Mapping of body surface potentials in patients with the idiopathic long QT syndrome

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ABSTRACT  Body surface potential maps were recorded from 140 chest leads in 25 patients affected by the idiopathic long QT syndrome (LQTs) and in 25 healthy control subjects matched for age and sex. Potential time integrals of the QRST and ST-T intervals were calculated at each lead point and displayed as isointegral (ISOI) maps. The main abnormalities noted on the QRST and ST-T ISOI maps were one area of negative values larger than normal in the right anterior and inferior thorax and a complex multipeak distribution of the integral values. At least one abnormality was present in 19 (76%) of the patients with LQTs and four (16%) of the control subjects (p < .001). Each ISOI map was also represented as a weighted sum of nine fundamental components (eigenvectors) to detect and quantitate the nondipolar content. The percent contribution of the nondipolar eigenvectors (all eigenvectors beyond the third) was significantly higher in the LQTs group than in the control group (p < .005). Specifically, an abnormally high nondipolar content on the QRST ISOI maps was observed much more frequently for patients with LQTs than for control subjects (nine or 36% vs one or 4%), and this was also true on the ST-T ISOI maps (14 or 56% vs one or 4%). No correlation was found between the major abnormalities on body surface maps and syncopeal episodes. However, the high prevalence (76%) of these alterations among the patients with LQTs and their infrequent occurrence in the control population strongly suggests that they may be useful markers for the diagnosis of atypical cases. The prominent electronegative area on the anterior thorax can be related to delayed repolarization of a portion of the anterior wall of the heart. This finding is in agreement with the hypothesis that lower than normal right cardiac sympathetic activity is the main pathogenetic mechanism of LQTs. Multipolar distribution and high nondipolar content suggest regional electrical disparities in the ventricular recovery process. This may in part account for the high susceptibility of patients with LQTs to malignant arrhythmias.

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THE ELECTROPHYSIOLOGIC alterations underlying the idiopathic long QT syndrome (LQTs) are still unknown. Clinical and experimental observations1–3 support the hypothesis that the most likely pathogenetic mechanism of LQTs is an imbalance in the sympathetic innervation of the heart. Specifically, the basic defect might be lower than normal right cardiac sympathetic activity with reflexly high activity of the left cardiac sympathetic nerves. These concepts are reflected in the current therapy for LQTs.4

The recovery process of myocardial fibers is markedly influenced by sympathetic activity and regional variations in sympathetic drive result in local changes in recovery times.5 This may alter the sequence of ventricular repolarization and provoke greater disparities in electrical potential among myocardial areas. A more diverse pattern of repolarization may produce a more complex, perhaps multipolar potential distribution at the body surface that would not be revealed by the conventional 12-lead electrocardiogram (ECG), but only by potential mapping of the entire chest.

In patients with LQTs the standard ECG shows various nonspecific abnormalities of the T wave in addition to QT prolongation; in some cases the ECG may even be normal.4 Body surface potential maps (BSPMs), which have been proven to provide diagnostic information undetectable by the conventional 12-lead ECG,6–11 might be a suitable method for revealing even small abnormalities of ventricular recovery in patients with LQTs.
The aim of this study was to describe the characteristic features of BSPMs of patients with LQTS and to establish whether BSPMs would reveal abnormalities that could be related to an altered sequence of ventricular recovery and to electrical disparities that might favor development of ventricular arrhythmias. Preliminary data on this subject have been presented previously.12

Methods

Body surface potential recordings. By means of vertical rubber straps, 140 silver–silver chloride electrodes were applied to the chest surface. The probes were positioned as shown in figure 1, i.e., 105 electrodes were placed on the anterior chest wall from the right midaxillary line to the left posterior axillary line and 35 electrodes were placed on the back of each subject. Wilson’s central terminal was taken as the reference point for measurement of chest potentials. Recordings from groups of 35 electrodes plus a reference lead (standard lead II) were obtained at one time with an automated instrument (Cardimap II, Battaglia-Rangoni) that performs on-line amplification, multiplexing (at 500 Hz/channel), and digital conversion of the signals. The amplifiers used had different gain values (500, 1000, 2000, and 5000), common mode rejection rate greater than 90 dB, a high time constant (>8 sec), and a sample and hold circuit. An eight-bit logarithmic analog-to-digital converter (AM 6070) was used that had a better resolution for the lowest amplitude signals (equivalent to 12 bits or 1 to 2 μV) than for higher signals. The digital data were then decoded into a microvolt linear scale according to the transfer functions of the analog-to-digital converter. The UP segment was taken as the “zero” reference line for all measurements. The noise level of the overall recording system was 10 to 12 μV, peak to peak. The blocks of data from four successive recordings, relating to four cardiac cycles at the end of a normal expiration, were processed together after time alignment on a Nova 4/C Data General computer connected to the recording instrument. The time of the highest absolute value of the first derivative of lead II of the ECG was taken as a reference point for time alignment. Maps of the potential values from 140 chest points were thus obtained every 2 msec of the cardiac cycle and displayed as shown in figure 1.

