Unsuspected Echocardiographic Abnormality in the Long QT Syndrome
Diagnostic, Prognostic, and Pathogenetic Implications

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Background. The idiopathic long QT syndrome (LQTS) is characterized by electrocardiographic abnormalities and by a high incidence of lethal arrhythmias. The present case/control study demonstrates the frequent occurrence of unusual and specific ventricular wall motion abnormalities in LQTS and their association with history of syncope or cardiac arrest. These abnormalities were present in 23 of 42 LQTS patients (55%) and in two of 42 healthy controls (5%, \( p < 0.0001 \)) matched for age, sex, height, and weight.

Methods and Results. Two new measurements were developed to assess quantitatively the abnormalities observed. The first, Th1/2, is an index of the rapidity of the early contraction phase; the second, TSTh, is an index of the presence of a slow movement in the late thickening phase. Th1/2 was smaller in LQTS patients (15.0 ± 4.1 versus 19.9 ± 3.9% of the cardiac cycle, \( p < 0.001 \)), indicating that they reach half-maximal systolic contraction more rapidly than controls. TSTh was greater in LQTS patients (9.37 ± 6.82 versus 2.88 ± 4.46%, \( p < 0.001 \)), indicating that they spend more time at a very low thickening rate. A peculiar double peak pattern of late thickening was present in 11 patients and in no controls. These abnormalities were more frequent in symptomatic than in asymptomatic patients (20 of 26, 77%, versus three of 16, 19%, \( p < 0.005 \); relative risk, 2.75). They were not affected by \( \beta \)-blockade or by left cardiac sympathetic denervation. The same echocardiographic abnormalities were produced by right stellactomy in nine of nine anesthetized dogs, were not dependent on cycle length, and were not modified by subsequent left stellactomy.

Conclusions. This study demonstrates a previously unsuspected abnormality in the ventricular contraction pattern of LQTS patients and, for the first time, provides evidence that a noninvasively detected cardiac abnormality is associated with a higher risk for syncope/cardiac arrest. The experimental reproduction of this echocardiographic abnormality by right stellactomy indicates that this newly found clinical characteristic of LQTS does not contradict the “sympathetic imbalance” hypothesis. (Circulation 1991;84:1530–1542)

The idiopathic long QT syndrome (LQTS) is a well-defined clinical entity with a high lethality among untreated patients.\(^1\)\(^6\) The main clinical features, besides the occurrence of syncope/cardiac arrest mostly in young individuals and in association with stressful events,\(^7\) are several unusual electrocardiographic characteristics. They include prolongation of the QT interval,\(^8\) episodes of T wave alternans,\(^9\) low heart rate in relation to age,\(^1\) sinus pauses unrelated to sinus arrhythmia,\(^10\) and notched or bifasic T waves.\(^2,3,6,10–12\) Traditional cardiologic examination, including cardiac dimensions and dynamics, has always been considered normal in LQTS patients. To date no single cardiac abnormality has been found to correlate with prognosis.\(^4,6,13\)

For several years our institute has been a major referral center for LQTS patients, who are seen either as routine controls or as new patients. All undergo routine examinations, and their electrocardiograms have never generated special interest. Because of unusual circumstances, it was noted one day that a young LQTS patient had a quite uncommon echo-
cardiographic pattern. The analysis and discussion that followed that serendipitous observation generated the present clinical case/control study, which provides the first evidence for a significant left ventricular motion abnormality in LQTS. At the same time, an experimental study was undertaken with the objective of investigating whether that clinical observation contradicted one of the two major pathogenetic hypotheses for LQTS, the “sympathetic imbalance” hypothesis. Here we report both the clinical and the experimental portions of our study. Preliminary data have been presented.

Methods

Clinical Study

Study population. This prospective echocardiographic study involved 42 patients affected by the LQTS and 42 healthy controls. To provide a case/control study, patients and controls were matched for sex, age, height, and weight. The LQTS patients were consecutively admitted to our center either for periodic follow-up visits or for the occurrence of syncope or cardiac arrest, during a period of approximately 18 months. They were predominantly women (74%) (50% <18 years), relatively young (mean age, 23 ±14 years; median, 18; range, 2–64), with a prolonged ventricular repolarization (QTc, 504±54 msec). The majority (74%) were affected by the familial type of LQTS, and only one had congenital deafness. A history of documented syncope or cardiac arrest was present in 24 patients (57%), defined here as “symptomatic.” The state of therapy at the time of the study was as follows: β-adrenergic blockade (mostly propranolol, 2–3 mg/kg/day) in nine patients, β-blockade and left cardiac sympathetic denervation in 10 patients, and no therapy in 23 patients. Of the last 23, seven were studied with and without β-blockade. All patients on therapy had a history of syncope or cardiac arrest.

