Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk

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Received 25 November 2013; revised 1 July 2014; accepted 12 August 2014; online publish-ahead-of-print 9 September 2014

Aim
Prolonged and dispersed left-ventricular (LV) contraction is present in patients with long-QT syndrome (LQTS). Electrical and mechanical abnormalities appear most pronounced in symptomatic individuals. We focus on the ‘electromechanical window’ (EMW; duration of LV-mechanical systole minus QT interval) in patients with genotyped LQTS. Profound EMW negativity heralds torsades de pointes in animal models of drug-induced LQTS.

Methods and results
We included 244 LQTS patients from three centres, of whom 97 had experienced arrhythmic events. Seventy-six matched healthy individuals served as controls. QT interval was subtracted from the duration of Q-onset to aortic-valve closure (QAoC) midline assessed non-invasively by continuous-wave echocardiography, measured in the same beat. Electromechanical window was positive in controls but negative in LQTS patients (22 ± 19 vs. −43 ± 46 ms; P < 0.0001), being even more negative in symptomatic than event-free patients (−67 ± 42 vs. −27 ± 41 ms; P < 0.0001). QT, QTc, and QAoC were longer in LQTS subjects (451 ± 57, 465 ± 50, and 408 ± 37 ms, P < 0.0001). Electromechanical window was a better discriminator of patients with previous arrhythmic events than resting QTc (AUC 0.77 (95% CI, 0.71–0.83) and 0.71 (95% CI, 0.65–0.78); P = 0.03). In multivariate analysis, EMW predicted arrhythmic events independently of QTc (odds ratio 1.25; 95% CI, 1.11–1.40; P = 0.001). Adding EMW to QTc for risk assessment led to a net reclassification improvement of 13.3% (P = 0.03). No EMW differences were found between the three major LQTS genotypes.

Conclusions
Patients with genotype-positive LQTS express EMW negativity, which is most pronounced in patients with documented arrhythmic events.

Keywords
Long-QT syndrome • Arrhythmia • Sudden death • Ion channels • Echocardiography

Introduction
The congenital long-QT syndromes (LQTS) are caused by mutations in genes encoding for cardiac ion-channel subunits or ion-channel-associated proteins. To date, at least 15 different genes have been causally implicated. Long-QT syndromes-related ion-channel defects predispose to cardiac action-potential prolongation and accentuate regional and temporal dispersion of repolarization. Genotype-specific pro-arrhythmic conditions can exacerbate repolarization dispersion and lead to the occurrence of...
afterdepolarizations, premature ventricular ectopic beats, and re-entrant excitation. These mechanisms can precipitate torsades de pointes (TdP) in susceptible LQTS patients, but their exact contribution to arrhythmogenesis remains often obscure. Additional mechanisms, including mechano-electrical triggers, appear relevant, but remain to be fully elucidated.2

There have been reports of altered ventricular mechanics in (subsets of) LQTS patients. Using the M-mode, Nador et al.3 demonstrated rapid early contraction and an extended phase of LV-wall thickening before rapid relaxation in 55% of LQTS patients, being most overt in symptomatic individuals. In some, mostly symptomatic, patients a peculiar double-peak pattern of LV-wall thickening before rapid relaxation in 55% of LQTS patients, being observed, possibly the mechanical correlate of early afterdepolarizations. These LQTS-related mechanical abnormalities were normalized by Ca++-channel blocker treatment.4 Similar results were obtained using tissue-Doppler imaging techniques.5,6 Strain-imaging revealed longer contraction duration in the subendocardium than the midmyocardium of symptomatic LQTS-mutation carriers (but less so of asymptomatic or healthy individuals), indicating accentuated transmural mechanical dispersion in the former.7 Prolonged contraction duration and augmented longitudinal mechanical dispersion were superior to QTc for arrhythmia-risk assessment.5,8

Only few studies have addressed indices of electromechanical coupling in LQTS patients. In 1991, Vincent et al.9 reported on the ratio of electrical to mechanical systole in an ungenotyped Romano-Ward family. By measuring QT interval and time from Q-wave to second heart sound (QS2), they demonstrated a prolonged QT/QS2 ratio in rest increasing during exercise (1.12 to 1.45) in Romano-Ward patients with a resting QTc of 490 ms. In controls, QT/QS2 increased only modestly from a rest ratio of <1.0. The relation of QT/QS2 to major arrhythmic events was not examined.9