![Diagram](http://circ.ahajournals.org/)

**FIGURE 1.** Schema illustrating the anterior and posterior chest surfaces explored. The electrode sites are indicated by dots: 105 probes are located from the right midaxillary line to the left posterior axillary line and 35 are on the back. Anteriorly, highest and lowest rows correspond to the levels of the suprasternal notch and umbilicus.

**Instantaneous potential maps.** For each subject instantaneous potential distributions during the QRS and the ST-T interval were examined. In particular, the following variables were considered: location of the potential maximum* and minimum* and their voltages at each eighth of the ST-T interval and the highest absolute values reached by the potential extrema during repolarization and times at which they occurred.

The beginning and the end of the QRS and the end of the T wave were determined by visually inspecting the maps of instantaneous potential distribution. The onset of the QRS was taken as the instant of appearance, at the end of PQ interval, of a potential maximum in the sternal–left mammary region that progressively increased in voltage. The end of QRS was taken as the instant when ventricular excitation potentials (maximum and/or minimum) disappeared, even when clear-cut repolarization potentials were already identifiable in previous instants. The definition of the end of the T wave presents some difficulties because of the possible presence of a U wave. When the potential extrema progressively decreased from the appearance of the peak T value until measurable potentials disappeared, we considered this instant the end of the T wave. In most cases, the potential maximum during the final phases of the T wave, after decreasing to a low potential level, showed a period of stability or a new increase (U wave). In this case we considered the end of the T wave the last instant at which a decrease in voltage was observed.

**Integral maps.** The potential time integral relating to a given interval of the cardiac cycle was calculated at each lead point as the algebraic sum of all potentials, from the instant of onset to the instant of offset, multiplied by the sampling interval. The values were expressed in microvolts per second and transferred to a diagram that represented the thoracic surface and was similar to that used for displaying the instantaneous potential distribution (figure 1). On each map of time integral values, isointegral contour lines were drawn manually (isointegral maps).

The integrals of the QRST (from the onset of QRS to the offset of the T wave) and ST-T (from the end of QRS to the end of the T wave) intervals were calculated. Group mean maps were calculated by use of the respective mean values at each lead point. The mean difference map was obtained by subtracting the mean map of the control subjects from that of the patients with LQTS.

**Eigenvector analysis.** Integral maps obtained in our study population were examined by means of principal component analysis. This technique was originally used with the aim of representing electrocardiographic tracings from the thoracic surface by means of a limited number of fundamental waveforms.13 In this study we applied the principal component analysis proposed by Lux et al.14 to quantitatively characterize surface potential (or potential time integral) distributions with a few principal patterns. A detailed description of the mathematical procedures used is given in the Appendix.

In this kind of analysis each individual map is represented as a weighted sum of a limited number of fundamental patterns common to both control subjects and patients. From the entire set of data (including data from control subjects and patients with LQTS) we calculated 15 fundamental types of spatial distributions, also called “eigenvectors,” that were transferred on the same diagram used for the individual maps. In addition, for each individual isointegral map a set of coefficients was calculated that represented the contribution of each fundamental pattern to the spatial distribution shown on that map. Mean values for the coefficients relating to each eigenvector were separately

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*We defined the maximum or minimum as a point on the thoracic surface at which the potential value (or the potential time integral value) was higher or lower in relation to all the surrounding points.
DE AMBROGGI et al.
calculated for the two study groups to show the mean contribution of each eigenvector to the maps of the two groups.

**Study population.** BSPMs were obtained from a population of 50 subjects, 25 patients with LQTS and 25 healthy control subjects, matched as specified below.

