Transmural Differences in Myocardial Contraction in Long-QT Syndrome
Mechanical Consequences of Ion Channel Dysfunction

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Background—Long-QT syndrome (LQTS) is characterized by prolonged myocardial action potential duration. The longest action potential duration is reported in the endomyocardium and midmyocardium. Prolonged action potential duration in LQTS may cause prolonged cardiac contraction, which can be assessed by strain echocardiography. We hypothesized that myocardial contraction is most prolonged in subendocardial myofibers in LQTS patients and that inhomogeneous transmural contraction is related to the risk of spontaneous arrhythmia.

Methods and Results—We included 101 genotyped LQTS mutation carriers and 35 healthy individuals. A history of cardiac arrhythmias was present in 48 mutations carriers, and 53 were asymptomatic. Myocardial contraction duration was assessed by strain echocardiography as time from the ECG Q wave to peak strain in 16 LV segments. Strain was assessed along the longitudinal axis, predominantly representing subendocardial fibers, and along the circumferential axis, representing midmyocardial fibers. Mean contraction duration was longer in LQTS mutation carriers compared with healthy individuals (445 ± 45 versus 390 ± 40 milliseconds; P < 0.001) and longer in symptomatic compared with asymptomatic LQTS mutation carriers (460 ± 40 versus 425 ± 45 milliseconds; P < 0.001). Contraction duration by longitudinal strain was longer than by circumferential strain in symptomatic LQTS patients (460 ± 45 versus 445 ± 45 milliseconds; P = 0.008) but not in asymptomatic patients and healthy individuals, indicating transmural mechanical dispersion. This time difference was present in a majority of LV segments and was most evident in patients with LQT2 and the Jervell and Lange-Nielsen syndrome.

Conclusion—Contraction duration in symptomatic LQTS mutation carriers was longer in the subendocardium than in the midmyocardium, indicating transmural mechanical dispersion, which was not present in asymptomatic and healthy individuals. (Circulation. 2010;122:1355-1363.)

Key Words: echocardiography ■ long QT syndrome ■ torsade de pointes ■ transthoracic echocardiography ■ arrhythmia

The long-QT syndrome (LQTS) is due to inherited cardiac ion channel defects and predisposes to life-threatening ventricular arrhythmias and sudden cardiac death. Its prevalence has been estimated as 1 in 2000.1 LQTS-related ion channels defects lead to prolonged cardiac action potential duration (APD). The degree of action potential prolongation and dispersion in timing of action potential repolarization have been considered the major mechanisms behind the ventricular arrhythmias in these patients. Earlier invasive studies have indicated that the duration of the cardiac action potential is not homogeneous throughout the myocardium in either normal or genetically altered myocardial tissue.2-3 The longest APD in LQTS models has been reported in endocardial Purkinje cells and in subendocardial to midmyocardial cells (M cells).4-5 Transmural differences in APD have been considered to be of major importance in arrhythmogenesis in LQTS patients.6 However, it has been challenging to assess APD and dispersion in patients. Attempts to estimate action potential dispersion in terms of QT dispersion have not been clinically useful.7

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Left ventricular (LV) function has been considered normal in LQTS patients. There is, however, support for the assumption that subtle electric changes may cause mechanical dysfunction. Nador et al8 and De Ferrari et al9 have reported wall motion abnormalities in LQTS patients. We recently
reported prolonged myocardial contraction duration and pronounced mechanical dispersion assessed by echocardiographic velocity measurements in patients with LQTS, and these mechanical abnormalities were associated with a higher risk of cardiac arrhythmias. These results supported that the electric mechanisms for arrhythmia in LQTS may be translated into mechanical contraction abnormalities, including prolongation and dispersion of myocardial contraction duration.

Myocardial strain measurements have been proven to be superior for assessment of regional LV function. The subendocardium consists mainly of longitudinal myocardial fibers, whereas the midmyocardium consists mainly of circumferentially oriented fibers. As a result of this myocardial fiber geometry, strain measurements are able to indirectly discriminate between transmural contraction differences (ie, differences between subendocardial and midmyocardial layers).

We hypothesized that myocardial contraction is inhomogeneously prolonged throughout the LV in LQTS patients and that the longest contraction duration is located in the subendocardium where the longest APD has been reported. Furthermore, we wanted to investigate whether the heterogeneity of prolonged contraction is related to specific genotypes and the risk for spontaneous arrhythmia in LQTS patients.

