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Clinical Research

Determination of the QT Interval in Left Bundle Branch Block: Development of a Novel Formula

Jacky K.K. Tang, BSc (Pharm), and Simon W. Rabkin, MD, FRCPC, FCCS, FESC, FACC

Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

Background: Determination of the prolonged QT interval in left bundle branch block (LBBB), which should be of special concern to identify individuals at high risk of potentially fatal cardiac arrhythmia risk, has been problematic.

Methods: Electrocardiograms (ECGs) (n = 17) in intermittent LBBB were used to develop a new formula for the calculation of QTc in LBBB. This formula and 5 others were compared in a population with LBBB (n = 2610). The QT was corrected for heart rate (HR) using the Bazett formula (QTcBZT) and the spline QT formula (QTcRBK), which is relatively independent of HR. The JT interval was significantly related to HR.

Results: The new approach ($QTc_{LBBB}NEW = 0.945*QTcRBK_{LBBB} - 26$) in LBBB showed the highest correlation with intrinsic QTc (without LBBB) and had minimal HR dependency. Previous formulae to

RÉSUMÉ

Contexte : La mesure de l'allongement de l'intervalle QT dans le bloc de branche gauche (BBG), auquel on devrait accorder une attention particulière pour repérer les individus présentant un risque élevé d'arythmie cardiaque dont l'issue peut être fatale, pose certaines difficultés.

Méthodologie : Des électrocardiogrammes (ECG) (n = 17) ont été réalisés chez des patients présentant un BBG intermittent pour élaborer une nouvelle formule de calcul du QTc dans le BBG. Cette formule et 5 autres ont été comparées dans une population de patients atteints de BBG (n = 2610). Le QT a été corrigé en fonction de la fréquence cardiaque (FC) à l'aide de la formule de Bazett (QTcBZT) et de la formule d'interpolation spline QTcRBK, qui est relativement indépendante de la FC. L'intervalle JT était lié de façon significative à la FC.

Prolongation of the QT interval, a measurement of ventricular repolarization, is a significant risk factor for fatal arrhythmias and sudden cardiac death.[1,2] Left bundle branch block (LBBB) is also associated with a high risk of cardiac mortality.[3,4] Identifying prolonged ventricular repolarization in the setting of LBBB, which should be of special concern in identifying individuals at high risk of potentially fatal cardiac arrhythmias, has produced a number of challenges. These include appropriate methods to adjust for the contribution of the increased QRS duration due to the LBBB, the recognized heart rate dependency of the QT interval, and the impact of delayed depolarization on repolarization. Although the first issue has received some attention, the second issue is poorly investigated in LBBB, and the third issue may not be readily solvable on the standard electrocardiography.

Several formulae have been proposed to correct for delayed depolarization in LBBB, which contributes to increasing the QT interval because the QT interval encompasses the increased QRS duration.[5-9] However, the use of heart rate correction formulae in patients with LBBB has only rarely been studied. Calculation of the JT interval as an indicator of the QT interval, in LBBB, was proposed to be a reasonable approach based on electrophysiological studies of right ventricular (RV) apex pacing to induce LBBB.[9] However, we found that JT in RV pacing still maintains heart rate dependency, limiting its use alone for QT assessment.[10] We instead proposed a heart rate correction for the QT interval before the calculation of the JT interval.[10] Rautaharju et al.[7] examined the relations among the RR, JT, and QT intervals in 11,739 adult men and women with normal ventricular conduction, and in 1251 subjects with major ventricular conduction defects, they found that the JT interval retained a strong residual correlation with ventricular rate and concluded that it was an "ill-advised" approach to estimate the QT interval. Instead, they proposed a formula that included a linear function of the RR interval, as well as different constants for men and women. Yankelson et al.[8] proposed a JT interval measurement with a heart rate correction using the Bazett formula while adding different fixed constants for the "normal" QRS duration for men and for women. Bogossian et al.[5] proposed a formula based on electrophysiological studies in patients who had RV pacing and concluded that

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Corresponding author: Dr Simon W. Rabkin, University of British Columbia, 9th Floor, 2775 Laurel St, Vancouver, British Columbia V5Z 1M9, Canada. Tel.: +1-604-875-5847; fax: +1-604-875-5849.

E-mail: simon.rabkin@ubc.ca

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determine the QT interval in LBBB showed significant HR dependency except for one proposed by Rautaharju et al. Inclusion of an HR correction factor in existing formulae blunted HR dependency but not if the QT interval was adjusted by the QTcBZT. In men and women, use of the QTcBZT markedly increases the proportion of individuals with prolonged QTc, which was more evident with increasing HR. The 99th and 97.5th percentiles for QTc_{LBBB}NEW for men and women identified abnormal QT prolongation in LBBB.

Conclusions: A new formula that modifies the QT and JT intervals in LBBB predicts the QT interval in the absence of LBBB. Abnormal QT intervals in the 99th and 97.5th percentiles can identify patients with LBBB who have QT interval prolongation.

Résultats : La nouvelle approche (QTc_{BBG}NOUVEAU = 0,945* $QTcRBK_{BBG}$ − 26) dans le BBG a montré la corrélation la plus élevée avec le QTc intrinsèque (sans BBG) et une dépendance minimale à la FC. Les formules utilisées antérieurement pour mesurer l'intervalle QT dans le BBG étaient fortement dépendantes de la FC, sauf celle proposée par Rautaharju et ses collègues. L'inclusion d'un facteur de correction de la FC dans les formules existantes estompait la dépendance à la FC, sauf si l'intervalle QT était ajusté par la formule QT cRBK. Chez les hommes et les femmes, l'utilisation de la formule QTcBZT a entraîné un accroissement marqué de la proportion des individus présentant un allongement du QTc qui était plus manifeste lorsque la FC augmentait. Les 99^{e} et 97,5^{e} centiles du QTc_{BBG}NOUVEAU correspondaient à une prolongation anormale de l'intervalle QT chez les hommes et les femmes présentant un BBG.