The members of the control group were thought to be normal on the basis of a negative clinical history, a complete and negative clinical examination, and a normal 12-lead ECG. They were excluded if any abnormality in the traditional echocardiographic parameters, including mitral valve prolapse, was present.

Echocardiographic Study. A complete M-mode, two-dimensional, and Doppler examination was performed, in a 30° right anterior oblique position, with an ATL MK 600 echocardiograph (Advanced Technology Labs Inc., Bellevue, Wash.) equipped with 2.5 and 5 MHz probes. All examinations and measurements were recorded at end-tidal volume, following the standards developed by the American Society for Echocardiography. The echocardiographic tracings were recorded, together with a modified lead II ECG, at a speed of 100 mm/sec, with a fiber-optic recorder.

Since the most relevant measurements were performed in the M-mode long-axis parasternal view, we standardized this approach. Care was taken to obtain simultaneous recordings of the interventricular septum and of the left ventricular posterior wall in a section of the left ventricle below the maximal deflection of the mitral valve leaflets, and to direct the ultrasound beam perpendicular to the posterior wall. It became apparent that an alteration in the thickening pattern of the left ventricle was often present. This was most easily recorded in the posterior wall. Accordingly, for our measurements we used a recording of the left ventricular posterior wall in which the endocardium could be identified with precision. The investigator responsible for the identification of the endocardial contour was blinded as to the subject’s identity (case or control) and to the presence of symptoms. The endocardial movement of a 100-mm/sec recording was followed with a graphic pen (Cardio 200, Kontron Instruments, Eching, Munich, FRG). The signal was stored in the built-in computer that also calculated the first derivative of wall thickening. We evaluated both early and late systolic phases of ventricular wall thickening and, because of the absence of specific quantitative methods of analysis, one of us (G.M.D.F.) developed two new measurements. The first is the time to reach half of maximal systolic thickening, derived from the endocardial tracing. This is an index of the rapidity of the early contraction phase and will be referred to as “Th1/2” (A–B in Figure 1).

The second is the time spent during late thickening before rapid relaxation at a rate smaller than 1 cm/sec, calculated from the first derivative of the endocardial tracing. This is an index of the presence of slow thickening in the late systolic phase, and will be referred to as “TSTh” (C–D in Figure 1). The reversal of the movement of the endocardium (i.e., the point at which the first derivative definitely crosses the zero line in the downward direction) was taken as the end of this period. Figure 1 shows a normal echocardiographic tracing and indicates how these measurements were made.

Because of the possibility that different heart rates might influence the comparability of these indexes, we decided to express them as percentage of the cardiac cycle.

Experimental Study

A sympathetic imbalance, secondary to a lower than normal right cardiac sympathetic activity, is a possible pathogenetic mechanism of LQTS. We have evaluated whether the reproduction of such a sympathetic imbalance would induce changes in the movement of the ventricular wall, and whether these changes would have any similarity with the abnormalities observed in the LQTS patients.

In 12 adult mongrel dogs weighing 12–18 kg, anesthesia was induced by sodium thiopental and was maintained by α-chloralose (80 mg/kg bolus, plus 15 mg/kg/hr after the first 3 hours); the dogs were then ventilated with room air by use of a Harvard respirator (Harvard Apparatus, South Natick, Mass.). A midline sternotomy was performed, the
pericardium was opened, and the heart was suspended in a pericardial cradle. The cervical vagosympathetic trunks and both stellate ganglia were carefully isolated. A polyethylene sheathing was suspended over the heart to form a cradle that was filled with 37°C saline and was in gentle contact with the heart surface. This allowed the heart to be examined directly, but avoided compression by the probe. An M-mode and two-dimensional examinations were performed with the same equipment as used in the clinical study. The long-axis view was used for the measurements of the indexes described above.

