Electrocardiographic risk stratification in families with congenital long QT syndrome

Gerold Mönnig1,2*, Lars Eckardt1,2, Horst Wedekind1,2, Wilhelm Haverkamp1,2+, Joachim Gerss3, Peter Milberg1,2, Kristina Wasmer1, Paulus Kirchhof1,2, Gerd Assmann2, Günter Breithardt1,2, and Eric Schulze-Bahr1,2

1 Department of Cardiology and Angiology, Medizinische Klinik und Poliklinik C, University Hospital Münster, Albert-Schweitzer-Str. 33, D-48149 Münster, Germany; 2 Department of Molecular Cardiology, Leibniz-Institute of Arteriosclerosis Research at the University of Münster, Germany; and 3 Coordinating Centre for Clinical Trials, University Hospital Münster, Germany

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Aims The QT interval in the surface ECG is one of the most often used risk stratifiers in families with congenital long QT syndrome (LQTS). The best ECG lead for clinical management of LQTS families remains unclear.

Methods and results The predictive power of the QTc interval in all ECG leads was studied in 200 consecutive genotyped LQTS family members to identify mutation carriers (n = 103; age: 35 ± 19 years) and high-risk LQTS patients (n = 16 with survived sudden cardiac arrest) using receiver operating curve (ROC) analysis (ROC = area under curve). Additionally, the risk for events (syncope and sudden cardiac arrest) was calculated for QTc decile in all individuals. The predictive power was highest in lead II and lead V5 for identifying carriers in LQTS families. These ECG leads were optimal for risk stratification (ROC range 0.83–0.87). In these leads, positive predictive value (PPV) and negative predictive value (NPV) were highest for suggested QTc cut-offs (440 and 500 ms) for identification of LQTS mutation carriers and high-risk patients (PPV between 78–81 and 73–80%, respectively). The risk for events in QTc deciles increased exponentially from 10 to 80% and was 40% for QTc > 500 ms.

Conclusion On the basis of these data, QTc is the best diagnostic and prognostic ECG parameter in LQTS families. A single measurement should be obtained in lead II if measurable and then in left precordial leads (preferably V5) as a second choice.

Introduction
The long QT syndrome (LQTS) is characterized by a prolonged QT interval in the surface ECG and the propensity to life-threatening ventricular tachyarrhythmias.1,2 Molecular and structural investigations have revealed mutations in seven genes which cause altered expression, function, or regulation (LQT4) of cardiac ion channels.3,4 As the first manifestation of this disease may be fatal, it is crucial to identify clinical markers for asymptomatic family members.5 While diagnostic genetic testing remains still laborious due to the extensive genetic heterogeneity, the diagnosis of LQTS relies primarily on determination of the rate-corrected QT interval (QTc) from a standard 12-lead ECG, T-wave morphology, and on clinical presentation. For this reason, it is helpful for clinical management of these individuals to have a risk stratification algorithm above the genotype.6 Priori et al.6 reported that all mutation carriers with a QTc interval of >500 ms are at high risk for syncope, cardiac arrest, or sudden death and therefore need prophylactic therapy (except for female patients with LQT3 genotype). In that study, all measurements were only obtained in lead II without analysing the predictive power of QTc in other ECG leads for risk stratification. However, the selection of the optimal ECG lead may be crucial because the correct measurement of QTc in these individuals is of great importance for further therapeutic decisions. It is well known that ECG lead selection influences QTc measurement and thereby limits the reliability and accuracy of ECG risk stratification if performed in inconsistent leads.7,8 Therefore, we tested the diagnostic value of QTc interval measured in all 12 ECG leads in identifying LQTS mutation carriers and high-risk LQTS mutation carriers. The goal of the present study was to optimize risk stratification as well as to identify the ideal ECG lead with the best predictive power for established cut-offs for QTc in the management of LQTS families.