**Methods**

**LQTS Mutation Carriers**
A total of 101 genotyped LQTS mutation carriers were included in this study. Sixty-four patients were heterozygous for a mutation in the LQT1 locus and 26 in the LQT2 locus. Only 1 patient was heterozygous for a mutation in the LQT3 locus and 1 in the LQT5 locus. A relatively high proportion of the study patients (n=9) were homozygotes or compound heterozygotes for mutations in the LQT1 locus (Jervell and Lange Nielsen syndrome [JLNS]). In all, 48 (48%) had a history of documented arrhythmia, syncope, or cardiac arrest, defined here as symptomatic, and 53 (52%) were asymptomatic mutation carriers who were recruited from family cascade genetic screening. β-Blocker medications at the time of the examination used in the study were metoprolol succinate in 37 patients (113±47 mg/d), timolol in 7 patients (15±3 mg/d), propranolol in 6 patients (188±106 mg/d), and bisoprolol (10±0 mg/d) in 2 patients. In addition to β-blocker therapy, 6 mutation carriers were treated with an implantable cardioverter-defibrillator and 3 with an atrial pacemaker. One JLNS patient was also treated with left sympathetic denervation. None of the LQTS patients had structural heart disease of other origin. We did not include asymptomatic mutation carriers <18 years of age because we regarded them as too young to be classified as truly asymptomatic.

**Control Group**
Healthy individuals from the hospital staff (n=35) with age and sex corresponding to the patients were recruited as a control group for the echocardiographic measurements. ECG, heart rate correction of the QT interval (QTc), and echocardiography showed normal findings in all healthy individuals.

Written informed consent was given by all study participants. The study was approved by the Regional Committee for Medical Research Ethics.

**Electrocardiography**
Twelve-lead ECG was obtained at the time of echocardiographic examination. The Bazett formula was used for QTc. QTc dispersion was measured as the difference between longest and shortest QTc intervals in any of the 12 ECG leads.

**Echocardiographic Studies**
The echocardiographic studies were performed on a Vivid 7 (GE Healthcare, Horten, Norway). Data were analyzed with EchoPAC (GE Healthcare). LV ejection fraction was assessed with the Simpson method from 2-dimensional echocardiography.
Myocardial Strain Measurements

We assessed longitudinal and circumferential strains by the speckle tracking technique\textsuperscript{17} with a frame rate of 76±18 frames per second. Three cardiac cycles were analyzed.

We assessed the following parameters from myocardial strain: maximum myocardial shortening (Figure 1); global strain calculated as the average of longitudinal maximum myocardial shortening from 16 LV segments; time from ECG onset of the Q wave (onset of the R wave if the Q wave was absent) to maximum myocardial shortening defined as contraction duration (Figure 1); SD of the 16 longitudinally measured and 6 circumferentially measured contraction durations calculated as parameters of mechanical dispersion; time difference between the longest and shortest contraction durations defined as delta contraction duration in the longitudinal and circumferential directions; and transmural mechanical dispersion expressed by the time difference in longitudinal and circumferential contraction durations of the 6 basal LV segments (Figure 2).

Because tissue Doppler imaging (TDI) had higher temporal resolution (129±28 frames per second) compared with speckle tracking measurements, TDI recordings of the LV were obtained from the apical 4-chamber, 2-chamber, and long-axis views as previously described.\textsuperscript{10}

Heart rate was recorded at time of echocardiographic examination, and all echocardiographic time measurements were corrected for heart rate with the Bazett formula.\textsuperscript{14} Myocardial strain could be assessed in 98\% of the myocardial segments in LQTS mutation carriers and in 94\% of the segments in the healthy individuals. The primary analysis was done by a single observer and repeated in a blinded fashion. For contraction duration, intraobserver, interobserver, and test-retest intraclass correlations were 0.96, 0.96, and 0.87, respectively; for mechanical dispersion, they were 0.98, 0.89, and 0.79, respectively. The corresponding QTc and QTc dispersion test-retest intraclass correlations were 0.82 and 0.67, respectively.