Conclusions : Une nouvelle formule qui modifie les intervalles QT et JT dans le BBG prédit l'intervalle QT en l'absence de BBG. Les intervalles QT anormaux des 99^{e} et 97,5^{e} centiles permettent de repérer les patients présentant un BBG avec prolongation de l'intervalle QT.

subtracting 48.5% of (pacing-induced) LBBB duration would predict intrinsic QRS duration. Wang et al.[6] studied patients with intermittent (pacing-induced) LBBB and estimated that the proportionate contribution of the QRS duration was 86% minus a fixed amount attributed to the LBBB. Most but not all of these formulae ignore the impact of heart rate. Rautaharju et al.[7] suggested a specific correction factor, whereas others proposed using the Bazett formula.[6] The Bazett formula has been criticized as it demonstrates heart rate dependency that is most evident at faster heart rates.[11,12] We have proposed a newer QT adjustment formula (QTcRBK) based on a spline equation to adjust for heart rate effects on the QT interval in 13,600 individuals in the National Health and Nutrition Examination Survey (NHANES US) population study and found that it was relatively independent of heart rate and superior to other QTc formulae.[13]

The objective of this study was several-fold. First, we proposed to examine the contribution of LBBB to QT duration in persons with intermittent LBBB. Second, we sought to compare 6 different proposed formulae in LBBB, compared with the normal ventricular conduction, after correcting for heart rate dependency. In this way, we would provide a modification of existing formulae to best address the impact of heart rate. In addition, we sought to compare the impact of the various LBBB QT formulae in a large population of patients with complete LBBB and to define an abnormally prolonged JT interval corrected for heart rate from the large population study.

Methods

Cases with intermittent LBBB

Patient selection. The study population consisted of 17 patients (mean age 74.7 ± 9.5 years, standard deviation [SD]; 47.1% male) who met the entry criteria, screened retrospectively from a list of all unique patients (n = 37) identified through an electronic search of electrocardiograms (ECGs) with a diagnosis of "intermittent LBBB" that were confirmed by a reading cardiologist at Vancouver General Hospital and University of British Columbia Hospital between January 1, 2004, and March 31, 2018 (Table 1). Details of the inclusion and exclusion criteria are present in the Supplemental Methods.

ECG measurements. The details of the ECG measurement are provided in the Supplemental Methods.

Population-based LBBB

The study population consisted of 2610 patients (mean age 74.1 ± 12.5 [SD] years; 50.6% male) identified retrospectively with an ECG diagnosis of LBBB from our ECG database between January 1, 2004, and March 31, 2018 (Table 1). Details of the populations are presented in the Supplemental Methods.

Data analysis

Six different formulae or approaches were compared:

(1) QT_{LBBB}BOG proposed by Bogossian et al.,[5] where $QT = QT_{LBBB} - 48.5\% * QRS_{LBBB}$.
(2) QT_{LBBB}WANG proposed by Wang et al.,[6] where $QT = QT_{LBBB} - (0.86 * QRS_{LBBB} - 71)$.
(3) QTc_{LBBB} RAUT proposed by Rautaharju et al.,[7] where $QT = QT_{LBBB} - 155 * (60/HR - 1) - 0.93 * (QRS_{LBBB} - 139) + k$ ($k = -22$ ms for men; $k = -34$ ms for women).
(4) JTc_{LBBB}, where the JT interval is calculated as JTc = QTc − QRS,[9,10] where the QTc is calculated and the QRS duration is subtracted leaving the estimated JTc.
(5) QT_{LBBB}YANK proposed by Yankelson et al.,[8] where QT = JT + QRS, when QRS duration was set at 95 ms for males and 88 ms for females.
(6) QTc_{LBBB}NEW, where QTcRBK = 0.945*QTc RBK_{LBBB} − 26. This QTc formula was derived from using the constants from the linear relationship between $QTcRBK_{LBBB}$ in intrinsic conduction to QTcRBK in LBBB.

The equations, except for those that already had a heart rate correction, were then modified to adjust for heart rate

Table 1. Baseline characteristics of the 2 study populations

Intermittent left bundle branch block (LBBB) (n = 17)*		
Sex	M = 47.1%; F = 52.9%	
Age	74.7 ± 9.5 y	
	Intrinsic QRS	LBBB
Heart rate	74.4 ± 15.6 bpm	80.5 ± 22.7 bpm
QRS duration	100.5 ± 9.3 ms	152.7 ± 18.7 ms
QT interval	387.9 ± 40.1 ms	431.0 ± 52.7 ms
QTcBZT	427.0 ± 43.4 ms	487.8 ± 37.2 ms
QTcRBK	406.5 ± 33.8 ms	457.9 ± 28.4 ms
Population-based LBBB (n = 2610)		
Sex		M = 50.6%; F = 49.4%
Age		74.1 ± 12.5 y
Heart rate		74.7 ± 17.6 bpm
QRS duration		147.1 ± 16.0 ms
QT interval		444.0 ± 45.4 ms
QTcBZT		487.4 ± 34.1 ms
QTcRBK		462.3 ± 28.3 ms

The data are the mean ± standard deviation.