*Corresponding author. Tel: +49 251 8347645; fax: +49 251 834 7864. E-mail address: moennig@uni-muenster.de
+ Present address. Department of Cardiology, Campus Virchow Clinic, Charité—University Medicine Berlin, Germany.
Methods

Study patients

Between 1991 and 2004, 39 consecutive and unrelated LQTS families with mutations in the genes coding for cardiac ion channels (12 LQT1; 24 LQT2; 1 LQT3; 2 LQT5) were included in the study. All of them presented to our department for LQTS risk assessment. Altogether 200 individuals, LQTS patients and their family members, with available 12-lead ECG, complete history, and family history were analysed. The family size of analysed individuals ranged between three and 11 family members (mean 5.1). In 16 of the families, there was a history of sudden cardiac death (SCD). The study population was divided into five groups according to genotype and phenotype (carriers/non-carriers; symptomatic/asymptomatic; high risk) (Figure 1). LQTS gene carriers were defined by the presence of a mutation in the genes known to cause LQTS. Non-carriers were defined by the absence of the family-specific LQTS mutation. Symptomatic patients were defined as patients with history of LQTS-specific syncope and/or survived cardiac arrest (SCA), those with SCA were defined as high risk. QTc is the heart rate corrected QT interval in milliseconds.

As QTc mean multiplied with uncorrected dispersion of QT. This parameter has been shown to put additional and independent power on (QTmax - longest and the shortest value measured in each of the 12 leads). The QT dispersion was calculated as the difference between the lead mean of the rate corrected QT interval in all 12 ECG leads. Rate using Bazett's equation.10 QTc mean was defined as the inter-index patients. All available family members were genetically screened for the presence of the family-specific mutation.

ECG analysis

In all individuals studied, the baseline ECG off-without any repolarization-prolonging drugs or beta-blockers was analysed by a single investigator, blinded to clinical symptoms and results of genetic analyses, using a Houston Instruments graphic pad (HIPAD Plus™, model: 9012E-00). The exact ECG analysis procedure has previously been reported.9 QT interval was corrected for heart rate using Bazett’s equation.10 QTc mean was defined as the inter-lead mean of the rate corrected QT interval in all 12 ECG leads. The QT dispersion was calculated as the difference between the longest and the shortest value measured in each of the 12 leads (QTmax – QTmin). For all individuals, the QT product was calculated as QTc mean multiplied with uncorrected dispersion of QT. This parameter has been shown to put additional and independent power on identification of mutation carriers when adjusted for sex and age in a logistic regression analysis in a prior analysis.9 Leads in which the end of the T-wave could not be precisely defined were excluded from analysis. The QTc of >440 ms was defined as being prolonged11 and was tested for identifying LQTS mutation carriers in this cohort. Data from the international LQTS registry suggested a QTc of >470 ms with the best positive predictive value (PPV) in LQTS families.12 Therefore, we tested this cut-off to further categorize LQTS patients according to symptoms. A QTc of >500 ms has been shown to be associated with high risk for cardiac events in LQTS patients6 and was chosen for SCA risk stratification in this study.

DNA amplification and sequencing

Genomic DNA was extracted from peripheral blood leukocytes following standard procedures.7 The KCNQ1 (LQT1), HERG (LQT2), SCN5A (LQT3), KCNE1 (LQT5), and KCNE2 (LQT6) genes were analysed by direct sequencing (BDT 3.0, Applied Biosystems) following pre-defined analysis levels (A: LQT1 + 2; B: LQT3; C: LQT5 + 6). In each level, all coding gene regions of the probands DNA were completely analysed by polymerase chain reaction and followed by direct sequencing on a solid support as described.9 Analysis was stopped after a level was completed and a mutation was identified. In family members, analysis was only performed in the mutant region.

Statistical analysis

Continuous data are presented as mean ± standard deviation. Univariate analysis was performed on the basis of generalized linear models. In the case of discrete and continuous parameters, a logit and identity link function was established, respectively, corresponding to binomial and normally distributed outcomes. Parameter estimation was performed by means of GEE (generalized estimating equations), followed by Wald-type hypothesis tests. Family relations were accounted for by assuming an exchangeable working correlation structure.

