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Lidocaine attenuation testing: An *in vivo* investigation of putative LQT3-associated variants in the *SCN5A*-encoded sodium channel

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Abstract

BACKGROUND—Long QT syndrome type 3 (LQT3) accounts for 5%–10% of long QT syndrome and results from gain-of-function mutations in the *SCN5A*-encoded sodium channel. Approximately 2% of healthy individuals host rare *SCN5A* variants of uncertain significance (VUS). Distinction of true LQT3-causative mutations from background genetic noise is essential.

OBJECTIVE—The purpose of this study was to assess the use of the lidocaine attenuation test (LAT) in evaluating patients with possible LQT3.

METHODS—We reviewed the LAT results and medical records for 25 patients with a possible LQT3-associated *SCN5A* variant. The LAT involved a loading dose of 1 mg/kg of intravenous lidocaine followed by continuous infusion at 50 µg/(kg•min) for 20 minutes. If the corrected QT interval shortened by ≥30 ms, the LAT was defined as positive.

RESULTS—Sixteen patients (64%) had a positive LAT, 6 of which demonstrated the E1784K variant. A positive LAT correlated in 86% of cases with abnormal *in vitro* channel function (mean corrected QT interval attenuation 43 ± 3 ms vs 25 ± 5 ms for wildtype variants; *P* = .03). Four of 5 patients (80%) with a VUS had a positive LAT (T1304M [2 patients], L1786P, and R800L). The T1304M variant demonstrated abnormal *in vitro* function and a positive LAT, opening the door for a potential variant promotion from VUS to likely pathogenic.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.hrthm.2017.04.020>.

CONCLUSION—The LAT may help distinguish true LQT3-causative mutations from an otherwise noncontributory VUS. Given that lidocaine acts as a late sodium current blocker, a positive LAT may enable the early identification of a pathological accentuation of the late sodium current that could be targeted therapeutically.

Keywords

Long QT syndrome; Long QT syndrome type 3; Lidocaine attenuation test; VUS; *SCN5A*

Introduction

Long QT syndrome (LQTS) is an inherited disorder characterized by abnormal ventricular repolarization that can precipitate ventricular arrhythmias leading to syncope or sudden cardiac death.^{1,2} LQTS occurs in ~1:2000 individuals.³ Approximately 5%–10% of LQTS is caused by gain-of-function mutations in the *SCN5A*-encoded Na_v1.5 sodium channel and is designated as LQTS type 3 (LQT3).⁴ Bona fide LQT3-causative mutations result in either a delay of sodium channel inactivation, increased late sodium current, or increased window current. While many disease-causing mutations in *SCN5A* are associated with LQT3, distinguishing pathologic mutations from background noise is extremely important. In fact, 2% of ostensibly healthy individuals host rare variants of *SCN5A*, making variant interpretation, disease management, and family screening challenging.⁵

In LQT3, sodium channel blockers such as lidocaine and mexiletine have been shown to shorten the QT interval by attenuating the persistent, pathologic sodium channel current.^{6–8} In 2004, Chauhan et al⁹ described the use of lidocaine/potassium infusion for the evaluation of patients with borderline prolonged corrected QT (QTc) interval values at baseline. In this study, a patient with suspected

LQT3 demonstrated increased sensitivity to lidocaine infusion as compared to patients with other LQTS genetic subtypes. The combined sensitivity of lidocaine/potassium infusion for the diagnosis of LQTS was 88%, and the specificity was 100%; however, the sensitivity and specificity for isolated lidocaine infusion for LQT3 have not been established. At our institution, we have used the protocol for lidocaine infusion and continuous cardiac monitoring as described in Chauhan's study as a lidocaine attenuation test (LAT) to evaluate patients who have possible LQT3.