In nine dogs, the echocardiographic study was performed in basal conditions, after bilateral vagotomy, and after ablation of the right stellate ganglion. Atrial pacing was performed after right stelllectomy to correct for the heart rate decrease that follows removal of the right-side sympathetic nerves.\textsuperscript{17,18} In two of these dogs, the quantitative measurement could not be done accurately in control conditions, whereas it was made in the other two conditions.

In three dogs, bilateral vagotomy was followed by left stelllectomy. This was done to verify whether the changes induced by right stelllectomy were merely representing the effect of a nonuniform sympathetic innervation. In five of the 12 dogs, a bilateral stelllectomy was performed; specifically, in three, the right stellate ganglion was removed after left stelllectomy, and in two, left stelllectomy was performed after removal of the right stellate ganglion.

Stelllectomy is an irreversible procedure. The potential reversibility of the phenomenon observed was examined in one experiment. In this dog, the echocardiographic study was performed during cold blockade of the right stellate ganglion and was repeated after rewarming; afterward, the ganglion was removed as in the other experiments. Effectiveness of the blockade and restoration of neural function after rewarming were established by observing the typical heart rate changes expected in the two conditions.

In each condition, the QTc is the average of five QT intervals from nonconsecutive beats, corrected for heart rate according to Bazett’s formula.

**Data and Statistical Analysis**

For the case/control comparison of the variables under study we used, whenever possible, data taken in pharmacological washout. This was the case for the seven patients studied with and without therapy with β-blockers. Therefore, the control group was compared with the LQTS group that included 23 patients without or off therapy and 19 under therapy with β-blockers, of whom 10 also had had left cardiac sympathetic denervation. Unless stated differently, the two echocardiographic indexes are expressed as
TABLE 1. Echocardiographic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>LQTS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>44.9±5.7</td>
<td>46.5±6.4</td>
<td>0.076</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>28.8±4.2</td>
<td>29.1±4.5</td>
<td>0.58</td>
</tr>
<tr>
<td>SF (%)</td>
<td>35.7±3.5</td>
<td>37.4±3.9</td>
<td>0.028</td>
</tr>
<tr>
<td>Septum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT (mm)</td>
<td>7.9±1.7</td>
<td>8.4±2.6</td>
<td>0.13</td>
</tr>
<tr>
<td>ST (mm)</td>
<td>11.2±2.0</td>
<td>11.6±2.5</td>
<td>0.21</td>
</tr>
<tr>
<td>TF (%)</td>
<td>42.4±16</td>
<td>43.3±22</td>
<td>0.84</td>
</tr>
<tr>
<td>Posterior wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT (mm)</td>
<td>7.3±1.8</td>
<td>7.4±2.1</td>
<td>0.67</td>
</tr>
<tr>
<td>ST (mm)</td>
<td>13.3±2.6</td>
<td>13.6±2.6</td>
<td>0.35</td>
</tr>
<tr>
<td>TF (%)</td>
<td>84.8±31</td>
<td>90.2±30</td>
<td>0.37</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>135.8±61</td>
<td>149.0±82</td>
<td>0.26</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>82.4±20.6</td>
<td>93.8±47.7</td>
<td>0.081</td>
</tr>
</tbody>
</table>

EDD, end diastolic diameter; ESD, end systolic diameter; SF, shortening fraction; DT, diastolic thickness; ST, systolic thickness; TF, thickening fraction; LV, left ventricle.

percent of the cardiac cycle. Mean comparison was performed by Student’s t test on paired (if applicable) or independent samples. Frequency comparison was performed by χ² test with Yates correction. For the experimental study, analysis of variance for repeated measures was applied; then, differences between interventions were assessed with Student’s t test for paired data with the Bonferroni correction. Data are expressed as mean±SD. A value of p<0.05 was considered the limit for significance.

Results

Clinical Study

General characteristics. The LQTS patients and controls had exactly the same mean age (22.7±14.4 and 22.7±14.8 years, respectively), the same height (155.3±20 and 155.6±19.3 cm), and a very similar weight (53.5±19.8 and 51.3±16.0 kg). As expected by the characteristic pathophysiology of this disease and by the β-blocking treatment in some patients, mean cardiac cycle length was longer in LQTS patients (996±193 versus 836±115 msec, p<0.01). The QT interval (500±73 versus 352±23 msec) and QTc (504±54 versus 389±26 msec) were also markedly longer in LQTS patients (both p<0.001).

