Assessment of Prolonged QT and JT Intervals in Ventricular Conduction Defects

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The JT interval or Bazett's QTc − QRS has been advocated for detection of prolonged repolarization in ventricular conduction defects (VCDs). However, the use of neither JT nor QTc − QRS has been validated, and normal limits for rate-adjusted JT have not been established for VCDs or for normal ventricular conduction. Functional relations among RR, JT, and QT intervals were evaluated in 11,739 adult men and women with normal ventricular conduction and in 1,251 subjects with major VCD. The results showed that JT adjustment obtained as QTc − QRS retained a strong residual correlation with ventricular rate (r = 0.54), making its use ill-advised. In contrast, QT adjustment as a linear function of the RR interval for VCD as $QT_{RR,QRS}$ = QT − 155 × (60/heart rate − 1) − 0.93 × (QRS − 139) + k, with k = −22 ms for men and −34 ms for women, removed the rate dependence and produced upper 2% and 5% normal limits at 460 and 450 ms, respectively, which are identical to those in normal conduction. As an alternative, equally effective linear JT adjustment formulas were derived, including newly required normal standards. Thus, detection of prolonged repolarization in VCD requires the use of the JT interval or a bivariate model for QT with RR and QRS intervals as covariates. ©2004 by Excerpta Medica, Inc.

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QT interval prolongation is recognized as a clinically and epidemiologically important ventricular repolarization abnormality with important prognostic implications. Prolonged excitation time in ventricular conduction defect (VCD) induces secondary prolongation of the QT interval, and the use of the JT interval instead of the QT interval has been advocated.[1,2] However, information about the functional dependence of the JT interval on QRS and ventricular rate in VCD and in normal ventricular conduction is limited. In addition, normal limits for rate-adjusted JT intervals have not been established for VCDs or for normal ventricular conduction. Rate-invariant normal standards for the QT interval for normal ventricular conduction based on percentile distributions have been established in a previous study.[3]

We evaluated functional relations among QT, JT, RR, and QRS intervals in 11,739 normal men and women with normal ventricular conduction and in 1,251 subjects with VCDs. The objectives of the present investigation were to derive (1) optimal formulas for the adjustment of QT and JT intervals for ventricular rate and for removing the dependence of repolarization time on QRS duration in VCDs and (2) rate-invariant normal standards suitable for detection of prolonged repolarization in VCDs.

METHODS

Study population: Source data for this investigation were derived from 3 different population studies previously described in detail: the Third National Health and Nutrition Examination Survey,[3] the Cardiovascular Health Study,[4] and the Atherosclerosis Research In Communities Study.[5] Subjects with a history of heart attack, coronary bypass surgery, or coronary angioplasty were excluded. Electrocardiographically based exclusions for the group with normal conduction included a QRS interval ≥120 ms and other major electrocardiographic abnormalities according to the Minnesota Code[6] (myocardial infarction by electrocardiogram: Minnesota codes 1.1, 1.2, or 1.3 with codes 4.1, 4.2, 5.1, or 5.2; isolated ST-T abnormalities: codes 4.1, 4.2, 5.1, or 5.2; and electronic pacemakers: code 6.8). This selection process produced a group of 11,739 subjects (4,742 men and 6,997 women, ages 40 to 99 years) considered normal for the purposes of the present study.

Subjects for the group with major VCD were selected by using the Novacode classification criteria for VCD[7]: (1) left bundle branch block (LBBB; Novacode 3.1): QRS ≥125 ms, R-peak time or R′-peak time ≥60 ms in leads I, aVL, V_5, or V_6, and no ventricular preexcitation; (2) right bundle branch block (Novacode 3.2): QRS ≥120 ms and R-peak or R′-peak time ≥60 ms in leads V_1 or V_2 and S duration greater than or equal to R duration in leads I or V_6, and no ventricular preexcitation; and (3) indeterminate-type ventricular conduction delay (Novacode 3.3): QRS ≥120 ms and no LBBB or right branch bundle

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block and no ventricular preexcitation. The indeterminate-type ventricular conduction delay category includes LBBB patterns with QRS intervals of ≥120 to 124 ms. An additional exclusion criterion was the presence of Q waves suggesting possible old myocardial infarction (Q-wave score ≥25 as defined by the Novacode). These selection criteria yielded a total of 1,251 subjects (795 men and 456 women, ≥40 years old) with major ventricular conduction delays (342 with LBBB, 593 with right branch bundle block, and 316 with indeterminate-type ventricular conduction delay).