Herein, we sought to describe the results of the LAT in patients with suspected LQT3 and correlate those results with the phenotype and pathogenicity of *SCN5A* variants to evaluate the use of the LAT to potentially distinguish true LQT3-causative mutations from ambiguous *SCN5A* variants.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. All patients with LQT3 who underwent a clinical diagnostic LAT were included in this study. A total of 25 patients met inclusion criteria. Demographic data, LAT results, *SCN5A* variant status, and current LQTS-directed treatment (ie, β -blocker, mexiletine, implantable cardioverter-

defibrillator) were obtained from review of the electronic medical record. A schematic of the LAT study protocol is shown in Figure 1A. The test is performed with the patient in a fasting state in the cardiac electrophysiology laboratory. After placing an intravenous line and electrocardiographic (ECG) leads, baseline QT, QTc, and RR intervals are obtained. At the start of the test, a lidocaine bolus of 1 mg/kg (maximum 100 mg) is administered followed by an infusion of 50 µg/(kg•min) (maximum 3 mg/min) for 20 minutes.⁹ QT intervals, RR intervals, and the derived Bazett's heart rate-corrected QTc values are recorded at 1-minute intervals for 7 minutes followed by recordings at the 10th, 15th, and 20th minute after the start of the test (Figure 1A). Recovery recordings are performed at 5-, 10-, and 20-minute intervals after lidocaine discontinuation. All values are obtained from lead II as a mean of 3 consecutive beats. All ECGs were reevaluated for this study by a physician (H.N.A.) blinded to genotype. The LAT is considered positive for the pathologic late sodium current if the QTc interval shortened by ≥ 30 ms from baseline at any time point during the infusion.

A Schwartz score for the diagnosis of LQTS was ascribed to each patient.¹⁰ Patients with a score of ≥ 1 point were considered to have a low probability of LQTS, patients with a score of 1.5–3 points had an intermediate probability, and patients with a score of ≥ 3.5 points were considered to have high probability. This often-used score was used to ascribe a numerical value to the clinical phenotype of each patient for the purpose of analysis and genotype correlation.

Identified *SCN5A* variants were classified for pathogenicity using in vitro data as well as presence/absence in the Exome Aggregation Consortium databases¹¹ according to the classification algorithm presented in Supplemental Table 1. Overrepresentation in cases vs controls for variant classification was determined using the Fisher statistical method. In vitro function was established previously using whole-cell patch-clamp analysis performed in our laboratory or by review of the available literature.^{12–15} For 2 missense variants—R53Q and L1786—in vitro analysis data were not available at the time of this evaluation. Abnormal in vitro function was defined as a reduction in current density, a >5-mV shift in $V_{1/2}$ in activation/inactivation, or a statistically significant >100% increase in sodium late current (Supplemental Table 2).

In vitro results, variant classification, and clinical phenotype (via Schwartz score) were compared with the LAT result. Continuous data were analyzed using the Student *t* test for comparison of mean data and the analysis of variance for comparison of LAT results with variant classification. Categorical data, including LAT and in vitro study results, were analyzed using a 2-tailed Fisher exact method. A receiver operating characteristic curve was constructed to analyze LAT test characteristics including sensitivity and specificity. A *P* value of <.05 was considered statistically significant.

Results

Study cohort

Between 2002 and 2013, a total of 25 patients with a diagnosis of possible or probable *SCN5A*-mediated LQT3 had a LAT performed during their evaluation at Mayo Clinic. The demographic characteristics of the study cohort are summarized in Table 1. The mean age

was 22 ± 11 years, and approximately half (52%) were female patients. The mean baseline QTc interval was 459 ± 30 ms. None of the patients had an LQTS-triggered event (ie, syncope, seizures, and cardiac arrest) before the diagnosis of LQT3. Seventeen patients (68%) had a family history of diagnosed LQTS (48%) or sudden cardiac death (48%).

Genetic analyses

Thirteen unique *SCN5A* variants were identified (Supplemental Table 3). The most common variant was E1784K (9 of 25 [36%]) followed by N1325S (3 of 25 [12%]). R190Q, G615E, and T1304M were identified in 2 patients, and the remaining variants (E48K, R53Q, L461V, R800L, M1320V, R1644H, and L1786P) were seen once. Among these, both patients with R190Q, all 3 with N1325S, and 2 of the 9 patients with E1784K were related.