Experimentally, Gallacher et al.9,10 demonstrated in anesthetized dogs that under baseline conditions the LV-pressure duration outlasts both QT interval and LV-endocardial monophasic-action-potential duration, thus creating a positive so-called ‘electromechanical window’ (EMW).10 Electromechanical window turned very negative during pharmacological I,Ks block just prior to the induction of TdP by beta-adrenergic stimulation.9,10 Within this negative EMW, sizeable LV aftercontractions arose consistently if TdP ensued. This led us to investigate the EMW in a large population of LQTS probands and their asymptomatic genotype-positive family members, under clinically stable conditions. We compared LQTS patients with healthy controls, with and without beta-blocking therapy. All underwent echocardiography with simultaneous standard 3-lead ECG recording to determine the EMW non-invasively. We hypothesized that the EMW is more negative in LQTS patients than in healthy controls, and that profound EMW negativity correlates significantly with major arrhythmic events.

Methods

This study was carried out in accordance with the ethical guidelines of the Declaration of Helsinki. Patients gave written informed consent for DNA diagnostics and echocardiographic research. IRB approval for the retrospective analysis of genotype and echocardiographic phenotype data was provided for the patients evaluated at Mayo Clinic.

Study population

In this case–control, multicentre study, 244 genotype-positive LQTS index cases and asymptomatic family members, and 76 healthy controls were included. A heterozygous KCNQ1 mutation was present in 107 individuals (LQT1), a KCNH2 mutation in 84 (LQT2), a SCN5A mutation in 41 (LQT3), a KCN1E mutation in 8 (LQT5), a KCN2E mutation in 1 (LQT6), and double heterozygous mutations (KCNQ1 + KCNH2) in 2 patients. The remaining patient was double heterozygote for KCN1Q mutations with clinical features of Jervell and Lange-Nielsen syndrome (JLNS). Mutations were considered ‘pathogenic’ or ‘variants of uncertain significance’ (VUS) based on literature reports and molecular-genetic assessment. Class-3 VUS-positive patients were included after exclusion of other causative gene mutations. In all probands, the clinical diagnosis of LQTS was made using the Schwartz criteria.11 Arrhythmic events were scored as syncpe, documented ventricular tachyarrhythmia (VT), aborted cardiac arrest, and/or sudden death. We included subjects older than 10 years. The use of antiarrhythmic drugs and history of implantable cardioverter defibrillator (ICD) or pacemaker implantation at the time of echocardiography were noted. If possible, EMW measurements were made prior to the initiation of antiarrhythmic therapy.

The healthy control group is described in detail in Supplementary material online.

Echocardiography

Echocardiographic examinations were performed on a Vivid 7 (General Electric Healthcare, Horten, Norway) or IE33 system (Philips, Eindhoven, The Netherlands) and data were analysed by R.M.A.t.B. and K.H.H., blinded to the patient’s diagnosis.

Electromechanical window calculation

Continuous-wave Doppler images in the apical long-axis view assessing the aortic-valve flow and concurrent 3-lead ECG tracings were used for EMW calculations (Figure 1). We measured (i) the interval from QRS-onset to the aortic-valve closure midline [Q-onset to aortic-valve closure (Q AoC) interval], (ii) QT interval in lead II, for the same beat. The EMW (ms) was calculated by subtracting QT from the Q AoC interval. Q-onset to aortic-valve closure incorporates the LV—excitation contraction coupling delay, isovolumetric contraction, and ejection time and is taken as an arbitrary derivative of the duration of LV-mechanical systole.12 It is generally accepted to measure the QT interval in ECG lead II or any longest QT time at the precordium. Here, we assessed lead II because this is also available in commercial ultrasound systems, whereas precordial ECG recordings are normally not. Hypothetically, a longer precordially derived QT would lead to more profound EMW negativity when QAoC remains unaltered. In 6% of our subjects, the 3-lead-echo-related QT interval could not be determined accurately. Instead, contiguous 12-lead ECG-derived QT was obtained at an equivalent RR interval (≤25 ms difference). Bazett’s formula was used to correct QT for heart rate.