Electrocardiographic methods: Electrocardiograms were recorded in a resting supine state according to a comparable and strictly standardized procedure for electrocardiographic acquisition, including electrode placement[8] in each study. All electrocardiograms received at the Central ECG Laboratory (EPICARE Center, Wake Forest University, Winston-Salem, North Carolina) were inspected visually to detect technical errors, missing leads, and inadequate quality, and such records were rejected from electrocardiographic data files. Two electrocardiographic programs were used for QT measurement as an enhanced quality control procedure, Marquette 12SL (GE Marquette, Milwaukee, Wisconsin) and the Dalhousie Program.[9] These programs measure the QT as a global interval, the Marquette 12SL from the median complex derived and the Dalhousie Program from a complex obtained with selective averaging of all normally conducted complexes. The programs use derived composite magnitude functions from independent components of standard 12-lead electrocardiograms and their approximate first and second derivatives. The global QT interval derived from these ancillary functions reduces measurement uncertainties due to small T-wave amplitudes in any patient lead.

QT measurements by the 2 programs differed by ≥40 ms in 305 of the 11,739 subjects (2.6%) in the normal group and in 30 of the 1,252 subjects (2.4%) with VCDs. A special algorithm was used for these 2.4% of electrocardiograms for QT selection after rate adjustment. In the group with normal conduction, the QT measurement that was closer to the median rate-corrected QT of the group was chosen. In the group with VCDs, the selection was based on that program's JT interval that was closer to the median rate-corrected JT interval of the group. In all other cases, the QT and JT measurements by the Marquette 12SL program were retained for the analyses because the overall variability of the rate-adjusted QT interval was smaller for the Marquette 12SL than for the older Dalhousie Program.

Data analysis: The QT and JT intervals' prediction accuracy were evaluated by comparing R^2 values of the fit on QT and JT distributions by different prediction functions. From the different power functions evaluated, all with exponents between 1/3 (used in Fridericia's formula[10]) and 1 (linear function of the RR interval) had close, equally good prediction accuracy for the QT and JT intervals, with R^2 values differing by <1%, provided that a regression intercept and adjustment for gender were incorporated into the prediction formula. Subsequently, formulas with linear function for the RR interval were selected for more detailed analyses because of their suitability for obtaining rate-invariant normal limits. All analyses, including descriptive statistics and graphics, were performed with Microsoft Excel 5.0 (Microsoft Corporation, Redmond, Washington).

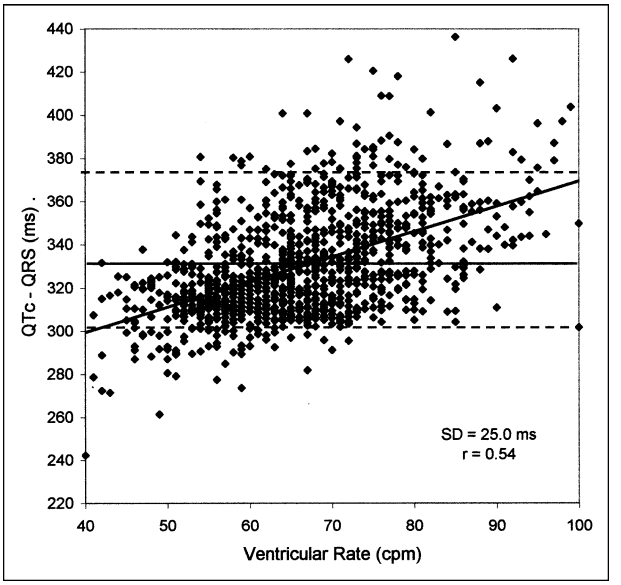

FIGURE 1. Rate- and gender-adjusted JT (JTc) obtained as JTc = QTc − QRS versus ventricular rate in pooled group of 1,252 men and women with major VCDs. Normal limits for rate-adjusted JT *(dashed lines)* are not valid because of the strong residual correlation between QTc − QRS and the ventricular rate (r = 0.54). cpm = complexes per minute; QTc = Bazett's rate-corrected QT.