In vitro data were available for 11 of 13 variants (85%), with abnormal in vitro function found in 5 of 11 tested variants (45%) (R800L, T1304M, N1325S, R1644H, and E1784K) (Supplemental Table 2).

Based on these results and genetic population data on these 13 variants, 4 variants (R53Q, R800L, T1304M, and L1786P) were classified as variants of uncertain significance (VUS) (Supplemental Table 3). Two variants were classified as pathogenic (N1325S and E1784K), 1 as likely pathogenic (R1644H), 2 as likely benign (E462A and M1320V), and 4 as benign (E48K, R190Q, L461V, and G615E).

Positive LAT

Sixteen patients (64%) had a positive LAT. There were no significant phenotypical differences between patients with a positive and a negative LAT (Table 1). The mean baseline QTc interval was 462 ± 33 ms for patients with a positive LAT as compared with 452 ± 25 ms for patients with a negative LAT. For patients with a positive LAT, the mean QTc interval shortening observed was 49 ± 15 ms (range 30–91 ms) as compared with 21 ± 7 ms (range 10–29 ms) for patients with a negative LAT (Table 1).

SCN5A variants associated with overlap syndrome

Several *SCN5A* variants have been documented in association with both LQT3 and Brugada syndrome (BrS). In our study, E1784K, G615E, and L1786P have the potential for BrS “overlap.”¹⁶ To assess whether these patients might have an underlying BrS phenotype, we reviewed QRS interval on the baseline ECG for all patients. There was no significant difference in QRS interval between patients with a positive and a negative LAT (Table 1). In addition, when comparing the mean QRS change during lidocaine infusion, there was no significant difference between the potential overlap syndrome variants and LQT3-only variants. In fact, patients with an “overlap” variant demonstrated a predominance toward a slight decrease in QRS duration with a mean difference of -1 ms while those with an LQT3-only variant demonstrated a mean difference of 0 ms ($P = .6$). None of the patients with a possible *SCN5A* overlap variant showed an ECG or QRS interval suggestive of $\text{Na}_v1.5$ loss of function in general or BrS in particular with the standard precordial lead position or high lead placement.

LAT-phenotype correlation

A score based on the Schwartz criteria¹⁰ was provided to each patient to provide an objective measure of the veracity of the LQTS clinical phenotype. The mean Schwartz score for all patients was 2.68 ± 1.13 . Patients with a positive LAT had a mean Schwartz score of 2.97 ± 0.27 , while those with a negative LAT had a Schwartz score of 2.17 ± 0.36 ($P = .087$). One patient had both a negative LAT and a low Schwartz score (< 1), while 2 patients had a low Schwartz score but a positive LAT. These 2 patients had G615E and T1304M variants with LAT values of 44 and 42 ms, respectively. Seven patients had both a positive LAT and a high Schwartz score (ie, ≥ 3.5). When using a Schwartz score of ≥ 1.5 as a criterion standard for clinical diagnosis of at least intermediate probability of LQTS, this gives a positive predictive value of 88% and a negative predictive value of 11%.

Comparison of LAT results with in vitro data and variant classification

A positive LAT correlated in 86% of cases with in vitro evidence of abnormal channel function (13 of 15) ($P = .03$) (Figure 2). Variants with abnormal in vitro functional status demonstrated a mean QTc interval shortening of 43 ± 3 ms as compared with 25 ± 5 ms for variants with wild-type functional status ($P = .003$). The LAT results were analyzed using receiver operating characteristic analyses, with in vitro function as the reference standard for comparison. Based on this analysis, 30 ms was determined to be the optimal cutoff value to predict a positive LAT (area under the curve 0.86) (Figure 3). This cutoff value resulted in a sensitivity of 81% and a specificity of 71%. In our study, 2 patients with the pathogenic E1784K variant had a negative LAT but displayed a QTc interval attenuation of 25 and 29 ms, respectively. If these 2 cases were categorized as a positive LAT by lowering the cutoff value to 25 ms, this would increase the sensitivity to 94% but specificity would decrease significantly to 57%. Therefore, in order to maximize both sensitivity and specificity, 30 ms provides the optimal cutoff value. However, if the LAT is used as a screening test, a cutoff value of 25 ms may be more reasonable to maximize sensitivity.

