Provocation of sudden heart rate oscillation with adenosine exposes abnormal QT responses in patients with long QT syndrome: a bedside test for diagnosing long QT syndrome

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Received 8 July 2005; accepted 25 July 2005; online publish-ahead-of-print 16 August 2005

Aims As arrhythmias in the long QT syndrome (LQTS) are triggered by heart rate deceleration or acceleration, we speculated that the sudden bradycardia and subsequent tachycardia that follow adenosine injection would unravel QT changes of diagnostic value in patients with LQTS.

Methods and results Patients (18 LQTS and 20 controls) received intravenous adenosine during sinus rhythm. Adenosine was injected at incremental doses until atrioventricular block or sinus pauses lasting 3 s occurred. The QT duration and morphology were studied at baseline and at the time of maximal bradycardia and subsequent tachycardia. Despite similar degree of adenosine-induced bradycardia (longest R–R 1.7 ± 0.7 vs. 2.2 ± 1.3 s for LQTS and controls, \( P = \text{NS} \)), the QT interval of LQT patients increased by 15.8 ± 13.1%, whereas the QT of controls increased by only 1.5 ± 6.7\% (\( P < 0.001 \)). Similarly, despite similar reflex tachycardia (shortest R–R 0.58 ± 0.07 vs. 0.55 ± 0.07 s for LQT patients and controls, \( P = \text{NS} \)), LQTS patients developed greater QT prolongation (QTc = 569 ± 53 vs. 458 ± 58 ms for LQT patients and controls, \( P < 0.001 \)). The best discriminator was the QTc during maximal bradycardia. Notched T-waves were observed in 72% of LQT patients but in only 5% of controls during adenosine-induced bradycardia (\( P < 0.001 \)).

Conclusion By provoking transient bradycardia followed by sinus tachycardia, this adenosine challenge test triggers QT changes that appear to be useful in distinguishing patients with LQTS from healthy controls.

KEYWORDS
Long QT syndrome; Adenosine; Torsade de pointes; Electrocardiogram

Introduction
The diagnosis of the long QT syndrome (LQTS) is straightforward when torsade de pointes is documented at the time of symptoms in a patient with obvious prolongation of the QT interval.1,2 More often, however, diagnosing an LQTS is problematic for several reasons. First, arrhythmic symptoms related to an LQTS occur infrequently, making it difficult to document torsade de pointes. Secondly, considerable overlapping in the duration of the QT interval exists between carriers of LQTS mutations and healthy controls.3,4 Hence, a common scenario is the referral of patients with borderline or slightly prolonged QT segment who have symptoms suggestive of arrhythmias but no arrhythmia documentation. Thirdly, although genetic testing may confirm the diagnosis when a cardiac channel malfunction is identified, this testing may take months to conclude and is performed only in specialized centres. Moreover, failing to identify a mutation does not exclude the diagnosis of LQTS.5 Thus, diagnosing a congenital LQTS remains a clinical challenge.1

Sudden changes in heart rate affect the QT segment of patients with LQTS profoundly.6 In fact, sudden acceleration, or sudden deceleration, of the heart rate can trigger torsade de pointes. In the first scenario, sinus tachycardia (as seen during stress) leads to T-wave alternans7 and ultimately triggers ‘adrenergic-dependent’ (tachycardia-dependent) torsade de pointes.8 Similarly, sudden heart rate slowing (as during post-extrasystolic pauses)1,9 leads to post-pause ‘U-wave augmentation’9,10 and eventually causes ‘pause-dependent’ (bradycardia-dependent) torsade de pointes.11,12

The adenosine compounds [adenosine and adenosine triphosphate (ATP)] are nucleotides that, when injected

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intravenously, block atrioventricular (AV) nodal conduction for a few seconds. Physicians take advantage of this property to terminate supraventricular tachycardias or to identify the presence of dual AV node physiology or accessory pathways.14,15 When injected during sinus rhythm, the adenosine compounds cause dose-dependent bradycardia either due to sinus pauses or due to transient AV block. This short-lasting bradycarrhythmia is soon followed by marked sinus tachycardia.16 We aimed to take advantage of the sudden deceleration–acceleration sequence that invariably follows the injection of adenosine during sinus rhythm to evaluate whether these heart rate oscillations would unravel pathologic QT changes in patients with LQTS.