Echocardiographic analysis. No abnormality was found in LQTS patients as to ventricular chamber size, wall thickness (in reference to the normal range for age, sex, and body mass), and Doppler examination. Table 1 shows the comparison between LQTS and controls in left ventricular measurements. The only difference, albeit small, that reaches statistical significance is the shortening fraction of the left ventricle (37.4±3.9% versus 35.7±3.5%, p=0.028). Of potential importance is a trend among the patients for a greater end-diastolic diameter of the left ventricle and for a greater cardiac mass index (p=0.076 and p=0.081, respectively).

The critical finding was a striking difference between patients and controls in the pattern of ventricular wall thickening. Both the early contraction and the late phase of wall thickening were affected. Briefly, in LQTS patients the early contraction was more rapid and the late wall thickening before rapid relaxation was slower.

The index of the rapidity of thickening in the early phase, Th1/2, was significantly smaller in LQTS patients (15.0±4.1% versus 19.9±3.9% of the cardiac cycle, p<0.001). This indicates that LQTS patients reach half-maximal systolic contraction more rapidly than controls.

The measure of the slow-speed thickening in late systole, TSTh, was significantly greater in patients than in controls. Mean TSTh was 9.37±6.82% versus 2.88±4.46% of the cardiac cycle in patients and in controls, respectively (p<0.001). This indicates that LQTS patients spend much more time than controls at a very low thickening rate before rapid relaxation. Two main aspects of this latter abnormality were seen in LQTS patients: a uniform slowing of thickening, leading to a rectilinear “plateaulike” morphology, and a dip in the late part of contraction followed by a second anterior movement of the endocardium producing a double peak image. In the few cases in which the second peak exceeded the first, it was considered to be the maximal thickening and was used for the determination of Th1/2.

Figure 2 illustrates a representative example from a LQTS patient. Segment AB, corresponding to Th1/2, is short. On the other hand, the segment CD, corresponding to the index of slow thickening, TSTh, is prolonged and the late thickening phase results in a plateau. Figure 3 shows one extreme example of the double peak morphology. A very long time is spent at a thickening rate less than 1 cm/sec, and there is even a phase of reversal, as indicated by the negative value of the derivative of wall thickening.

Data related to the cardiac cycle are probably better suited for comparison; nonetheless, we also calculated the corresponding absolute value for the two indexes (Th1/2 and TSTh). Because of the longer RR intervals in LQTS patients, using absolute values instead of percent changes, the difference in Th1/2, although still present, decreases and no longer reaches statistical significance (137±36.9 versus 148.6±25.4 msec, p=0.08), whereas the difference in TSTh increases further (81.8±63.4 versus 18.6±23.7 msec, p<0.001). Thus, the quantitative difference between LQTS patients and controls, particularly in TSTh, does not depend significantly on the type of analysis used.

Twenty-three of the 42 LQTS patients (55%) were found on the basis of qualitative analysis to have an abnormal movement, whereas this occurred in only two of the 42 controls (5%, p<0.001). Of these 23 patients, 11 had the double peak morphology; this was never observed among the controls. When the recordings were analyzed by an independent investigator, blinded to the identity and history of patients,
who was asked to define the contraction pattern as either normal or abnormal, the same percentages of abnormality were identified. Figure 4 shows the values of Th1/2 and TSTh in LQTS patients and in controls.

A second surprise was the finding that among LQTS patients the abnormal movement of the left ventricular posterior wall was definitively more frequent in symptomatic patients (20 of 26, 77%) compared with asymptomatic (three of 16, 19%; p<0.001). Indeed, the presence of the movement abnormality carried a significantly greater probability of syncope or cardiac arrest (relative risk, 2.75; 95% confidence interval, 1.60–4.72). The double peak morphology was even more strongly correlated with cardiac events, as they were present in 10 of these 11 patients (91%).

When symptomatic and asymptomatic patients were compared for quantitative measures, it was found that no significant difference was present in early systolic thickening (Th1/2, 14.5±3.7% versus 15.9±4.7%). Interestingly, symptomatic patients had a longer “plateau” phase, as shown by the greater TSTh (11.8±6.3% versus 6.2±5.9% of the cardiac cycle, p<0.01). Figure 5 shows the values of the Th1/2 and TSTh in the 26 symptomatic patients and in their own matched controls.