Statistical analysis

Continuous data were tested for normality of distribution and depicted as mean ± SD. Comparison of means in Gaussian-distributed groups was performed by unpaired Student’s t-test. For non-parametric methods the Mann—Whitney U-test was used. For multiple comparisons, one-way ANOVA was applied. Receiver-operating characteristic (ROC) curve and logistic regression analysis were established to assess predictive accuracy. The optimal cut-off value for EMW at highest accuracy, sensitivity, and specificity for the optimal cut-off value was determined. The area under the curve (AUC) and 95%-confidence interval (CI) were
Results

Clinical characteristics

Clinical characteristics of the LQTS population and healthy controls are illustrated in Table 1. Of the LQTS population 163 (67%) were female and 97 (40%) were classified as ‘symptomatic’, with 31 patients having cardiac arrest [documented TdP/ventricular fibrillation (VF) in 23; mean TdP/VF episodes per patient 2.8 ± 5.9; electrical storm in six], resulting in death in two. The remaining 66 patients experienced at least one syncopal event, with documented non-sustained (polymorphic) VT in nine. Long-QT syndrome patients had lower mean heart rates (66 ± 13 vs. 73 ± 14 b.p.m. in controls; \( P < 0.0001 \)).

Seventy-five percent harboured a pathogenic mutation in one or more LQTS-related genes, whereas 25% had a VUS, being equally present in symptomatic and event-free subjects. Long-QT syndrome patients had longer QT intervals and QTc compared with controls (QT: 451 ± 57 vs. 357 ± 29 ms; QTc: 465 ± 50 vs. 391 ± 27 ms; \( P < 0.0001 \)), with less exaggerated QTc because of inclusion of asymptomatic mutation-positive relatives (i.e. a representative population at the Cardiogenetics Clinic). Q-onset to aortic-valve closure was significantly longer in LQTS patients (408 ± 37 vs. 379 ± 31 ms; \( P < 0.0001 \)). Combined, these parameters led to negative EMWs in LQTS patients as opposed to positive values in controls (43 ± 46 vs. 22 ± 19 ms; \( P < 0.0001 \); Figure 2).

Patients (\( n = 16 \)) with double LQTS mutations, a history of pacemaker implantation or stellectomy, or on mexiletine treatment did not influence the general outcomes of this study. The inter- and intra-observer variability of EMW measurements had a correlation coefficient of 0.91 (95% CI, 0.65–0.98) and 0.99 (95% CI, 0.97–1.0). Serial EMW measurements were similar in 25 clinically stable patients, after a mean of 48 ± 37 months (−30 ± 49 vs. −24 ± 30 ms; \( P = 0.33 \)). There was no difference between echocardiogram-related and standard-ECG lead-II-derived QT and RR intervals (QT: 450 ± 57 vs. 459 ± 59 ms, \( P = 0.76 \); RR: 949 ± 181 vs. 973 ±

![Figure 1](image)

Figure 1: Representative electromechanical window calculations in the same beat during continuous-wave Doppler echocardiography of the left ventricular-outflow tract. (Left panel) Electromechanical window positivity (yellow bar) in a healthy individual. (Middle panel) Electromechanical window negativity (red bar) in an asymptomatic long-QT syndrome subject. (Right panel) Profound electromechanical window negativity in a symptomatic patient. Q-onset to aortic-valve closure, interval from initiation of QRS to aortic-valve closure; EMW, electromechanical window; RV, right ventricle; LV, left ventricle; LA, left atrium; Ao, ascending aorta.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy individuals (n = 76)</th>
<th>LQTS patients (n = 244)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37 ± 12</td>
<td>38 ± 16</td>
<td>0.57</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>51 (67)</td>
<td>163 (67)</td>
<td>0.97</td>
</tr>
<tr>
<td>Antiarrhythmic drug at time of echocardiogram</td>
<td>Beta-blocker, n (%)</td>
<td>0</td>
<td>100 (41)</td>
</tr>
<tr>
<td></td>
<td>Mexiletine, n (%)</td>
<td>0</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>845 ± 157</td>
<td>950 ± 182</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QT interval, ms</td>
<td>357 ± 29</td>
<td>451 ± 57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>391 ± 27</td>
<td>465 ± 50</td>
<td>&lt;0.0001</td>
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<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
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<tr>
<td>LV-ejection fraction, %</td>
<td>63 ± 7</td>
<td>63 ± 5</td>
<td>0.83</td>
</tr>
<tr>
<td>QAoC interval, ms</td>
<td>379 ± 31</td>
<td>408 ± 37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EMW, ms</td>
<td>22 ± 19</td>
<td>−43 ± 46</td>
<td>&lt;0.0001</td>
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</table>

