Utility of a Simplified Lidocaine and Potassium Infusion in Diagnosing Long QT Syndrome among Patients with Borderline QTc Interval Prolongation

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Background: Congenital long QT syndrome (LQTS) is caused by mutations in the cardiac Na⁺ or K⁺ channels that result in a prolonged QTc interval and increased QT dispersion. Na⁺ channel blockers and K⁺ can reverse the repolarization abnormalities in the Na⁺ channel variant (LQT3) and K⁺ channel variant (LQT1, LQT2), respectively. The phenotype of LQTS can be difficult to recognize, especially when the QTc interval is mildly prolonged. Additional noninvasive testing methods are needed to enhance the diagnosis of LQTS. This study compared the response of the QTc interval and QT dispersion to a sequential lidocaine/K⁺ infusion in LQTS patients with borderline QTc interval prolongation and control patients as a means of diagnosing LQTS.

Methods: In this study, eight LQTS patients with borderline QTc, defined as QTc < 470 ms, and 10 healthy controls received sequential lidocaine/K⁺ infusion.

Results: At baseline, LQTS patients had a longer QTc (446 ± 29 vs 416 ± 28 ms, P < 0.05) but similar QT dispersion (43 ± 14 vs 29 ± 10 ms) compared to controls. After lidocaine administration, baseline QTc and QT dispersion did not change in either LQTS or controls. One LQTS patient had a 54 ms (12%) reduction in his QTc but no change in QT dispersion. Following K⁺ infusion, baseline QTc and QT dispersion decreased by 9% (P < 0.005) and 45% (P < 0.005), respectively in LQTS. No effect was seen in control patients, where QTc and QT dispersion shortened by 1% (5 ± 14 ms) and 20% (6 ± 7 ms), respectively, compared to baseline. The combined lidocaine/K⁺ infusion had a sensitivity, specificity, and accuracy of 88%, 100%, and 94%, respectively, in diagnosing LQTS.

Conclusions: A simplified sequential lidocaine/K⁺ challenge is accurate in diagnosing LQTS among patients with borderline QTc prolongation.

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antiarrhythmic agents; arrhythmia, electrophysiology; potassium

Congenital long QT syndrome (LQTS) is an inherited disorder of ventricular repolarization that can result in syncope and sudden death.¹ This condition is caused by mutant cardiac Na⁺ or K⁺ channels, encoded by the SCN5A (LQT3), KVLQT1 (LQT1), or HERG (LQT2) genes, that prolong ventricular repolarization time; thereby increasing the propensity for lethal torsade de pointes and ventricular fibrillation.²⁻⁵ Other repolarization abnormalities identified in this syndrome include increased QT dispersion on the 12-lead ECG⁶ and abnormal ST-T wave morphology.⁷⁻⁹ The diagnosis of LQTS may be problematic in up to 30% of patients who present

with symptoms but borderline QTc interval prolongation and normal T wave morphology.¹⁰

In LQT3, the Na⁺ channel variant of LQTS, Na⁺ channel blockers such as lidocaine and mexilitine have been shown to shorten the QTc interval by decreasing the pathologic late-persistent Na⁺ current.¹¹⁻¹⁸ In contrast, patients with the K⁺ channel LQT2 mutation exhibit QTc interval shortening with K⁺ infusion.¹⁸ In the case of LQT2, reduced I_{Kr}, can be augmented by increasing serum K⁺ concentrations in patients leading to a normalization of their QTc interval and QT dispersion.¹⁹⁻²² For LQT1, reduced I_{Ks} is not directly influenced

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by elevated serum K⁺ but other repolarizing currents such as I_{Kr} and I_{K1} can increase, leading to a shortening in repolarization time.^{23,24} In contrast, control subjects with normal repolarization have shown little change in QTc interval and QT dispersion with mexilitine or K⁺.