The possible correlation between the duration of the QT interval (as an index of duration of ventricular repolarization) and the time spent in the plateau phase (TSTh) was evaluated (Figure 6). The analysis of the 84 subjects indicates a moderately positive correlation among QTc and TSTh (r=0.57, p<0.001) (Figure 7).

Electrocardiographic analysis. QTc was not significantly different between symptomatic (514±61 msec) and asymptomatic patients (487±38 msec, p=0.10). In the 32 patients in whom the ECG was obtained at the same time as the echocardiographic recording, an analysis of the notched T wave was also performed. The alteration in wall thickening and the morphological abnormality in the T wave were correlated, as indicated by the fact that the notched T wave was present in 15 of the 17 patients with the echo abnormality (88%) and in only four of the 15 patients without the echo abnormality (27%, p<0.001). Moreover, 10 of 11 (91%) patients with the double peak also had a notched T wave.

Effect of β-blockade. Seven patients were studied both with and without chronic therapy with β-blockers. β-Blockade did not significantly influence the two indexes. Th1/2 was 15.9±3.9% of cardiac cycle without and 15.4±3.9% with β-blockers, and TSTh was 7.14±5.0% without and 6.39±5.9% with β-blockers. Th1/2 was different if expressed in absolute rather than relative values (140.7±47.3 versus 174.7±40.8 msec, p<0.05), probably as a consequence of the longer cycle length (1,144.7±127.3 versus 878.1±181.3 msec, p<0.005) produced by β-blockers. From a morphological point of view, in one patient the abnormality was less marked after β-blockers.

Effect of left cardiac sympathetic denervation. In five patients the echocardiographic abnormality was pres-
ent before and after left cardiac sympathetic denervation, without any significant difference.

**Experimental Study**

Heart rate in control condition was 164±22 beats/min and increased to 195±18 beats/min after bilateral vagotomy ($p<0.05$). The ablation of the right stellate ganglion reduced heart rate by 57 beats/min to 138±29 beats/min ($p<0.001$). Subsequent removal of the left stellate ganglion did not change heart rate further. The $QT_c$ did not change after vagotomy (331±5 versus 342±21 msec, NS), while it increased

**FIGURE 3.** Extreme example from LQTS patient. M-mode examination form the long-axis parasternal view. In this case, the main abnormality is represented by a major prolongation of the time spent in the late thickening phase and especially by the occurrence of a dip followed by a second anterior movement of the endocardium, resulting in a double peak morphology. For details see Figure 1. LVPW, left ventricular posterior wall.

**FIGURE 4.** Bar graph showing mean percent values (±1 SD) of the early systolic thickening (Th1/2) and of the time spent in the late thickening phase (TSTh) in control subjects and LQTS patients.
after right stellectomy to 415±30 msec (*p<0.001 versus vagotomy) and did not change further after left stellectomy.

The thickening velocity in the early phase, Th1/2, and the slow thickening in the late systolic phase, TSTh, did not change after vagotomy (from 19.6±4.2% to 19.2±2.4%, NS, and from 1.4±0.7% to 1.4±0.6%, NS, respectively). By striking contrast, after right stellectomy, left ventricular wall thickening was markedly altered in all the dogs, and the alteration impressively mimicked the echocardiographic abnormalities observed in LQTS patients (Figure 8). Compared with postvagotomy conditions, the early contraction was more rapid and the late systolic phase was slower. After right stellectomy, Th1/2 was reduced (from 20.4±3.4% to 10.2±2%, *p<0.0001), whereas TSTh was markedly prolonged (from 1.8±0.8% to 21.8±7.5%, *p<0.0001). These abnormalities provoked a typical plateau morphology, very similar to that observed in the LQTS patients. The overall changes induced by right stelllectomy are shown in Figure 9. It is worth noting the similarity between the pattern present in the LQTS patients compared with the healthy controls and the pattern present in the dogs after right stellate ganglion ablation compared with the same dogs with QTc < 440, 440 < QTc < 480, and QTc > 480.
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FIGURE 7. Scatterplot of the relation between QTc and the time spent in the late thickening phase (TSTh) in the controls (○), in asymptomatic LQTS patients (◇) and in symptomatic LQTS patients (■). Individuals with greater values of QTc had a TSTh occupying a greater portion of the cardiac cycle.

intact cardiac sympathetic innervation. Also in the experimental study, the QTc and the echocardiographic indexes were moderately correlated (r=0.60 and 0.63, p<0.01) (Figure 10).

