Risk of Life-Threatening Cardiac Events in Patients with Genotype-Confirmed Long-QT Syndrome and a Normal-Range QTc

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Word count: 4749 words (including text, references, and figure legends).

Running title: Phenotype-negative long-QT syndrome

Abstract

Objectives: The study was designed to assess the clinical course and to identify risk factors for life-threatening events among long-QT syndrome (LQTS) patients with normal corrected QT intervals (QTc).

Background: Current data regarding the outcome of patients with concealed LQTS are limited.

Methods: We examined clinical and genetic risk factors for aborted cardiac arrest (ACA) or sudden cardiac death (SCD) from birth through age 40 years among 3,386 genotyped subjects from 7 multinational LQTS registries, categorized as LQTS with normal-range QTc (≤440 msec [n=469]; LQTS with prolonged QTc (>440 msec [n=1392]); and unaffected family members (genotyped-negative with ≤440 msec [n=1525].

Results: The cumulative probability of ACA or SCD among LQTS patients with a normal-range QTc (4%) was significantly lower than among those with a prolonged QTc (15%; p<0.001), but higher than among unaffected family members (0.4%; p<0.001). Risk factors ACA or SCD among patients with a normal-range QTc included mutation characteristics (transmembrane-missense vs. non-transmembrane or non-missense mutations: HR=6.32 [p=0.006]) and the LQTS genotypes (LQT1:LQT2, HR=9.88 [p=0.03]; LQT3:LQT2, HR=8.04 [p=0.07], whereas clinical factors, including gender and QTc duration, were associated with a significant increase in the risk for ACA or SCD only among patients with a prolonged QTc (female >13 yrs: HR=1.90 [p=0.002]; QTc duration: 8% risk-increase per 10 msec increment [p=0.002])

Conclusions: Genotype-confirmed patients with concealed LQTS make up about 25% of the at-risk LQTS population. Genetic data, including information regarding mutation characteristics

and the LQTS genotype, identify increased risk for ACA or SCD in this overall lower-risk LQTS subgroup.

Key words: long-QT syndrome • corrected QT interval • sudden cardiac death

Condensed Abstract

The present study was designed to assess the clinical course and to identify risk factors for life-threatening events among long-QT syndrome (LQTS) patients with a normal range QTc (≤440 msec). Normal-range QTc patients are shown to comprise 25% of 1,863 genetically-confirmed LQT1-3 patients from the International LQTS Registry, and to have a 4% cumulative probability of aborted cardiac arrest or sudden cardiac death from birth through age 40 years. We show that genetic data, including knowledge of mutation location and type, can help identify increased risk for life-threatening events in this lower subset of the LQTS population.

Abbreviations and acronyms

ACA = aborted cardiac arrest

ECG = electrocardiogram

LQTS = long QT syndrome

LQT1,2,3 = long QT syndrome types 1,2, and 3

QTc = corrected QT

SCD = sudden cardiac death

Congenital long QT syndrome (LQTS) is an inherited channelopathy, characterized by a prolonged corrected QT interval (QTc) at rest, that is associated with an increased predisposition for polymorphic ventricular arrhythmias and sudden cardiac death (SCD) in young individuals without structural heart disease (1). To date, more than 500 mutations have been identified in 12 LQTS-susceptibility genes, with the LQT1-3 genotypes comprising more than 95% of genotype positive LQTS and approximately 75% of all LQTS (2). Risk assessment among affected LQTS patients relies primarily on a constellation of electrocardiographic (ECG) and clinical factors, including QTc and age-gender interactions (3-6). In addition, there is increasing evidence that genetic information and the molecular/cellular properties of the LQTS-causative mutation may identify subjects with increased risk for cardiac events (7-10). Despite these recent advancements, however, currently there are limited data regarding the clinical course and risk factors for life-threatening events among LQTS patients with normal resting QTc values, so-called silent mutation carriers, concealed LQTS, or normal QT interval LQTS.

In the present study we employed combined data from 7 national LQTS registries to: 1) compare the clinical course of LQTS patients who have a normal-range QTc to that of patients with a prolonged QTc and of genotype-negative unaffected family members; and 2) identify specific clinical and genetic risk factors for life-threatening cardiac events among LQTS patients with a normal-range QTc.

Methods

Study Population

The study population comprised 3,386 genotyped subjects drawn from the Rochester, NY enrolling center (center #1) of the International LQTS Registry (n=2,630), the Netherlands LQTS Registry (n=391), and the Japanese LQTS Registry (n=205), as well as from data submitted by

other investigators specifically for this collaborative mutation analysis project: Denmark (n=90), Italy (n=28), Israel (n=25), and Sweden (n=17). Patients were derived from 552 proband-identified *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) families. The proband in each family had otherwise unexplained, diagnostic QTc prolongation or experienced LQTS-related symptoms. Patients were excluded from the study if they had 1) > 1 LQTS identified mutation (n=70); 2) Jervell and Lange-Nielsen syndrome with deafness and 2 *KCNQ1* mutations or one known *KCNQ1* mutation and congenital deafness (n=2); and 3) no identified mutation on genetic testing with prolonged QTc (> 440 msec [n=428]).

Data Collection and End Point

Routine clinical and rest ECG parameters were acquired at the time of enrollment in each of the registries. Measured parameters on the first recorded ECG included QT and R-R intervals in milliseconds, with QT corrected for heart rate by Bazett's formula (11). Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, ECG findings, therapies, and events during long-term follow-up. Data common to all LQTS registries involving genetically tested individuals were electronically merged into a common database for the present study. In addition, information regarding QT prolonging medications and triggers for cardiac events was collected through a specific questionnaire for patients enrolled the US portion of the registry.

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising aborted cardiac arrest ([ACA] requiring external defibrillation as part of the resuscitation or internal defibrillation in patients with an implantable cardioverter defibrillator [ICD]), or LQTS-related sudden cardiac death ([SCD] abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a non-witnessed

setting such as sleep). In the multivariate models, follow-up was censored at age 41 years to avoid the influence of coronary disease on the occurrence of cardiac events. We also evaluated a secondary end point that included the occurrence of a first cardiac event of any-type during follow-up (comprising syncope [defined as transient loss of consciousness that was abrupt in onset and offset], ACA, or SCD).

Phenotype Characterization

For the purpose of this study, the QTc was categorized as normal-range (≤ 440 msec) or prolonged (> 440 msec) according to accepted criteria for the phenotypic definition of LQTS (12). Employing this definition, the study population were categorized into 3 genotype/QTc subgroups: 1) LQTS with normal-range QTc (n=469): comprising patients identified to have a LQT1-3 mutation with QTc ≤440 msec; 2) LQTS with prolonged QTc (n=1392): comprising patients with a LQT1-3 mutation with QTc >440 msec; and 3) unaffected family members (n=1525): comprising registry subjects from genotype-positive proband-identified families who were genetically tested and found negative for the LQTS-associated mutation, with QTc ≤ 440 msec (i.e. genetically and phenotypically unaffected family members).