The 25 patients with LQTS (18 female and seven male) ranged in age from 8 to 45 years (mean 20.2 ± 13.3). Seventeen patients were asymptomatic and had had syncopal episodes and/or cardiac arrest and documented ventricular tachyarrhythmias; eight patients were asymptomatic, but had siblings or parents who had LQTS associated with major cardiac events or sudden death (table 1). As the upper limit of normal for the QT interval corrected for the heart rate according to Bazett’s formula, we used QTc = 440 msec. Three patients had a QTc within normal limits in lead II, but were considered to have LQTS on other grounds. Specifically, they all had demonstrated syncope, and other family members showed the full picture of LQTS. Two patients had prolonged QTc intervals in leads other than lead II and one had a prolonged right ventricular endocardial monophasic action potential.

Thirteen patients were receiving long-term treatment with propranolol and four had undergone high thoracic left sympathectomy. The asymptomatic patients were not treated, in keeping with our policy for the management of these patients.

Twenty-five healthy subjects were matched for sex, age (±2 years), and body habitus (height ± 10 cm; weight ± 5 kg) with the patients with LQTS. None had history of cardiac disease; results of physical examination and the 12-lead ECG were within normal limits.

**Statistical analysis.** Data are presented as the mean ± 1 SD. Comparisons of sample mean values were made by means of Student’s t test for unpaired data. Proportions were compared by means of the chi-square test.

When eigenvector analysis (see Appendix) is used, derivation of precise probability density functions for the coefficients (qk) and for the percent content of the various eigenvectors (PCqk) is quite difficult and the normality of distribution is uncertain. Accordingly, mean values of these coefficients were compared by means of a nonparametric test (Wilcoxon test for unpaired data).

**Results**

The observation of at least one abnormality either on the isointegral maps or in the eigenvectors was more frequent among patients with LQTS than among control subjects (19/25 or 76% vs 4/25 or 16%, p < .001).

In view of the absence of thorough reports on body surface potentials in patients with idiopathic LQTS,

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ISOI map = isointegral map; Neg = large anterior negativity; Mul = multipolar distribution of the integral values; 0 = no apparent abnormality; Pos = high-amplitude maximum; ND = nondipolar content in QRST ISOI maps (+ = values >7.2; - = values <7.2) and in ST-T ISOI maps (+ = values >6.5; - = values <6.5); Sym = symptomatic patient, syncope; Asym = asymptomatic patient; Fam = familial type of LQTS; JLN = Jervell-Lange-Nielsen type of LQTS (congenital deafness); BB = β-blockers; HTLS = high thoracic left sympathectomy.
we present here a detailed analysis of the various and complex patterns observed.

**Instantaneous potential maps**

*Control subjects.* The potential distribution during the ST-T interval was similar to that already described for normal subjects.\(^{15-17}\)

During the T wave, the potential minimum was consistently observed in the right clavicular or scapular area and the maximum was located in the precordial region. In the great majority of cases, slight shifts in the potential extrema were observed during the entire T wave; however, in four subjects 10 to 14 years old the maximum migrated from the sternal area to the left axilla and again toward the parasternal region during the last instants of the T wave. In one subject, a second maximum appeared in the lower left lateral wall 130 msec after the end of the QRS. This maximum moved superiorly to the axilla and became the principal maximum.

In all but one control subject, potential distributions temporally related to the U wave on the surface ECG could be identified; the potential distributions were similar to those previously described by Spach et al.\(^{18}\)

Generally, we observed a period of transition from the T to the U wave lasting 20 msec or more, during which the amplitude of the voltages remained stable. Thereafter, the maximum slightly increased (the highest value varied from 38 to 176 µV, mean value 76 ± 36) for a varying interval of time, and then progressively decreased. Throughout the U wave, the potential maximum was in the same position as the T wave maximum, or slightly to its right. Negative potentials of low voltage were measured all around the maximum.

*Patients with LQTS.* During the initial phase of repolarization (initial two-eighths of the ST-T interval), the potential maximum was normally located in all but three patients. The potential minimum was ill-defined, as in control subjects.

At three-eighths of the ST-T interval in the great majority of patients the potential maximum was located in the midsternal or left mammary area; the minimum lay within a negative area covering the right scapular, axillary, or mammary region.

During the phases that followed until the end of repolarization the potential distribution was substantially unchanged in seven patients, with only slight shifts of the location of the potential extrema.

In 14 patients, at five- to six-eighths of the ST-T interval a migration of the maximum toward the left axillary region was observed; in five of these patients the maximum persisted in this region until the end of the ST-T interval, whereas in the remaining nine pa-

tients it again moved toward the left mammary or parasternal region during the last eighth of the ST-T interval.