In order to perform sensitivity analysis of the lead selection procedure, a resampling approach was applied. Bootstrap samples were randomly generated from original data by drawing with replacement 200 patients each. Using each such sample, ECG leads were ranked corresponding to respective values of 'area under curve (AUC) + measurability'. Analysing 100 bootstrap samples in this way, each ECG lead was assigned 100 ranks ranging from 1 to 12, respectively. The set of ranks of a certain ECG lead shows its

Figure 1 Subgroups of analysed LQTS families. LQTS gene carriers were defined by the presence of a mutation in the genes known to cause LQTS. Non-carriers were defined by the absence of the family-specific LQTS mutation. Symptomatic patients were defined as patients with history of LQTS-specific syncope and/or SCA, those with SCA were defined as high risk. QTc is the heart rate corrected QT interval in milliseconds.
predictive power, subject to population changes. The results of sensitivity analyses (data not shown) confirm the main results derived from original data (discussed subsequently).

All results are interpreted exploratively. $P$-values are regarded as explorative metrics that are considered statistically significant in the case of $P < 0.05$. No adjustment of significance levels for multiple testing is conducted.

Receiver operating curve (ROC) analysis was performed for interlead QT, mean QT dispersion, QT product, and for QTc, in each ECG lead to evaluate the discriminative power between LQTS mutation carriers and non-carriers as well as high and low-risk LQTS patients. Results are interpreted descriptively. A test which perfectly discriminates between affected and unaffected individuals with an AUC of 1.0, whereas a test with no discriminatory power shows an AUC of 0.5. The optimal ECG lead for management of LQTS families is that with best measurability of QT interval and with best identification of mutation carriers and high-risk LQTS patients. Therefore, the sum of relative measurability and AUC in ROC analysis was calculated for each lead. Those ECG leads with high sum values are most diagnostic and prognostic in combination with a good measurability. Statistical evaluations were performed by means of software packages SPSS 10.0 (SPSS Inc., Chicago, IL, USA), S-PLUS 7.0 (Insightful Corp., Seattle, WA, USA), and SAS 8.2 (SAS Institute, NC, USA).

Results

Some of the clinical characteristics and ECG measurements of genotyped LQTS individuals are summarized in Tables 1 and 2.

All symptomatic LQTS patients [age: 36.4 ± 19; 35 female (67%)] had a typical history of syncope (mean 7.4 ± 10.3 SD; median 3; range: 1–50 syncopes). Most syncopal episodes occurred with adrenergic arousal such as physical activity ($n = 20$), intense emotions ($n = 19$), auditory stimuli ($n = 3$), or swimming ($n = 5$) whereas only 11 occurred under rest or during sleep. No cause of syncope other than suspected or documented Torsade de Pointes could be identified in cardiologic and neurologic workup. In 13 of them (25%), a Torsade de Pointes arrhythmia could be documented. There was a family history of SCD in 30 patients (57.7%, age at SCD: 38.4 ± 15 years). All symptomatic patients were treated with beta-blocker after diagnosis of LQTS. In addition, 14 patients received an implantable cardioverter/defibrillator because of recurrent syncope on beta-blocker therapy or SCA. Sixteen patients (30.7%) had survived a cardiac arrest. This subgroup was defined as high-risk LQTS group.

In the asymptomatic patient group, there were 25 males and 26 females with detected LQTS mutations. Mean age was 32 ± 19 years. By definition, none of these patients had a history of a typical syncope, of malignant ventricular arrhythmias, or of SCA in the past. Two patients had reported a short loss of consciousness during an episode of orthostatic dysregulation. Beta-blocker was advised to all asymptomatic patients after establishing the diagnosis and identification of the familial mutation but only 32 of them (63%) accepted this therapy.

In the non-carrier subgroup, there were 52 males and 45 females (mean age 35 ± 18 years). Ten of these individuals (10%) had a history of syncope (0.5 ± 1.8) not related to LQTS, mostly due to orthostatic dysregulation. None of them presented with documented ventricular tachycardia or SCA.

There were marked differences in the baseline ECGs of these four groups analysed (Tables 1 and 2). In symptomatic patients, the spontaneous cycle length was longer compared with asymptomatic and non-carriers (908, 852, and 841 ms respectively, $P < 0.001$). Comparing cycle length between all LQTS mutation carriers and non-carriers, there was no significant difference (880 vs. 841 ms). QTc interval in all ECG leads, as well as QTc mean, QT product, and QT dispersion, was significantly prolonged in LQTS mutation carriers compared with non-carriers (Table 1). These ECG parameters were longest in symptomatic LQTS carriers compared to all other groups (Table 2). The QTc was prolonged in symptomatic patients for all single ECG leads. QTc interval and QT product were significantly different between all groups (symptomatic, asymptomatic, and non-carrier). There was a trend to even longer ECG parameters in high-risk LQTS carriers compared with the other symptomatic LQTS patients (Table 2).