*In 14 of the cases, the rhythm was sinus, and in 3 cases, the rhythm was atrial fibrillation.

using 2 approaches. First, the QT intervals were corrected for heart rate with the Bazett approach (QTcBZT). QTcBZT was chosen because it is the heart rate correction formula in most widespread usage and several of the QT LBBB correction formula also proposed using the Bazett correction factor.[8] The second QTc formula was the new spline formula (QTcRBK) that was developed based on the ECGs from approximately 13,600 individuals in the NHANES US population study and was shown to be relatively independent of heart rate and superior to other QTc formulae.[13] We used the nomenclature for QTc abbreviations that specified the first 3 syllables of the first authors name.[14] LBBB data were corrected for heart rate for all 4 methods that had not included a heart rate correction approach. The one proposed by Rautaharju et al.[7] already includes heart rate correction in the formula. The QT interval was measured from the lead with the longest QT interval, and the prolonged QTc interval was defined as greater than 450 milliseconds and 460 milliseconds for men and women, respectively, according to AHA/ACCF/HRS recommendations.[15]

Statistical analysis

Linear regression analyses were performed to examine both heart rate dependency and the relation of each formula to intrinsic (non-LBBB) conduction. The linear correlation approach was selected because it has been used by several authors to establish the validity of their correction formula for LBBB. The F statistic was used for relative comparisons. If the correction formula completely removes the effect of heart rate, the F statistic will be 0. Large values of F indicate that the heart rate dependency is still evident.

Results

Relationship between heart rate and QT or JT in LBBB

Examining the QT-heart rate relationship in LBBB on the ECG with intermittent LBBB, showed a significant relationship ($P < 0.001$) between QT and heart rate, for the Bogossian (QT_{LBBB}BOG), Wang (QT_{LBBB}WANG), JT (JT_{LBBB}), and Yankelson (QT_{LBBB}YANK) formulae (Fig. 1). In contrast, the new proposed formula (QT_{LBBB}New) and the Rautaharju formula (QT_{LBBB}RAUT) did not demonstrate any significant relationship with heart rate.

Relationship between heart rate and QT or JT in intrinsic conduction

The relationship between heart rate and the QT or JT interval was examined in QRS complexes that did not show evidence of LBBB on the ECG with intermittent LBBB (Supplemental Figure S1). There was a significant inverse relationship between heart rate and QT ($P = 0.020$) or JT ($P = 0.017$). The Bazett formulae reduced the level of significance to the 10% level for QTcBZT ($P = 0.085$) and JTcBZT ($P = 0.070$) as a trend for heart rate dependency was still evident. In contrast, the new correction formulae removed the impact of heart rate on the QT ($P = 0.559$) or JT ($P = 0.508$).

JT interval

Because the JT interval demonstrates significant heart rate dependency in LBBB ($P < 0.001$) and intrinsic QRS complexes ($P = 0.017$), a correction approach is necessary, as we have previously demonstrated[10] and as found in the absence of LBBB (Supplemental Figure S1). The QTcBZT correction followed by JT calculation did not correct the heart rate dependency of the JT interval (Supplemental Figure S2). Following the approach of applying a QTc spline adjustment equation (QTcRBK) and then calculating the JT interval,[10] we found that there was no significant heart rate dependency of the JT interval. In contrast, there remained a significant ($P = 0.005$) heart rate dependency using the Bazett correction approach.

LBBB QT correction vs intrinsic QT value

We next sought to determine the correlation between each of 6 proposed formulae on the measured QT interval in LBBB with the QT interval in the absence of LBBB (or intrinsic QRS complexes). To adjust for the effect of heart rate, the 2 different correction formulae were used for intrinsic complexes for all formulae except for the 2 formulae that had internal correction factors. Each formula was modified by either QTcBZT or QTcRBK and the appropriate comparator that was the related QTc in the intrinsic QRS complexes (Fig. 2). Each of the formulae showed a significant correlation between the QT in LBBB and QT without LBBB. The range of correlations varied from $r = 0.611$ for $JTcBZT_{LBBB}$ to $r = 0.794$ for QTc_{LBBB}NEW.

Correlation itself is not necessarily the ultimate best formula as QTcBZT is not independent of heart rate, so a good correlation with a suboptimal QTc is not a proof of a best index. Use of the new proposed approach demonstrated the highest correlation overall, followed by the formulae proposed by Bogossian, Rautaharju, Wang, Yankelson, and then the JTc method (Fig. 2).

