricular tachycardia, long-term follow-up data for patients with the long QT syndrome who have undergone sympathectomy are scanty. In prior reports, changes in the QT interval after sympathectomy were variable and were not predictive of clinical outcome.

This report deals with 10 consecutive patients with the long QT syndrome who underwent sympathectomy over a 6 year period. The study aimed to assess the long-term effects of sympathectomy on changes in the corrected QT interval (QTc), ventricular arrhythmias, and symptoms.

Materials and methods

The study was a retrospective analysis of 10 patients with the long QT syndrome who underwent left cervicothoracic sympathectomy during the years 1977 to 1982 at either the University of California Medical Center, San Francisco (six patients), or Stanford Medical Center (four patients). During this period we evaluated a total of 18 symptomatic patients with a definite diagnosis of the long QT syndrome: eight responded to the β-blockers but 10 required sympathectomy because of a poor response to the β-blockers or severe manifestations of the syndrome. The study population comprised the latter 10 patients. The clinical characteristics of the 10 patients are summarized in table 1. There were nine women and one man, with an age range of 13 to 56 years (30.5 ± 12). The syndrome was familial in four and idiopathic in six. All patients had a history of cardiac arrest (nine patients), syncope (nine patients), or both (eight patients). Polymorphous ventricular tachycardia or fibrillation was documented as the cause of symptoms in each patient. Based on the history, physical examination, electrocardiogram, chest x-ray, two-dimensional echocardiogram (three patients), and cardiac catheterization with coronary angiography (three patients), seven patients had no demonstrable structural heart disease, two had mild systemic hypertension without left ventricular hypertrophy, and one had mitral valve prolapse. Seven
of the 10 patients had also undergone electrophysiologic stimulation studies before sympathectomy; none had inducible sustained ventricular tachycardia or fibrillation although nonsustained polymorphic ventricular tachycardia was induced in four patients. We have previously reported detailed findings on the results of electrophysiologic testing.12

All patients demonstrated prolongation of the resting QT interval (mean 548 ± 51 msec, range 480 to 620) and the QTc (mean 556 ± 43 msec, range 500 to 610). The prolongation of the QT interval was unrelated to drugs, electrolyte abnormalities, myocardial ischemia, or a central nervous system lesion. The upper limit of normal for the QT interval was determined by the frequency distribution table of Simonson et al.13 The QTc interval was obtained by dividing the measured QT interval by the square root of the preceding R-R interval in seconds (Bazett’s formula).14 The upper limit of normal of QTc was defined as 450 msec.

The indications for sympathectomy were the following: seven patients (Nos. 1 to 3, 5 to 7, and 9) underwent surgery because of symptoms refractory to full doses of β-blockers (table 1). Two patients (Nos. 8 and 10) underwent sympathectomy after their first episode of cardiac arrest before an adequate trial of β-blockers. The remaining patient (No. 4) underwent sympathectomy because of severe central nervous system intolerance (fatigue, nightmares, and depression) to propranolol (800 mg/day) and because lower doses of propranolol failed to control symptoms.

A left cervicothoracic sympathectomy was performed via the supraclavicular approach in all patients. The dissection was carried out posteriorly to the transverse process of the lower cervical spine where the stellate ganglion was identified. The dissection was then carried inferiorly to the limits of exposure to identify the upper thoracic sympathetic ganglia. The left stellate ganglion in its entirety and the first three to four thoracic sympathetic ganglia were excised in all but one patient (No. 2), in whom only the left stellate ganglion was resected. Postoperatively, all patients developed a left-sided Horner’s syndrome. No complications were encountered.

All patients were followed by one of the authors or the referring physicians at intervals of 3 to 6 months.

Values are expressed as mean ± 1 SD. The two-tailed t test for paired data was used to compare QTc values before and after surgery in the same patient.