### Diagnostic and prognostic value of ECG parameters in LQTS families

In ROC analysis, QTc interval (QTc mean) was best for identifying LQTS mutation carriers within the LQTS families compared with QT dispersion and QT product (Figure 2). Additionally, QTc mean presented with the best predictive power in identifying high-risk carriers (ROC 0.86) compared with QT dispersion (ROC 0.65) and QT product (ROC 0.71). The predictive power of QTc in identifying LQTS mutation carriers was best in leads II, aVR, and V5 (Table 3).

Sensitivity and specificity was highest (80 and 83%) for a cut-off of 440 ms to separate LQTS carriers from non-carriers. The PPV and negative predictive value (NPV) were best for these (II, aVR, V5) leads (Table 3). Two of these leads (II and V5) were even optimal to identify high-risk LQTS patients, whereas nearly all chest leads (V2–6)
presented with similar sum of ROC and measurability (Table 4). A cut-off value of QTc >500 ms presented with the highest sensitivity and specificity to identify high-risk patients (75 and 81%, respectively). The PPV and NPV were best for these leads in this subgroup (Table 4). Although there was an overlap in QTc between symptomatic and asymptomatic carriers as well as non-carriers, the best predictive power was reached by QTc mean in ROC analysis (ROC 0.72) to identify mutation carriers at risk for symptoms (SCA and syncope). Likewise, leads II and V5 were most prognostic for symptomatic carriers (ROC 0.74 and 0.73, respectively) and a cut-off of 470 ms presented with the best sensitivity (70%) and specificity (73%).

In conclusion, leads II and V5 were optimal for clinical management of LQTS families in terms of measurability, identification of mutation carriers, and risk stratification, whereas other leads had similar diagnostic values in risk stratification (e.g. V2/3) or identification (aVR) alone.

**Risk stratification for cardiac events by QTc**

The risk for cardiac events such as syncope or SCA increased nearly exponentially for QTc deciles in analysed LQTS families (Figure 3). However, even at the first QTc decile, there were two symptomatic LQTS mutation carriers with syncope and six non-carriers were found in the last three deciles. SCA was present not before the sixth decile with QTc range from 441 to 455 ms. There was a trend to younger age at first cardiac event with longer QTc. At the eighth decile, with a QTc of more than 470 ms, the risk for cardiac events was >20%.

**Discussion**

Our data demonstrate that QTc interval is the best diagnostic and prognostic ECG parameter in LQTS families. Although there is an overlap, this study has proven the cut-off for QTc of >440 ms for identifying LQTS patients, QTc >470 ms classifies LQTS patient with risk for symptoms and a QTc of >500 ms for life-threatening events, respectively. In our cohort, the risk for cardiac events has clearly demonstrated a nearly exponential increase for QTc interval. In this large database, the highest diagnostic and prognostic value (ROC and measurability) in LQTS families has been observed for QTc in leads II and V5 of 12-lead ECGs. Thus, QTc should be obtained in one of these leads if measured in only one ECG lead. However, other leads presented with similar diagnostic (aVR) or prognostic (V2/3) value alone.

The sensitivity of the selected cut-offs was higher in other than the selected leads, especially in risk stratification (e.g. 95% in lead aVL compared with 75% in V5) (Table 4). However, the QT interval in aVL is only measurable in 80% of the whole cohort and in 96% in lead V5. From the clinical point of view, this might be a big difference: the lower the measurability, the more complex is the T-wave morphology.
Table 4  Predictive power of QTc in each ECG lead in identifying high-risk LQTS patients with survived sudden cardiac arrest among LQTS mutation carriers