The response of the QTc interval and QT dispersion to lidocaine or K⁺ has not previously been studied in LQTS patients with borderline QTc interval prolongation. We considered a QTc interval ≤ 470 ms to be borderline prolonged because the probability of LQTS is intermediate in such patients if no other ECG or clinical feature of LQTS are present, according to Schwartz et al.²⁵ We hypothesized that lidocaine or K⁺ infusion would shorten the QT interval and QT dispersion to a greater extent in LQTS patients with borderline prolonged QTc intervals than normal controls. The combined lidocaine/K⁺ infusion should provide a simple test to unmask repolarization abnormalities and facilitate the diagnoses of LQTS in such patients. To investigate this hypothesis, we sequentially infused lidocaine followed by K⁺ in a LQTS population with a QTc interval ≤ 470 ms and in control subjects in order to compare the resultant changes in repolarization.

METHODS

Subjects

Eight patients with LQTS (5 females, mean age 31 ± 14 years) and QTc intervals ≤ 470 ms were enrolled. LQTS patients were included if they scored at least 4 points according to the 1993 LQTS diagnostic criteria, indicating definite LQTS.²⁵ Patients were drawn from five kindreds with known LQTS and all had a history of exercise-induced syncope. Four LQTS patients were genotyped using chromosomal analysis and were found to carry a mutation in HERG. The mean QTc interval of the LQTS population was 446 ± 29 ms (range 394–470 ms), which was unrelated to antiarrhythmic agents, electrolyte abnormalities, or any other cause of QT prolongation.

The control group included 10 patients (5 females, mean age 41 ± 9 years) with structurally normal hearts undergoing catheter ablation for supraventricular tachycardia. These patients were studied during the recovery period following successful radiofrequency catheter ablation, at which time their resting ECGs were normal with no ev-

idence of preexcitation or bundle branch block. The research protocol was reviewed and approved by our ethical review board, and written informed consent was obtained from participants.

Infusion Protocol

Intravenous access was obtained through a large forearm vein. Subjects rested supine for 60–90 minutes and then were studied. Following baseline ECG and serum K⁺, each patient received a 1.5 mg/kg bolus of lidocaine followed by a 3 mg/min infusion for 20 minutes. After a 40 minute lidocaine washout period, serum K⁺ was increased with po KCl 60 mEq, iv KCl 10 mEq/h for 4 hours, and po spironolactone 200 mg followed by a second dose of 100 mg 2 hours later. Twelve-lead ECGs were recorded after lidocaine and K⁺ infusion. Serum K⁺ was measured prior to the K⁺ infusion and then again at 2 and 4 hours after the K⁺ infusion.

QT Analysis

The QT interval was measured manually by a single observer using calipers from ECGs recorded at 25 mm/s. For each of the 12 leads, the QT interval was defined from the beginning of the QRS complex to the intersection of the tangent of the steepest downslope of the dominant repolarization wave with the isoelectric baseline.²⁶ U waves were not included in the measured QT interval. Leads were excluded from analysis only when the end of the T wave was not clearly distinguishable or less than 0.1 mV in amplitude. No more than two leads were excluded from any 12-lead ECG in the analysis. The QT interval was rate corrected using Bazett's formula.²⁷ QT dispersion was defined as the difference between the maximum and minimum QT interval from the 12-lead ECG.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD. Because of the small sample size, the Wilcoxon signed-rank test for paired data was used to compare intrapatient differences. The Mann-Whitney test was used to compare differences between LQTS patients and controls. Comparisons between categorical variables were made using chi-square tests or Fisher's exact test when appropriate. The sensitivity, specificity, and accuracy of the combined lidocaine/K⁺ infusion in diagnosing LQTS were determined using cutoffs derived from the

Table 1. Baseline Patient Characteristics

Variable	Controls (n = 10)	LQTS (n = 8)
Age (year)	41 ± 9	31 ± 14
Age range (year)	32–51	16–53
Females (%)	5 (50)	5 (63)
HR (bpm)	72 ± 18	54 ± 7*
QTc interval (ms)	416 ± 28	446 ± 29*
QT dispersion (ms)	29 ± 10	41 ± 16
β-blocker use (%)	0	7 (87)**

*P < 0.05 (vs control); **P < 0.001 (vs control).

control population. LQTS patients who exhibited a change in QTc interval with lidocaine or K⁺ greater than 2 standard deviations above the mean change seen in the controls were considered to have a positive lidocaine response or a positive K⁺ response, respectively. All tests were two sided and differences were significant at P < 0.05.

