International Journal of Cardiology 174 (2014) 535–540

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

New age- and sex-specific criteria for QT prolongation based on rate correction formulas that minimize bias at the upper normal limits

Pentti M. Rautaharju [a,*], Jay W. Mason [b], Toshio Akiyama [c]

[a] Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC, USA
[b] Cardiology Division, University of Utah, Salt Lake City, UT, USA
[c] Cardiology Division, University of Rochester, NY, USA

ARTICLE INFO

Article history:
Received 24 January 2014
Received in revised form 9 March 2014
Accepted 11 April 2014
Available online 21 April 2014

Keywords:
QT prolongation
Sex differences
Aging
Normal standards

ABSTRACT

Background: Existing formulas for rate-corrected QT (QTc) commonly fail to properly adjust the upper normal limits which are more critical than the mean QTc for evaluation of prolonged QT. Age- and sex-related differences in QTc are also often overlooked. Our goal was to establish criteria for prolonged QTc using formulas that minimize QTc bias at the upper normal limits.

Methods and results: Strict criteria were used in selecting a study group of 57,595 persons aged 5 to 89 years (54% women) and to exclude electrocardiograms (ECG) with possible disease-associated changes. Two QT rate adjustment formulas were identified which both minimized rate-dependency in the 98th percentile limits: QTcmod, based on an electrophysiological model (QTcMod = QTx(120 + HR)/180)), and QTcLogLin, a power function of the RR interval with exponents 0.37 for men and 0.38 for women. QTc shortened in men during adolescence and QTcMod became 13 ms shorter than in women at age 20–29 years. The sex difference was maintained through adulthood although decreasing with age. The criteria established for prolonged QTc were: Age <40 years, men 430 ms, women 440 ms; Age 40 to 69, men 440 ms, women 450 ms; Age ≥ 70 years, men 455 ms, and women 460 ms.

Conclusions: Sex difference in QTc originates from shortened QT in adolescent males. Upper normal limits for QTc vary substantially by age and sex, and it is essential to use age- and sex-specific criteria for evaluation of QT prolongation.

1. Introduction

Prolonged QT interval can potentially precipitate malignant arrhythmias and QT prolongation is of concern in a variety of conditions, including coronary heart disease (CHD), sudden cardiac death (SCD), left ventricular hypertrophy (LVH), congenital and acquired long QT syndrome (LQTS) and in evaluation of drugs and other cardioactive agents. In adults, SCD mortality risk increases with age and parallels that of CHD mortality because 80% of SCD occurs in persons with CHD [1]. Excluding sudden infant syndrome which peaks between birth and 6 months of age, SCD accounts for 19% of sudden deaths in children between 1 and 13 years of age and 30% between 14 and 21 years of age [2]. Although a multiplicity of factors other than prolonged QT are involved in the mechanism of CHD and SCD, prolonged QT is of concern both in pediatric and adult cardiology.

A variety of formulas for rate-adjusted QT (QTc) with large differences in their functional form have been introduced in electrocardiographic literature [3], including Bazett's formula (QTcBz) [4], Fridericia's cube root formula (QTcFri) [5], the Framingham formula (QTcFra) [6] and the formula of Hodges (QTcHg) [7]. Bazett's formula continues to be the most commonly used formula for QT rate correction in spite of the fact that it severely overcorrects at high heart rates [8] in adults and in children who normally have high heart rates. Numerous studies have compared various formulas for rate-adjusted QTc. In these comparative QTc evaluations the mean QTc is commonly found to be rate-independent. However, these studies have often overlooked the residual rate dependence of the upper normal limits which are more important than the mean values because they are used for diagnosing prolonged QT. Age-dependence of these upper normal limits is also overlooked. In addition, QTc is known to be longer in women than in men reported to result from QT shortening in adolescent males with no change in adolescent females [9]. The attainment of a widely applicable QTc formula with bias-free mean values and upper normal limits valid for both sexes and over a wide age range has been an elusive goal.