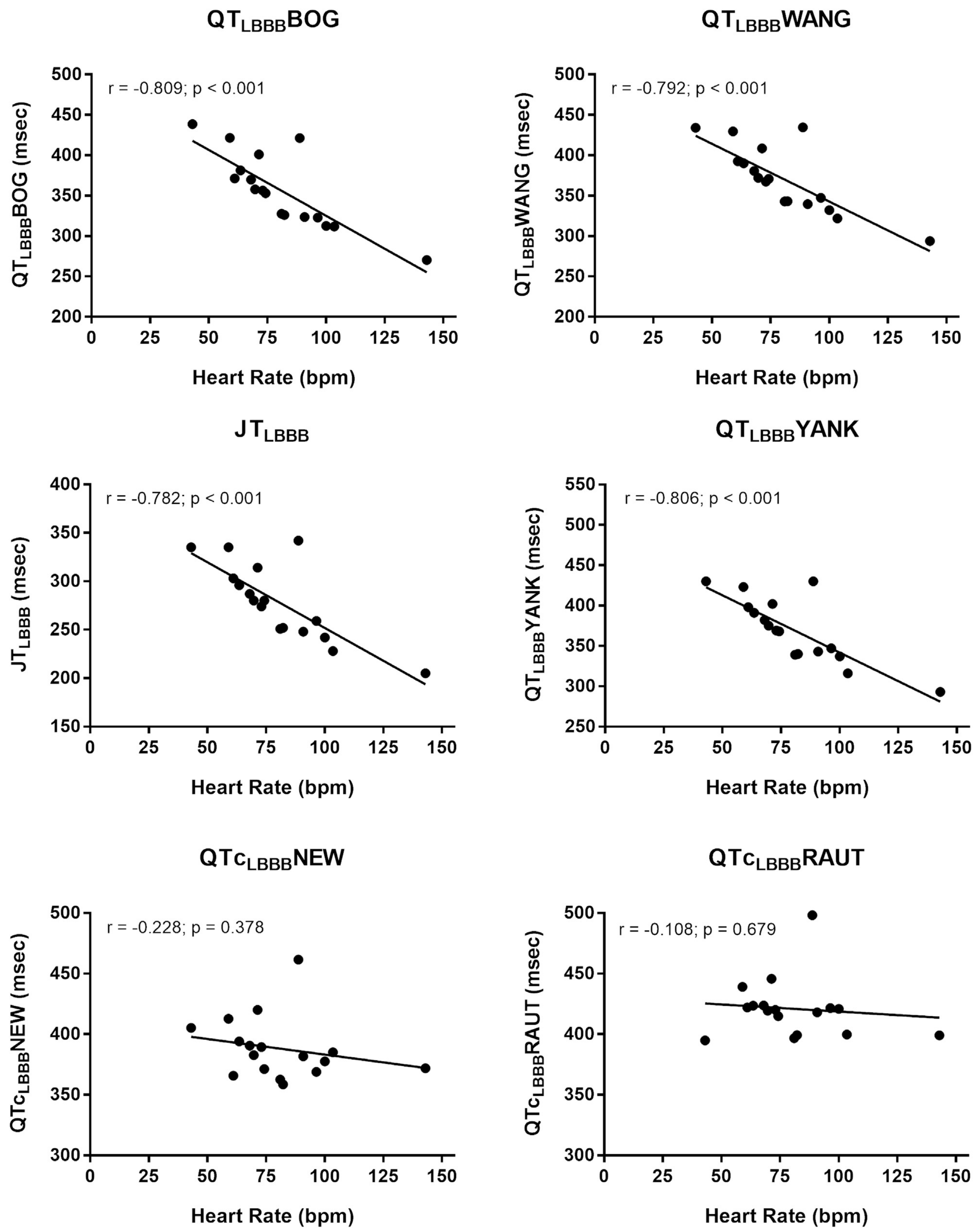

Figure 1. The relationship between heart rate and QT or JT interval in left bundle branch block (LBBB) for the different formulae: QTc (formulae) and JT.