To exclude the possibility that the reduction in heart rate produced by the ablation of the right stellate ganglion might have affected wall thickening, the echocardiographic examination was repeated while, by atrial pacing, heart rate was kept at the same level present before right stellectomy (n=8). The abnormalities in the wall thickening of the left ventricle were observed also in these conditions (Figure 8), as Th1/2 and TSTh were similar to those observed without pacing (8.9±1.7% and 26.4±7.2%, respectively).

FIGURE 8. Anesthetized dog. M-mode examination from the long-axis parasternal view at a speed of 100 mm/sec. The three tracings provide images after bilateral vagotomy, after right stellectomy without atrial pacing (RSGx), and after right stellectomy with atrial pacing (RSGx+pacing). After ablation of the right stellate ganglion there is the appearance of an abnormal movement of the posterior wall of the left ventricle very similar to that observed in the LQTS patients. When the heart rate reduction consequent to right stellectomy is counteracted by atrial pacing, the abnormality in the wall thickening of the left ventricle remains evident. Note the appearance of the double peak morphology; for example, the contour of the endocardium in the last beat of the right stellectomy plus pacing condition.
The removal of the left stellate ganglion performed after right stellectomy did not correct or induce any further change in the ventricular wall thickening. In the three experiments in which left stellectomy was performed as first intervention, heart rate and QTc did not change significantly (from 187±6 to 177±16 beats/min, NS, and from 336±9 to 339±1 msec, NS). More importantly, left stellectomy did not alter the wall thickening of the left ventricle. Neither Th1/2 nor TSTh changed (from 20±2.3% to 18.9±2.2%, NS, and from 1.6±0.7% to 1.3±0.6%, NS). Right stellectomy performed after left stellectomy induced the same modifications of left ventricular wall thickening as produced by unilateral right stellectomy with the contralateral left stellate ganglion intact. When heart rate was brought back by atrial pacing to the same level observed before right stellectomy, the abnormalities in the wall thickening of the left ventricle remained present.

Blockade by cold of the right stellate ganglion induced a decrease in heart rate similar to that observed with the subsequent surgical ablation of the same ganglion, and the typical abnormality in the left ventricular wall thickening also became evident. Rewarming the ganglion restored the previous normal pattern in the ventricular wall thickening as well as in heart rate.

**Discussion**

The present study has disclosed an unsuspected abnormality of left ventricular posterior wall thickening among patients affected by the long QT syndrome. The presence of this abnormality is associated with a higher risk for syncope/cardiac arrest, thus constituting the first cardiac abnormality with prognostic value identified in this disease. Two different indexes of ventricular wall thickening were developed and have allowed the necessary quantitative assessment of the movement abnormality. These specific movement abnormalities were reproduced experimentally by selective removal of the right stellate ganglion. The data presented have implications for the diagnosis, the prognosis, and the pathogenesis of LQTS.

**Echocardiographic Abnormality**

Our measurements centered on the posterior wall movement because of the better visual definition of the endocardial layer in this region and because, when analyzed by M-mode, the abnormality was more clearly visible in the posterior wall. This does not imply a regional abnormality because the lack of any dyssnergy, as observed with the two-dimensional approach, suggests strongly that the phenomenon involves the entire left ventricle.

Because of the limitations inherent in a purely morphological observation and description of the contraction pattern, easily affected by subjective bias and by interobserver variability, we thought it necessary to use a quantitative assessment. We developed two mathematical indexes that could adequately describe the abnormality observed in the LQTS patients. Independently of LQTS, these new indexes may become useful in other conditions and may contribute to a more complete echocardiographic assessment of cardiac dynamics.
The first index, Th1/2, provides a measurement of the rapidity of the first part of ventricular wall thickening; the faster the early contraction, the smaller the time required to reach half of maximal systolic thickening. The LQTS patients have a more rapid early contraction, as indicated by the significantly smaller Th1/2.