Statistical Analyses

Continuous data are presented as mean±SD or as median (range). Comparisons of means between groups of patients were performed by unpaired Student t test (SPSS 15.0, SPSS Inc, Chicago, Ill). The paired t test was used for all comparisons within the same patient. Comparisons of proportions were performed by the Fisher exact test. Receiver-operating characteristic (ROC) curves were created for longitudinal mechanical dispersion and QTc to determine the discrimination of these parameters, ie, the ability to distinguish between LQTS mutation carriers with and without cardiac events (documented arrhythmia, syncope, or cardiac arrest). The optimal cutoff value for mechanical dispersion was defined as the value from the ROC curve closest to the top left corner. The sensitivity and specificity for the optimal cutoff value were reported. For QTc, the established cutoff value of 460 milliseconds was used.\textsuperscript{18} The area under the ROC curve (AUC) was calculated for both parameters, and comparison between AUCs\textsuperscript{19} was performed with the Analyze-it software. For all statistical analyses, P values were 2 sided. Values of \( P<0.05 \) were considered statistically significant.

Results

Myocardial Function in LQTS Patients

Clinical characteristics and echocardiographic data are presented in Table 1. Age and heart rate were similar in LQTS

<table>
<thead>
<tr>
<th></th>
<th>Healthy Individuals (n=35)</th>
<th>LQTS Patients (n=101)</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>34±10</td>
<td>37±16</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±10</td>
<td>65±13</td>
<td>0.27</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>20 (57)</td>
<td>71 (70)</td>
<td>0.21</td>
</tr>
<tr>
<td>EF, %</td>
<td>64±5</td>
<td>64±6</td>
<td>0.83</td>
</tr>
<tr>
<td>Global strain, %</td>
<td>−22.6±2.0</td>
<td>−21.4±1.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean contraction duration, longitudinal, ms</td>
<td>390±40</td>
<td>445±45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean contraction duration, circumferential, ms</td>
<td>385±45</td>
<td>430±50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical dispersion, longitudinal, ms</td>
<td>20±7</td>
<td>36±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical dispersion, circumferential, ms</td>
<td>14±11</td>
<td>36±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta contraction duration, longitudinal, ms</td>
<td>55±20</td>
<td>110±50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta contraction duration, circumferential, ms</td>
<td>25±25</td>
<td>88±55</td>
<td>&lt;0.001</td>
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</table>

\( \text{EF} \) indicates ejection fraction. Values are mean±SD when appropriate. \( P \) values are from unpaired t test and Fisher exact test.
patients and healthy individuals. Ejection fraction was normal in LQTS subjects regardless of previous arrhythmias. LQTS patients had longer QTc compared with healthy individuals (480±45 versus 390±20 milliseconds; \( P<0.001 \)). Despite apparently normal systolic LV function, mean contraction duration was significantly longer in LQTS patients compared with healthy individuals in longitudinal and circumferential measurements (both \( P<0.001 \)). The abnormal myocardial function in LQTS mutation carriers was further confirmed by a significantly more pronounced mechanical dispersion (heterogeneous contraction) compared with healthy individuals (\( P<0.001 \)). Finally, delta contraction duration, reflecting the difference between the longest and shortest contraction durations, was prolonged in LQTS patients (\( P<0.001 \)). Global strain as a marker of systolic function was within normal range in LQTS patients but was significantly reduced compared with healthy individuals (\( P=0.009 \)).