RESULTS

The first relevant point to consider is the possible adequacy of the use of QTc − QRS, appropriately denoted as JTc for rate adjustment. The plot of JTc versus ventricular rate in the VCD group (Figure 1) shows that this adjustment retained a profound dependence of the adjusted JT interval on ventricular rate, with a high residual correlation (r = 0.54). This level of residual correlation was even higher than in subjects with normal ventricular conduction (r = 0.32).[3]

In considering possible solutions to the above problem, the effect of QRS duration on the QT and JT intervals was evaluated in light of the results from a previous modeling study.[11] In linear models regressing the RR interval and QRS as covariates on QT and JT intervals, the regression coefficients for QRS are related by the following expressions: QT = a1 × RR + b1 × QRS + c1 and JT = a2 × RR + b2 × QRS + c2, whereby b2 = (1 − b1) because JT = QT − QRS. Consequently, if QRS duration has a prominent influence on the QT interval as expected in VCDs, its effect on the JT interval will be correspondingly weaker. The data presented in Table 1 support this assertion. R^2 values in regression models for QT pre-

TABLE 1 R^2 Values for Linear QT and JT Prediction Models in 11,739 Adults With Normal Ventricular Conduction and in 1,252 Subjects With Major Ventricular Conduction Defects*

		Normal Subjects		Subjects With Ventricular Conduction Defects			
Interval	Prediction Model	Men (n = 4,742)	Women (n = 6,997)	LBBB (n = 342)	RBBB (n = 593)	IVCD (n = 316)	All (n = 1,251)
QT	QT = k1 × RR + k2	0.78	0.70	0.57	0.60	0.52	0.50
	QT = k1 × RR + k2 × QRS + k3	0.78	0.71	0.69	0.69	0.57	0.66
JT	JT = k1 × RR + k2	0.72	0.66	0.64	0.61	0.55	0.60
	JT = k1 × RR + k2 × QRS + k3	0.77	0.70	0.64	0.63	0.55	0.60

*In normal conduction, QRS interval contributes substantially to JT prediction but not to QT prediction. In VCDs, the opposite is true: QRS contributes substantially to QT prediction but the contribution to JT prediction is negligible.
IVCD = indeterminate-type ventricular conduction delay; RBBB = right bundle branch block.

TABLE 2 Reduction of Variance-Related Parameters in Normal Conduction and in Ventricular Conduction Defects by Adjustment Functions for JT and QT

Adjustment Function	Mean	SD	CV	IQR
Normal conduction				
Unadjusted JT in men	308	31.7	10.3	42
Unadjusted JT in women	316	29.2	9.2	40
1. QT_{RR} = QT − 185 × (60/HR − 1) + 6 ms for men	420	15.8	3.8	19
2. $JT_{RR,QRS}$ = JT − 183 × (60/HR − 1) + 0.73 × (QRS − 89) + 8 ms for men	331	15.6	4.7	20
3. JT_{RR} = JT − 176 × (60/HR − 1) + 14 ms for men	333	16.9	5.1	22
Bundle branch blocks				
Unadjusted JT	293	31.3	10.7	42
4. JT_{RR}* = JT − 155 × (60/HR − 1) + k; k = 34 ms for men, 22 ms for women	333	19.0	5.7	23
5. $QT_{RR,QRS}$ = QT − 155 × (60/HR − 1) − 0.93 × (QRS − 139) + k; k = −22 for men, −34 for women	420	20.0	4.8	24
6. JTc* = QTc − QRS + 3 ms	333	25.0	7.6	34

*The JT formulas in VCDs adjust the mean values of JTbz and JT_{RR} to 333 ms, equal to the mean value of JT_{RR} in normal conduction. Upper 2% and 5% normal limits for JT_{RR} are 370 and 350 ms, respectively, and those for QT_{RR} and $QT_{RR,QRS}$ are 460 and 450 ms, respectively. QT and JT intervals are in milliseconds.
CV = coefficient of variation = 100 × SD/mean; HR = heart rate (60/HR = RR interval in seconds); IQR = interquartile range.

diction in conduction defects increased from 0.50 to 0.66 with the inclusion of QRS compared by adjusting the QT interval for the RR interval alone. The effect was strongest in LBBB, as seen from the increase in R^2 value from 0.57 to 0.69. In comparison, the effect of QRS on the JT interval was practically negligible in all VCD categories, as seen by comparing the respective R^2 values with and without the QRS term. The situation was reversed in normal conduction. QRS duration had a notable effect on the JT interval in men and in women, but the influence of QRS duration on the QT interval was negligible.

QRS duration and adjustment for QT and JT intervals in normal conduction: These considerations suggest that, for JT adjustment, an adjustment for QRS duration needs to be considered in normal ventricular conduction and that it can be omitted in VCDs. The starting point for comparing various JT and QT adjustment functions is the single-parameter QT adjustment function in normal conduction derived in our previous study[3] (formula 1 in Table 2). This formula and a 2-parameter JT adjustment function (formula 2) reduced the SD of the adjusted interval to nearly 1/2 compared with that of the unadjusted interval.