QT data from two large previously documented normal reference groups [10,11] with different characteristics of QT distributions were pooled into one data file in the present investigation with the expectation that this would improve the prospect of procuring a QTc formula

* Corresponding author at: 737 Vista Meadows Dr. Weston, FL 33327, USA. Tel./fax: +1 954 385 5622.
E-mail address: pentti.rautaharju@gmail.com (P.M. Rautaharju).

http://dx.doi.org/10.1016/j.ijcard.2014.04.133
0167-5273/

which would be applicable in diverse population groups. The special focus of our investigations was to secure a QTc formula which would minimize the rate-dependent bias in the upper normal limits. The primary objective of the study was to establish criteria for prolonged QT by sex and age which would be valid from childhood to old age.

2. Methods

QT data for the first reference group were obtained from the study group of Mason et al. [8]. The study group was dominantly North-American and European (91%) and 53% were women. The reference group was selected by excluding from the initial QT data file ($N = 79{,}743$) ECGs of persons with possible disease-associated ECG effects, including the following reasons: evidence of a cardiac pacemaker on ECG ($n = 256$), screen failure for any reason ($n = 756$ of the remaining), enrollment in a clinical trial of cardiovascular ($n = 7066$ of the remaining), diabetes ($n = 9190$ of the remaining), or hyperlipidemia therapy ($n = 6571$ of the remaining). The disease target of the therapy under study identified 41 disease states in the remaining patients. From this group, an additional 1320 subjects were excluded because of noncardiac disorders that could affect electrocardiographic intervals: end-stage renal disease ($n = 392$), hypertension ($n = 451$), and acute stroke ($n = 477$). From the remaining group of 54,584 subjects, an additional 8455 were removed because of one or more specific diagnoses on ECG: nonsinus rhythm (4286); acute, recent, or remote myocardial infarction ($n = 1050$); ventricular preexcitation ($n = 20$); a diagnosis of right or left ventricular hypertrophy with both voltage and associated abnormalities ($n = 229$); complete right bundle branch block (RBBB) ($n = 833$), complete left bundle branch block (LBBB) ($n = 261$), IVCD ($n = 1761$), and technical issues ($n = 35$). This process left 46,129 in the reference range subset. From this group 65 adults older than 90 years and 105 children younger than 5 years were excluded from the present analyses, leaving the remaining group of 45,959 persons aged 5 to 89 years. All ECGs were procured by standardized methods through a core ECG laboratory and all measurements were performed on digital data by board-certified cardiologists using computerized workstations with high resolution.

Previously documented source data for the second reference group [9] consisting of 11,739 persons 40 to 96 years old (60% women) were obtained from the Third National Health and Examination Survey *NHANES3) [12], the Cardiovascular Health Study (CHS) [13] and the Arteriosclerosis Study in Communities (ARIC) study [14]. All ECGs were recorded using strictly standardized procedures for ECG acquisition, and all ECGs were processed in a central ECG laboratory. Visual and automatic computer procedures were used for quality control with special attention to the accuracy of ECG interval measurements. This reference group represents subgroups of community-based populations considered free from cardiovascular heart disease. Excluded were persons with a history of heart attack, coronary artery bypass surgery or angioplasty. ECG-based exclusions included QRS duration 120 ms or longer and major ECG abnormalities according to the Minnesota Code [15], including myocardial infarction (Code 1.1, 1.2, or Code 1.3 with Code 4.1, 4.2, 5.1 or 5.2), or electronic pacemaker (Code 6.3). Excluded from the remaining group of 11,739 were 37 persons with incomplete data and 66 persons 90 years old or older, leaving 11,636 persons in the remaining group.

The pooled reference group of 57,595 persons was stratified by age or HR (HR) for evaluation of age- and HR-dependence of QTc.