### Results in Symptomatic Compared With Asymptomatic LQTS Mutation Carriers and Arrhythmia Risk Evaluation

Symptomatic LQTS mutation carriers had longer QTc (\( P<0.001 \)) and pronounced QTc dispersion (\( P=0.04 \)) compared with asymptomatic mutation carriers (Table 2). Mean contraction duration was longer in symptomatic LQTS mutation carriers compared with asymptomatic carriers in longitudinal (\( P<0.001 \)) and circumferential (\( P=0.03 \)) measurements. In symptomatic LQTS patients, mean contraction duration measured by longitudinal strain was significantly longer compared with circumferential strain (460±45 versus 445±45 milliseconds; \( P=0.008 \)), reflecting transmural mechanical dispersion. Significant differences between subendocardial and midmyocardial contraction durations were present in the following segments in symptomatic LQTS mutation carriers: posterior septal: 465±60 milliseconds for longitudinal versus 415±50 milliseconds for circumferential, \( P<0.001 \); anterior septal: 470±65 milliseconds for longitudinal versus 440±60 milliseconds for circumferential, \( P=0.04 \); anterior segment: 485±65 milliseconds for longitudinal versus 445±65 milliseconds for circumferential, \( P=0.02 \); posterolateral segment: 480±50 milliseconds for longitudinal versus 425±65 milliseconds for circumferential, \( P=0.01 \); and posterior segment: 480±65 milliseconds for longitudinal versus 440±65 milliseconds for circumferential, \( P=0.003 \). In asymptomatic LQTS mutation carriers and healthy individuals, there were no significant differences in mean contraction duration measured by longitudinal compared with circumferential strain (\( P=0.31 \) and \( P=0.99 \), respectively), indicating an absence of transmural mechanical dispersion.

Mechanical dispersion, assessed as the SD of contraction duration, was significantly greater in symptomatic LQTS mutation carriers compared with asymptomatic patients in both strain directions (\( P<0.001 \); Table 2 and Figure 3). The time differences between the longest and the shortest contraction durations longitudinally and circumferentially (delta contraction durations) were significantly longer in symptomatic LQTS mutation carriers (\( P<0.001 \)). As determined by ROC analysis, longitudinal mechanical dispersion could better discriminate between LQTS mutation carriers with and without cardiac events compared with QTc with an AUC of 0.87 (95% confidence interval [CI], 0.79 to 0.94; Figure 4). The AUC for mechanical dispersion was significantly higher compared with the AUC for QTc (AUC, 0.71; 95% CI, 0.61 to 0.81; \( P<0.01 \)). QTc ≥460 milliseconds showed a sensitivity of 42% (95% CI, 29 to 57) and a specificity of 81% (95% CI, 67 to 91) for identifying mutation carriers with a history of events. The optimal cutoff value for mechanical dispersion was ≥33 milliseconds and identified mutation carriers with a history of events with a sensitivity of 76% (95% CI, 61 to 87) and a specificity of 91% (95% CI, 78 to 98). There was a modest but significant correlation between QTc dispersion by ECG and mechanical dispersion by echocardiography (\( r=0.30 \), \( P=0.007 \)).

The echocardiographic study was repeated in 10 patients after a median of 16 months (range, 6 to 38 months). No changes in medication were initiated in these patients between the 2 echocardiographic studies. Contraction duration and mechanical dispersion did not change significantly over time. Contraction durations at the first and second echocardiographic studies were 465±65 and 435±30 milliseconds, respectively (\( P=0.12 \)). Mechanical

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### Table 2. Clinical Characteristics and Echocardiographic Findings in 53 Asymptomatic and 48 Symptomatic LQTS Mutation Carriers

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic LQTS Patients (n=53)</th>
<th>Symptomatic LQTS Patients (n=48)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±14</td>
<td>32±16</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±13</td>
<td>64±13</td>
<td>0.22</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>32 (60)</td>
<td>39 (81)</td>
<td>0.03</td>
</tr>
<tr>
<td>EF, %</td>
<td>64±6</td>
<td>64±5</td>
<td>0.50</td>
</tr>
<tr>
<td>Global strain, %</td>
<td>−21.2±1.6</td>
<td>−21.5±1.9</td>
<td>0.41</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>460±30</td>
<td>495±50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc dispersion, ms</td>
<td>48±17</td>
<td>56±23</td>
<td>0.04</td>
</tr>
<tr>
<td>LQT1, n (%)</td>
<td>40 (75)</td>
<td>24 (50)</td>
<td>0.005</td>
</tr>
<tr>
<td>LQT2, n (%)</td>
<td>12 (23)</td>
<td>14 (29)</td>
<td>0.81</td>
</tr>
<tr>
<td>LQT3, n (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>LQT5, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.48</td>
</tr>
<tr>
<td>JLNS, n (%)</td>
<td>0 (0)</td>
<td>9 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean contraction duration, longitudinal, ms</td>
<td>425±45</td>
<td>460±40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean contraction duration, circumferential, ms</td>
<td>415±55</td>
<td>440±45</td>
<td>0.03</td>
</tr>
<tr>
<td>Mechanical dispersion, longitudinal, ms</td>
<td>27±12</td>
<td>45±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical dispersion, circumferential, ms</td>
<td>26±21</td>
<td>46±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta contraction duration, longitudinal, ms</td>
<td>85±40</td>
<td>130±50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta contraction duration, circumferential, ms</td>
<td>55±50</td>
<td>100±55</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction. Values are mean±SD when appropriate. \( P \) values are from unpaired t test and Fisher exact test.
dispersions at the same occasions were 43±19 and 37±10 milliseconds (P=0.17).