Table 1: Characteristics of healthy individuals and long-QT syndrome patients

LQTS, long-QT syndrome; LV, left ventricular; QAoC, interval from QRS-onset to aortic-valve closure; EMW, electromechanical window.
185 ms; \( P = 0.15 \)). Subgroup analysis of 76 patients with concealed LQTS (i.e. QTc \( > 440 \) ms, being on average 412\( + 23 \) ms) yielded an EMW of \( 28 + 32 \) ms (\( P < 0.0001 \) vs. controls), which was most pronounced in symptomatic individuals (Figure 3).

Electromechanical window and arrhythmic events

Age, gender, and genetic diagnosis were similar for symptomatic and asymptomatic LQTS patients (61 vs. 28% beta-blocker therapy, respectively, at the time of echocardiography; Table 2). QT and QTc were longer in the former (QT: 479 \( \pm 56 \) vs. 432 \( \pm 49 \) ms; QTc: 488 \( \pm 50 \) vs. 450 \( \pm 44 \) ms; \( P < 0.0001 \)). Q-onset to aortic-valve closures were similar in both groups. Consequently, symptomatic LQTS patients had a more negative EMW: \(-67 \pm 42\) vs. \(-27 \pm 41\) ms (\( P < 0.0001 \); Table 2 and Figure 2). Interestingly, when plotting EMW against QTc (Figure 3), symptomatic and asymptomatic LQTS patients had more negative EMWs for any given QTc than control subjects, which coincided with a more negative slope of the linear relation and a leftward shift of its crossing of the abscissa.

By ROC analysis, EMW proved a better discriminator for arrhythmic events than QTc, with an AUC_{EMW} 0.77 (95% CI, 0.71–0.83), AUC_{QTc} 0.71 (95% CI, 0.65–0.78), and AUC_{QT} 0.74 (95% CI, 0.68–0.81; \( P = 0.03 \); Figure 4). The optimal cut-off value for EMW with 72% accuracy was \(-62\) ms, identifying symptomatic patients with 84% sensitivity and 54% specificity. Logistic regression analysis identified EMW, QTc, and beta-blocker therapy as univariate predictors of arrhythmic events (Supplementary material online, Table S1).

After multivariate analysis, EMW (but not QTc) remained an independent predictor [odds ratio for 10-ms EMW decrease 1.25 (95% CI, 1.11–1.40; \( P = 0.001 \)]. Adding EMW to QTc in LQTS risk assessment resulted in 12 individuals being correctly reclassified into a higher risk category, when compared with a model without EMW. Seven subjects were incorrectly reclassified into a lower risk category. Similarly, 25 asymptomatic individuals were correctly reclassified into a lower risk category, whereas 13 were incorrectly reclassified into a higher risk category. The NRI was 13.3% (\( P = 0.03 \)) when adding EMW.

Beta-blocker therapy

In healthy individuals, beta-blocker treatment was associated with longer QAoC despite similar QT/QTc (QAoC: 413 \( \pm 42 \) vs. 379 \( \pm 31 \) ms; \( P < 0.01 \); QT: 371 \( \pm 42 \) vs. 357 \( \pm 29 \) ms; \( P = 0.20 \); QTc: 377 \( \pm 34 \) vs. 391 \( \pm 27 \) ms; \( P = 0.06 \)). Consequently, their EMW increased to \( 43 \pm 25 \) ms (\( P < 0.01 \)). For beta-blocker-treated LQTS subjects, both QT and QAoC were longer than in untreated patients (QT: 470 \( \pm 57 \) vs. 437 \( \pm 52 \) ms; QAoC: 416 \( \pm 33 \) vs. 400 \( \pm 32 \) ms; \( P < 0.001 \) for both), rendering the EMW more negative (\(-54 \pm 51\) vs. \(-36 \pm 41\) ms; \( P = 0.004 \)). Also, QTc was longer (478 \( \pm 53 \) vs. 457 \( \pm 46 \) ms; \( P = 0.002 \)). In 26 symptomatic patients, beta-blocker therapy was initiated directly after echocardiography. In 15 of these, mostly LQT1 and LQTS patients repeat echocardiography confirmed preferential QAoC (over QT) prolongation by the addition of therapy, resulting in a trend towards
reduced EMW negativity (EMW_preBB $-32 \pm 33$ vs. EMW_postBB $-19 \pm 33$ ms; $P = 0.06$). In total, 88% of the symptomatic patients of this study were ultimately treated with beta-blockers.