A single-parameter JT adjustment function (JT_{RR}, formula 3) did not perform quite as well in normal conduction but nevertheless was fairly satisfactory. It produced upper and lower second and fifth percentile normal limits for the JT interval that remained rate invariant within 5 ms over the range of ventricular rates from 40 to 90 complexes/min (Figure 2). The stability of the normal limits for the JT interval over various sinus heart rates appeared equal to that for QT_{RR} in a previous investigation.[3]

QRS duration and JT and QT adjustments in VCDs: Various prospective JT adjustment functions in VCDs are compared in the lower half of Table 2. As expected, the best adjustment was obtained with category-specific coefficients (data not shown), with SD and the coefficient of variation being 19.0 ms and 5.7%, respectively, in the pooled VCD group. However, the adjustment accuracy was similar to a common set of coefficients, with SD and the coefficient of variability being 19.2 ms and 5.8%, respectively.

JT_{RR} values from formula 4 in Table 2 obtained with the pooled coefficients were plotted against the ventricular rate in the VCD group (Figure 3). The adjusted JT interval exceeded the upper second percentile normal limit in 51 subjects (4.1%) and the upper fifth percentile in 210 subjects (16.8%) with VCDs.

The adjusted QT values in the VCD group by the $QT_{RR,QRS}$ model (formula 5) are graphed against QRS duration in Figure 4. The chart shows that QT dependence of QRS duration in VCD was removed. It also indicates that the upper and lower percentile limits established in the normal conduction group are applicable to the VCD group, although the sample size in VCD subgroups with more pronounced QRS duration is smaller. Of the 1,251 subjects with VCDs, 44

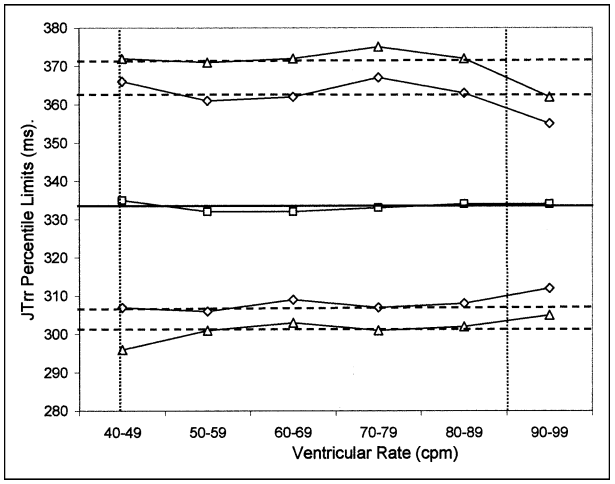

FIGURE 2. Mean values *(squares)* with upper and lower second *(triangles)* and fifth *(diamonds)* percentile normal limits for the JT interval adjusted for the RR interval (60/HR) by the formula: JT_{RR} = JT − 176 × (60/HR − 1) + 14 ms adjustment for men. The normal limits established in 11,739 normal subjects ≥40 years old remain stable within 5 ms in the range of sinus rates from 40 to 90 complexes/min (cpm). HR = heart rate.

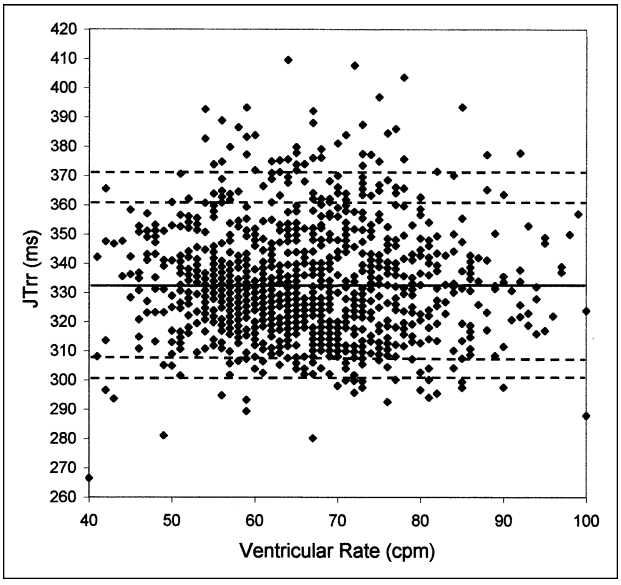

FIGURE 3. The JT interval adjusted as a linear function of the RR interval (JTrr = JT − 155 × [60/HR − 1] +k, with k = 34 ms for men and 22 ms for women) in pooled group of subjects with VCD. *Dashed lines,* upper and lower second and fifth percentile limits from Figure 1 established with the $JT_{RR,QRS}$ formula in the normal group. Abbreviations as in Figure 2.