All longitudinal time measurements were repeated by the TDI method because of the higher temporal resolution. These time measurements showed results similar to those of speckle tracking (data not presented). The intraclass correlation between contraction duration by TDI and the speckle tracking technique was 0.84.

β-Blocker therapy was more common in symptomatic LQTS mutation carriers (85%) compared with asymptomatic carriers (21%; P<0.001). However, heart rate at the time of echocardiographic examination was not significantly different in the 2 groups (Table 2).

**Genotype Subgroup Analyses**

Subgroup analyses of LQT1 (n=64) and LQT2 (n=26) single-mutation carriers did not show significant differences in QTc (470±35 versus 470±30 milliseconds; P=0.85) or mean contraction duration longitudinally (435±45 versus 445±50 milliseconds; P=0.50) or circumferentially (430±55 versus 420±45 milliseconds; P=0.40). Longitudinal mechanical dispersion tended to be more pronounced in LQT2 compared with LQT1 patients (37±14 versus 31±14 milliseconds; P=0.10). In double-mutation carriers (JLNS patients; n=9), QTc was prolonged compared with single-mutation carriers (560±50 versus 470±35 milliseconds; P=0.001). Mean longitudinal contraction duration was prolonged (475±35 versus 440±45 milliseconds; P=0.02), but not in the circumferential direction (430±45 versus 430±50 milliseconds; P=0.98), compared with single-mutation carriers. Longitudinal mechanical dispersion was more pronounced in JLNS patients compared with single-mutation carriers (54±13 versus 34±14 milliseconds; P=0.002).

Figure 5 demonstrates that transmural mechanical dispersion was prominent in LQT2 patients in the posterior septal, anterior septal, and anterior segments. Transmural mechanical dispersion was not present in asymptomatic LQT2 mutation carriers. In JLNS patients, significant transmural mechanical dispersion was present in the posterior septal, anterior septal, anterior, posterolateral, and posterior segments. In LQT1 single-mutation carriers, transmural mechanical dispersion did not reach significant levels in analysis of symptomatic LQT1 patients separately.

**Discussion**

This study confirms that LQTS patients have myocardial contraction abnormalities. A novel observation in the present study was that LQTS patients have abnormally prolonged contraction in the LV long axis, which reflects the function of myocardial fibers located predominantly in the subendocar-
The symptomatic LQTS patients in our study had longer contraction duration in the subendocardial layer compared with the mid layer of the ventricular wall, indicating transmural mechanical dispersion. Transmural differences in contraction durations were present in most LV segments, were related to risk for cardiac arrhythmias, and were most evident in LQT2 and JLNS patients. This study indicates that regional myocardial dysfunction may reflect electric disturbances and may be helpful in exploring arrhythmogenesis in these patients.

Electric Dysfunction and Mechanical Consequences in LQTS
Ion channel defects in LQTS lead to prolonged APD. Ion channels are not homogeneously distributed throughout the myocardium. Defective ion channels will therefore lead to an inhomogeneous prolongation of APD and will ultimately result in dispersion of electric repolarization.2 Findings from LQTS patients have implicated a specific role for early afterdepolarizations and dispersion of electric repolarization in ventricular arrhythmogenesis.20,21 Furthermore, there is strong evidence that early afterdepolarizations lead to prolonged repolarization, which has been linked to myocardial contraction abnormalities.8,26 The findings in our study support that prolonged APD results in prolonged regional ventricular contraction and are in accordance with previous studies.8–10 The pronounced mechanical dispersion found in our LQTS patients was related to ventricular arrhythmias and is likely to reflect electric dispersion. Heterogeneous ventricular contraction can also be caused by fibrosis in myocardial tissue and has been related to ventricular arrhythmias22 and death23 in patients after myocardial infarction.