In two patients minor variations in this pattern were observed. In one patient (No. 19), the sternal maximum did not migrate to the left axilla, but a second maximum appeared at four-eighths of the ST-T in the left axilla and it progressively increased while the first maximum vanished. In the second patient (No. 14), at five-eighths of the ST-T interval the maximum migrated to the left posterior axillary line and to the back and then it moved again to the initial position, while the most negative potentials remained confined within the right lower half of the back.

In the remaining two patients the sequence of potential patterns was quite different from those previously described. In one (patient 7), a second minimum appeared below the maximum at three-eighths of the ST-T and it increased progressively to become the principal potential minimum. Meanwhile, the sternal maximum vanished and a new maximum appeared on the back. Also, the migration of the extrema was complex: at the five- to six-eighths of the ST-T interval the dorsal maximum migrated toward the axilla and the left mammary region, shifting the minimum from the sternal area to the right clavicular region. In the other patient (No. 13), during the first two-eighths of the ST-T the minimum was observed in the left axillary-mammary region and the maximum was located in the right clavicular area. The maximum then moved backward and it reached the left axilla at five-eighths of the ST-T, while the negative potentials covered the entire right thorax with a minimum located along the left lower sternal border. During the final phase the potential maximum reached the sternal area, while the minimum migrated to the right submammary region.

The mean highest voltages attained by the potential extrema during repolarization were not significantly different from those in control subjects (592 ± 292 and -327 ± 151 µV vs 631 ± 193 and -292 ± 94 µV), but the positive and negative peak values were attained significantly later after the QRS onset than in control subjects (380 ± 71 and 402 ± 58 msec, respectively, vs 294 ± 39 and 297 ± 35 msec, p < .001).

In seven patients U wave potentials were identified on the basis of the following pattern: during the final phase of the T wave, the potential maximum progressively decreased and after a period of stability it increased again, reaching a value ranging from 39 to 137 µV (mean value 96 ± 38). In four patients the T wave maximum decreased to a
voltage level of 70 to 100 μV, and then remained stable for quite some time (70 to 110 msec) before decreasing again. This potential pattern was considered to be an expression of partial TU overlapping.

The potential distribution during the U interval was characterized, as it was in control subjects, by one maximum in the mid lower sternal or left mammary region and by low-level negative potentials without a clear-cut minimum that could be found anywhere around the maximum.

In 14 patients U wave potentials could not be distinguished because the potential extrema progressively decreased from the peak T value until measurable repolarization potentials disappeared. It is possible that in these cases the U wave was part of a larger TU complex. This fusion probably influenced the magnitude of the last T wave potentials, but it did not seem to give rise to complex potential distributions. In particular, the multipolar distribution observed in some patients with LQTS appeared earlier during the T wave than the presumed occurrence of the U wave. Thus, this would not have affected our results.

**QRST integral maps**

*Control subjects.* The mean isointegral map from the control subjects showed a bipolar distribution of the integral values with a minimum in the upper sternal area and a maximum in the left submammary region (figure 2). The mean values ± SD for the maximum and minimum were 111 ± 41 and −47 ± 18 μV·sec, respectively. The individual isointegral maps showed only slight variations in the locations of the maximum and minimum except in one subject in whom the minimum was in the lower sternal area (figure 3). In none of the control subjects did negative values cover the entire anterior right thorax; however, in one subject the negative area reached the epigastric region.

*Patients with LQTS.* The mean isointegral map from the patients with LQTS showed a potential distribution similar to that of the mean isointegral map from the controls. Nevertheless, the difference map (mean map from patients with LQTS minus the mean control map) showed that patients with LQTS had lower values on the inferior half of the trunk and on the right anterior thorax and higher values on the left anterior thorax compared with control subjects (figure 2).

The average values for maximum and minimum potentials were 124 ± 50 (NS) and −65 ± 34 μV·sec (p < .05 vs control subjects), respectively.

With respect to the individual isointegral maps, in nine patients the distribution of the integral values was apparently normal.

In 13 patients the negative values entirely or almost entirely covered the right anterior thorax (figure 4). Most of the minima were concentrated in the upper sternal or in the lower sternal region; the maxima were located in the left mammary or axillary region (figure 3).

In six patients there was multipeak distribution of the integral values: four patients showed two minima and one maximum (figure 5) and two patients had two maxima and one minimum. In three of the six patients a large negative area was also present.