RESULTS

Baseline Clinical and ECG Characteristics

The age and gender distribution was similar between the LQTS patients and controls (Table 1). The LQTS group had longer QTc intervals but similar QT dispersion at baseline compared with control subjects. T-wave morphology was normal in the controls whereas the LQTS group had one patient with bifid T waves and another with late-onset T waves. Resting heart rates were lower in LQTS due to beta-blocker therapy in seven of the eight patients (87%).

Effect of Lidocaine on QTc interval and QT dispersion

The total lidocaine dose given to LQTS and control patients was similar (Table 2). Some patients

Table 2. Lidocaine/K⁺ Infusion

Variable	Controls (n = 10)	LQTS (n = 8)
Total lidocaine dose (mg)	160 ± 0	158 ± 7
Total K ⁺ dose (mEq)	96 ± 8	100 ± 0
Spironolactone (mg)	290 ± 32	300 ± 0
Baseline K ⁺ (mEq)	3.9 ± 0.2	4.1 ± 0.2**
2-hour K ⁺ (mEq)	4.4 ± 0.5*	5.3 ± 0.4*,**
4-hour K ⁺ (mEq)	4.4 ± 0.3*	5.1 ± 0.5*,**
ΔK ⁺ at 4 hours (mEq)	0.5 ± 0.4	1.0 ± 0.5

*P < 0.01 (vs baseline K⁺); **P < 0.01 (vs control).

Figure 1. Mean ± SD QTc interval dynamics in response to lidocaine and a 4-hour K⁺ infusion in LQTS patients and normal controls. Lidocaine failed to shorten QTc in both LQTS and controls. The 4-hour K⁺ infusion significantly shortened QTc compared to baseline among LQTS patients. In contrast, no response was seen in the normal controls. P < 0.005 for LQTS group (vs baseline).

experienced oral parasthesias near the end of the infusion but the dosing was otherwise well tolerated. After administration of lidocaine, baseline QTc did not significantly decrease in either the LQTS patients (3%, 15 ± 21 ms) or control subjects (−1%, −3 ± 19 ms) (Figs. 1 and 2). No change was noted in baseline QT dispersion in both groups (Figs. 2

Figure 2. Mean ± SD QT dispersion dynamics in response to lidocaine and a 4-hour K⁺ infusion in LQTS patients and normal controls. Lidocaine failed to shorten QT dispersion in both LQTS and controls. The 4-hour K⁺ infusion significantly shortened QT dispersion compared to baseline among LQTS patients. In contrast, no response was seen in the normal controls. P < 0.005 for LQTS group (vs baseline).

Figure 3. Mean $\pm$ SD shortening of baseline QTc interval and QT dispersion with lidocaine among LQTS patients and normal controls. The extent of shortening in QTc interval and QT dispersion was similar between LQTS patients and normal controls.

and 3). Note that one LQTS patient had a 12% (54 ms) reduction in QTc but no change in QT dispersion. This patient had late onset T waves with marked sinus bradycardia off beta-blockers, suggestive of LQT3.⁷

Effect of K⁺ on QTc interval and QT dispersion

Following lidocaine washout, QTc and QT dispersion returned to baseline values (Figs. 1 and 3). Subsequently, the total dose of K⁺ and spironolactone given to LQTS and control patients were similar (Table 2). The K⁺ infusion was reduced in two control patients due to nausea in one and peripheral intravenous irritation in the other. Baseline serum K⁺ was lower in the controls compared to the LQTS patients (3.9 ± 0.2 vs 4.1 ± 0.2 mEq, $P < 0.01$). After the 4-hour K⁺ infusion, serum K⁺ rose significantly compared to baseline in both controls (3.9 ± 0.2 to 4.4 ± 0.3 mEq, $P < 0.01$) and LQTS patients (4.1 ± 0.2 to 5.1 ± 0.5 mEq, $P < 0.01$). The rise in serum K⁺ in controls (0.5 ± 0.4 mEq) and LQTS patients (1.0 ± 0.5 mEq) was similar. During the 4-hour K⁺ infusion, the QTc and QT dispersion significantly decreased in LQTS by 9% (42 ± 12 ms, $P < 0.005$) and 45% (20 ± 13 ms, $P < 0.005$), respectively, compared to baseline. No effect was seen in control patients, where QTc and QT dispersion shortened by 1% (5 ± 14 ms) and 20% (6 ± 7 ms), respectively, compared to baseline (Figs. 1, 3, and 4).