Genotype Characterization

The *KCNQ1*, *KCNH2*, and *SCN5A* mutations were identified with the use of standard genetic tests performed in academic molecular-genetic laboratories including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, TX; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN; Boston Children's Hospital, Boston, MA; Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; and Department of Clinical Genetics, Academic

Medical Center, Amsterdam, Netherlands, and Molecular Cardiology Laboratory, Policlinico S. Matteo and University of Pavia, Pavia, Italy.

Genetic alterations of the amino acid sequence were characterized by location and by the type of the specific mutation. The transmembrane region of each of the 3 LQTS channels was defined as: (i) amino acid residues from 120 through 355 in the *KCNQ1*-encoded Kv7.1 channel (S1-6 region); (ii) amino acid residues from 398 through 657 (S1-S6 region) in the *KCNH2*-encoded Kv11.1 channel; and (iii) amino acid residues 129 through 417, 713 through 940, 1201 through 1470, and 1523 through 1740 in the *SCN5A*-encoded Nav1.5 channel (13). Based on prior studies that demonstrated the functional and clinical importance of missense mutations which are located in the transmembrane region of these LQTS-associated channels (9,10), mutation categories were pre-specified in the primary analysis as transmembrane-missense (mutations of the missense-type in any of the 3 transmembrane regions described above) vs. non-transmembrane or non-missense (i.e. any other identified LQT1-3 mutation that is not transmembrane-missense).

Statistical Analysis

The clinical characteristics of study patients were compared by genotype/QTc categories using the chi-square test for categorical variables, and the t-test and the Mann-Whitney-Wilcoxon test for continuous variables. The Kaplan-Meier estimator was used to assess the time to a first life-threatening event and the cumulative event rates by risk groups and risk factors, and groups were compared using the log-rank test.

Cox proportional hazards regression analysis was carried out in the total study population, and separately in the subset of patients with genotype-positive LQTS. Prespecified covariates in the total population model included the 3 genotype/QTc categories, gender, and

time-dependent beta-blocker therapy. The models comprising genotype-positive patients included the following prespecified covariates: QTc category (normal-range- [≤440 msec] vs. prolonged- [>440 msec] QTc), the LQT1-3 genotypes, mutation location/type, gender, QTc duration (assessed both as a continuous measure [per 10 msec increase] and as a categorical covariate [dichotomized at the median value of each QTc category, and assessed in separate models]), time-dependent beta-blocker therapy, and a family history of SCD in a first degree relative. The effect of each covariate on outcome in each QTc category (i.e. among LQTS patients with normal-range- and prolonged- QTc) was assessed using interaction-term analysis, with interactions tested one at a time. Estimates of predictor hazard ratios in the separate normal/prolonged QTc categories were obtained using these interactions. To avoid violation of the proportional hazards assumption due to gender-risk crossover during adolescence, we employed an age-gender interaction-term in the multivariate models.

Because almost all the subjects were first- and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership (14). All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc, Cary, NC). A 2-sided 0.05 significance level was used for hypothesis testing.

Results

The spectrum and number of LQT1-, LQT2-, and LQT3-associated mutations by the pre-specified location and type categories are presented in Supplementary Appendix Table 1. A total of 100, 177, and 41, different mutations were identified in the *KCNQ1*-encoded Kv7.1, *KCNH2*-

encoded Kv11.1, and *SCN5A*-encoded Nav1.5 ion channels, respectively. Study patients with an identified LQTS mutation exhibited a very wide QTc distribution (Fig. 1), ranging from a minimum of 350 msec to a maximum of 800 msec (mean [±SD]: 450 ± 56; median 440 msec [interquartile-range: 410 msec to 480 msec]). QTc distribution was similar among the 3 LQTS genotypes. Four hundred and sixty-nine LQTS mutation positive patients exhibited a normal-range QTc, comprising 25% of identified cases.

The clinical characteristics of the total study population by genotype/QTc subgroup are shown in Table 1. The frequency of probands (defined in the registry as the first person in a family, living or deceased, identified to have LQTS by the enrollment center) was highest among patients with a prolonged QTc, whereas most patients with a normal-range QTc (92%) were asymptomatic at the time of genetic testing. The frequency of females was similar between the unaffected subjects and LQTS patients with a normal-range QTc, and higher among patients with a prolonged QTc. Among mutation carriers, the frequency of the 3 main LQTS genotypes was similar between patients with- and without- a prolonged QTc. However, LQT1 and LQT2 patients with a prolonged QTc having a higher frequency of transmembrane-missense mutations as compared with the corresponding genotype carriers who had normal-range QTc. LQTS related therapies were administered to a significantly higher frequency of patients with a prolonged QTc than to subjects in the other 2 subgroups (Table 1).

Clinical Course by Genotype/QTc Subgroup

Kaplan-Meier survival analysis (Fig. 2) demonstrated a relatively low rate of ACA or SCD among LQTS patients with a normal-range QTc (4% at age 40 years and 10% at age 70 years). Event rates were significantly higher among patients with a prolonged QTc (15% and 24% at age

70 years; log-rank p-value <0.001 for the comparison with the normal-range QTc subgroup), and significantly lower among unaffected family members (0.4% and 1% at age 70 years; log-rank p-value <0.001 for the comparison with the normal-range QTc subgroup and for the overall difference among the 3 subgroups). Notably, life-threatening events among patients with a normal-range QTc occurred mostly after age 10 years, whereas patients with a prolonged QTc exhibited an earlier onset of life-threatening events (Fig. 2).

After multivariate adjustment for gender, time-dependent beta-blocktherapy, and a family history of SCD in a first degree relative, LQTS patients with a normal-range QTc were shown to have a significant 72% (p<0.001) lower-risk of ACA or SCD as compared with patients with a prolonged QTc, but also exhibited a >10-fold increase on the risk of life-threatening events as compared with unaffected family members (Table 2). A history of syncope was present in 62% of LQTS patients with a normal-range QTc who had a life-threatening event during follow-up. Accordingly, when the composite secondary end point of a first cardiac event of any type was assessed (comprising mainly non-life-threatening syncopal episodes), patients with a normal-range QTc were consistently shown to be at a lower risk as compared with those who had a prolonged QTc (HR=0.47 [95% CI 0.33 – 0.59]; p<0.001).and at a higher risk as compared with unaffected family members (HR=5.20 [95% CI 4.19-6.44]; p<0.001).