The second index, TSTh, provides a measurement of the time spent during late thickening at a rate slower than 1 cm/sec, in a “plateaulike” phase, before rapid relaxation; it reflects the presence of slow thickening during late systole. In LQTS patients, a much longer part of the cardiac cycle is spent at a very low thickening rate, as indicated by the significantly greater TSTh.

Thus, the previously unsuspected echocardiographic abnormality now described in 55% of LQTS patients combines two morphologically distinct aspects: a rapid early contraction and a very prolonged phase of slow thickening before rapid relaxation. The latter is the most pronounced abnormality and can often be identified by a visual inspection. In almost 25% of the patients, the slow contraction instead of a rectilinear plateau shows a “double peak” morphology with the two peaks interrupted by a dip.

Peculiar ventricular wall movement patterns that may, to a certain extent, resemble the one described here have been reported in association with some cardiovascular diseases. The ventricular preexcitation of the Wolff-Parkinson-White syndrome produces an early peak in the initial phase of wall thickening that may result in an increased steepness of the first part of the endocardial profile.19 This pattern is limited to the wall where the Kent bundle terminates. Patients with mitral valve prolapse sometimes show a distinct late systolic “dip” in ventricular wall motion20,21 that pro-
roduces a pattern similar to the one defined here as “double peak.” This abnormality has been described only in the left ventricular posterior wall; indeed, two-dimensional imaging allows its location within the posterior and posterobasal regions and discloses a distinct dyssynergy in the overall contraction. This feature clearly differentiates the pattern present in the patients with mitral valve prolapse from that found in the patients with LQTS. Among the latter, the abnormality appears to be global rather than regional.

Mechanisms

We do not have a ready and simple explanation for the phenomenon observed; however, reasonable speculations can be made.

A prolongation of the action potential duration is associated with an increase in the tension developed by the ventricular muscle and with a greater intracellular influx of calcium leading to a prolonged contraction.\(^2\)\(^3\)\(^4\)\(^5\) Given the probable presence of early afterdepolarizations (EAD) in LQTS,\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\) the double peak could represent the mechanical equivalent of an EAD. This would fit with the fact that most patients with the double peak also had a notched T wave, provided that the notch on the T wave does indeed represent an EAD. The moderate but significant correlation between the mechanical abnormality and QT, \(r=0.57\) may suggest that the duration of ventricular repolarization does contribute to the phenomenon observed, possibly by facilitating the availability of intracellular calcium.

The reproduction of the echocardiographic abnormality by removal of the right, but not the left, stellate ganglion demonstrates that a nonuniform sympathetic output to the heart can induce the phenomenon. However, the experimental results are not easy to interpret despite their great internal consistency. The data clearly indicate that the wall thickening abnormality is dependent on the incompleteness of the right cardiac sympathetic innervation; the left nerves seem to be completely uninfluential because the movement abnormality is neither induced by unilateral left stellectomy nor is it corrected when left stellectomy is performed after right stellectomy. The latter finding excludes the possibility that a reflex increase in the activity of the left-side nerves is involved in the occurrence of the abnormality following right stellectomy; this is at variance with several of the findings observed with unilateral right stellectomy.\(^1\)\(^8\)

The experiments with atrial pacing prove that the phenomenon is independent of heart rate, and the experiment with cold blockade indicates that the phenomenon is not irreversible if the right sympathetic outflow to the heart is restored. The clinical data with and without propranolol suggest that the wall thickening abnormality is not significantly dependent on overall sympathetic tone, and specifically on activation of \(\beta\)-adrenergic receptors. They actually seem to support the experimental finding that the phenomenon depends on a selectively reduced sympathetic activity and also fit with the fact that the left stellectomy does not correct the abnormality once it is induced by right stellectomy. This latter point is further substantiated by the presence of the abnormality in the patients who underwent left cardiac sympathetic denervation.

Diagnostic Implications

The presence of a marked QT interval prolongation in a child who faints during emotional or physical stresses and has family members already diagnosed as having the LQTS, clearly poses no diagnostic difficulty. Often, however, the clinical presentation is not so obvious, and a set of major and minor diagnostic criteria has been provided.\(^3\) Additionally, the existence of abnormal patterns of ventricular repolarization, as evidenced by body surface mapping,\(^2\)\(^6\)\(^7\) and of quantitative abnormalities in the duration of repolarization\(^2\)\(^8\) has been identified in many LQTS patients. Nonetheless, the diagnosis of the patient with stress-induced syncope, no family history, and borderline QT interval prolongation, remains difficult.