Figure 4. Mean $\pm$ SD shortening of baseline QTc interval and QT dispersion with K⁺ infusion among LQTS patients and normal controls. The extent of shortening in QTc and QT dispersion was significantly greater in the LQTS patients than the normal controls. $P < 0.05$ (vs controls).

Diagnostic Utility of Lidocaine/K⁺ Infusion

Based on the QTc shortening in the control group, a positive lidocaine response in the LQTS group corresponded to a reduction in QTc > 35 ms, which was seen in one LQTS patient but no controls. This LQTS patient was suspected of having LQT3 based on his late-onset T waves.⁷ For the K⁺ infusion protocol, a positive response in the LQTS patients was defined by a reduction in QTc > 33 ms, which was apparent in seven out of the eight LQTS patients. In all control subjects, QTc shortening was less than 33 ms (range -19 to 19 ms). The genotype of the single LQT2 patient with a negative K⁺ response was HERG. This patient had an adequate rise in serum K⁺ of 0.7 mEq during the 4-hour K⁺ infusion.

Overall in our study population, the utility of the combined lidocaine/K⁺ infusion in diagnosing LQTS was high with a sensitivity of 88%, a specificity of 100%, and an accuracy of 94%.

DISCUSSION

Main Findings

A simplified lidocaine/K⁺ infusion protocol was highly accurate in diagnosing LQTS in our patient population with borderline QTc prolongation (≤ 470 ms). Lidocaine infusion alone identified one patient with LQTS while the remaining patients were identified with the K⁺ infusion. The combined drug challenge was well tolerated in our

study group and required half a day of monitoring to complete.

Clinical Significance

The diagnostic criteria for LQTS relies on several ECG and clinical parameters such as the extent of QTc prolongation, torsade de pointes, abnormal T-wave morphology, a history of syncope or a family history of LQTS.²⁵ In patients without a positive family history who present with presyncope or syncope but with borderline QTc interval prolongation and normal T-wave morphology, the diagnosis of LQTS remains difficult. The prevalence of such patients may be as high as 30% according to the LQTS registry.¹⁰ Although genetic testing provides a gold standard for the diagnosis of congenital LQTS, it is still too costly and time-consuming to be a practical clinical tool. In addition, many patients represent sporadic cases or previously undescribed mutations. By measuring QT dynamics in response to lidocaine/K⁺, the present infusion protocol provides a provocative test to aid in the diagnosis of LQTS for patients with borderline QTc interval prolongation.

Our study is the first to measure QT dynamics with lidocaine and K⁺ in LQTS patients without marked QTc interval prolongation. In contrast, Schwartz et al. investigated the effect of mexilitine in 15 LQTS patients whose baseline QTc interval was 534 ± 57 ms.¹⁸ Similarly, Compton et al. studied the response of the QTc interval to K⁺ infusion in seven LQT2 patients whose baseline QTc interval was 627 ± 90 ms.²¹

Differential Response to Lidocaine and K⁺ in LQTS

Lidocaine like other class Ib drugs preferentially blocks the inactivated-state of the Na⁺ channel. In cellular models of LQT3 involving heterologous expression of the inactivation-defective Na⁺ channel mutants, lidocaine stabilizes inactivation thereby decreasing the late-persistent I_{Na} that prolongs repolarization.^{11–14} In contrast, the robust early I_{Na} transient, which is responsible for phase 0 of the action potential, changes minimally. Similarly, mexilitine abbreviates the action potential duration of ventricular myocytes in a drug model of LQT3 using anthopleurin, an inhibitor of Na⁺ channel inactivation.^{15–17} Among LQT3 patients, mexilitine shortens their QTc interval, a response not seen in patients with LQT2.¹⁸ The effect of Na⁺ chan-