<table>
<thead>
<tr>
<th>ECG lead</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>aVR</th>
<th>aVL</th>
<th>aVF</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
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<tbody>
<tr>
<td>Measurable QTc (%)</td>
<td>95.1</td>
<td>97.1</td>
<td>70.0</td>
<td>92.2</td>
<td>80.5</td>
<td>86.4</td>
<td>92.2</td>
<td>96.1</td>
<td>98.0</td>
<td>94.2</td>
<td>96.1</td>
<td>92.2</td>
</tr>
<tr>
<td>ROC AUC</td>
<td>0.82</td>
<td>0.85</td>
<td>0.85</td>
<td>0.86</td>
<td>0.94</td>
<td>0.86</td>
<td>0.81</td>
<td>0.83</td>
<td>0.83</td>
<td>0.81</td>
<td>0.83</td>
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<tr>
<td>Standard error</td>
<td>0.05</td>
<td>0.05</td>
<td>0.051</td>
<td>0.025</td>
<td>0.046</td>
<td>0.069</td>
<td>0.052</td>
<td>0.053</td>
<td>0.052</td>
<td>0.054</td>
<td>0.056</td>
<td></td>
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<tr>
<td>95% confidence interval</td>
<td>0.71-0.94</td>
<td>0.75-0.95</td>
<td>0.74-0.96</td>
<td>0.76-0.96</td>
<td>0.90-0.99</td>
<td>0.78-0.96</td>
<td>0.68-0.95</td>
<td>0.73-0.93</td>
<td>0.71-0.92</td>
<td>0.73-0.93</td>
<td>0.72-0.93</td>
<td>0.72-0.95</td>
</tr>
<tr>
<td>ROC + measurability</td>
<td>1.77</td>
<td>1.82</td>
<td>1.55</td>
<td>1.78</td>
<td>1.75</td>
<td>1.72</td>
<td>1.73</td>
<td>1.79</td>
<td>1.79</td>
<td>1.77</td>
<td>1.79</td>
<td>1.75</td>
</tr>
<tr>
<td>Sensitivity (QTc &gt; 500)</td>
<td>62</td>
<td>68</td>
<td>78</td>
<td>81</td>
<td>93</td>
<td>66</td>
<td>73</td>
<td>69</td>
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<td>73</td>
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<tr>
<td>Specificity (QTc &gt; 500)</td>
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<td>84</td>
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<td>82</td>
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<td>79</td>
<td>80</td>
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<td>PPV (QTc &gt; 500)</td>
<td>73</td>
<td>80</td>
<td>67</td>
<td>80</td>
<td>93</td>
<td>73</td>
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<td>73</td>
<td>60</td>
<td>80</td>
<td>73</td>
<td>67</td>
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<td>NNP (QTc &gt; 500)</td>
<td>70</td>
<td>65</td>
<td>43</td>
<td>70</td>
<td>51</td>
<td>70</td>
<td>68</td>
<td>62</td>
<td>62</td>
<td>70</td>
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</table>

ROC analysis was performed for QTc in all ECG leads of 103 LQTS mutation carriers to identify those with survived sudden cardiac arrest (ROC AUC). The percentage of measurable QTc intervals is given for each lead as well as the sensitivity and specificity for a cut-off of 500 ms. In this subanalysis, high-risk LQTS patients can be best identified in lead II and in most of the precordial leads (V2/3/5) according to measurability and predictive power (high 'ROC + measurability', italicized).
In daily clinical practice, QTc measurement in these leads may be associated with high intraobserver as well as interobserver variability and therefore have low predictive accuracy. Therefore, ROC analysis together with measurability might be a better parameter to identify the ‘optimal’ ECG lead.

The clinical identification of potential LQTS mutation carriers as well as risk stratification for syncope and SCD is a challenging task for management of LQTS families. This is important for clinical practice even in the genetic era because genotyping is time-consuming and expensive if it is performed in all family members. Furthermore, family members at risk for SCD should be identified as early as possible and put on adequate treatment.