The present report provides a new marker that, when present, strongly points to the LQTS. Particularly among symptomatic patients, only one fourth can be expected not to have this abnormality. The fact that this marker is identified noninvasively makes this new diagnostic tool easily available. Echocardiographic screening for the specific wall motion abnormality described here should become part of the routine clinical evaluation for patients potentially affected by the LQTS.

Prognostic Implications

Risk stratification for patients affected by LQTS has so far been elusive. The only data available come from the International Prospective Registry and Study\(^1\)\(^3\) and suggest a markedly greater risk only for the few patients affected by congenital deafness. The importance of the actual length of the QT interval, despite its probable role in arrhythmogenesis, has not yet been clearly defined.\(^1\)\(^3\) The anomaly in left ventricular wall motion represents the first cardiac abnormality associated with a significantly higher risk (2.75 times higher) for cardiac events.

Our study does not yet provide data that actually demonstrate that among asymptomatic patients, those with the wall thickening abnormality are more likely to develop syncope/cardiac arrest than those without. This essential step requires a prospective study, currently ongoing, in which asymptomatic and untreated patients are characterized for the echocardiographic abnormality and followed for an adequate period of time.

Pathogenetic Implications

Currently, two pathogenetic mechanisms are the most credited. One, the “sympathetic imbalance” hypothesis, suggests that the primary defect is a congenitally lower-than-normal right cardiac sympathetic activity accompanied by left sympathetic hy-
peractivity. The other, the “intracardiac abnormality” hypothesis, suggests that the primary defect is a not yet identified alteration in K⁺ or Ca²⁺ currents, possibly involving the repolarizing current Iₛ or the plateau current Iₐ,L. In either case, the triggering event for the life-threatening arrhythmias would be a sudden increase in sympathetic activity. The clinical efficacy of β-blockade and of left cardiac sympathetic denervation fits with both hypotheses. Moreover, they are not mutually exclusive, because incomplete development of sympathetic innervation leads to probably irreversible alterations in regulatory G proteins that control several ionic currents and pumps.

So far, the intellectually more attractive “cardiac abnormality” hypothesis has been so vaguely formulated that it is actually difficult to test it. By contrast, the seemingly simplistic “sympathetic imbalance” hypothesis is more amenable to testing because removal of the right-side cardiac sympathetic nerves should reproduce its main features. Accordingly, we tested whether the echocardiographic abnormality just discovered in the LQTS patients did or did not contradict the “sympathetic imbalance” hypothesis.

The experimental results demonstrate that a wall thickening abnormality almost identical to that found in half of the patients with LQTS can be reproduced by removal of the right stellate ganglion, that is, by a sympathetic imbalance of the type proposed as one possible mechanism for the LQTS. Two differences exist between the experimental and the clinical findings. The echocardiographic abnormality produced by right stellectomy occurred in all the dogs tested and was quantitatively greater, as is evident from a comparison of Figures 4, 5, and 9. This is not at all surprising because, according to the “sympathetic imbalance” hypothesis, among the patients with LQTS one would expect the right cardiac sympathetic activity to be just lower than normal and not totally absent, as happens with right stellectomy.

The reproduction of the echocardiographic abnormality by right stellectomy has to be placed in context with the previous studies. Indeed, right stellectomy has been found to prolong the QT interval, to lower the threshold for ventricular fibrillation, to lower heart rate at rest and during exercise, to facilitate the occurrence of ventricular tachyarrhythmias during emotional stress and during exercise, to favor the appearance of T wave alternans, and to induce the appearance of sinus pauses. All these effects are consistent with the clinical presentation of the LQTS.

The evidence that right stellectomy reproduced with an amazing similarity the clinical echocardiographic abnormality is no way proves that this specific asymmetry in cardiac sympathetic innervation is the cause of LQTS. However, it demonstrates that even this new feature of LQTS does not contradict the “sympathetic imbalance” hypothesis. Unavoidably, this lends further support to the concept that a genetically controlled abnormality in the development of cardiac sympathetic innervation is critically involved in the pathogenesis of LQTS.

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References


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