Further analysis demonstrated the association between the LAT result and the combined variant frequency and in vitro analysis data. Sixty-eight percent of positive LATs were associated with a rarity to absence of the variant in public exomes (or significant overrepresentation in cases vs controls) as well as abnormal in vitro function. Another 12% of positive LATs were associated with either a low population frequency variant data or abnormal in vitro data ($P = .03$). Conversely, 60% of the negative LAT results were associated with common variants and wild type in vitro function ($P = .03$). Based on the composite variant classification as described in Supplemental Table 1, among the patients with variants classified as pathogenic or likely pathogenic, 77% (10 of 13) had a positive LAT as compared with only 28% of patients (2 of 7) with benign or likely benign variants ($P = .02$) (Figure 4).

Variants of uncertain significance

Of the 13 variants, 4 were classified as VUS (31%), which included R53Q, L1786P, R800L, and T1304M (2 patients). The T1304M variant had abnormal in vitro function, and both patients with this variant had a markedly positive

LAT.—A QTc interval shortening of 42 and 50 ms was observed for patients with this variant, opening the door for potentially upgrading it from a VUS to a likely pathogenic variant. Similarly, this could be done for the L1786P variant, which demonstrated a QTc interval attenuation of 91 ms, though no in vitro data are currently available for this variant. However, mexiletine treatment was recommended because the patient demonstrated extreme QTc interval shortening. R800L also had a positive LAT (QTc interval attenuation 37 ms). Conversely, the R53Q variant was associated with a negative LAT, which could potentially justify its demotion from VUS to likely benign.

Discussion

Although our knowledge on the pathogenetics, clinical features, treatment, and outcomes of LQTS has grown significantly, risk stratification and variant interpretation remain challenging, especially when novel variants are classified as a VUS. Previous studies have provided information about risk stratification in LQTS and demonstrated the additional value of drug provocation tests in the clinical evaluation of LQTS.^{17–19} While these studies provided an evaluation of patients with potassium channel-mediated LQTS particularly *KCNQ1*-mediated LQT1, they do not address abnormal sodium channel function (*SCN5A*) as seen in patients with LQT3. Lidocaine attenuates abnormal sodium channel function in LQT3, thereby shortening the QTc interval during the infusion.⁸ Therefore, the LAT may provide similar use in the evaluation of patients with suspected LQT3 as exercise or epinephrine testing provide in the evaluation of suspected LQT1. Our study describes the LAT use in patients with *SCN5A* variants and its association with genotype.

Positive LAT

In vitro analyses have been used to describe the functional status of variants implicated in LQTS. However, these data are not available for novel variants and variant classification can be variable based on the type of algorithm used.²⁰ We compared data from in vitro analysis and variant classification with the LAT result to provide additional insight into the predictive value of the LAT. Notably, the LAT result correlated closely with both, and the majority of patients with a positive LAT also had abnormal in vitro function. Using a combination of in vitro results and variant classification, the LAT result has a positive predictive value of 85% and a negative predictive value of 67%. Furthermore, using a cutoff value of 30 ms, the LAT demonstrates a sensitivity of 81% and a specificity of 71%. Exercise or epinephrine infusion testing has provided similar correlation with LQT1 or LQT2, but no existing testing modality has provided this information for LQT3.^{18,19,21} Our data suggest that the LAT can provide significant ancillary information to assist with variant adjudication and to anticipate the patient's responsivity to oral mexiletine therapy.^{22,23}

We identified 8 unique *SCN5A* variants associated with a positive LAT, including E1784K, N1325S, T1304M, E48K, G615E, L1786P, R1644H, and R800L. A number of these variants have been described previously in patients with suspected LQTS. However, several variants such as L1786P and E48K have not been associated previously with LQT3 on review of the existing literature.^{12–15} While functional data were not available for the L1786P variant, a variant, involving the same amino acid (L1786A), yields a dysfunctional sodium current.²⁴

In line with the L1786P being pathogenic as well, the patient with L1786P had a positive LAT.