**Results**

The response of QTc to sympathectomy is shown in table 2. The mean QTc shortened significantly from a baseline of 556 ± 43 to 508 ± 65 msec immediately

### Table 1
Clinical characteristics of 10 patients with the long QT syndrome who underwent left cervicothoracic sympathectomy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Syndrome</th>
<th>Presync.</th>
<th>Symptoms syn.</th>
<th>Cardiac arrest</th>
<th>Duration of symptoms (mo)</th>
<th>Therapy (mg/day)</th>
<th>QTc/QTc (msec)</th>
<th>DOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^</td>
<td>58/F</td>
<td>Idio.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
<td>48</td>
<td>Prop. (160)</td>
<td>600/600</td>
<td>3/77</td>
</tr>
<tr>
<td>2</td>
<td>13/F</td>
<td>Fam.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
<td>12</td>
<td>Prop. (160)</td>
<td>520/610</td>
<td>10/78</td>
</tr>
<tr>
<td>3</td>
<td>30/F</td>
<td>Fam.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
<td>12</td>
<td>Prop. (160)</td>
<td>520/610</td>
<td>3/79</td>
</tr>
<tr>
<td>4^</td>
<td>26/F</td>
<td>Idio.</td>
<td>+ + +</td>
<td>+ +</td>
<td>-</td>
<td>10</td>
<td>Prop. (360)</td>
<td>500/540</td>
<td>3/79</td>
</tr>
<tr>
<td>5^</td>
<td>22/M</td>
<td>Fam.</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>3</td>
<td>Prop. (160)</td>
<td>600/550</td>
<td>8/79</td>
</tr>
<tr>
<td>6</td>
<td>25/F</td>
<td>Idio.</td>
<td>+ + +</td>
<td>+ +</td>
<td>+</td>
<td>4</td>
<td>Prop. (240)</td>
<td>520/515</td>
<td>11/80</td>
</tr>
<tr>
<td>7^</td>
<td>34/F</td>
<td>Idio.</td>
<td>+ + +</td>
<td>+ +</td>
<td>+</td>
<td>12</td>
<td>Prop. (160)</td>
<td>620/600</td>
<td>11/81</td>
</tr>
<tr>
<td>8^</td>
<td>33/F</td>
<td>Fam.</td>
<td>+ + +</td>
<td>+ +</td>
<td>+</td>
<td>96</td>
<td>Nad. (360)</td>
<td>480/500</td>
<td>5/82</td>
</tr>
<tr>
<td>9^</td>
<td>30/F</td>
<td>Idio.</td>
<td>+ + +</td>
<td>+ +</td>
<td>+</td>
<td>72</td>
<td>NAD. (360)</td>
<td>600/550</td>
<td>9/82</td>
</tr>
<tr>
<td>10</td>
<td>34/F</td>
<td>Idio.</td>
<td>+ +</td>
<td>-</td>
<td>+</td>
<td>2</td>
<td>520/500</td>
<td>10/82</td>
<td></td>
</tr>
</tbody>
</table>

Idio. = idiopathic; Fam. = familial; Presync. = presyncope; Syn = syncope; Prop = propranolol; Nad = nadolol; DOS = date of left cervicothoracic sympathectomy; HTN = systemic hypertension; MVP = mitral valve prolapse; DPH = diphenylhydantoin; + = 1 episode; ++ = two to five episodes; +++ = more than five episodes.

^ Patients underwent electrophysiologic testing before sympathectomy.

### Table 2
QTc before and after sympathectomy in 10 patients with the long QT syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Preop.</th>
<th>Early postop.</th>
<th>Late postop.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCL</td>
<td>QTc</td>
<td>SCL</td>
</tr>
<tr>
<td>1</td>
<td>1000</td>
<td>600</td>
<td>860</td>
</tr>
<tr>
<td>2</td>
<td>750</td>
<td>600</td>
<td>700</td>
</tr>
<tr>
<td>3</td>
<td>730</td>
<td>610</td>
<td>600</td>
</tr>
<tr>
<td>4</td>
<td>850</td>
<td>540</td>
<td>1000</td>
</tr>
<tr>
<td>5</td>
<td>1200</td>
<td>550</td>
<td>925</td>
</tr>
<tr>
<td>6</td>
<td>1030</td>
<td>515</td>
<td>750</td>
</tr>
<tr>
<td>7</td>
<td>1070</td>
<td>600</td>
<td>1400</td>
</tr>
<tr>
<td>8</td>
<td>1200</td>
<td>550</td>
<td>1000</td>
</tr>
<tr>
<td>9</td>
<td>920</td>
<td>500</td>
<td>900</td>
</tr>
<tr>
<td>10</td>
<td>1080</td>
<td>500</td>
<td>1000</td>
</tr>
</tbody>
</table>

Mean 983 ± 556 913 ± 508^a 1045 ± 513^a

SD ± 167 ± 43 ± 219 ± 65 ± 194 ± 49

Values expressed in milliseconds.