Methods

Patient groups

The ‘LQTS group’ consisted of patients with 'definite LQTS' or 'high probability for LQTS'. Patients with high probability of LQTS are patients with 'International LQTS Registry Score' of ≥4 points. The patients with definite LQTS have, in addition, documented torsade de pointes and/or an LQTS mutation. The ‘control group’ consisted of consecutive patients prospectively undergoing an adenosine or ATP challenge test for identifying the presence of dual AV node physiology or concealed accessory pathway as previously described.14,15 None of the controls had a history of syncope or a familial history even reminiscent of LQTS, none were receiving medications known to impair myocardial repolarization and none of them had evidence of organic heart disease including left ventricular hypertrophy. Patients and controls provided informed consent according to the study protocol reviewed by our Institutional Review Committee. A history of bronchial asthma was an exclusion criterion.

Interventions

LQTS patients and controls underwent the adenosine or ATP test as a bedside test during continuous electrocardiographic recording. ATP (Striadyne, Ayerst Laboratories, France) or adenosine (Adenocor, Sanofi-Winthrop) was injected through an antecubital vein as a rapid bolus, followed by a 20 mL flush of normal saline. The initial dose was 10 mg of ATP or 6 mg of adenosine. Repeated injections (using 10 mg or 6 mg increments, for ATP or adenosine, respectively) were given until one of the following events occurred: (i) transient AV nodal block of second or third degree, (ii) sinus bradycardia or sinus arrest leading to ≥3 s asystole, (iii) the patient requested termination of the test because of side effects, or (iv) a maximal dose of 40 mg ATP or 24 mg adenosine was reached. Only patients developing bradycardia (as described earlier) were included in the final analysis.

Measurements

To avoid reader bias, one investigator first photocopied and coded four electrocardiograms for each patient that were recorded at the following points in time: (i) at baseline, (ii) at the time of maximal bradycardia, (iii) at the time of maximal tachycardia, and (iv) at the maximal QT effect (at the time of the most obvious changes in T-wave morphology during the reflex tachycardia phase). All the coded electrocardiograms (four traces per patient) were then presented in random order to a second investigator who performed the QT measurements. Thus, the ‘QT reader’ was unaware not only of the patient allotment but also of the patient’s baseline QT when measuring the QT interval recorded during adenosine-induced bradycardia or tachycardia. The following measurements were made in all 12 leads at each point in time: (i) QT and QT(peak) (the intervals from the onset of the QRS to the end of the T-wave and to the peak of the T-wave, respectively); (ii) QT(peak-end) [the difference between QT and QT(peak)]; (iii) QTc [the mean QT (of 12 leads) divided by the root square of the preceding R–R interval]; (iv) the presence of abnormal T-waves (T-wave inversion and notched T-waves) and the amplitude of all the T-wave components were noted: T2 signifies that there were notched or double T-waves, T2 > T1 signifies that the second T-wave component was taller than the first component by any value and T2 ≥ T1 signifies that T2 was considerably taller than T1 (by >0.1 mV).

Statistics

Data are displayed as mean ± SD for continuous variables and as number and percentage for categorical variables. To examine the hypothesis that administrating adenosine influences the QT parameters of LQT patients and controls differently, ANOVA in a mixed inter–intra model was performed twice, with the QT and the QTc as the dependent variables, and with two independent variables: (i) the stage in relation to adenosine injection (i.e. baseline, maximal bradycardia, maximal tachycardia, and maximal QT effect) was entered as a repeated measure variable and (ii) the subject’s status (LQTS or control) was entered as a between-subject variable. Contrast analysis was then performed to compare QT parameters in relation to baseline, separately for the LQTS and the control groups. Finally, discriminant analysis was performed to examine the best separation solution between the two groups. For this purpose, 70% of the total sample was randomly selected and a discriminant U function was applied in a stepwise method, i.e. only variables that minimized the lambda score were entered. The results were then applied to all cases to examine how good the model performs. For all categorical variables, the χ² phi and Cramer’s V statistics were used. Two-tailed P-value ≤ 0.05 was considered significant. The SPSS statistical package was used to perform all statistical evaluation (SPSS Inc. V12 Chicago, IL, USA).