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**FIGURE 2.** Mean isointegral maps of QRST and ST-T intervals in the control and LQTS groups. The respective difference maps are illustrated in the third column. Values are expressed in μV·sec.
ST-T integral maps

Control subjects. The mean isointegral map from the 25 control subjects showed a smooth distribution of the integral values, with a maximum in the left mammary region and a minimum in the upper sternal area (figure 2). The average values for the maximum and minimum were 88 ± 31 and -33 ± 12 μV·sec, respectively. The individual maps showed a slight variability in the patterns. The location of the minimum (figure 3) was the right scapular region in four subjects, whereas it lay on the right clavicular or upper sternal areas in 21 subjects. The maxima were located in the left parasternal–mammary region in all subjects (figure 3); in two a second maximum was observed in the left axillary region (in one it was in the upper portion and in the other in the mid lower portion).

Patients with LQTS. The mean isointegral map for patients with LQTS showed a distribution of values similar to that on the map for control subjects (figure 2), but the difference map showed that, on average, the integral values were lower in the patients than in control subjects in a large area covering the right thorax and the inferior half of the trunk (figure 2), a finding similar to that observed on the QRST difference map.

The amplitudes of the potential extrema were 113 ± 59 and -45 ± 28 μV·sec and did not differ significantly from those observed in the control group.

With respect to the individual maps, the distribution of the integral values was very similar to that in the control subjects in nine patients. In nine patients the area of negative values covered entirely or almost entirely the right anterior thorax, extending to the left beyond the midsternal line in some cases (figure 4). In another six patients and in two patients in the last subgroup described, a complex distribution of the integral values was observed: among these eight patients, four had two maxima and one minimum (figure 6), two had two maxima and two minima (figure 5), one had two minima and one maximum, and in one patient there were three minima (the highest minimum was in the right scapular region and the remaining two were located anteriorly, one to the right of the maximum, and the second inferiorly; figure 7). On the 12-lead ECG of this patient the T waves did not show any abnormal pattern, although the isointegral map revealed definite repolarization abnormalities.

Finally, in one patient (No. 16) the distribution of integral values was different from those previously
described: a high-amplitude maximum lay on the left sternal border and positive values covered all of the anterior thorax except the clavicular and the upper regions. The minimum was located in the right scapular area.

**Eigenvector analysis.** The results obtained from the eigenvector analysis are illustrated in figures 8 and 9. Only the first nine eigenvectors were considered since each eigenvector beyond the ninth accounted for a very small proportion of the total information content of the maps obtained in our study population (less than 0.25%; see Appendix for calculation methods). The first three eigenvectors relating to QRST and ST-T isointegral maps, displayed as "eigenvector contour maps," showed smooth bipolar distributions with different locations of the peak values, whereas the eigenvectors beyond the third showed a more complex multipeak distribution (figure 8). Mean values of coefficients relative to the first nine eigenvectors on QRST and ST-T isointegral maps from control subjects and patients with LQTS are shown in table 2.

Significant differences were found between the average values of coefficients for control subjects and values for patients with LQTS for the third and the sixth eigenvectors. The third eigenvector contour map showed a minimum potential in the lower sternal-epigastric region and a maximum in the left subclavicul-
FIGURE 6. Patient 7. QRST isointegral map shows a large negative area on the anterior thorax. On the ST-T isointegral map two positive peaks are present.

Discussion

In this study the analysis of body surface potentials in patients with LQTS often showed an anterior thoracic area of negative potentials larger than normal during repolarization and a potential distribution more complex than normal. Although in some cases these characteristics were already evident on inspection of the sequence of instantaneous potential maps, in most instances they could be recognized only from the distribution of the QRST and ST-T integrals or after eigenvector analysis.

Instantaneous potential maps. The visual inspection of BSPMs revealed that the instantaneous potential distributions were grossly abnormal either with respect to the location of the extrema or to the simultaneous presence of multiple peaks in only a few patients with LQTS. In these cases the maps strongly suggested the existence of marked alterations in the normal sequence of ventricular recovery that are likely to give rise to electrical disparities in the heart. On the other hand, in most patients BSPMs revealed less marked abnormalities in the instantaneous distribution.

With respect to the potential minimum, in several patients with LQTS the negative potentials covered, during the entire repolarization, an area on the anterior thorax larger than that covered in control subjects. The pattern of prominent anterior negativity could indicate that some portions of the anterior wall and/or of the septum repolarized later than other cardiac regions.