Risk Factors for ACA or SCD in LQTS Patients With and Without a Prolonged QTc

Interaction-term analysis demonstrated significant differences in risk factors for life-threatening events between the 2 LQTS subgroups (Table 3). Among patients with a normal-range QTc, the LQT1 and LQT3 genotypes were associated with a respective 10-fold and 8-fold increase in the risk of life-threatening events as compared with the LQT2 genotype. In contrast, among patients

with a prolonged QTc, the LQT1 genotype was associated with half the risk of the LQT2 genotype (p=0.002) with a statistically significant genotype-by-QTc subgroup interaction (p=0.006, Table 3; first row), and the LQT3 genotype showed a similar risk to the LQT2 genotype without a statistically significant a genotype-by-QTc subgroup interaction (Table 3; second row).

The location-type of the LQTS mutation was shown to be a significant risk factor for ACA or SCD among patients with a normal-range QTc. In this LQTS subset, transmembrane-missense mutations were associated with a pronounced > 6-fold (p=0.006) increase in the risk of ACA or SCD as compared with non-transmembrane or non-missense mutations. In contrast, among patients with a prolonged QTc transmembrane-missense mutations were not independently associated with outcome (Table 3; third row). Notably, when the secondary end point of cardiac events of any-type was assessed, transmembrane-missense mutations were shown to be an independent risk factor in both LQTS subgroups (normal range QTc: HR=1.71 [95% CI 1.16-2.34]; prolonged QTc; HR=1.39 [95% CI 1.17–1.65]).

Consistent results, demonstrating an association between transmembrane-missense mutations and the risk of ACA or SCD among patients with a normal-range QTc, were shown when the reference group (comprising non-transmembrane or non-missense mutations) was further divided into 3 subcategories, including non-missense mutations in the transmembrane region, missense mutations in the non-transmembrance region, and non-missense mutations in the non-transmembrane region (HR > 4.0 for all 3 comparisons). Accordingly, patients with a normal-range QTc with transmembrane-missense mutations experienced a relatively high rate of ACA or SCD during follow-up (9% at age 40 years and 21% at age 70 years), whereas normal-range QTc patients with other mutations had a very low event rate through age 40 years (1% at

age 40 years and 5% at age 70 years; log-rank p-value for the overall difference = 0.005 [Fig. 3A]). In contrast, among patients with a prolonged QTc there was no statistically significant difference in the rate of ACA or SCD between the 2 mutation categories (16% and 14%, respectively; p=0.18 [Fig. 3B]).

Clinical and electrocardiographic factors, including gender and QTc duration, were shown to be associated with a significant increase in the risk for ACA or SCD only among patients with a prolonged QTc (Table 3; rows 4-6). In contrast, among patients with a normal-range QTc, gender was not a significant risk factor, and QTc duration was not independently associated with a significant increase in the risk of ACA or SCD when assessed both a continuous measure or when dichotomized at the median value (≥420 msec).

As suggested previously (15), the presence of a family history of SCD in any first degree relative was not shown to be an independent predictor of ACA or SCD among patients with either a normal-range QTc (HR=0.89 [95% CI 0.63-1.25]; p=0.50) or a prolonged QTc (HR=1.40 [95% CI 0.32-6.17]; p=0.65) after adjustment for genetic and clinical factors.

Beta-blocker therapy was administered to 38% of patients who had a normal-range QTc as compared with 54% of the patients who had a prolonged QTc (p<0.001; Table 1). Treatment with beta-blockers was associated with an overall significant 25% reduction in the risk of ACA or SCD in the total study population (95% CI 0.70 – 0.80; p=<0.001), with similar effects in patients with a normal-range QTc and those with a prolonged QTc (p-value for β-blocker-by-LQTS subset interaction = 0.45).

Characteristics of fatal/near-fatal cases with a normal-range QTc

The characteristics of the patients with a normal-range QTc who experienced ACA or SCD during follow-up are shown in Table 4. The mean (±SD) age of the lethal/near-lethal event in this population was 25.9 ± 4.5 years. Nine of the patients (53%) who experienced the event were women; and 4 (24%) were treated with beta-blockers are the time of the event. Among patients with a normal-range QTc with available data regarding therapies and triggers at the time of the event, none reported as being treated with a QT prolonging drug at the time of ACA or SCD, and the majority of the lethal/near-lethal events were not associated with exercise or arousal triggers (Table 4).

Discussion

In this study, we assessed the clinical course and risk factors for life-threatening events among patients with one of the three most common LQTS genotypes who do not exhibit the disease's phenotypic hallmark of QT prolongation, otherwise referred to as concealed LQTS, normal QT interval LQTS, or genotype-positive/ECG phenotype negative LQTS. Similar to prior reports (16), we have shown that patients with LQT1-3 exhibit a wide QTc distribution, with approximately 25% having QTc values well within the normal-range. The rate of ACA or SCD among LQTS patients with a normal-range QTc was shown to be very low (4% from birth through age 40 years, corresponding to an approximate event rate of ~0.13% per year). Comparatively however, this very low risk subset of the LQTS population still exhibited a >10-fold increase in the risk of life-threatening events when compared with genetically and phenotypically unaffected family members. Importantly, predictors of life-threatening events were shown to be significantly different between LQTS patients with- and without- a prolonged QTc. In the latter LQTS subgroup, genetic data, including knowledge of genotype and mutation characteristics, were shown to identify the risk of ACA or SCD, whereas in the former LQTS

subgroup, female gender in the post-adolescence period and QTc duration were identified as the predominant risk factors for life-threatening events.

The clinical course of patients with LQTS is variable due to incomplete penetrance (17). It is influenced by age, genotype, gender, environmental factors, therapy, and possibly other modifier genes (1-10). Recent studies from the International LQTS Registry that assessed the risk for life-threatening events in LQTS patients have consistently demonstrated that ECG and clinical risk factors, including the QTc and age-gender interactions, identify increased risk in the LQTS population (3-5). These studies, however, included mainly phenotype-positive LQTS patients with a QTc $\geq$ 450 msec. Thus, the effect of genetic data on outcomes in these studies was not statistically significant after adjustment for the ECG and clinical factors. The current study population, comprising 1,861 genetically-confirmed patients with the LQT1-3 genotypes, extends the data derived from prior studies, and demonstrates that risk factors for life-threatening events are significantly different between LQTS patients with- and without- QTc prolongation. Consistent with prior studies, we have shown that among LQTS patients who exhibit a prolonged QTc duration, ECG information and clinical factors can be used to identify the risk for life-threatening events. In contrast, among mutation positive subjects with a normal-range QTc, genetic factors, including knowledge of the LQTS genotypes and the mutation location-type, identified patients who were at an increased risk for ACA or SCD after adjustment for ECG and clinical data.

Gender was not a significant risk factor for cardiac events among patients with a normal-range QTc. Furthermore, patients with a normal-range QTc displayed a similar frequency of women as unaffected family members, whereas the frequency of women was significantly higher among patients with a prolonged QTc. These findings are in accordance with earlier evidence of

a longer QTc interval in LQTS women than in men (18), resulting in a marked female predominance in phenotypically affected patients (3-5). The biologic basis for this sex difference might be the down-regulation of expression of cardiac potassium-channel genes by female sex hormones, which have been shown to prolong the QT interval in both congenital- and drug-induced LQTS (19,20). These hormonal effects may explain the present findings of a lower frequency of LQTS women with a normal-range QTc.