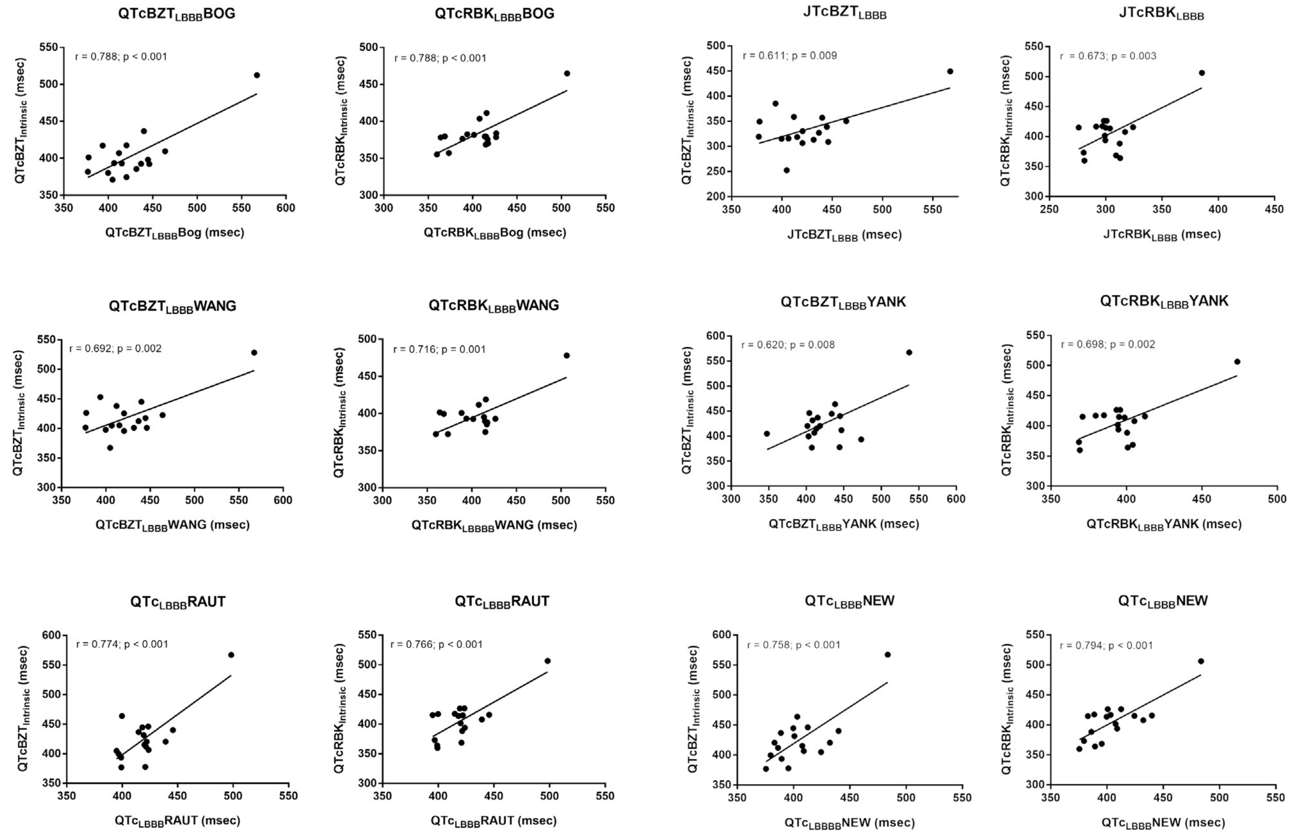

Figure 2. The relationship between the QT interval in the absence or presence of left bundle branch block (LBBB) for the proposed formulae.

Implication of the heart rate correction formulae in LBBB

The inverse relationship between QT interval and heart rate was evident with a high correlation ($r = 0.781$; $F = 4087$) in the population of 2610 patients with LBBB (Fig. 3). Significant QT-heart rate relationships were evident for $QTBOG_{LBBB}$ ($r = 0.790$; $F = 4623$), $QTWANG_{LBBB}$ ($r = 0.798$; $F = 4568$), and $QTYANK_{LBBB}$ ($r = 0.778$; $F = 4646$). QTcBZT blunted the impact of heart rate but with a correlation that was still meaningful ($r = 0.436$; $F = 611.9$; $P < 0.001$), so $QTcBZT_{LBBB}BOG$, QTcBZT $_{LBBB}WANG$, and QTcBZT $_{LBBB}YANK$ continued to show meaningful relationships with heart rate. $QTcRAUT_{LBBB}$ definitely blunted the heart rate dependency ($r = 0.150$; $F = 144.3$) but not as much as $QTcRBK_{LBBB}$ ($r = 0.109$; $F = 31.7$). The JT interval showed a high heart rate dependency in LBBB ($r = 0.793$; $F = 4422$). It was reduced by Bazett correction, but JTcBZT was still highly significantly related to heart rate ($r = 0.525$; $F = 992.2$). In contrast, the heart rate dependency was almost obliterated by correction with JTcRBK ($r = 0.038$; $F = 3.79$).

To assess the impact of the various QTc_{LBBB} formulae on the percentage of individuals who would have prolonged QTc, the data were analysed separately for men and women with cutoff values of 450 milliseconds and 460 milliseconds, respectively.[15] In women, use of the QTcBZT was associated with a markedly greater proportion of individuals with a QTc more than 460 milliseconds for $QTcBZT_{LBBB}BOG$, $QTcBZT_{LBBB}WANG$, and $QTcBZT_{LBBB}YANK$ (Fig. 4). This is most likely due to the heart rate dependency of QTcBZT. $QTcBZT_{LBBB}YANK$ had the highest proportion of cases with QTc > 460 milliseconds, followed by $QTcBZT_{LBBB}WANG$, $QTc_{LBBB}RAUT$, and then $QTcBZT_{LBBB}BOG$. In men, use of the QTcBZT was similarly associated with a significant increase in proportion of individuals with a QTc more than 450 milliseconds for $QTcBZT_{LBBB}BOG$, $QTcBZT_{LBBB}WANG$, and $QTcBZT_{LBBB}YANK$ (Fig. 4). $QTcBZT_{LBBB}YANK$ shows the highest proportion of cases with prolonged QTc, followed by $QTc_{LBBB}RAUT$, $QTcBZT_{LBBB}WANG$, and then QTc $BZT_{LBBB}BOG$, which is a different rank order compared with women. In all cases, the addition of QTcRBK heart rate modification, that reduced heart rate dependency, produced considerably lower proportion of cases with prolonged QTc > 460 milliseconds in women and > 450 milliseconds in men.

To explore the impact of heart rate on the prevalence of prolonged QTc, the QTc intervals were evaluated across the heart rate spectrum (Fig. 5). It was evident that greater heart rates were associated with a higher percentage of men and women with prolonged QTc when using the Bazett correction factor.

The distribution of the QTc interval and the JTc interval provides data to define criteria for normal intervals (Supplemental Figure S3). The 99th percentile for $QTcNEW_{LBBB}$ was 496.5 and 471.3 milliseconds for men and women, respectively, whereas the 97.5th percentile was 479.9