Results

Twenty patients with LQTS and 22 controls agreed to participate in the study. One LQT patient developed cough and mild expiratory wheezing (that resolved without therapy). A second patient, as well as two controls, withdrew their consent to participate after the first or second dose of adenosine. These patients were excluded from further analysis because the adenosine doses given failed to provoke any bradycardia. Thus, the effects of adenosine were evaluated in 18 patients with LQTS and 20 controls. All but one of the LQT patients had LQTS score ≥ 4 (mean score 5.1 ± 1). The only patient with LQTS score < 4 (3 points) has an LQT2 mutation. Seven patients were genotyped: five patients have LQT2, one has LQT1, and one has LQT3. The LQTS group includes six patients with documented torsade de pointes or ventricular fibrillation and seven patients with a history of syncope.

Patients and controls were similar in terms of their demographic and electrocardiographic characteristics except for the QT interval, which (as expected) was longer in patients with LQTS (Table 1). It should be noted that 10 (56%) of the LQT patients had a mean QTc < 460 ms, whereas seven of the controls had a mean QTc > 410 ms. Thus, 17 (45%) of the study population had QTc values that would be considered ‘borderline’ because, in large genotyped populations, such QT intervals can be seen in LQTS-mutation carriers or healthy individuals.3,18 In addition, the adenosine doses administered to both patient groups were similar. Moreover, the sudden changes in heart rate that
were induced by adenosine were of similar magnitude in both groups (Table 1).

### Bradycardia-induced QT changes

Despite similar degrees of adenosine-induced bradycardia (Figure 1), there were striking differences in the response of the QT interval between the two groups: During maximal bradycardia, the QT interval of controls increased by only 1.5 ± 6.7%, whereas a 15.8 ± 13.1% increment in QT interval was seen among LQT patients (P < 0.001) (Figures 1–3). Because of the marked increase in R–R interval, the QTc of both groups actually decreased during bradycardia, yet significantly less among LQT patients (the QTc shortened by 13 ± 18 and by 32 ± 17% for LQT patients and controls, respectively, P = 0.002). At the time of maximal bradycardia, the QT was 366 ± 39 ms for controls and 487 ± 69 ms for LQT patients (P < 0.001), and the QTc was 269 ± 69 ms for controls and 395 ± 79 ms for LQT patients (P < 0.001) (Figure 1).

### Tachycardia-induced QT changes

The adenosine-induced transient bradycardia was invariably followed by sinus tachycardia that reached a maximal rate 21 ± 9 s after the deepest bradycardia. The maximal heart rate during the tachycardia phase was similar for LQT patients and controls (R–R interval 582 ± 70 ms for LQTs vs. 543 ± 67 ms for controls, P = NS). The maximal changes in T-wave morphology and QT duration were not seen at the time of maximal tachycardia but rather 11 ± 9 s later, when the sinus rate began to return towards the baseline rate. Although the heart rate at the time of maximal T-wave changes was similar between LQTs patients and controls (Figure 1), the QT and the QTc of LQT patients were much longer than those of the controls (QT = 458 ± 55 vs. 348 ± 57 ms, P < 0.001 and QTc = 569 ± 53 vs. 458 ± 58 ms, P < 0.001, for LQT patients and controls, respectively) (Figures 1 and 4).

### Adenosine-induced changes in T-wave morphology

T-wave inversion following adenosine injection was of no diagnostic value because it occurred in five (28%) LQT patients and six (32%) controls (P = NS) at the time of maximal effect. In contrast, double T-waves (T-wave notches) were noted in at least one lead in 10 (56%) of LQT patients and two (10%) of controls (P = 0.003) at baseline. Moreover, during the bradycardia phase of the adenosine challenge, the percentage of patients with double T-waves increased to 72% among LQT patients but decreased to 5% in controls (P < 0.001). During the tachycardia phase, 72% of LQT patients and 30% of controls had notched T-waves. However, T2 > T1 was seen in 12 (67%) of LQT patients but in only two (10%) of controls (P < 0.001) and T2 >> T1 was seen at the time of maximal effect in eight (44%) of LQT patients and in only one (5%) of controls (P = 0.004). One LQT patient developed ventricular extrasystoles that appeared to represent triggered activity from early after-depolarizations because they were pause-dependent and originated from the terminal part of the QT segment (Figure 4, bottom trace) and one LQT patient developed T-wave alternans during the tachycardia phase of the test (Figure 5).