Recent genotype-phenotype studies have shown that missense mutations located in the transmembrane region, that is responsible for forming the ion conduction pathway of the channel, are associated with a significantly higher risk of cardiac events as compared with mutations that are located in other regions of the LQTS channel (9,10). The current study also shows that transmembrane-missense mutations are associated with a significantly higher risk for cardiac events of any-type (predominated by syncopal episodes) among LQTS patients with both a normal-range- and a prolonged- QTc. However, our findings suggest that data regarding mutation characteristics are important for the assessment of life-threatening events (comprising ACA or SCD) mainly among patients with a normal-range QTc, in whom information derived from ECG and clinical data is more limited. In this LQTS subset, missense mutations located in the transmembrane region were shown to be associated with > 6-fold increase in the risk of life-threatening events, and with a clinically meaningful rate of ACA or SCD (9%) from birth through age 40 years.

The mechanisms relating to the occurrence of life-threatening ventricular tachyarrhymias among phenotype-negative LQTS patients are not clear. In the present study none of the patients with a normal-range QTc who experienced ACA or SCD took a QT prolonging medication at the time of the event. Furthermore, most events among patients with a normal-range QTc were not

related to exercise or arousal triggers (Table 4). An ECG tracing from a patient with the *KCNQ1(S349W)* mutation who developed arrhythmic events despite a normal-range QTc, showed spontaneous generation of polymorphic ventricular tachycardia without preceding extrasystolic pauses or sudden sinus rate acceleration (Fig. 4), possibly explaining the occurrence of ACA or SCD in study patients with a normal-range QTc who were treated with beta-blockers at the time of the event.

Study limitations

Most study patients did not undergo comprehensive genetic testing for all currently known mutations that may predispose to arrhythmic risk. Thus, it is possible that the co-existence of modifier genes affected the outcome of LQTS patients with a normal-range QTc who experienced life-threatening cardiac events. In addition, in order to provide an estimation of event rates among unaffected family members, we included in the control group subjects who were both genotype-negative and also had a normal-range QTc (and excluded genotype-negative subjects with a prolonged QTc due to possible unidentified mutations in this subset). Therefore, the overall frequency of genotype-positive subjects in the total population may not represent the true penetrance of LQTS in affected families.

The threshold value of 440 ms for the definition of a normal-range QTc in the present study was based on the diagnostic criteria for LQTS proposed in by Schwartz and Moss, that define prolonged QTc as ≥450 msec in males or ≥460 msec in females (12). We chose to use a uniform approach by selecting 440 msec as the upper limit of normal rather than having separate phenotypic definitions for males and females. It should also be noted that 2.5% of infants and 10

– 20% of adults exceed this cut-off (21). Thus, the 440 ms value is not meant to suggest an LQTS diagnosis on its own.

Conclusions and clinical implications

The present study shows that LQTS patients who exhibit a normal-range QTc comprise approximately 25% of the LQTS population and have a significantly lower risk of life-threatening events as compared with phenotypically affected patients, but also exhibit a significant increase in the risk of ACA or SCD as compared with unaffected family members. Missense mutations in the transmembrane regions of the ion channels, mainly among patients with LQT1 and LQT3, were shown to identify patients with a normal-range QTc who have an increased risk for ACA or SCD. In contrast, increments in QTc duration were not shown to be significantly associated with increased risk for life-threatening events in this population. These findings suggest that 1) risk assessment among phenotype-negative family members of LQTS probands should include genetic testing, since a positive genetic test in a family member with a normal-range QTc implies an overall >10-fold increase in the risk of ACA or SCD as compared with a negative test in an unaffected family member; 2) genetic data may be used to identify phenotype-negative LQTS patients who are at increased risk for fatal ventricular tachyarrhythmias independently of QTc duration; and 3) LQTS mutation positive patients with a normal-range QTc who are identified as having increased risk for life-threatening events based on genotype and mutation characteristics (i.e. LQT1 and LQT3 with transmembrane-missense mutations) should be carefully followed-up and receive a similar management strategy as phenotype-positive LQTS patients, including avoidance of QT-prolonging medications (22), routine therapy with β-blockers, and possibly ICD therapy among those who remain symptomatic despite medical therapy. Conversely, patients with the lowest risk profile of

already low risk, concealed LQTS (i.e. concealed LQT2 and non-transmembrane-missense LQT1- and LQT3) may represent the nominally near zero risk subpopulation(s) of LQTS in need of only preventative health recommendations such as QT drug avoidance.

Funding/Support:

This work was supported by research grants HL-33843 and HL-51618 from the National Institutes of Health, Bethesda, Md.

Disclosures:

None

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Figure Legends

Figure 1: Distribution of QTc Duration in Genotype-Positive LQTS Patients

Distribution of QTc interval durations among genotype-positive study patients.

QTc = corrected QT interval.

Figure 2: Rate of ACA/SCD by Genotype/QTc Category

Kaplan-Meier cumulative probabilities of ACA and SCD by genotype/QTc subgroup.

ACA = aborted cardiac arrest; LQTS = long QT syndrome; QTc = corrected QT interval; SCD = sudden cardiac death.

Figure 3: Rate of ACA/SCD in Patients with Normal- and Prolonged- QTc by Mutation Location-Type

Kaplan-Meier cumulative probabilities of ACA and SCD by mutation location-type in LQTS patients with (A) QTc ≤ 440 msec; and (B) QTc > 440 msec.

ACA = aborted cardiac arrest; LQTS = long QT syndrome; QTc = corrected QT interval; SCD = sudden cardiac death.

Figure 4: Polymorphic Ventricular Tachycardia in a Patient with a Normal-Range QTc

Spontaneous generation of polymorphic ventricular tachycardia in an LQT1 patient with a normal-range QTc. (A) The patient had QTc duration of 410 msec on baseline ECG; (B) Electrocardiographic tracing at the time of arrhythmic event demonstrates sinus rate with an RR interval of 1000 msec without significant QT prolongation prior to the arrhythmia; and (C) The patient was treated with nadolol and received an ICD, but continued to exhibit arrhythmic

episodes that were recorded on ICD interrogation (C).