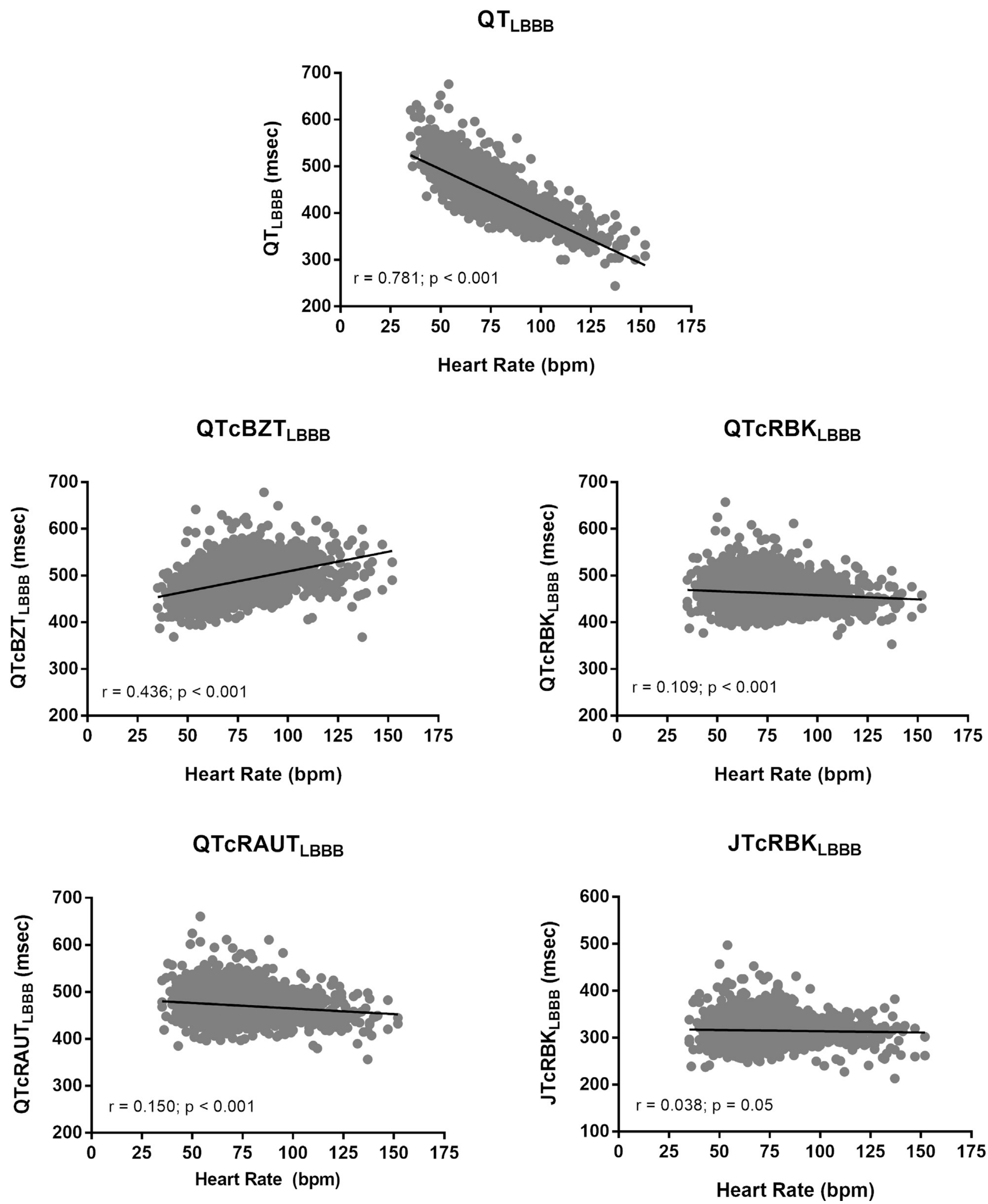

Figure 3. The relationship between heart rate and QT in 2610 cases of left bundle branch block (LBBB) in the absence of a correction factor (**top panel**) and with the Bazett correction (QTcBZT) (**middle-left panel**), $QTcRAUT_{LBBB}$ (**lower-left panel**), $QTcRBK_{LBBB}$ (**middle-right panel**), and JTcRBK (**lower-right panel**).

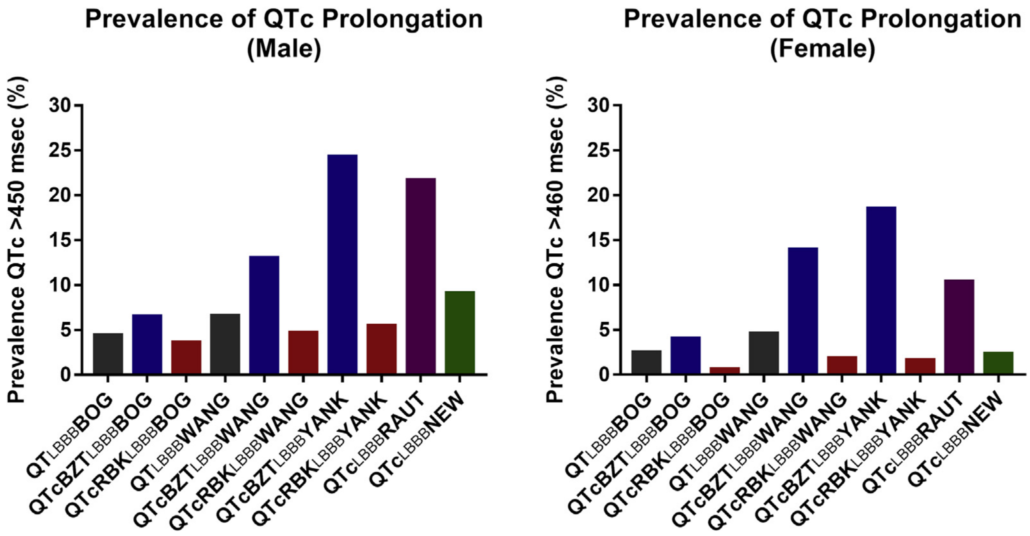

Figure 4. The prevalence of QT prolongation for different QT formulae for men using the criteria of a QTc greater than 450 milliseconds and for women using the criteria of greater than 460 milliseconds. LBBB, left bundle branch block.

and 458.2 milliseconds for men and women, respectively (Table 2). The corrected JT interval JTcRBK at the 99th percentile was 398 milliseconds for men and 381 milliseconds for women, and at the 97.5th percentile, it was 377 milliseconds for men and 364 milliseconds for women. The age dependency of QTc[13] was not evident in these data ($P = 0.40$ for women and $P = 0.12$ for men), permitting the use of the percentile numbers without reference to age, because of the relatively small variation in age of this older population. The mean age was 76.0 years (95% confidence interval, 75.3-76.6) for women and 72.3 years (95% confidence interval, 71.6-73.0) for men.

