

# Statistical Identification of Delayed Repolarization: Applicability in Long QT Syndrome (LQTS) Population

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## Abstract

*Based on digitized electrocardiogram recordings and multiregression methods adjusting the QT interval for RR interval, age, and gender, in normal population (N = 578) a new measurement called 'adjusted QT' (QTa) was determined. QTa is expressed in normal population standard deviation units, and in percentiles (%QTa). The QTa was applied to our LQTS multicenter registry (N = 2000) treating probands (N = 326) and family members (N = 1674) separately.*

*This new concept based on digitized electrocardiograms and statistical probabilistic methods adjusting for RR, age and gender is a new approach that should permit improved identification of delayed repolarization and long QT syndrome.*

## Introduction

The time honored electrocardiographic criterion for diagnosis of delayed repolarization is  $QTc > 0.44 \text{ sec}^{1/2}$  by Bazett's formula ( $QTc = QT/\sqrt{RR}$ ) (1). This arbitrary cutoff based on few references with small number of individuals (2), creates a gray zone that contributes to false-positive and false-negative classification errors. Besides, with the use of this formula the correction is not always accurate, especially at slow or fast heart rates, resulting in under or overcorrection of the measured QT interval. Other formulas have been proposed to adjust the QT interval for heart rate (3, 4).

While heart rate is the major determinant of the QT interval duration, a large variability in QTc interval also exists relative to gender and age (5, 6), leading to the conclusion that the QT interval must be corrected not only for heart rate but also for age and gender.

The purposes of this study were: 1) to establish normal standards for QT interval, based on a large normal population, using high quality digitized electrocardiogram

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recordings, and statistical probabilistic approach adjusting for heart-rate, age and gender ; 2) to apply this approach to the LQTS international registry.

## Methods

### Study population

**a. Normals:** The study population consisted of 578 normal subjects, who had digitized 12-lead electrocardiographic recordings on a MAC-12 recorder (Marquette Electronics, Inc., Milwaukee, Wisconsin.). Two data sets were provided: 1) 420 healthy adults (222 males and 198 females; age 16-81 years; median age - 35 years); 2) 158 healthy children (80 males and 78 females; age 1-15; median age - 9 years).

**b. LQTS population:** The International LQTS Registry consisted 2000 individuals, 326 probands and 1674 family members. A proband was defined as the first family member diagnosed to have LQTS by a  $QTc > 0.44 \text{ sec}^{1/2}$ . Among probands, 69% were females, age 1-73 years, median age 16 years. Among the family members, 52% were females, age 1-92 years, median age 27 years.

### Electrocardiographic variables

Digitized electrocardiograms were recorded on a MAC-12 system that simultaneously acquires and digitizes two limb leads (L1, L2) and six precordial leads (V1 through V6) for 10 seconds, at a sampling frequency of 250 Hz and with a resolution of  $5 \mu\text{V}$ . QT interval was measured as the time interval from the earliest Q wave onset to the latest T wave offset or the next P wave onset (whichever occurred earlier) on the median beat in any of the 12 leads used (8 acquired and 4 constructed). The averaged RR interval observed during the 10-second original recording was used.

## Statistical analysis

The baseline characteristics of the study population were compared using where appropriate, either a chi-square test, two sample t-test, or analysis of variance. Results of continuous variables are reported as mean  $\pm$  SD. A two-sided p-value of less than 0.05 was considered statistically significant.

Based on multiregression methods, formulas relating QT to RR, gender and age were developed for 578 normals. After exploring the possibilities of various measurement scales for the variables, three regression formulas were settled (in natural logarithm): one for adult males, one for adult females, and one for adult children (in whom no gender difference was found), as follows:

$$\ln QT = a + b \cdot \ln RR + c \cdot \ln AGE + d \cdot \ln RR \cdot \ln AGE + \text{Residual}$$

where  $\ln$  - in natural logarithm; a, b, c, and d are the coefficients determined from the data by regression methods (one set of values for each of the three equations). The residual is that part of the  $\ln QT$  that cannot be explained by the regression equation. Thus, for an individual who fits best the regression, the residual is zero. For each individual a standardized residual (QT residual in  $\ln$  units / SD of the residual) was determined, named 'adjusted QT' (QTa), as follows:

$$QTa = [\ln QT - (a + b \cdot \ln RR + c \cdot \ln AGE + d \cdot \ln RR \cdot \ln AGE)] / SD$$

The standardized residual in healthy population is expected to have an approximately normal (Gaussian) distribution (Figure 1), with QTa expressed in normal population standard deviation units. The QTa measurement can be converted to a percentile QTa (%QTa), from normal distribution tables. Thus, a QTa of 1.96 SD has a %QTa of 2.5%, with the interpretation that 2.5% of normals have a higher QT, after adjusting for RR, gender, and age; and a QTa of 2.326 SD identifies patients in the top 1% of the normal population.

## Results

### Comparability of study population

The baseline characteristics of the normal study population (N = 578), separately for children (N = 158), adult males (N = 220), and adult females (N = 198) are presented in Table 1. The percentage of females among the adult population was similar to the percentage of

females among children, 43% vs 49%, respectively. QTc was longer among adult females than among adult males,  $0.420 \pm 0.018$  vs  $0.409 \pm 0.014$  sec, respectively,  $p < 0.001$ . QTc  $> 0.440$  sec<sup>1/2</sup> was noted in 5.7% of the children, 8.6% of adult females, but not among adult males.