Table 1. Baseline and follow-up characteristics of the study population by genotype-phenotype

CHARACTERISTICS	UNAFFECTED FAMILY MEMBERS (N=1525)	LQTS WITH NORMAL-RANGE QTC (N=469)	LQTS WITH PROLONGED QTC (N=1392)
Female	52%	48%	61%*†
Family history of SCD	8%	12%	19%*†
QTc (msec)			
Mean ± SD	412 ± 22	419 ±20	501 ± 48
Median (IQ range)	420 (400-430)	420 (410-440)	490 (470-520)
Proband	8%	8%	29%*†
RR (msec)			
Mean ±SD	793 ±221	888 ±236	848 ±214 *†
Median (IQ range)	800 (640-930)	900 (740-1040)	840 (700-1000) *†
Genotype			
LQT1	NA	40%	39%
LQT2	NA	45%	47%
LQT3	NA	16%	14%
Mutation: TM-MS			
Overall	NA	35%	43%
LQT1	NA	45%	61%
LQT2	NA	16%	29%†
LQT3	NA	64%	31%†
Therapies			
beta-blockers	6.2%	38%	54%*†
Pacemaker	0.3%	0.6%	5%*†
LCSD	0.1%	0.2%	1.4%*†
ICD	0.6%	6%	14 %*†
Events			
Syncope	10%	21%	40%*†
ACA	0.2%	1.3%	8.4%*†
SCD	0.1%	1.5%	4.4%*†
ACA/SCD‡§	0.3%	2.8%	11.3%*

TM: Transmembrane, MS: Missense, ICD: implantable cardioverter defibrillator, ACA: aborted cardiac arrest, SCD: sudden cardiac death

*P<0.05 for the comparison among the 3 genotyped categories.

†P<0.05 for the comparison between genotype-positive patients with QTc ≤440 msec and genotype-positive patients with QTc >440 msec.

‡Appropriate ICD shocks comprised 0.04% of ACAs in genotype-positive/QTc ≤ 440msec patients, and 1.4% of ACAs in genotype-positive/QTc > 440msec patients

§Only the first event for each patient was considered.

Table 2. Multivariate analysis: Risk of ACA or SCD among the 3 genotype/QTc categories

GENOTYPE/QTC SUBGROUP	HAZARD RATIO	95% CONFIDENCE INTERVAL	P-VALUE
LQTS with prolonged QTc vs. Unaffected family members	36.53	13.35 – 99.95	<0.001
LQTS with normal-range QTc vs. Unaffected family members	10.25	3.34 – 31.46	<0.001
LQTS with normal-range QTc vs. LQTS\ with prolonged QTc	0.28	0.16 – 0.49	<0.001

*Model adjusted also for gender (female >13 yrs) and time-dependent β-blocker therapy.

Table 3. Risk factors for ACA/SCD among LQTS patients by QTc category.*

VARIABLE	LQTS/NORMAL-RANGE QTC		LQTS /PROLONGED QTC		
	HR (95% CI)	**P-Value**	**HR (95% CI)**	**P-value**	**P-Value for Interaction**
Genotype					
LQT1 vs. LQT2	9.88 (1.26 – 37.63)	0.03	0.53 (0.35 – 0.79)	0.002	0.006
LQT3 vs. LQT2	8.04 (0.85 – 36.03)	0.07	1.07 (0.70 – 1.63)	0.77	0.08
Mutation location and type					
Transmembrane-Missense vs. Non-Transmembrane-Missense	6.32 (1.71 – 23.33)	0.006	1.24 (0.88 – 1.76)	0.22	0.02
Gender					
Female >13 yrs vs. Male >13 yrs	1.32 (0.42 – 4.17)	0.64	1.90 (1.26 – 2.86)	0.002	0.53
QTc (msec)					
Per 10 msec increase	1.20 (0.81 – 1.78)	0.35	1.08 (1.05 – 1.10)	<0.001	0.58
≥median vs. < median†	1.03 (0.36 - 2.98)	0.95	2.96 (2.06 - 4.26)	<0.001	NA

*Cox proportional hazards regression modeling was carried out in models that included all patients with genotype-positive LQTS (n=1861). Covariates in the models included QTc category (i.e. ≤440 ms vs. >440 msec), genotype, mutation location/type, gender,

QTc (assessed as a continuous measure [per 10 msec increase]), time-dependent β-blocker therapy, and a family history of sudden cardiac death; the effect of each covariate in patients with normal- (QTc ≤440 ms) and those with prolonged- (>440 msec) QTc was assessed by interaction-term analysis, with interactions tested one at a time. Estimates of predictor hazard ratios in the separate normal/prolonged QTC groups were obtained using these interactions. Virtually identical results for all prespecified risk factors were also obtained from the models that did not include appropriate ICD shocks as part of the composite end point.

[†]Results were obtained from separate models that assessed the risk associated with QTc values ≥ median among LQTS patients with normal range QTc (median = 420 msec) and prolonged QTc (median = 500 msec).

Table 4. Characteristics of ACA/SCD cases with a normal-range QTc

CASE#	EVENT	EVENT AGE	FEMALE	QTC (MSEC)	BB	LCSD	PM	ICD	QT PD	TRIGGER*	GENOTYPE	MUTATION LOCATION-TYPE
1	SCD	0.5	-	390	-	-	-	-	-	NA	LQT3	Non-TMM
2	ACA	10	+	430	-	-	-	-	-	Exercise	LQT 1	TMM
3	ACA/Shock	11	+	400	-	-	-	+	-	Non-E/A	LQT 1	TMM
4	SCD	13	-	440	+	-	-	-	NA	NA	LQT 1	TMM
5	ACA	14	-	410	-	-	-	-	-	Exercise	LQT 1	Non-TMM
6	SCD	16	+	420	-	-	-	-	-	Non-E/A	LQT 3	TMM
7	ACA	16	+	440	-	-	-	-	-	Arousal	LQT 1	TMM
8	SCD	18	-	430	+	-	-	-	-	Non-E/A	LQT 1	TMM
9	ACA	18	+	410	-	-	-	-	-	Exercise	LQT 1	TMM
10	SCD	21	+	380	-	-	-	-	-	Arousal	LQT 2	Non-TMM
11	SCD	22	-	440	-	-	-	-	NA	NA	LQT 1	TMM
12	SCD	28	-	410	-	-	-	-	-	Exercise	LQT 1	TMM
13	ACA	35	+	420	-	-	-	-	-	Non-E/A	LQT 3	TMM
14	ACA	46	+	440	+	-	-	-	NA	NA	LQT 2	TMM
15	SCD	48	-	430	+	-	-	-	-	Non-E/A	LQT 2	Non-TMM
16	ACA	54	+	420	-	-	-	-	-	Non-E/A	LQT 3	Non-TMM
17	SCD	69	-	380	-	-	-	-	NA	NA	LQT 1	TMM

*Data regarding triggers for cardiac events and treatment with QT-prolonging medications were available for study patients who were enrolled in the US portion of the International LQTS Registry.

ACA = aborted cardiac arrest; BB = beta blocker therapy (at time of event); ICD = implantable cardioverter defibrillator (implanted prior to event); LCSD = left cardiac sympathetic denervation (performed prior to event); NA = not available; Non-E/A= non exercise/non-arousal trigger for event; PM = pacemaker (implanted prior to event); QT PD = QT prolonging drug; TMM = transmembrane-missense.