### Safety

All patients experienced the usual side effects of adenosine: chest pain, dyspnea, and/or flushing and, as mentioned earlier, three patients requested termination of the study because of these side effects, whereas in one patient, we terminated the study prematurely because of short-lasting wheezing. All the side effects terminated within seconds without intervention.

### Diagnostic value of the adenosine challenge

Adenosine challenge resulted in dissimilar response in LQT patients and controls. This was evident from the significant interaction between stage (baseline, bradycardia, tachycardia, and maximal effect) and patients’ group (LQTS vs. control) for both QT and QTc: (F(3,108) = 6.764, P < 0.0001 for QT and F(3,108) = 3.745, P = 0.013 for QTc). Contrast analysis revealed that the difference in QT and QTc between subjects with LQTS and controls was larger at all the three stages that followed adenosine injection (i.e. maximal bradycardia, maximal tachycardia, and maximal effect) than at baseline. The largest difference was seen during maximal bradycardia, where the difference between the mean QT values of the two groups was 121 ms (vs. a 59 ms difference at baseline) and the difference between the mean QTc values of the two groups was 125 ms (vs. a 55 ms difference at baseline) (Figure 1).

To reduce the influence of outliers, the median values of LQT patients and controls were also compared. Again, the best separation between groups was evident in the QTc at maximal bradycardia, where the difference between medians was 135 ms (vs. 67 ms at baseline). Because the QT of controls hardly changed while the R–R interval suddenly increased during adenosine-induced bradycardia, the QTc of controls actually shortened (Figure 1). On the basis of the current sample, the parameter that best distinguishes between two groups is the QTc measured during bradycardia. A QTc < 250 ms during maximal bradycardia nearly excludes LQTS, whereas QTc > 380 ms during bradycardia strongly implies LQTS. This is because only 5% of LQTS had a QTc ≤ 250 ms, whereas 95% of controls have QTc

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<th>Table 1 Baseline characteristics and response to adenosine in the study group</th>
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aSome patients received ATP: 10, 20, 30, and 40 mg of ATP were counted as 6, 12, 18, and 24 mg of adenosine, respectively.
bThe longest R–R and the shortest R–R denote the maximal bradycardia and the maximal tachycardia responses seen after adenosine administration, respectively.
380 ms at this stage. The second best distinguishing parameter was the QTc at the time of maximal QT effect.

At this stage, a QTc 490 ms nearly excludes LQTS (only 5% of LQTS had a QTc 490 ms during this stage), whereas a QTc 620 ms strongly implies LQTS (95% of controls have QTc 620 ms during this stage).

The area under the curve of the receiver operating characteristics (ROC) curves ranged between 0.933 and 0.969 for the QT measures at baseline, maximal effect, and maximal bradycardia values, and between 0.881 and 0.933 for the QTc measures at the same time points. From the ROC curve analysis, a QT of 0.41 s at maximal bradycardia time point had a sensitivity of 0.94 and a specificity of 0.9 to detect LQTS. At the time of maximal effect of adenosine on T-wave morphology, a QTc of 0.49 has a sensitivity of 0.94 and a specificity of 0.85 for detecting LQTS.

To build a predicting, explanatory model, we first randomly selected 70% of the sample and then applied discriminant analysis for both QT and QTc. For the QT, only the QT interval at maximal effect entered the final equation, with a lambda score of 0.366. This model correctly predicted 92.6% of the randomly selected cases (25/27 cases) and 89% (10/11 cases) of the remaining 30%.