Discussion

This study accomplished several aims. It (1) is the first in-depth analysis of the implications of competing approaches to measure the QT or JT interval in a large population of individuals with LBBB, (2) developed a new formula for the calculation of the QT interval in LBBB, (3) stressed the importance of the heart rate dependency of the QT interval and the JT interval in LBBB, (4) proposed a modification of existing approaches for the calculation of the QT interval for existing formulae, to adjust for heart rate dependency of the QT interval, and (5) proposed a new definition for QTc and JTc prolongation in LBBB.

We demonstrated that the QT interval in the absence of LBBB can be significantly predicted by the QT or JT interval in LBBB. Indeed, each of the formulae showed a significant correlation between the QT in LBBB and the QT without LBBB. Our newly developed approach to calculate the QT interval in LBBB was derived from using the constants from the linear relationship between QTcRBK in intrinsic conduction to QTcRBK in LBBB. It showed the highest correlation with intrinsic QTc compared with other approaches with the caveat that it was tested on the same data set.

Formulae for estimation of the QT interval in LBBB were initially suggested without incorporating heart rate corrections.[5,6,9] These approaches did not examine in detail the well-recognized heart rate dependency of the QT interval. Our data emphasize the need for an optimal heart rate correction in LBBB. Many different heart rate correction formulae have been proposed over the years (for a review, see the paper by Rabkin and Cheng[14]). The recent formula (QTcRBK) fit a spline function to ECGs from approximately 13,600 individuals in the NHANES US population study.[13] Previous formulae that used a linear, logarithmic, or an exponential fit of the data are only valid when the nature of the relationship is truly known and is constant over all heart rates. This is not the case with the QT-heart rate relationship. The relationship may be linear in one heart rate range and exponential in another range. The spline methodology is a better way to fit these kinds of relationships.[16] The QTcRBK formula was consistently better at adjusting the QT for heart rate compared with the other formulae and was also cross-validated in a separate population set,[13] so it was selected for use herein.

Calculation of the JT interval has been proposed to assess repolarization in LBBB with the suggestion that it is independent of the contribution of the increased QRS duration due to LBBB.[9] The JT interval, however, is dependent on heart rate as we show here, and previously demonstrated in the LBBB pattern induced by RV pacing[10] and noted by others.[7] Following the approach of applying the QTc spline adjustment equation and then calculating the JT interval,[10] we found that there was no significant heart rate dependency of the JTc interval. Calculation of the JTc in LBBB with a heart rate correction showed a high correlation with the intrinsic QT interval supporting the contention that QT in intraventricular conduction delay is mainly due to prolonged depolarization time, as the repolarization intervals were not significantly different.[17] This concept is also consistent with the suggestion that "QT deflection area was largely but not exclusively independent of ventricular activation sequence."[18]

In the absence of heart rate correction, the formulae for estimation of the QT interval in LBBB demonstrate a relatively high proportion of cases with QT prolongation. The