Dispersion of repolarization can occur between the apex and base, ie, longitudinally and transmurally, and can facilitate the generation of torsade de pointes arrhythmia.25 The measurement of QT dispersion on ECG as an indicator of dispersion of ventricular repolarization was presented as a promising tool in risk stratification of arrhythmias 2 decades ago.15,16 However, the method has not achieved the clinical value initially expected because of challenges in T-wave definition and relatively low reproducibility.7 Our study showed pronounced QTc dispersion in LQTS mutation carriers with arrhythmic events compared with those without arrhythmic events (Table 2). This is in accordance with previous studies showing pronounced QT dispersion in LQTS patients with recurrent arrhythmic events.16 The significant correlation to mechanical dispersion in our study supports the assumption that our echocardiographic findings may reflect electric dispersion of repolarization.

With the method presented in this study, we were able to quantify longitudinal (between the apex and base) and interregional (between the interventricular septum, lateral wall, anterior wall, and posterior wall) mechanical dispersion. In addition, we were able to provide a measure of mechanical transmural dispersion in comparisons of the duration of longitudinal strain with circumferential strain. The fiber orientation in LV is complex. In the subendocardium, the fibers have a predominantly longitudinal direction with an angle of 80° with respect to the circumferential direction.24,25 A recent experimental study demonstrated that differences in the timing of contraction between circumferential and longitudinal shortening in 1 LV segment were attributed to the electric sequence.25 The subendocardial fibers contribute mainly to longitudinal contraction, whereas the midmyocardium fibers contribute mainly to circumferential contraction.13 Therefore, differences in the timing of contraction in these directions reflect the transmural mechanical heterogeneity caused by electric dysfunction.

Mechanical Abnormalities in LQTS Patients
Mean contraction duration was prolonged in LQTS mutation carriers compared with healthy individuals and in symptomatic LQTS mutation carriers compared with asymptomatic carriers. Contraction duration by longitudinal strain (suben-
Electromechanical Interactions in LQTS

Sporadic but consistent awareness that electric alterations in LQTS patients have mechanical consequences has arisen during the past 20 years. We recently reported prolonged myocardial contraction duration and mechanical dispersion by myocardial velocities in LQTS patients that were associated with increased risk for ventricular arrhythmias. However, our recent report and earlier studies were not designed to distinctly quantify separate regions of the myocardium for comparison. In this study, we have used myocardial strain measurements instead of velocity measurements. Myocardial velocities have limited ability to reflect regional myocardial function. In contrast, myocardial strain measurements can identify myocardial dysfunction of a more regional character and can accurately assess myocardial shortening in a distinct part of the ventricle. With this method, we were able to investigate the regional nature of contraction prolongation in LQTS patients.

Clinical Implications

Genetic testing for LQTS has become more available; consequently, family screening has led to asymptomatic family mutation carriers making up a great number of consultations at the outpatient clinic. The overall risk that asymptomatic adult mutation-positive family members will experience spontaneous arrhythmias during their lifetime is low, and in these individuals, QTc has failed to be a significant predictor of outcome. Prophylactic treatment involves lifelong β-blocker therapy. Determining whether these family members are true silent mutation carriers and do not need prophylactic medication is often difficult. By ROC analysis, the best parameter for arrhythmia risk assessment in this study was longitudinal mechanical dispersion. This parameter reflects heterogeneity in regional contraction duration and was superior to QTc in discriminating between LQTS patients with and without arrhythmic events. Our findings suggest that echocardiography might be a complementary tool to QTc in risk stratification of LQTS mutation carriers and may provide added value in risk stratification of asymptomatic adult mutation carriers.