For the QTc, both QTc at maximal tachycardia and QTc at baseline entered the model, with a total lambda score of 0.25. This model correctly predicted 96.3% of the selected cases (26/27) as well as all the unselected cases (11/11).

Figure 1  Response of the R-R, QT, QTc, and QT(peak-end) to intravenous adenosine injection during sinus rhythm in patients with LQTS (black bars) and controls (white bars). All graphs show the mean (horizontal line) and SD (bar) during baseline, at the time of maximal adenosine-induced bradycardia, and the time that the maximal effect on the QT interval was observed during adenosine-induced tachycardia. QT(peak-end) is the interval between the peak of the T-wave and the end of the QT interval. *P < 0.01, **P < 0.001.

Figure 2  Typical response of the QT interval to sudden changes in heart rate provoked by adenosine in a control. Following the injection of 18 mg adenosine, there is transient complete AV block leading to 3.5 s of ventricular asystole. Despite the marked bradycardia, there is little change in the QT duration and morphology. Ten seconds later, reflex sinus tachycardia occurs. The amplitude of the T-wave slightly decreases during tachycardia but the T-wave morphology remains normal.
Accurate diagnosis of the LQTS is imperative because this is a potentially lethal disorder for which effective therapy exists. Among the numerous diagnostic tests proposed over the years,1 the two most commonly used tests, exercise19,20 and epinephrine challenge,21–23 take advantage of the poor accommodation of the QT interval in response to heart rate.

Figure 3  Response of the QT interval to adenosine-induced bradycardia in two patients with LQTS. The top trace is from a 40-year-old female. Her baseline QTc is 480 ms and her T-waves have normal morphology. Following injection of 30 mg ATP, she developed 4 s of AV block (P-waves are marked with arrowheads). During the bradycardia, the T-wave become notched (T2 > T1). The bottom trace is from a 22-year-old female. Her baseline QTc is 500 ms. The T-wave in lead V2 is followed by a second wave that most probably represents a ‘physiologic U-wave’10 because it is well defined, of small amplitude, and terminates much after the end of the QT interval defined from other leads (arrow). The maximal bradycardia, maximal tachycardia, and the maximal effects on the QT interval occur 20, 40, and 55 s after the ATP injection, respectively. During bradycardia, she develops notched T-waves in V2 [the amplitude of the second component increased and now terminates synchronously with the QT interval ends in other leads (arrow)]. During tachycardia, the T-wave assumes a bizarre morphology in lead V2, whereas abnormal ‘typical notched T-waves’ (T2 > T1) are noticed during tachycardia in lead V4.

Figure 4  Response of the QT interval to adenosine-induced tachycardia in three patients with LQTS. In the top trace (female, 47 years old), the QT interval not only fails to shorten during tachycardia but actually lengthens to the point that the end of the T-wave almost reaches the following P-wave. The middle trace is from a 50-year-old female with asymptomatic LQT2 mutation. Her QTc is only 430 ms at baseline and the T-wave morphology is normal. However, during the tachycardia phase of adenosine, the QT actually prolongs from 400 to 480 ms, the T-wave becomes frankly abnormal (*), and the QTc increases from 430 to 550 ms. The bottom trace is from a 56-year-old male. His baseline QT is only 420 ms. During the tachycardia phase of adenosine, he first developed notched abnormal T-waves (*) and eventually develops ventricular ectopy that looks typical of LQTS-related arrhythmias because the extrasystoles arise from the terminal part of the QT interval. Note that post-extrasystolic pauses trigger bizarre T-wave changes (**). The QTc reached a maximum of 560 ms before the onset of ventricular ectopy.

Discussion

Accurate diagnosis of the LQTS is imperative because this is a potentially lethal disorder for which effective therapy...
acceleration to improve the diagnosis of the LQTS. We report, for the first time, that the behaviour of the QT interval markedly differs between LQT patients and controls during the bradycardia- and the tachycardia-phase that follow an adenosine challenge test.