### Genotype subgroup analysis

For 107 LQT1, 84 LQT2, and 41 LQT3, averaged QTc was similar (467 $\pm$ 55, 467 $\pm$ 47, and 462 $\pm$ 45 ms; 40, 51, 7% beta-blocker therapy, respectively), Supplementary material online, Table S2. Q-onset to aortic-valve closure was slightly shorter in LQT3 (LQT3: 394 $\pm$ 37, LQT1: 413 $\pm$ 40, LQT2: 409 $\pm$ 33 ms; $P = 0.02$), which may be related to shorter RR and QT intervals in this subgroup. Altered $I_{Ks}/I_{Kr}$-dependent pacemaker activity $^{13}$ and imbalanced negative chronotropic therapy may have contributed to this. Electromechanical window negativity was similar for LQT1, LQT2, and LQT3, ($-243 \pm 47$, $-247 \pm 44$, and $-237 \pm 47$ ms) with longer QTc and unaltered QAoC in symptomatics, resulting in more profound EMW negativity (Table 3). Exclusion of the mexiletine-treated LQT3 patients did not alter these findings significantly.

The double-mutation and JLNS patients had the most profound EMW negativity: $-91 \pm 46$ ms ($n = 3$, all symptomatic). For the remaining 8 KCNE1 (LQT5) and 1 KCNE2 (LQT6)-mutation positive patients, an EMW of $-16 \pm 34$ ms was found.
Table 3  Genotype subgroup analysis

<table>
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<tr>
<th></th>
<th>LQT1 Asymptomatic (n = 69)</th>
<th>LQT1 Symptomatic (n = 38)</th>
<th>LQT2 Asymptomatic (n = 42)</th>
<th>LQT2 Symptomatic (n = 42)</th>
<th>LQT3 Asymptomatic (n = 31)</th>
<th>LQT3 Symptomatic (n = 10)</th>
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<td>Age, years</td>
<td>44 ± 15</td>
<td>34 ± 17*</td>
<td>37 ± 15</td>
<td>39 ± 17</td>
<td>32 ± 18</td>
<td>45 ± 13*</td>
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<td>Female sex, n (%)</td>
<td>42 (61)</td>
<td>26 (68)</td>
<td>26 (62)</td>
<td>31 (74)</td>
<td>19 (61)</td>
<td>9 (90)</td>
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<td>Antiarrhythmic drug at time of echocardiogram</td>
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<td>Beta-blocker, n (%)</td>
<td>22 (32)</td>
<td>21 (55)*</td>
<td>14 (33)</td>
<td>29 (69)*</td>
<td>0 (0)</td>
<td>8 (80)</td>
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<td>Mexiletine, n (%)</td>
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<td>6 (19)</td>
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<tr>
<td>RR interval, ms</td>
<td>943 ± 173</td>
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<tr>
<td>QT interval, ms</td>
<td>438 ± 52</td>
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<td>QTc, ms</td>
<td>454 ± 51</td>
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<th>Echocardiogram (-Mexiletine)</th>
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<tr>
<td>QAoC interval, ms</td>
<td>409 ± 33</td>
</tr>
<tr>
<td>EMW, ms</td>
<td>−29 ± 46</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

*Sympt. vs. asympt.: P < 0.05, §LQT3 vs. LQT1: P < 0.05, |Sympt. LQT3 vs. LQT1 and LQT2: P < 0.05.