nel blockers on QT dispersion in LQT3 has not been studied to date. Although the genotype of our single "lidocaine responder" is unknown, the presence of late-onset T waves and syncope at rest suggests LQT3.⁷ This patient's baseline QTc and QT dispersion were minimally prolonged which may account for the blunted response to lidocaine, with a 12% reduction in QTc and no change in QT dispersion. In contrast, Schwartz et al. noted a 17% change in the QTc interval of LQT3 patients treated acutely with mexilitine.¹⁸ The lidocaine response in LQT3 may also be allele specific. For instance, the QTc and QT dispersion in patients carrying the D1790G Na⁺ channel mutation do not change with lidocaine because a late persistent I_{Na} is not the pathophysiologic basis for their abnormal repolarization.²⁸ Instead, flecainide, an open-state Na⁺ channel blocker, improves repolarization. The mechanism of this differential response remains unclear.

Elevating serum K⁺ paradoxically augments the K⁺ repolarizing currents, I_{Kr} and I_{K1}, despite a decrease in electrochemical gradient.^{19,20} This results in a shortening of ventricular repolarization time. Among the seven LQT2 patients studied by Compton et al., QTc and QT dispersion fell by 24% and 68%, respectively with K⁺ infusion, a response that is more than twice that seen in our patients.²¹ The difference may be due to the greater serum K⁺ increase achieved in their patients (≥ 1.5 mEq) with the use of repeated doses of K⁺ and spironolactone which augment I_{Kr} to a greater extent. Our fixed-dose K⁺ infusion protocol was chosen as a simpler alternative to repeat dosing and serum K⁺ monitoring. In addition, the baseline repolarization abnormality was more severe among their LQT2 population with a mean QTc and QT dispersion of 627 and 133 ms, respectively. The K⁺ response may be blunted in patients with less repolarization prolongation, like our study patients, as suggested by the insignificant change in QTc and QT dispersion in the normal controls. It is unclear why the single LQTS patient with the HERG genotype was not a "potassium responder." This patient's QTc interval was 464 ms and the serum K⁺ rose adequately by 0.7 mEq after the 4-hour K⁺ infusion. We speculate that this LQT2 patient may carry a novel mutation that renders the K⁺ channel less sensitive to serum K⁺ elevations.

With respect to LQT1, the response of QTc and QT dispersion to K⁺ infusion has not previously been studied. Nonspecific augmentation of the K⁺

repolarizing currents, I_{Kr} and I_{K1}, with K⁺ should also shorten the QTc in LQT1 patients.^{19,20,23,24} By analogy, increasing the K⁺ repolarizing current, I_{K-ATP}, with the K⁺ channel opener, nicorandil, has been shown to improve the repolarization abnormalities in LQT1 patients.^{29,30}

Limitations

The number of patients in this study is small, with limited assessment of individual genotypes. Our observations require validation in larger numbers of genotyped patients. However, in the presence of typical ECG characteristics and event triggers, phenotypic predictors of genotype are adequate in predicting genotype in 88% of families with LQT1 and LQT2.^{7,8} A second limitation is that the specificity of the QTc response to K⁺ infusion for diagnosing LQTS was not assessed. In patients with QTc prolongation due to quinidine or congestive heart failure, K⁺ infusion nonspecifically shortens repolarization time by augmenting I_{Kr} and I_{K1}.³¹ However, antiarrhythmic exposure and heart failure can easily be excluded in an individual patient suspected of having LQTS by assessing the clinical history and left ventricular function. In such patients, who have borderline QTc prolongation, our simplified K⁺ protocol identified all but one patient with LQTS despite only a modest rise in serum K⁺.

In conclusion, sequential lidocaine and K⁺ infusion shortens the QTc interval to a greater extent in LQTS patients with borderline QTc prolongation than control subjects. This simplified drug challenge accurately diagnoses LQTS in patients with borderline QTc prolongation.

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