The E1784K variant was the most prevalent LQT3-associated variant seen and has been documented in patients with confirmed LQT3 previously.¹² Interestingly, 3 E1784K-positive patients had a negative LAT, suggesting that the correlation between genotype and phenotype may be complicated by other factors, which have not been well described. In addition, E1784K is not a pure LQT3-causative mutation as patients with E1784K can display isolated QT prolongation (ie, LQT3), isolated BrS, isolated cardiac conduction disease, or electrocardiographic features of all 3 phenotypes, thereby affecting the ability of this particular variant to respond to the LAT as predicted for a variant with pure LQT3 profile. Despite not reaching the cutoff value of 30 ms, 2 of these 3 patients approached our diagnostic threshold for a positive LAT (25 and 29 ms, respectively), suggesting a possible stronger correlation of a positive LAT and putative pathogenic variant status.

In 1985, Schwartz and colleagues developed a criterion for the diagnosis of LQTS, and in 1993, they refined it into a summative score denoting the probability of LQTS, given the patient's clinical findings and family history.^{25,26} This criterion was again updated in 2011 to include exercise stress testing.¹⁰ In our analysis, we sought to correlate this diagnostic score with the LAT results. Patients with a positive LAT did tend toward a slightly higher Schwartz score, but this did not reach statistical significance, possibly owing to a small number of patients in the study. The positive predictive value for our test using the Schwartz criteria as the criterion standard was excellent at 88%, but this also resulted in a low negative predictive value of 11%. Therefore, a positive LAT would increase suspicion for true LQT3 in patients with a *SCN5A* variant, but a negative test would be less useful.

Whether the test would be informative in patients with LQTS without a sodium channel variant remains to be determined but is doubtful on the basis of known cellular and molecular pathogenic mechanisms of potassium channel-mediated disease. It is possible that a positive LAT in a patient negative for LQT3 could suggest a final common pathway insult to the Na_v1.5 channel, prompting an index of suspicion for the presence of an LQT3 mimicker such as CAV3-LQTS (LQT9), SCN4B-LQTS (LQT10), or SNTA1-LQTS (LQT12). However, this has not been demonstrated thus far.

Potential clinical role of the LAT

In this study, we have shown that the LAT has a significant correlation with in vitro analysis and variant classification. Importantly, a positive LAT also has a close correlation with at least an intermediate clinical phenotype of LQTS (Schwartz score ≥ 1.5). The importance of the LAT becomes additionally evident when considering those variants stuck with a classification of VUS. In our study, there were 4 VUS (R53Q, R800L, T1304M, and L1786P), and 2 VUS (R53Q and L1786P) did not have in vitro data available. Previously, these patients had been treated on the basis of clinical history, family history, and ancillary testing as outlined in the "HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes,"²⁷ which did not comment on the potential role of this novel clinical test. Here, we have demonstrated that the

LAT can provide useful information about the potential presence of pathogenic sodium channel function.

For example, the T1304M variant demonstrated an abnormal in vitro function and both patients with this variant had a positive LAT. A QTc interval shortening of 42 and 50 ms was observed for these patients, opening the door for considering a variant upgrade from VUS to likely pathogenic. Similarly, this could be done for the L1786P variant, with the patient demonstrating a QTc interval attenuation of 91 ms on the LAT. Conversely, the R53Q variant was associated with a negative LAT, which could potentially justify its downgrade to “likely benign.” In all instances, the LAT facilitated the reclassification of a previously clinically uninformative/ambiguous variant to something that could help the diagnosis, treatment, and family screening for these patients.