Figure 5  Serial electromechanical window measurements in a LQT3 patient during different stages of treatment for recurrent torsades de pointes, and after clinical stabilization. (A) Beta-sympathomimetic therapy with isoproterenol resulted in marked electromechanical window negativity without torsades de pointes. (B) Interruption of isoproterenol with progressive electromechanical window negativity. (C) During extreme electromechanical window negativity torsades de pointes recurred. (D) ‘Normalized’, non-paced electromechanical window values after clinical stabilization.
Electromechanical window in long-QT syndrome patient with electrical storm

In a SCNSA-mutation-positive female (c.4850-4852delTCT; p.delPhe1617), we determined the EMW serially by means of tissue (TDI) and continuous-wave Doppler imaging during a phase with electrical storm, and after clinical stabilization (Figure 5). Acute TdP suppression was achieved by beta-sympathimetic treatment with isoproterenol, increasing her heart rate to 87 b.p.m. At that moment, EMW was −83 ms (after 27-ms correction for TDI-derived timing of aortic-valve closure, QTc 538 ms). After interruption of isoproterenol, EMW values deteriorated further to −163 ms within minutes (QTc 505 ms), followed by the recurrence of TdP. During these very negative EMWs, just prior to TdP, premature ventricular beats arose with mechanical activity initiating earlier than the measurable start of QRS, suggesting a mechanism other than excitation–contraction coupling. The patient was restabilized with isoproterenol and permanent right-atrial pacing after ICD implantation. In the months thereafter her EMW during intrinsic sinus rhythm markedly increased to −50 ms (QTc 508 ms) and no ventricular arrhythmias occurred.

Discussion

The present study focuses on electromechanical coupling in genotype LQTS patients, particularly the EMW, in relation to major arrhythmic events. Our results demonstrate that the physiological LV electromechanical sequence, in which aortic-valve closure occurs after T-wave completion, is reversed in LQTS. The consequent negative EMW occurs primarily by a prolonged QT interval in the absence of a correspondingly increased QAoC. Interestingly, in LQTS the EMW is more negative for any QTc suggesting repolarization-independent influences.

Electromechanical window negativity was most pronounced in patients with documented arrhythmic events and those with double heterozygous mutations (two KCNQ1 + KCNH2; one JLNS). Moreover, it appeared a better and independent discriminator of previous arrhythmic events than QTc. In one case with electrical storm, EMW was dynamic and very negative prior to TdP, but increased significantly after clinical stabilization. Our data confirm that inherited repolarization prolongation and instability are crucial factors for TdP, but they also hint towards the importance of mecanoelectric triggers, particularly in symptomatic LQTS patients at instances during their cardiac cycle when mechanical systole has ceased, but repolarization is still ongoing. Diastolic spontaneous Ca2+ release from the sarcoplasmic reticulum (SR) and mechanical aftercontractions can be pivotal arrhythmogenic factors, particularly when myocardial Ca2+ load is enhanced, as shown experimentally.

Interaction of electrical and mechanical systole

Under normal conditions, myocardial membrane depolarization precedes and initiates contraction through Ca2+-induced Ca2+ release from the SR, a process termed excitation–contraction coupling. Repolarization prolongation can increase cellular Ca2+ content by prolonging the inactivation phase of L-type Ca2+ current. Sympathetic stimulation, circulating catecholamines, and various positive-inotropic drugs enhance Ca2+ load. At the integrative level, preload and afterload are major determinants of myocardial inotropic state. To govern these mechanisms, electrical and mechanical activities are tightly linked. In healthy myocardium, mechanical relaxation terminates tens of milliseconds after repolarization. Likewise, we demonstrated a positive EMW value of 22 ± 19 ms in healthy controls, corresponding to a QT/QS2 ratio of 0.94. In clinical non-LQTS studies, the QT/QS2 ratio was used to investigate electromechanical coupling at resting heart rate, during adrenergic stimulation, changes in autonomic tone, and in coronary artery disease. In patients with prior myocardial infarction, the presence of QT > QS2 provided a risk indicator of mortality that was more potent than QTc.

In this LQTS study consisting of probands and asymptomatic family members, we observed an average EMW of −43 ± 46 ms (QT/QS2 ratio of 1.10), with symptomatic patients having more negative EMWs for a wide QTc range. We speculate that heterogeneous autonomic innervation and/or sympathetic hyperactivity could provoke EMW negativity by enhanced lusitropy in the presence of QT maladaptation, particularly in LQT1, LQT3, JLNS, or other conditions when cAMP-dependent kS cannot be adequately recruited to shorten repolarization. This may also apply to other LQTS genotypes if kS is intrinsically weak. In LQT3, increased late Na+ current may contribute to electromechanical divergence via altered myocardial Na+ and Ca2+ handling. Interestingly, a shorter QAoC was found to underlie the EMW in LQT3, being even shorter in symptomatic individuals (despite longer QTc). Any of these potential mechanisms requires further investigation.