SCL = sinus cycle length.

^p < .05 vs preoperative value.
after surgery (<6 weeks). Although the postoperative mean QTc value was shorter, the QTc interval remained abnormal in all patients except one (No. 4) (430 msec). There was no significant difference in the mean QTc between the early and late postoperative periods (>6 weeks).

After sympathectomy, nine of the 10 patients were initially discharged on no medication. One patient (No. 10) was treated with propranolol (160 mg/day) at the discretion of the referring physician.

The patients have been followed over a period of 17 to 65 months (mean 38.6 ± 19). After a mean symptom-free interval of 15.1 ± 12 months (range 1 to 36) recurrent symptoms developed in eight patients (table 3). Only two patients (Nos. 7 and 8) have remained asymptomatic after a follow-up period of 27 and 22 months, respectively. One of them (No. 8) has been on no drug therapy and the other (No. 7) has been treated with nadolol (240 mg/day) because of frequent (>30/hr) premature ventricular contractions (PVCs) on several 24 hr Holter monitor recordings.

Among the eight symptomatic patients, cardiac arrest recurred in three (30%), syncope in four (40%), and presyncope in six (60%). Cardiac arrest occurred at an interval of 24 (patient 1), 44 (patient 2), and 7 months (patient 10) from the date of surgery and proved fatal in one patient (No. 1). At the time of recurrent cardiac arrest, all three patients were taking maximally tolerated doses of β-blockers. Patient 1 took propranolol (160 mg/day) because of recurrent syncope that occurred 6 months before the fatal cardiac arrest. A 24 hr Holter monitor recording done 3 months before the cardiac arrest in this patient had demonstrated only three isolated PVCs. Patient 2 took nadolol (320 mg) and diphenylhydantoin (300 mg) because of symptoms of frequent syncope and presyncope that had developed 20 months before the cardiac arrest. Patient 10 took propranolol (160 mg/day) since the time of surgery and had been asymptomatic before cardiac arrest. No Holter recordings were available in the latter two patients. Only one of the patients with recurrent cardiac arrest (patient 2) showed evidence of regeneration of left adrenergic nerves (disappearance of Horner's syndrome).

Of the remaining five symptomatic patients, two (patients 4 and 5) developed frequent syncopal and presyncopal episodes after symptom-free intervals of 1 and 6 months, respectively, and three (patients 3, 6, and 9) had frequent presyncopal episodes. The symptoms were identical to those experienced preoperative-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Post-LCTS symptom-free interval (mo)</th>
<th>Recurrent symptoms during follow-up</th>
<th>Final therapy (mg/day)</th>
<th>Total follow-up (mo)</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 Syncope, cardiac arrest</td>
<td>Prop. (160)</td>
<td></td>
<td>24</td>
<td>Sudden death</td>
</tr>
<tr>
<td>2a</td>
<td>9 Syncope, presyncope, cardiac arrest</td>
<td>LCTSb</td>
<td></td>
<td>65</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>3</td>
<td>36 Presyncope</td>
<td>Atrial pacing Prop. (160)</td>
<td></td>
<td>61</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>4a</td>
<td>1 Syncope, presyncope</td>
<td>Repeat LCTS Atrial pacing Prop. (360)</td>
<td></td>
<td>61</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>5a</td>
<td>6 Syncope</td>
<td>Repeat LCTS Aten. (100)</td>
<td></td>
<td>52</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>6</td>
<td>24 Presyncope</td>
<td>Nad. (80)</td>
<td></td>
<td>39</td>
<td>Presyncope</td>
</tr>
<tr>
<td>7</td>
<td>27 None</td>
<td>Nad. (240)c</td>
<td></td>
<td>27</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>8a</td>
<td>22 None</td>
<td>None</td>
<td></td>
<td>22</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>9</td>
<td>1 Presyncope</td>
<td>Atrial pacing Nad. (360)</td>
<td></td>
<td>18</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>10</td>
<td>7 Cardiac arrest</td>
<td>AID</td>
<td></td>
<td>17</td>
<td>Cardiac arrest (nonfatal)</td>
</tr>
</tbody>
</table>