### Multiregression models-Adjusted QT (QTa)

Adjusted QT (QTa) was determined for the 3 subgroups of normals, using 3 separate multiregression models adjusting for RR, gender and age (Table 2). For children a gender difference was not found, however, an interaction term was found between age and RR; with age the RR interval increased.

The distribution of the QT standardized residuals (adjusted QTa) among the 578 normal individuals in the study is described in Figure 1, where QTa is expressed in normal population standard deviation units. For each individual in the study (child, adult male, adult female), the appropriate multiregression formula was applied. The QTa was found to be normally (Gaussian) distributed, with a mean of zero, which is corresponding to a %QTa of 50%. The vertical line of 1.96 SD units is corresponding to a %QT of 2.5%.

QTa was applied to our multicenter LTQS registry, treating probands (N = 326) and family members (N = 1674) separately (Figure 1). QTa is more skewed to the right for probands than for family members. Thus, a %QTa  $>$  upper 2.5% of normals was noted among 95.1% of probands but only among 36.8% of the family members, with the interpretation that those on the left side of the 1.96 SD line were false positively diagnosed as being probands.

## Discussion

The measurement of the QT interval and its correction or adjustment for cycle length, age and gender has been a difficult problem of the course of the past 70 years. The availability of digitized recordings on large normal population together with computerized statistical approach should permit improved identification of prolonged QT interval after adjusting for pertinent covariates. QTa is a prototype of an improved QTc measurement and may serve a role to identify more accurately delayed repolarization and LQTS.

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**Table 1: Baseline characteristics of normals (N = 578)**

<b>Variable</b>	<b>Children (N = 158)</b>	<b>Adult Males (N = 222)</b>	<b>Adult Females (N = 198)</b>	<b>p- value*</b>	<b>All (N = 578)</b>
Age (years)					
mean ± SD	9 ± 4	37 ± 13	40 ± 15	< 0.001	30 ± 18
range	1 - 15	16 - 81	16 - 76		1 - 81
Gender (%F)	49	0	100	< 0.001	48
RR interval (sec)					
mean ± SD	0.764 ± 0.111	0.955 ± 0.148	0.881 ± 0.126	< 0.001	0.877 ± 0.152
range	0.600 - 1.000	0.619 - 1.463	0.638 - 1.304		0.600 - 1.304
QT interval (sec)					
mean ± SD	0.367 ± 0.027	0.397 ± 0.030	0.392 ± 0.027	< 0.001	0.386 ± 0.031
range	0.308 - 0.424	0.328 - 0.512	0.328 - 0.476		0.308 - 0.512
QTc (sec <sup>1/2</sup> )					
mean ± SD	0.418 ± 0.017	0.409 ± 0.014	0.420 ± 0.018	< 0.001	0.415 ± 0.017
range	0.378 - 0.457	0.379 - 0.442	0.374 - 0.481		0.374 - 0.481
QTc > 0.44 sec <sup>1/2</sup> (%)	5.7	0	8.6	< 0.001	4.5

\* Among Children, Adult-males, Adult-females, by analysis of variance (ANOVA) or chi-square tests.

**Table 2: Multi regression formulae for adjusted QT (QTa) in 578 normals**

<b>Population</b>	<b>Formulae</b>	<b>r</b>
Children (N = 158)	$QTa = [0.820 + \ln(QT) - 0.781 \cdot \ln(RR) + 0.031 \cdot \ln(AGE + 1) + 0.164 \cdot \ln(RR) \cdot \ln(AGE + 1)] / 0.0367$	0.865 <sup>+</sup>
Adult-males (N = 222)	$QTa = [1.014 + \ln(QT) - 0.446 \cdot \ln(RR) - 0.031 \cdot \ln(AGE + 1)] / 0.031$	0.913 <sup>+</sup>
Adult-females (N = 198)	$QTa = [0.967 + \ln(QT) - 0.388 \cdot \ln(RR) - 0.022 \cdot \ln(AGE + 1)] / 0.040$	0.811 <sup>+</sup>

QT, RR intervals in seconds; AGE in years; ln (natural logarithm), <sup>+</sup> p < 0.0001

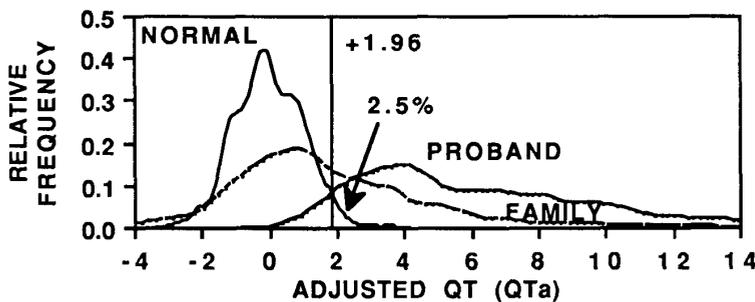


Figure 1: QTa distribution among normals, and among LQTS population; separately for probands (N = 326) and family members (N = 1674).

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