Beta-blockade is more efficacious in preventing recurrence of major arrhythmic events in LQT1 than LQT2 or LQT3 patients. While beta-blockers lend their antiarrhythmic actions primarily by dampening myocardial responses to sympathetic stimuli, shortening of QTc has also been demonstrated, mainly through heart rate slowing with minimal effects on QT. Based on our results in LQT5 patients and controls, increased contraction duration and a less negative EMW may confer additional antiarrhythmic protection in LQTS, in line with experimental data.

Electromechanical window negativity and pro-arrhythmic proclivity

Pro-arrhythmic aspects of EMW negativity have been evaluated in animal models of drug-induced LQTS. In anaesthetized drug-induced LQT1 dogs, kS blockade with HMR1556 or JNJ 303 markedly reduced EMW, but did not evoke TdP. Additional beta-adrenergic provocation with isoproterenol, exacerbated EMW negativity (to −109 ms) and led to the emergence of LV aftercontractions within the window, and subsequent TdP onset. Interventions (e.g. verapamil, esmolol, atenolol) that successfully prevented aftercontractions and/or rendered EMW less negative also prevented TdP. In anaesthetized guinea-pigs, the administration of drugs with documented TdP liability (i.e. quinidine, haloperidol, terfenadine, moxifloxacin, ciprofloxacin, and doxetilide) produced TdP only after substantial EMW negativity (< −50 ms) and infusion of adrenaline. Negative-control compounds did not cause EMW negativity or arrhythmia, even though repolarization prolongation...
was observed. TdP was typically preceded by aftercontractions. These aftercontractions, and their relation to TdP, suggest mechanoelectric influences during arrhythmogenesis. ²

Clinical implications
Along with other reports on the importance of mechanical abnormalities in LQTS, ²² our data indicate that the assessment of electromechanical coupling has added value for arrhythmia-risk analysis. The EMW, an easy-to-obtain parameter, proved a better and independent discriminator than resting QTc in our large LQTS population. A cut-off value of $< - 62$ ms predicted arrhythmic events with 72% accuracy. As such, it may be helpful to assess arrhythmia risk, guide arrhythmia maintenance therapy, and facilitate the timing of acute interventions in LQTS.

Limitations
The retrospective study design may have led to potential selection bias and confounding factors, among them possible under- and over-estimation of arrhythmic events. Echocardiographic examinations were performed at various times without standardization for diurnal sympathetic modulation of QT/QAoC and potential respiratory-cycle variation. This study did not allow for stratification according to beta-blocker therapy. A prospective cohort should confirm the association between EMW negativity and arrhythmic events, and address EMW dynamics over time.

Conclusions
There is mounting evidence of mechanical abnormalities in LQTS. Their quantitative analysis, besides QTc, has added value for arrhythmia-risk prediction. Using transthoracic echocardiography, we find that LQTS patients have a markedly negative EMW over a wide QTc range, which is most pronounced in those with documented arrhythmic events. In this study population, EMW proves superior to and independent from QTc in discriminating between a LQTS patient’s historical arrhythmic events. Hence, we propose to consider this parameter in the clinical management of LQTS patients.

Supplementary material
Supplementary material is available at European Heart Journal online.

Acknowledgements
The authors thank Roel L.H.M.G. Spåtjens, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, The Netherlands for figure optimization, and Margaret Ribe, Oslo University Hospital, Rikshospitalet, Norway, for data collection.

Funding
This work was supported by the Foundation ‘Sint Annadal’, Maastricht, The Netherlands (R.M.A.t.B.); a Vidi grant from the Netherlands Organization for Scientific Research, ZonMW 9170365 (P.G.A.V.), and funding by The Netherlands CardioVascular Research Initiative, CVON PREDICT (P.G.A.V.); the South-Eastern Norwegian health authorities (K.H.H.), Center for Cardiological Innovation (Norwegian Research Council) (T.E., K.H.H.), and Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program (M.J.A.).

Conflict of interest: M.J.A. is a consultant for Boston Scientific, Medtronic, St Jude Medical, and Transgenomic. Intellectual property resulted in license agreements (FAMILION-LQTS) in 2004 between Mayo Clinic Health Solutions and PSoxHealth. All other authors have no conflict of interest.

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