Noticeable shifts in the potential maximum, particularly during the latter portion of repolarization, were present much more often in patients with LQTS than in control subjects. The stable pattern during the later part of the normal ventricular recovery process has been related to the fact that boundaries of potential differences between areas at different stages of recovery are distributed in all or most of the ventricular mass and have a relatively stable location. Actually, the described shifting of the potential maximum during the T wave could reflect a relatively nonhomogeneous cardiac electric state, since it may result from greater than normal differences in the recovery times between different ventricular regions.

Since the differences between normal and LQTS potential maps were hardly quantifiable by inspection of the instantaneous potential distributions, we decided to use time integral analysis of the 140 electrocardiograms from which the instantaneous potential maps

FIGURE 7. Patient 5. The ST-T isointegral map (top) shows a complex multipeak distribution of the potential time integrals, whereas the ECG (bottom) does not reveal abnormal features of the T waves.
were generated. This approach has been proven to allow a reduction in the amount of data that must be analyzed without substantial loss of information.20-22

**QRST integral maps.** The integrals of QRST deflections are thought to provide valuable information on the ventricular recovery process.23-25 Areas of QRST deflection mainly reflect the intrinsic recovery properties and are largely, although not entirely, independent of the ventricular excitation sequence.25-28 Actually, at the body surface, negative QRST integrals should be recorded from areas facing myocardial regions with longer recovery durations, whereas positive values would be recorded from the thoracic surface facing cardiac regions with shorter recovery durations.

In the LQTS group the QRST integral values were, on average, lower than normal, particularly in the lower sternal-epigastric region (figure 2). In several individuals (13 of 25) this finding was particularly striking. These findings are in substantial agreement with those reported by Abildskov et al.29 in nine of 11 patients with LQTS, although in our population the most negative values were found in a somewhat lower location on the chest.

The prominent negative area on the anterior chest surface in patients with LQTS could result from the interplay of two factors: (1) the projection to that area, as in normal subjects, of negative potentials originating from the subendocardial layers, and (2) a delayed repolarization of the underlying anterior wall and/or septum so that it remains electronegative longer than other cardiac regions. This is consistent with the hypothesis of lower than normal right sympathetic activity as a possible pathogenetic mechanism for idiopathic LQTS.1-4 The effects of sympathetic activity on the ventricular recovery properties of the myocardium have been well demonstrated in the canine heart: ablation of the right stellate ganglion prolongs the recovery times in the anterior cardiac wall and lengthens the QT interval.5 Subsequently, this observation has been confirmed in cats,30 primates,31 and humans.32

**ST-T integral maps.** The analysis of ST-T integral

**FIGURE 8.** Spatial distributions of the third and sixth eigenvectors derived from QRST and ST-T isointegral maps of our entire study population.
maps may prevent concealment by the QRS integral of minor repolarization abnormalities. A potential limitation is the fact that these ST-T integrals are also influenced by the activation sequence. On the other hand, repolarization abnormalities may be important in creating electrical disparities that would favor the development of reentrant arrhythmias independent of their primary or secondary origin.

The large negativity and the multipolar distribution found on the ST-T maps was strikingly higher among the patients with LQTS compared with control subjects. Moreover, eight patients with LQTS who had a high nondipolar content did not have a multiplex distribution on their ST-T maps. This demonstrates that eigenvector analysis can detect nondipolar components not evident on ST-T maps.

Clinical correlates. The major abnormalities observed were found to have no correlation with syncopal episodes, with age, or with the type of treatment. Thus, it