In the past, several algorithms have been developed to identify affected LQTS family members (e.g. Schwartz score\textsuperscript{13}) and to estimate the risk for symptoms. Recently, Priori et al.\textsuperscript{6} reported a risk algorithm in a large series of LQTS patients. In this algorithm, QTc was by far the most predictive parameter for event-free survival except in LQT3 females but it was measured in only one or a few ECG leads. So far, the strategy of ECG lead selection for QTc measurement has been inconsistent. This is a challenge to the validity of the QTc measurement because it is known that QT interval differs markedly between different leads.\textsuperscript{8} Some investigators have adopted a specific lead (usually lead II) as the standard whenever it is measurable, then using lead V2 as a second choice, and so on. However, until now it is not known which ECG lead has the best predictive power to identify LQTS mutation carriers and those at high risk for symptoms. On the basis of our analysis, of all 12 ECG leads in LQTS families, leads II and V5 seem to be optimal in terms of simplicity and reproducibility. However, it is nearly impossible to estimate the risk for symptoms for LQTS family members only based on one ECG parameter. It is known since the molecular breakthrough in LQTS, that a strict cut-off of 440 ms will lead to misclassification\textsuperscript{12} and that computer-generated ECG interpretation alone will fail to identify LQTS family members at risk.\textsuperscript{14,15} Furthermore, T-wave morphology as well as family history and, last but not least, the identification of the causative

<table>
<thead>
<tr>
<th>QTc decile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with syncope/SCA</td>
<td>2/0</td>
<td>0/0</td>
<td>0/0</td>
<td>2/0</td>
<td>1/0</td>
<td>2/1</td>
<td>4/0</td>
<td>8/3</td>
<td>8/2</td>
<td>15/10</td>
</tr>
<tr>
<td>Mean age at first event</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>31</td>
<td>64</td>
<td>11</td>
<td>19</td>
<td>24</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>No. of LQT1/2/3/5</td>
<td>1/1/0/0</td>
<td>0/0/0/1</td>
<td>2/2/0/1</td>
<td>1/2/0/3</td>
<td>1/5/0/1</td>
<td>4/8/0/1</td>
<td>3/9/0/2</td>
<td>9/8/0/2</td>
<td>7/8/1/1</td>
<td>7/9/1/1</td>
</tr>
</tbody>
</table>

Figure 3  QTc deciles and risk for cardiac events. The risk for syncope and survived cardiac arrest (SCA) are given for all 200 analysed LQTS family members for the deciles of QTc interval. The overall risk in the cohort increased nearly exponentially by QTc deciles. Symptomatic LQTS patients were present in the first decile and non-carriers in the last decile.
mutation can complete sophisticated risk assessment, but only the first two of them are available for experienced cardiologists at the time of family screening.

In our cohort, the risk for cardiac events clearly demonstrated a nearly exponential increase with QTc interval. Interestingly, both curves, for syncope and SCA, run nearly parallel (Figure 3). Thus, QTc might serve as a reliable electrocardiographic predictor for both events. There was no SCA in the first five QTc deciles. In contrast, even a normal QTc might be associated with a risk for syncope in individuals of a LQTS family. This finding confirms that QTc interval is a useful LQTS risk stratifier but fails to exclude a risk for cardiac events (syncope) on its own. Our data confirm previous suggestions by the group of Priori et al.6 to identify LQTS patients with high risk not only for syncope but also for sudden cardiac arrest.

Until routine genetic testing for LQTS becomes available, the ECG will be the cornerstone in management of LQTS families. Our data demonstrate that QTc interval is superior to other ECG parameters in LQTS family analysis and risk stratification. If clinical circumstances require reduction of measurement of selected ECG leads, a single measurement should be obtained in lead II and in one of the left precordial leads (preferably V5) as a second choice. These detailed analyses of all 12 ECG leads confirm previously suggested risk stratification.9 Furthermore, clinical and electrocardiographic data are necessary to rate whether identified mutation carriers are at risk for tachyarrhythmias and sudden death or will stay asymptomatic.

Limitations

Our data were retrospectively analysed. Therefore, the estimated risk must be interpreted with caution because the values of individuals who have already died could not be included in our study (history of SCD in 16 of the analysed families). In contrast, all studies dealing with untreated LQTS patients must be retrospective, although there is an approved benefit of treatment in these patients.

Our genotyped LQTS cohort presents a relatively high number of index patients (n = 39) in relatively small families (average of 5.1 members per family). Those index patients have usually a more severe phenotype according to symptoms or ECG abnormalities than other affected family members, which is why they were the ﬁrst identiﬁed. This might therefore be a bias towards more symptomatic patients compared with the whole LQTS population. In contrast, this cohort is representative for a consecutive LQTS cohort in an electrophysiological specialized medical centre.

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