LCTS = left cervicothoracic sympathectomy; Nad. = nadolol; Prop. = propranolol; Aten. = atenolol; AID = automatic internal defibrillator.

*Horner’s syndrome disappeared during the follow-up period.

bInitial surgery was limited to left stellectomy.

cNadolol started because of frequent PVCs on Holter recordings.
ly but could be documented to be secondary to ventricular tachyarrhythmia in only one patient (No. 9). The symptoms were not responsive to the addition of β-blockers in any patient although they became less frequent than before sympathectomy.

In comparing the asymptomatic patients with those who had a recurrence of symptoms, we found no difference in the response of the QTc after surgery or the frequency of PVCs on the postsympathectomy Holter recordings. Among the six symptomatic patients with available Holter recordings, only one patient (No. 9) demonstrated frequent multifocal PVCs, often in pairs and triplets. The other five patients had either no or rare PVCs on numerous 24 hr recordings. One of the two asymptomatic patients (No. 7) also had frequent PVCs on Holter recordings.

Four patients (Nos. 2, 4, 5, and 8) experienced complete resolution of Horner’s syndrome after a mean interval of 16 ± 9 months (range 4 to 24) from the time of surgery. During follow-up the recurrent symptoms developed in three of them. One patient (No. 8), however, continues to be asymptomatic without drug therapy.

**Therapeutic intervention after sympathectomy.** One of the two survivors of cardiac arrest (patient 10) underwent implantation of an automatic internal defibrillator. The other patient (No. 2) underwent both permanent atrial pacemaker insertion and a sympathectomy. The previous surgery in this patient had been limited to removal of the left stellate ganglion with subsequent disappearance of Horner’s syndrome. Both patients have also continued β-blocker therapy. Patient 2 has had no recurrent symptoms since then (22 months) but patient 10 had another episode of syncope 3 months later that responded successfully to one shock delivered from the automatic internal defibrillator.

The control of symptoms in four of the other five symptomatic patients required, in addition to β-blockers, implantation of permanent atrial pacemakers in two (patients 3 and 9) and more extensive left thoracic sympathectomy up to the level of sixth ganglion (via transaxillary approach) in the other two patients (Nos. 4 and 5). One patient (No. 9) showed both relief of symptoms as well as dramatic decrease in both the frequency and complexity of ventricular arrhythmias after long-term atrial pacing (figure 1). This patient had significant sinus bradycardia with resting heart rate ranging from 42 to 55 beats/min. In the other two patients (Nos. 4 and 5) Horner’s syndrome had resolved after an interval of 4 and 16 months, respectively, from the first surgery. One patient (No. 6) continues to have infrequent presyncopal episodes on β-blockers alone.

**Discussion**

Left cervicothoracic sympathectomy was first used successfully in 1970 by Moss and MacDonald in a patient with the long QT syndrome who had symptoms.

**FIGURE 1.** Rhythm strips from patient 9 before and during long-term atrial pacing. The top two strips (simultaneous) were obtained 6 months after sympathectomy with the patient on nadolol (360 mg/day) and show frequent multifocal PVCs and ventricular tachycardia. The QT interval is prolonged to 520 msec. The rhythm in the bottom strip is completely atrial paced at 88 beats/min. Note the absence of PVCs and normalization of the QT interval.
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refractory to medical therapy. To date, the single largest surgical experience has been provided by the worldwide prospective registry started in 1979 by Schwartz, Moss, and Crampton.\textsuperscript{11} A total of 43 reported patients underwent sympathectomy because of symptoms refractory to \( \beta \)-blockers, and surgery was associated with a near total abolition of symptoms in all. Symptoms of recurrent syncope or presyncope were uncommon and appeared to resolve with \( \beta \)-blocker therapy.