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tbody>
<tr>
<td>Mean ± SD coefficients relating to the first nine eigenvectors of QRST and ST-T isointegral maps in the two groups</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eigenvector</th>
<th>Control subjects</th>
<th>Patients with LQTS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>458.1 ± 150.5</td>
<td>444.7 ± 212.6</td>
<td>NS</td>
</tr>
<tr>
<td>2nd</td>
<td>-2.5 ± 73.8</td>
<td>-18.3 ± 243.9</td>
<td>NS</td>
</tr>
<tr>
<td>3rd</td>
<td>-42.4 ± 83.2</td>
<td>62.9 ± 102.7</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>4th</td>
<td>9.4 ± 29.9</td>
<td>-0.4 ± 64.6</td>
<td>NS</td>
</tr>
<tr>
<td>5th</td>
<td>0.7 ± 35.3</td>
<td>8.5 ± 96.6</td>
<td>NS</td>
</tr>
<tr>
<td>6th</td>
<td>-18.3 ± 38.4</td>
<td>14.5 ± 44.9</td>
<td>p &lt; .005</td>
</tr>
<tr>
<td>7th</td>
<td>-3.5 ± 30.7</td>
<td>1.3 ± 33.3</td>
<td>NS</td>
</tr>
<tr>
<td>8th</td>
<td>-7.7 ± 24.2</td>
<td>3.6 ± 69.9</td>
<td>NS</td>
</tr>
<tr>
<td>9th</td>
<td>-1.1 ± 14.6</td>
<td>1.5 ± 33.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eigenvector</th>
<th>Control subjects</th>
<th>Patients with LQTS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>355.9 ± 111.1</td>
<td>368.3 ± 227.6</td>
<td>NS</td>
</tr>
<tr>
<td>2nd</td>
<td>-12.1 ± 85.5</td>
<td>-22.9 ± 183.1</td>
<td>NS</td>
</tr>
<tr>
<td>3rd</td>
<td>-14.1 ± 55.2</td>
<td>37.9 ± 105.6</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>4th</td>
<td>-0.7 ± 35.9</td>
<td>5.7 ± 52.1</td>
<td>NS</td>
</tr>
<tr>
<td>5th</td>
<td>-3.3 ± 22.8</td>
<td>3.6 ± 51.1</td>
<td>NS</td>
</tr>
<tr>
<td>6th</td>
<td>-16.0 ± 20.8</td>
<td>11.6 ± 34.7</td>
<td>p &lt; .005</td>
</tr>
<tr>
<td>7th</td>
<td>3.2 ± 14.5</td>
<td>-3.9 ± 30.6</td>
<td>NS</td>
</tr>
<tr>
<td>8th</td>
<td>-4.4 ± 19.8</td>
<td>0.5 ± 24.5</td>
<td>NS</td>
</tr>
<tr>
<td>9th</td>
<td>3.9 ± 16.4</td>
<td>0.6 ± 24.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

FIGURE 9. Nondipolar content of QRST and ST-T maps of control subjects and patients with LQTS. Mean and 1 SD are also indicated for the four groups. Significance levels were calculated by mean of a nonparametric test (Wilcoxon). High nondipolar content is present almost exclusively in the LQTS group, whereas a great overlapping between control and LQTS groups exists for the lower values.

The percent contribution of nondipolar eigenvectors to maps was strikingly higher among the patients with LQTS compared with control subjects. Moreover, eight patients with LQTS who had a high nondipolar content did not have a multiplex distribution on their ST-T maps. This demonstrates that eigenvector analysis can detect nondipolar components not evident on ST-T maps.

Eigenvector analysis. In 1981 Lux et al. proposed a method by which each potential map could be represented as a weighted sum of a few fundamental patterns (eigenvectors) and to quantitate the contribution of the spatial distribution of each eigenvector to the pattern of a given map. This method may also make possible the detection and quantitation of nondipolar components not evident on visual inspection of the isointegral map. This analysis assumes that any pattern of eigenvectors reflects, to some extent, the characteristics of the cardiac generator. Specifically, a more complex pattern would be likely to originate from more complex features of the cardiac generator.
seems unlikely that these abnormalities on BSPMs will be helpful for prognostic stratification or for identification of asymptomatic patients with LQTS who are at high risk of developing syncope. However, more data prospectively collected in a larger population of patients are needed.

On the other hand, the high incidence (76%) of these abnormalities among the patients with LQTs and their infrequent occurrence (16%) in the control population suggests that they may prove quite useful in diagnosing atypical cases. For example, one patient (No. 5, figure 7) in whom the QTC on the surface ECG was normal and in whom the diagnosis of LQTS was made on other grounds had clear-cut abnormalities on the BSPM.

Pathophysiologic implications. These findings are relevant to the pathogenesis of idiopathic LQTS and probably to the characteristic cardiac electrical instability associated with it. The large anterior negativity could indicate delayed repolarization of a portion of the anterior ventricular wall. This, as already noted, would fit well with the hypothesis that lower than normal right cardiac sympathetic activity is the basic pathogenetic defect of LQTS.