Limitations

The relationship between mechanical dispersion and electric dispersion should be studied in invasive electrophysiological studies. It may be speculated that β-blocker medication might influence contraction duration and our data. However, heart rate was not significantly different in asymptomatic and symptomatic patients, and all time measurements were corrected for heart rate by the Bazett formula. In addition, our recent study comparing healthy individuals on β-blocker medication with LQTS patients could not attribute prolonged contraction duration to the use of β-blocker medication. Our study did not provide data that demonstrated that LQTS patients with pronounced mechanical dispersion had a higher risk of future arrhythmic events. This requires a

docordial layers) was significantly longer than by circumferential strain (midmyocardial layers) in symptomatic LQTS patients. These findings indicate a transmural mechanical dispersion in symptomatic LQTS patients that was not present in asymptomatic and healthy individuals. These mechanical findings are in accordance with previous electric LQTS models reporting the longest APD in Purkinje cells and M cells located in the subendocardium and midmyocardium. The APD of subendocardial Purkinje fibers in vitro has been reported to be even longer than in the M cells, but the delayed repolarization of the Purkinje system has failed to register on the ECG. Purkinje cells are found in the His bundle and bundle branches and cover much of the endocardium. The transmural mechanical dispersion in this study may represent the transmural electric dispersion of repolarization that is shown to be present in LQTS models and is suggested to be a strong arrhythmogenic factor. In symptomatic LQT2 patients, the transmural dispersion was present in the interventricular septum and anterior LV wall. Septal cells may play a specific role in arrhythmogenesis in LQTS. It has been indicated that M cells in the interventricular septum are located in the deep subendocardium and exert a strong electrotonic influence to prolong APD in neighboring endocardial cells. Despite the limited number of genotype subgroup participants, transmural mechanical dispersion was pronounced in LQT2 patients and patients with JLNS. This finding may indicate genotype-specific differences in electric dispersion and are in accordance with the higher arrhythmic risk in patients with these genotypes.

Interestingly, our study indicates that novel echocardiographic methods can detect prolonged contraction in the subendocardial layers and support experimental electrophysiological reports. Our findings support the idea of LQTS as a regional disease, with the most prolonged contraction duration in the subendocardium in mutation carriers with arrhythmias. Future studies are needed to explore whether contraction abnormalities can add information about arrhythmogenicity in other channelopathies.

Global strain has been reported as a sensitive marker of systolic function. Global strain was within the normal range in LQTS patients but was reduced compared with healthy individuals. This finding may indicate that the contraction abnormalities in these patients may lead to subclinical impairment of myocardial function.
prospective study in which so far asymptomatic and untreated patients are followed up for an adequate period of time. This study design is difficult for ethical reasons.

Conclusions

LQTS patients have regional myocardial dysfunction that can be assessed by myocardial strain. Myocardial contraction duration is prolonged in LQTS mutation carriers and most prolonged in those with arrhythmic events. LQTS mutation carriers with arrhythmic events have longer contraction duration in the subendocardial layer compared with the mid layer of the ventricular wall, indicating transmural mechanical dispersion that is not present in asymptomatic LQTS mutation carriers and healthy individuals. Transmural dispersion is located predominantly in the interventricular septum and anterior LV wall in LQT2 patients and patients with JLNS.

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Disclosures

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We thank all the patients and control subjects who participated in this study.

References

The long-QT syndrome (LQTS) is due to inherited cardiac ion channel defects and predisposes to life-threatening ventricular arrhythmias and sudden cardiac death. Current risk stratification of ventricular arrhythmias is based on a history of syncope or documented arrhythmia, heart rate–corrected QT interval on the ECG (QTc), gender, and genotype. However, QTc is insufficient as a significant predictor of arrhythmic outcome. LQTS has traditionally been regarded as a purely electric disease. Strain by echocardiography can accurately quantify regional myocardial timing and function. Echocardiography was performed in 101 genotyped LQTS patients (53 asymptomatic and 48 with a history of cardiac arrhythmias) and 35 healthy control subjects. Left ventricular contraction pattern by strain was assessed as time from the ECG Q wave to maximum myocardial shortening in 16 LV segments. Strain was assessed along the longitudinal axis, predominantly representing subendocardial fibers, and along the circumferential axis, representing midmyocardial fibers. This study shows that LQTS patients have abnormal LV contraction patterns. Contraction duration was longer and more heterogeneous in symptomatic LQTS mutation carriers compared with asymptomatic patients. In addition, contraction duration was longer in the subendocardium than in the midmyocardium, indicating a pronounced transmural mechanical dispersion that was not present in asymptomatic and healthy individuals. Our findings suggest that echocardiography might be a complementary tool to QTc and may provide added value in risk stratification of LQTS mutation carriers.
Transmural Differences in Myocardial Contraction in Long-QT Syndrome: Mechanical Consequences of Ion Channel Dysfunction
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