Diagnostic value of the adenosine challenge test

Because this is the first use of adenosine to diagnose LQTS, we only studied patients with ‘definite’ or ‘high probability’ for LQTS and ‘definitively healthy’ controls (proof of concept design). As a consequence of this design, the QT parameters of the two groups were already dissimilar at baseline, making it more challenging to demonstrate the diagnostic value of the new diagnostic test. Nevertheless, the different response of the QT interval to the sudden heart rate changes provoked by adenosine augmented the difference between LQT patients and controls. The best discriminator proved to be the QTc measured during maximal bradycardia and the second best discriminator was the QTc at the time when the maximal effects of adenosine on QT morphology were evident during tachycardia. The magnitude of the difference between LQT patients and controls at any of these two stages was significantly larger than any difference noticeable at baseline. During maximal brady-cardia, QTc cut-off points of 250 ms and 620 ms provided excellent discrimination between LQT patients and controls because only 5% of LQTS (but almost 40% of controls) had QTc <250 ms, whereas <5% of controls (but 60% of LQTS) had QTc >620 ms. It should be noted that the best model that resulted in correct prediction of almost all the sample tested, including LQT patients and controls, was achieved by using both the baseline QTc and the QTc at maximal tachycardia. This emphasizes the clinical relevance of calculating QTc at this time points as well.

Mechanism of adenosine-mediated QT changes

The dependence of QT duration on heart rate is steeper in patients with LQTS than in controls. Thus, maladjustment of the QT interval to the heart rate oscillations induced by adenosine probably caused the striking QT changes in our LQT patients. However, the fact that the maximal effects on QT morphology did not occur at the time of maximal tachycardia, but shortly thereafter, suggests that rate-independent mechanisms also affected QT morphology. Adenosine has no direct effect on the ventricular action-potential duration and the changes in T-wave morphology induced by adenosine in this study are comparable to those reported with epinephrine. Because tachycardia, hypertension, and increased sympathetic nerve traffic follow the bradycardia response to adenosine only in awake patients (anaesthetized patients develop only bradycardia), it is likely that a reflex sympathetic surge, secondary to the chest pain and dyspnoea caused by adenosine, is responsible for the QT changes observed during the tachycardia phase of our adenosine challenge. Accordingly, adenosine could be better than epinephrine in simulating ‘physiologic stress’, the common trigger of arrhythmias in the LQTS.

Limitations

Experimental and clinical data suggest that LQTS patients with different genotypes respond differently to heart rate changes. Accordingly, patients with LQT3 would be expected to develop more QT changes during the bradycardia phase of the adenosine test, whereas LQT1 patients would be expected to show QT prolongation specifically during tachycardia. The small number of genotyped patients in our series precludes reaching any conclusions regarding this important point, and the relatively high proportion of patients with LQT2 in our series may have biased our results towards ‘more T-wave changes’. In addition, the study group consisted only of patients with high pre-test probability of LQTS. On one hand, this may have limited the diagnostic ‘added value’ of our test. On the other hand, the adenosine test may not necessarily perform as well in patients with less obvious LQTS or in patients with abnormal repolarization due to other causes (like left ventricular hypertrophy). Finally, because of the small number
of controls studied, the 'normal' response of the QT interval to adenosine has to be defined further.

Clinical implications

By performing rigorously controlled testing, two groups\textsuperscript{21,22,25,26} have established the epinephrine challenge test as the most useful test for diagnosing LQTS in borderline cases.\textsuperscript{23} By provoking 'reflex tachycardia', adenosine may be a better simulator of 'physiologic stress', the common trigger of arrhythmias in the LQTS, than exogenous epinephrine infusion. In addition, the adenosine challenge test provides additional diagnostic information during the bradycardia phase, which is absent during the epinephrine challenge. However, it is impossible to conclude which of these tests will provide the highest diagnostic value before comparison of our adenosine challenge test with the epinephrine protocols\textsuperscript{21,22} is performed in the same patients. The adenosine challenge test (like any challenge test performed in patients with suspected LQTS) should be performed only by personnel experienced and equipped for treating ventricular arrhythmias. We did not encounter serious side effects while using adenosine for diagnostic purposes in this and other studies.\textsuperscript{14,15} Nevertheless, it is worth remembering that cases of torsade de pointes during clinical use of adenosine have been described.\textsuperscript{30,31}

Conflict of interest: none declared.

References