The multiphasic distribution and a high nondipolar content noted on eigenvector analysis may indicate local disparities in recovery duration, thus providing a mechanism for vulnerability to malignant arrhythmias. Also, the presence of afterdepolarizations that may contribute to the genesis of arrhythmias in patients with LQTS would produce similar local disparities in duration of repolarization that would be consistent with the patterns observed in our patients. However, this nondipolar content should not be equated with the actual occurrence of arrhythmias, which still requires an initiating event. Rather, it suggests a condition in which an appropriate trigger, e.g., sympathetic hyperactivity, may more easily lead to the development of arrhythmias.

We express our gratitude to Ralph Lazzara, M.D., Oklahoma City, for helpful criticism and for reviewing the manuscript; to Dr. Emilio Macchi, Ph.D., Parma, for contributing to the eigenvector analysis; to Mrs. Carla Zanchetti for the art work; and to Dr. Laura Locati for typing the manuscript.

Appendix

The principal component analysis described by Lux et al. was performed on the integral maps obtained in our study population. The mathematical procedures adopted were the following.

Let \( M = \mathbf{M} \) be a 140 × \( p \) matrix, where \( p \) is the number of patients and 140 is the number of body surface lead points from each patient (1 < \( i \) < 140, 1 < \( j \) < \( p \)). Then \( m_{ij} \) represents the time integral of the potential at the \( i \)th lead point for the \( j \)th patient.

Let \( \mathbf{M}_j = [m_{1j}, m_{2j}, \ldots, m_{140j}] \) be the column vector representing the isointegral map for the \( j \)th patient. If a set of orthogonal vectors \( \mathbf{C}_k = [C_{1k}, C_{2k}, \ldots, C_{140k}] \) in a 140-dimensional space is chosen, then for each \( \mathbf{M}_j \):

\[
\mathbf{M}_j = \sum_{i=1}^{140} a_{ij} C_{ik} + \mathbf{E}_j
\]

where \( a_{ij} = \sum_{i=1}^{140} m_{ij} C_{ik} \).

It can be shown that if the vectors \( \mathbf{C}_k \) are the eigenvectors of the matrix of the mixed second moments of \( M \), there exists an integer \( q \) smaller than 140:

\[
\mathbf{M}_j = \sum_{i=1}^{q} a_{ij} C_{ik} + \mathbf{E}_j
\]

so that vector \( \mathbf{E}_j \), representing the truncation error, is minimized. Vectors \( \mathbf{C}_k \) are ordered according to the corresponding decreasing eigenvalues. In this way, we can represent each map as a weighted sum of a limited number (\( = q \)) of fundamental vectors \( \mathbf{C}_1, \ldots, \mathbf{C}_q \), but for a small representation error \( \mathbf{E}_j \).

The values of the elements of eigenvectors \( \mathbf{C}_1, \ldots, \mathbf{C}_q \) are reported in a format representing the thoracic surface (or eigenvector contour map) showing the body surface distribution relating to each eigenvector. Each coefficient \( a_{ij} \) indicates the weight of the pattern distribution represented by the eigenvector \( \mathbf{C}_k \) on the map of the \( j \)th subject. The elements of eigenvector \( \mathbf{C}_k \) are dimensionless, because the vector is normalized, and it shows only one type of distribution; the dimension of that distribution (\( \mu V/cm \) in our maps) is expressed by the coefficient \( a_{ij} \).

The first 15 eigenvalues and eigenvectors were calculated from the matrix of the mixed second moments of our entire sample (cases and controls) by means of an iterative method. The “information content” of the \( i \)th eigenvector as a percentage of the total information content of the sample matrix \( M \) was calculated as:

\[
\frac{\lambda_i}{\text{trace}(M)} \cdot 100
\]

where \( \lambda_i \) is the \( i \)th eigenvalue and \( K \) is the matrix of the mixed second moments of \( M \). Thus, further analyses were limited to the last eigenvector showing an information content greater than 0.25%.

Coefficients \( a_{ij} \) relating to each eigenvector and to each subject were calculated; mean values of these coefficients relating to each eigenvector were separately calculated for the two study groups. Moreover, the cumulative contribution of a group of eigenvectors to the total map content was calculated as:

\[
\text{PC}_{r,q} = \sum_{k=r}^{s} a_{ij}^2 \sum_{i=1}^{140} m_{ij} \cdot 100
\]

where \( \text{PC}_{r,q} \) represents the percent contribution of eigenvectors from \( C_r \) to \( C_s \) to the total map content of the \( j \)th subject.

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