Fig. 1

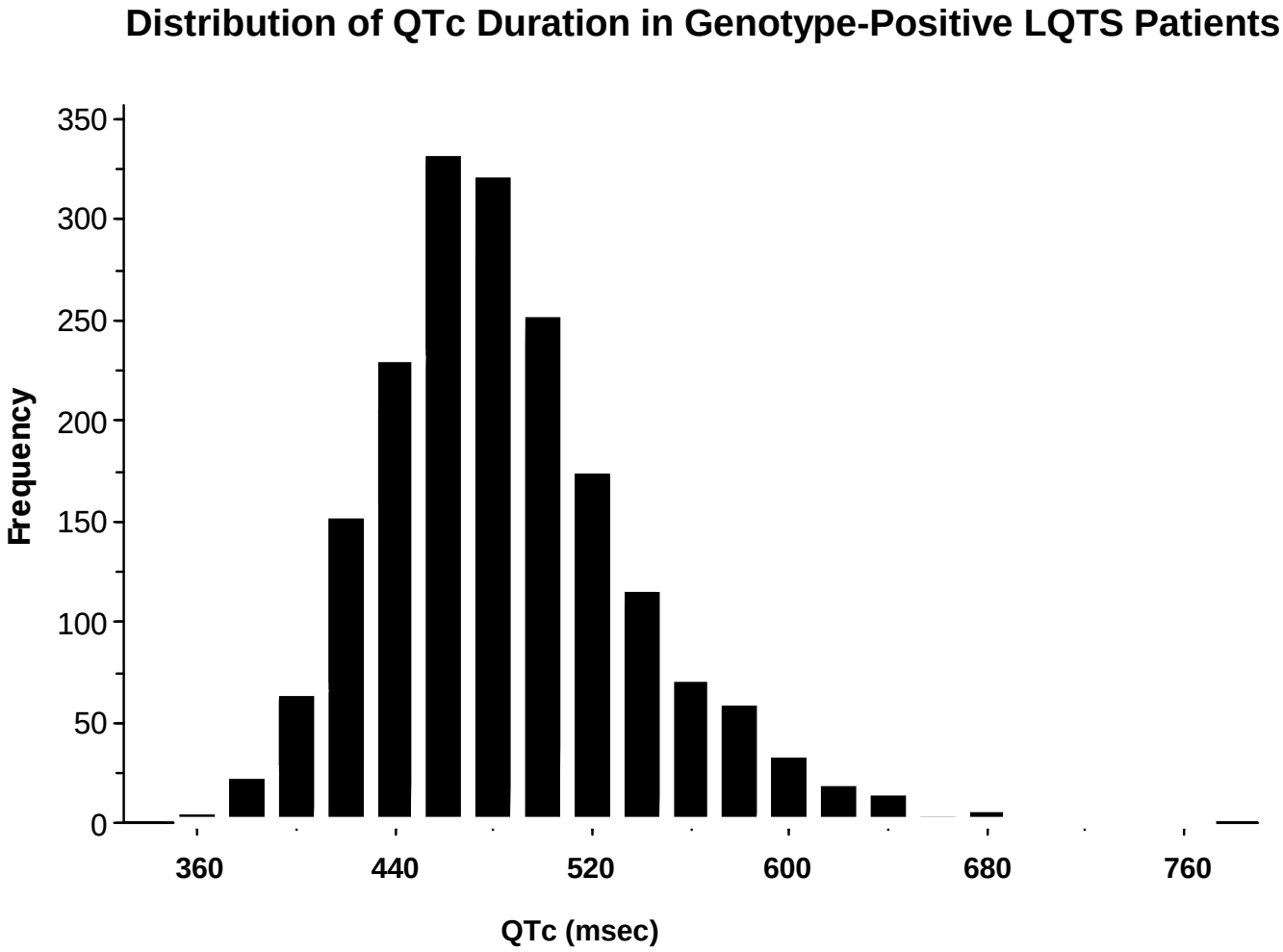
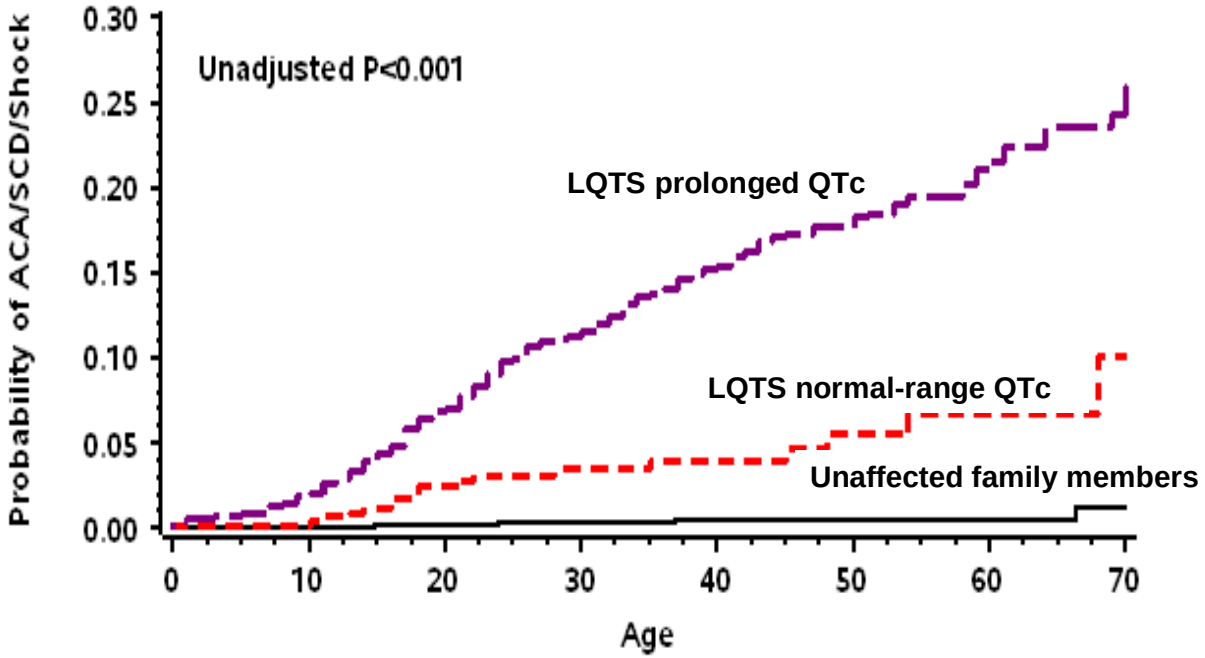

Distribution of QTc Duration in Genotype-Positive LQTS Patients
Frequency
350
300
250
200
150
100
50
0
360
440
520
600
680
760
QTc (msec)