Furthermore, we considered the implication this type of testing may have on treatment, particularly allowing for early treatment before a variant is identified and characterized. Mexiletine is an oral class IB sodium channel blocker whose mechanism of action closely mimics lidocaine with preferential attenuation of the late sodium current compared with peak sodium current block. This medication has been shown effective in the management of patients with LQT3.^{22,27,28} Howley et al detailed the case of an infant with prolonged QT on propranolol therapy who demonstrated progressive shortening of the QTc interval with lidocaine infusion, prompting clinical suspicion for LQT3, thus allowing for early initiation of mexiletine therapy before LQT3 was confirmed with genetic testing.²⁹ In our study, following the patient’s positive LAT, mexiletine was recommended in 13 patients (86%). The case reported by Howley et al as well as our data suggest that the LAT may provide a pregenetic test result strategy to identify patients with abnormal sodium channel function who might benefit from treatment with a sodium channel blocker such as mexiletine. However, additional studies to correlate the LAT result with the clinical use and effect of mexiletine are required to further evaluate this consideration.

Study limitations

This study provides information about the use of a standardized lidocaine infusion test for the evaluation of patients with suspected LQTS in the setting of a possible disease-associated *SCN5A* mutation. Specifically, a positive test correlates with abnormal in vitro function and provides a test with high sensitivity but low specificity. However, this study is limited by the small number of patients who have had this new test, making the results difficult to generalize to a larger population of patients with suspected LQTS. Additional prospective controlled studies in a larger population should be conducted to provide information about the use and indication for the evaluation of patients with suspected LQT3. In addition, this study shows the potential diagnostic information provided by this test, but further investigation would be needed to evaluate the impact on therapeutic responsiveness to treatment such as mexiletine.

Conclusion

The LAT provides a useful tool for the evaluation of patients with suspected LQT3. A positive LAT correlates with the composite variant classification and suggests the presence

of pathological accentuation of the late sodium current, which may be targeted with pharmacologic therapies such as mexiletine. In addition, the LAT result can potentially aid in the growing challenge of variant adjudication, particularly in those variants currently identified as *VUS*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic of the lidocaine attenuation test (LAT) protocol (A). Electrocardiographic (lead II) tracings for a patient during the LAT at (B) baseline, (C) 2 minutes into the infusion, and (D) 5 minutes into the recovery phase. QTc = corrected QT.

Figure 2.
Correlation of the lidocaine attenuation test (LAT) result with in vitro function.

Figure 3. Receiver operating characteristic curve of the lidocaine attenuation test using in vitro variant classification as the reference standard. AUC = area under the curve.

Figure 4.
Correlation of the lidocaine attenuation test (LAT) result with mutation classification. VUS = variants of uncertain significance.

Table 1

Demographic characteristics of cohorts with a positive LAT and a negative LAT

Characteristic	Study cohort	Positive LAT	Negative LAT	P
No. of patients	25	16	9	–
Sex: female	13 (52)	7 (44)	6 (67)	.4
Age at LAT (y)	22 ± 10	21 ± 10	22 ± 11	.8
Age at LQTS diagnosis (y)	19 ± 11	18 ± 11	22 ± 11	.4
Baseline QTc interval (ms)	459 ± 30	462 ± 33	452 ± 25	.4
Baseline QRS interval (ms)	82 ± 8	82 ± 6	82 ± 10	.9
Symptomatic	1 (4)	0 (0)	1 (10)	.4
Family history of LQTS	12 (48)	9 (56)	3 (33)	.2
Family history of SCD	12 (48)	8 (50)	5 (56)	1.0
QT interval shortening (ms)	38 ± 19 (10–91)	49 ± 15 (30–91)	21 ± 7 (10–29)	–
Time to maximum shortening (min)	5 ± 3 (1–15)	4 ± 3 (1–10)	5 ± 4 (1–15)	.6
Schwartz score for the diagnosis of LQTS	2.7 ± 1	3.0 ± 0.3	2.2 ± 0.4	.09

Values are presented as mean ± SD (range) or as n (%).

LAT 5 lidocaine attenuation test; LQTS 5 long QT syndrome; QTc 5 corrected QT; SCD 5 sudden cardiac death.