3. Statistical methods

Multiple QTc formulas were evaluated in the pooled reference group in subgroups stratified by HR. We established a minimum requirement that the variation in the 98% limits be no more than 10 ms across the physiological range of HR from 50 to 99/min and in all subgroups by age. Sex differences in QT evolution with age were evaluated for these formulas and normal ranges were established for subgroups stratified by age and sex. Normal ranges were also established for rate-and age-adjusted QT. Data analyses including descriptive statistics and graphics were done using Microsoft Excel 2007version 5.0 (Microsoft Corporation, Redmond, Washington).

A new classification structure was used for categorization of the QTc formulas as linear or inverse based on their generic forms and QT prediction functions (Table 1). QTc formulas are categorized as inverse if QT adjustment is done by dividing QT by a QT prediction function and as linear if a QT adjustment term is added to QT as a linear proportion of the difference of the predicted QT from the reference interval or HR (RR = 1 s or HR = 60)

4. Results

Table 2 shows the distributions of HR, QRS duration and unadjusted QT in men and women in the study population by age. The sample size is large, even in the smallest age subgroups. Comparing age groups 10–14 and 15–19 years, QRS duration increased in adolescent boys by 11 ms and in girls by 6 ms. QRS duration was 6 ms longer in men at age group 20–24 years and the 6 ms sex difference was retained through adulthood.

Unexpectedly many of the commonly used QTc formulas that we evaluated failed to meet the minimum performance criterion set for rate-independence of the 98th percentile normal limits even with the coefficients optimized for the pooled reference group. The performance of the Framingham formula [5] with linear adjustment of QT to the RR interval and the formula of Hodges [6] with linear QT adjustment to HR was unsatisfactory (not shown) as was the performance of power functions of RR with exponents ranging from 0.5 (QTcB) to 0.33 (QTcF).The bias in the upper normal limits with QTcB and QTcF (Fig. 1) shows that the rate-dependence was particularly strong for QTcB. Medians and 98th percentiles for three of the QTc formulas with a more satisfactory performance are listed in Table 3. Recalling the

Table 1
Categorization of QTc formulas as linear and inverse based on their generic forms and QT prediction functions.

QTc formula label	QT prediction function	Generic form of QTc in terms of QT prediction function (QTpr)	Men		Women	
			C*	k†	C	k
‡Linear						
‖QTcRR	RR^k	QTc = QT + Cx(QTpr-1)	154	1	168	1
#QTcHR	HR^k	QTc = QT + Cx(60-QTpr)	2.0	1	2.07	1
**QTcLog Lin	RR^k	QTc = QT + Cx(QTpr-1)	398	0.37	409	0.38
§Inverse						
††QTcB	RR^k	QTc = QT/CxQTpr	1	0.5	1	0.5
‡‡QTcF	RR^k	QTc = QT/CxQTpr	1	0.33	1	0.33
§§QTcLogInv	RR^k	QTc = QT/CxQTpr	1	0.37	1	0.38
QTcMod	$1/(120 + HR^k)$		180	1	180	1

RR = RR interval; HR = heart rate.
‖ QTcRR = QTc as a linear function of RR with coefficients derived from the reference group of the present study.
QTcHR = QTc as a linear function of HR.
|||| QTcMod = Modular QTc prediction formula.
* C = slope coefficient of QTc formula.
† k = exponent of the QT prediction function.
‡ In linear adjustment of QT, the adjustment term is added to QT as a linear proportion of the difference of the prediction function from the reference interval or HR (RR = 1 or HR = 60).
§ In inverse adjustment QT is divided by the prediction function.
** QTcLogLin = logarithmic QTc formula with linear QT adjustment (logarithmic refers to natural (base e) logarithm).
†† QTcB = Bazett's formula
‡‡ QTcF = Fridericia's formula
§§ QTcLogInv = logarithmic QTc formula with inverse QT adjustment (logarithmic refers to natural (base e) logarithm).