(3.5%) exceeded the upper 2% normal limit and 103 (8.2%) the upper 5% normal limit established in the group with normal ventricular conduction. A closer examination of the distribution of the subjects exceeding the upper 5% normal limit in various types of conduction defects showed that the allocation was 42 (12.3%) in LBBB, 32 (5.4%) in right branch bundle block, and 29 (9.2%) in indeterminate-type ventricular conduction delay. The distribution was similar when group-specific coefficients were applied.

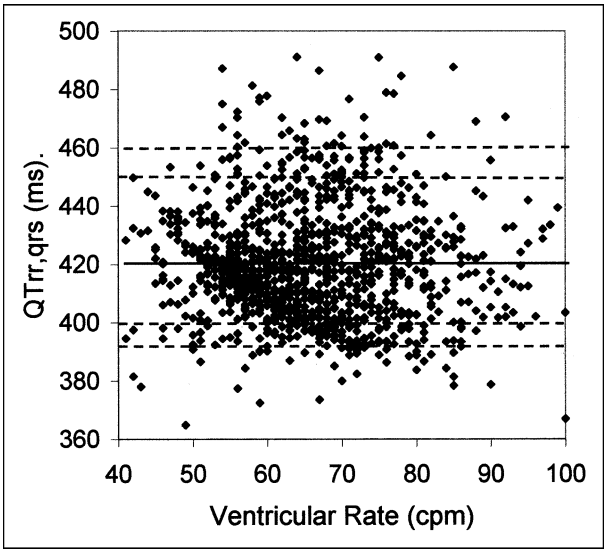

FIGURE 4. QT adjusted for ventricular rate, QRS interval, and gender graphed against ventricular rate in 1,251 subjects with VCD: $QT_{RR,QRS}$ = QT − 155 × (60/HR − 1) − 0.93 × (RR − 139) + k, where k = −22 for men and −34 ms for women. *Dashed lines,* the upper and lower 2% and 5% normal limits established in the group with normal ventricular conduction.

DISCUSSION

A critical result from the present investigation was that QT adjustment in VCDs obtained as QTc − QRS retained a strong residual correlation with ventricular rate (r = 0.54). The correlation was even larger than that for QTc in normal conduction (r = 0.32).[3] This renders the use of QTc − QRS in VCDs as disadvantageous, and its potential retention of risk information[2] does not remove its fundamental flaws by statistical manipulations. In contrast, QT adjustment for VCD as $QT_{RR,QRS}$ = QT − 155 × (60/heart rate − 1) − 0.93 × (QRS − 139) + k, with k = −22 ms for men and −34 ms for women, removed the rate dependence and produced upper 2% and 5% normal limits at 460 and 450 ms, respectively, identical to those in normal conduction.

As an alternative to the 2-parameter $QT_{RR,QRS}$ function, the JT interval, adjusted for the RR interval only (formula 1 in Table 2), produced similar adjustment accuracy. Adding QRS duration did not notably improve JT prediction in VCDs. In normal ventricular conduction, including QRS, it slightly improved the prediction accuracy but a single-parameter model with the JT interval as a function of the RR interval can be considered fairly satisfactory. The use of the QT adjustment formula has the advantage that the upper 5% and 2% normal limits, which are already familiar to electrocardiographers (450 and 460 ms, respectively), apply for normal conduction and for VCDs. Further, electrocardiographers are more familiar with using the QT interval than the JT interval for detection of prolonged repolarization. If the formula for JT adjusted for RR is used, the new upper normal limits for the adjusted JT interval established in the present investigation have to be used.

Normal limits for the QT interval established in

most previous investigations have been based on the use of the mean $\pm$ 2 $\times$ SD based on the erroneous assumption that the adjusted QT distributions at different ventricular rate subintervals have a constant variance and are Gaussian normal. Our previous investigation demonstrated that QT distributions are variably skewed and heteroclastic (variance not constant at different ranges of ventricular rate) and that earlier normal standards for QT intervals may be in error.[3] In addition, if QTc $-$ QRS is used in VCDs instead of an appropriate adjustment function, even the correctly derived normal standards for the JT interval are not valid if the ventricular rate deviates from 60 complexes/min.

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