Fig. 2

Rate of ACA/SCD by Genotype/QTc Category



Patients at Risk					
Gen-/Phen-	1525	1377 (0)	728 (0)	348 (0)	92 (0.01)
Gen+/Phen-	469	406 (0)	236 (0.04)	97 (0.06)	20 (0.10)
Gen+/Phen+	1392	1235 (0.02)	729 (0.11)	334 (0.18)	94 (0.24)

Fig. 3A

Rate of ACA/SCD in Patients with Normal-Range QTc by Mutation Location-type

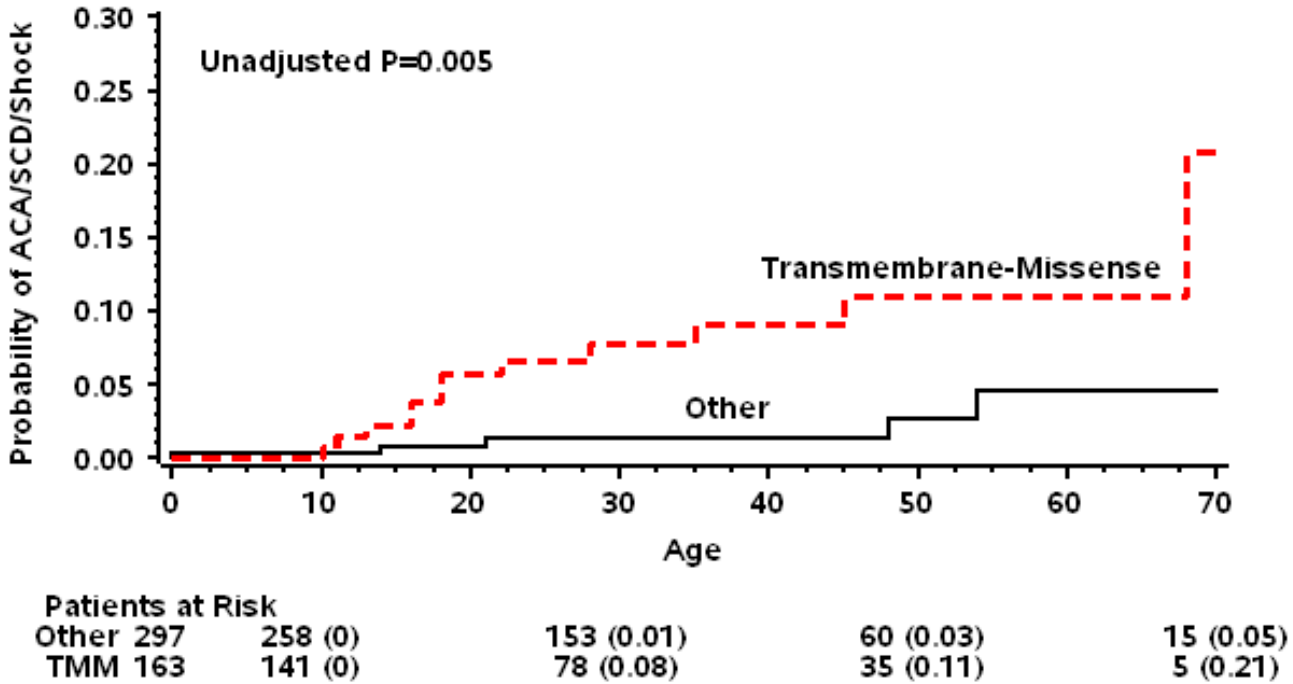


Fig. 3B

Rate of ACA/SCD in Patients with Prolonged QTc by Mutation Location-type

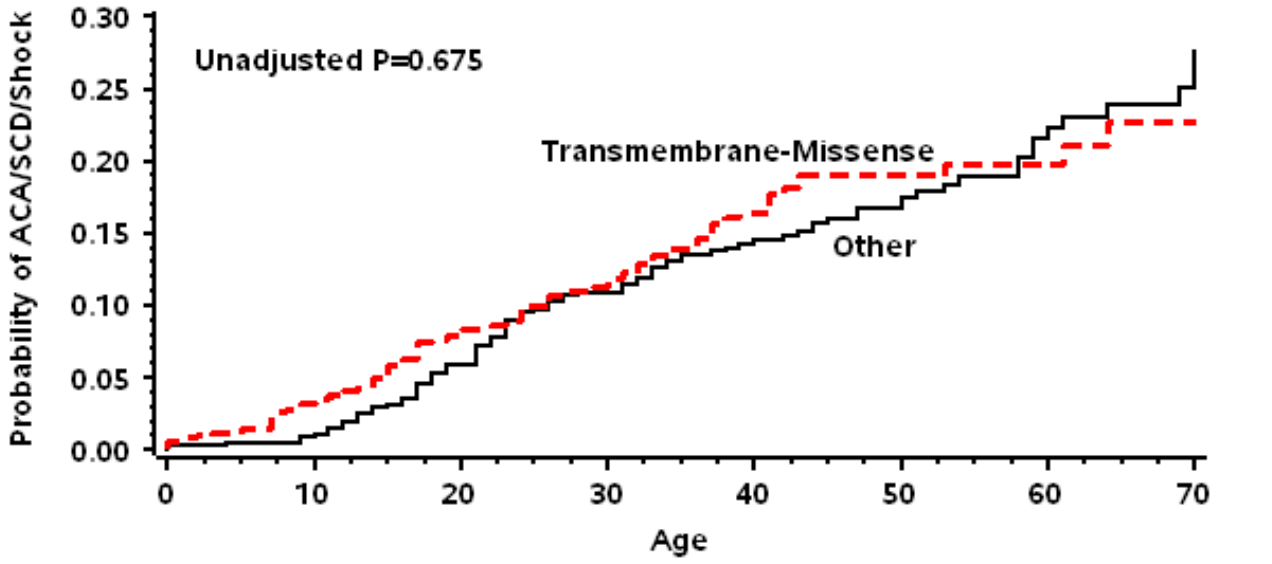


Fig. 4A

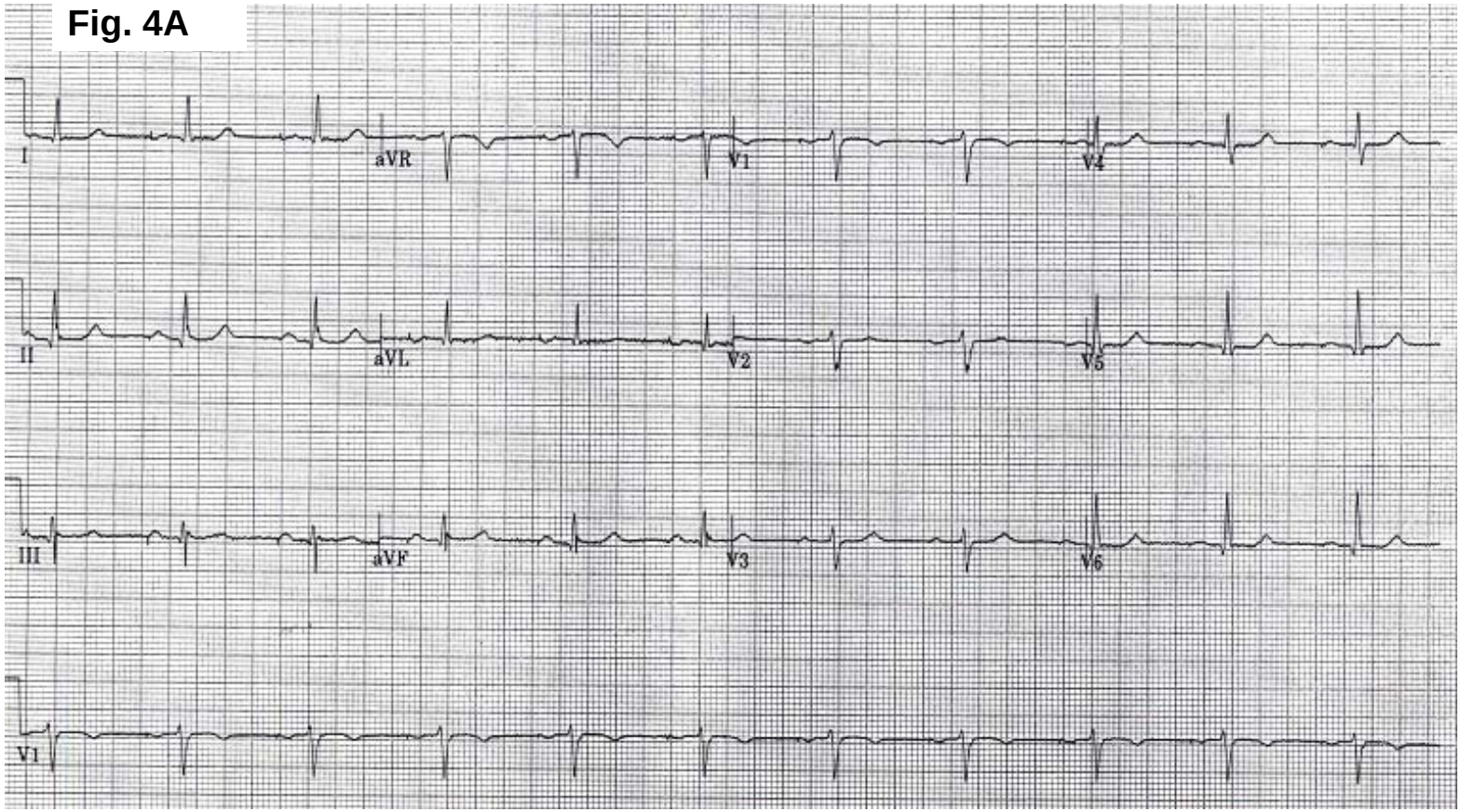


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Fig. 4B

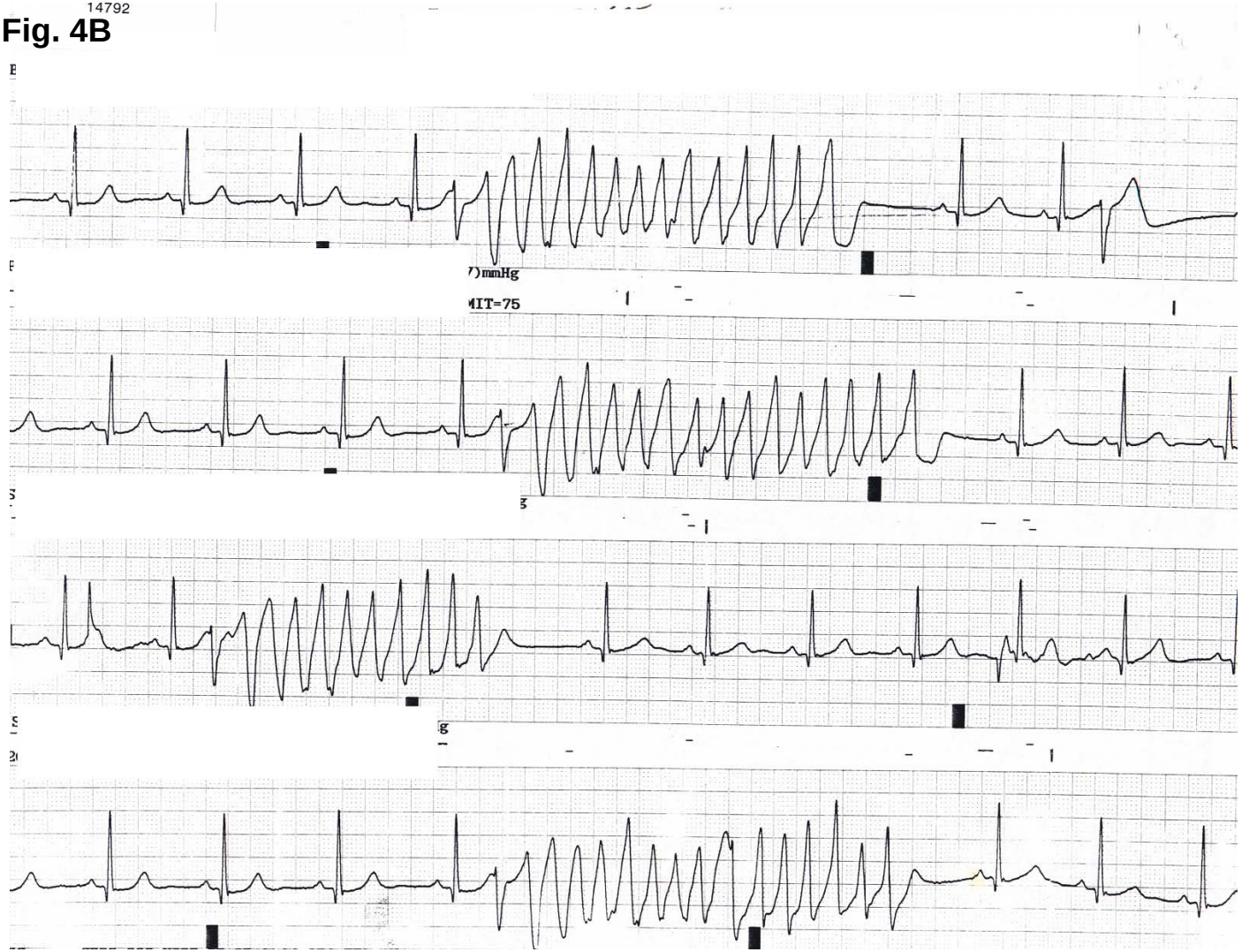

Fig. 4C