Our experience with sympathectomy was not as favorable as that reported by others.\textsuperscript{7-11} Our patients were comparable to those previously reported in both the magnitude of QT prolongation as well as in clinical manifestations of the syndrome. However, the sympathectomy provided long-term relief of symptoms in only two patients (20%), while the other eight patients (80%) developed recurrent symptoms that included cardiac arrest in three (30%), repetitive syncope in four (40%), and presyncope in six (60%). One patient experienced sudden death at an interval of 24 months after surgery. Therefore, left stellectomy or standard left cervicothoracic sympathectomy does not by itself provide permanent relief of symptoms to all patients with this syndrome.

The addition of \( \beta \)-blockers has been reported to be beneficial in stellactomized patients with recurrent symptoms.\textsuperscript{1-11} However, \( \beta \)-blockers proved relatively ineffective in the control of recurrent symptoms in our patients. All three episodes of cardiac arrest occurred while patients were taking maximally tolerated doses of \( \beta \)-blockers. \( \beta \)-Blockers also failed to abolish syncope and presyncope in the other four patients, although the frequency of the symptoms diminished significantly. The control of symptoms often required other therapeutic modalities such as long-term atrial pacing or use of an automatic internal defibrillator.

The reasons underlying the difference between our experience and that of others are unclear. Although there was an initial period (mean 15.1 \( \pm \) 12 months) of symptom control in the majority of patients, this beneficial effect was not sustained over a longer follow-up period. Conceivably, failure of sympathectomy to provide sustained benefit was related to regeneration of the cardiac sympathetic nerves. Among the symptomatic patients, the initial Horner’s syndrome resolved in three patients despite complete removal (histologically documented) of the left stellate ganglion in each. One of them had undergone left stellactomy alone (patient 2), and the development of syncope and cardiac arrest may have been caused by an inadequate sympathectomy. The two other patients who showed evidence of regeneration (Nos. 4 and 5) also appeared to respond to more extensive thoracic sympathectomy with removal of up to sixth thoracic ganglion. However, recurrence of symptoms in the other five patients who had undergone adequate sympathectomy with removal of the first three to four thoracic ganglia was not associated with any clinical evidence of regeneration of sympathetic nerves. The clinical significance of disappearance of Horner’s syndrome in one of the asymptomatic patients (No. 9) also remains unclear.

The inability of sympathectomy to provide sustained protection against cardiac arrest and syncope in all patients with the long QT syndrome was an unexpected finding. The rationale for unilateral sympathectomy is based on the presumption of relative dominance of the left-sided cardiac adrenergic activity.\textsuperscript{15-18} The evidence in favor of this hypothesis comes from the observation that the stimulation of the left-sided or ablation of the right-sided stellate ganglion is associated with prolongation of the QT interval as well as an induction of ventricular arrhythmias in dogs. Left stellactomy not only prevents QT prolongation but also decreases the ventricular arrhythmias and increases the ventricular fibrillation threshold.\textsuperscript{19-21} The inefficacy of sympathectomy in most of our patients raises important questions regarding the pathogenesis of the syndrome. A mechanism other than congenital sympathetic imbalance may be operative in some patients. For example, the fundamental problem may be at the myocardial level, involving electrophysiologic mechanisms that are merely modulated, to an extent by neural activity.\textsuperscript{21-24} In that case, empiric therapy with sympathectomy may prove to be of limited value for some patients with the long QT syndrome.

In summary, standard sympathectomy alone or in combination with \( \beta \)-blockers proved to be disappointing in providing sustained relief of symptoms for most patients with the long QT syndrome. Neither changes in the QT interval nor Holter recordings were predictive of the clinical response. Limited experience with the use of long-term atrial overdrive pacing for those who failed to respond with sympathectomy and had significant sinus bradycardia appears to be promising. The role of long-term atrial pacing or automatic internal defibrillators without sympathectomy remains to be determined.

References
THERAPY AND PREVENTION—ARRHYTHMIA

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