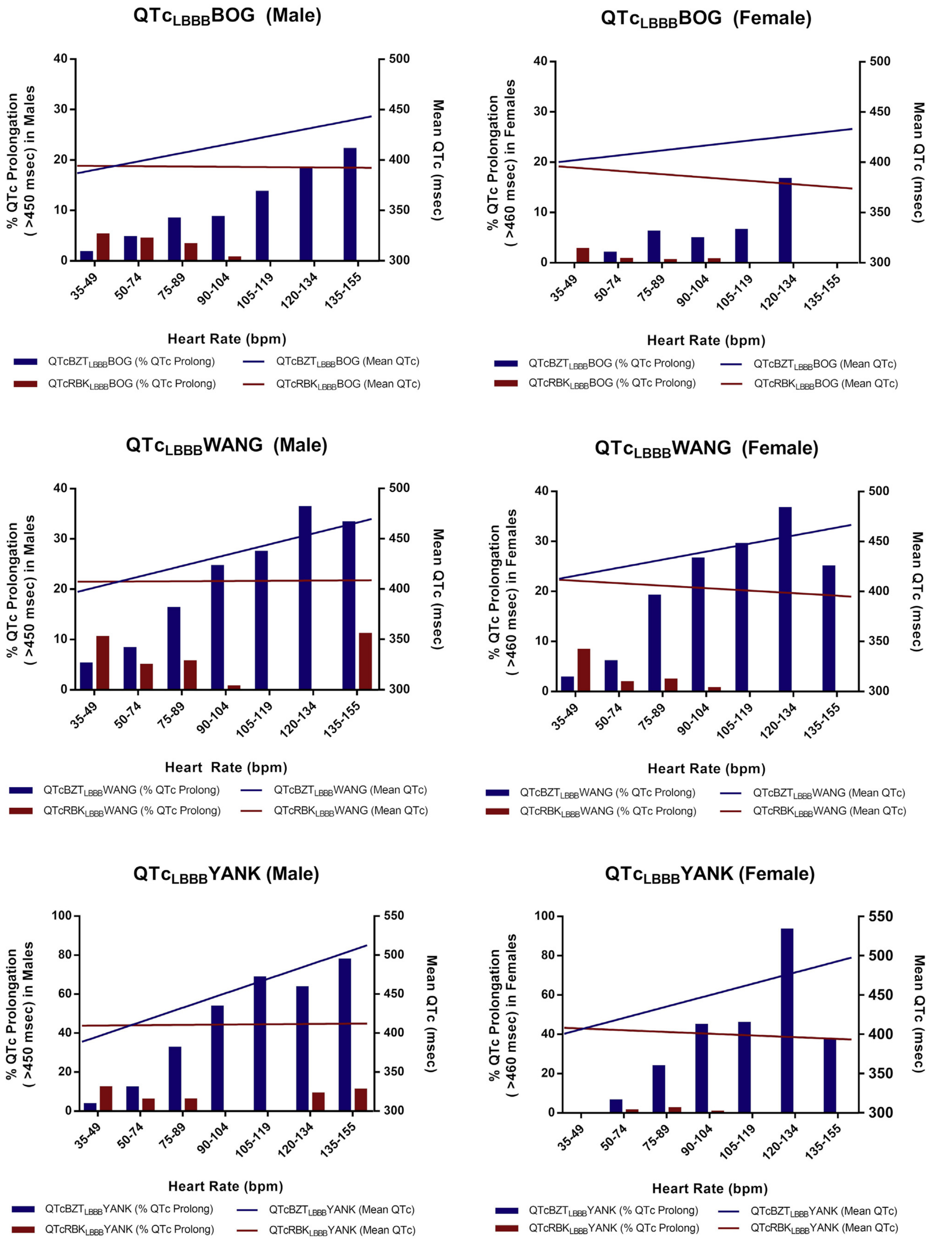

Figure 5. The proportion of men with a QTc over 450 milliseconds and women with a QTc over 460 milliseconds across the heart rate spectrum of 3 different QTcLBBB formulae with the Bazett correction (QTcBZT) (**left bar**) or spline correction (QTcRBK) (**right bar** of each set of bars). The mean heart rate in each interval is also displayed. LBBB, left bundle branch block.

Table 2. The 99th and 97.5th percentile for QTc

	99th percentile (ms)	97.5th percentile (ms)		99th percentile (ms)	97.5th percentile (ms)
Male					
$QTcBZT_{LBBB}$	593.96	566.22	$QTcRBK_{LBBB}$	553.15	535.58
$QTcBZT_{LBBB}BOG$	492.04	470.28	$QTcRBK_{LBBB}BOG$	475.92	455.70
$QTcBZT_{LBBB}WANG$	509.93	487.24	$QTcRBK_{LBBB}WANG$	488.80	469.76
$QTcBZT_{LBBB}YANK$	521.75	499.47	$QTcRBK_{LBBB}YANK$	493.09	471.98
$JTcBZT_{LBBB}$	426.75	404.47	$JTcRBK_{LBBB}$	398.09	376.98
$QTc_{LBBB}RAUT$	518.05	497.88	$QTc_{LBBB}NEW$	496.45	479.86
Female					
$QTcBZT_{LBBB}$	574.15	557.75	$QTcRBK_{LBBB}$	526.44	512.63
$QTcBZT_{LBBB}BOG$	483.49	469.82	$QTcRBK_{LBBB}BOG$	450.58	440.08
$QTcBZT_{LBBB}WANG$	506.05	489.71	$QTcRBK_{LBBB}WANG$	470.43	456.16
$QTcBZT_{LBBB}YANK$	516.51	499.67	$QTcRBK_{LBBB}YANK$	469.81	452.35
$JTcBZT_{LBBB}$	428.51	411.67	$JTcRBK_{LBBB}$	381.81	364.35
$QTc_{LBBB}RAUT$	495.45	481.06	$QTc_{LBBB}NEW$	471.28	458.19

LBBB, left bundle branch block.

data suggest that failure to correct for heart rate can lead to overestimation of QT duration and may lead to inappropriate clinical decisions. Once the QT interval had been well corrected for heart rate (with QTcRBK), the proportion with the prolonged QT interval was more constant across the different formulae. However, even in the presence of QTc heart rate correction, there is considerable variability in the proportion of individuals with prolonged QTc depending on the heart rate correction formula used. Formulae corrected by QTcBZT were associated with a significantly larger proportion of individuals with QTc prolongation. Based on our data correlating QTc formulae with heart rate, it is reasonable to infer that this increased proportion of individuals identified is a result of the significant residual heart rate dependency with the QTcBZT formula, especially in the higher heart rate ranges. Indeed, we demonstrate an increasingly higher proportion of individuals with prolonged QTc at higher heart rates using the QTcBZT formula. Our data suggest that the QTcBZT is not appropriate for heart rate correction in patients with LBBB and can lead to drastic overestimation of QTc prolongation at higher heart rates. We propose a modification of existing formulae to incorporate a better heart rate adjustment method.

We found that the formula proposed by Rautaharju et al showed a higher proportion of QTc prolongation in men than in women. This may be due to the larger constant subtracted from the QRS duration for women than men in contrast to the other approaches. Furthermore, the use of Rautaharju et al's formula identified a significant proportion of patients with QTc prolongation. Two possible reasons include the age differences in the population studied and the fact that Rautaharju et al based their formula on patients with LBBB, right bundle branch block (RBBB), and indeterminate ventricular conduction defect, and actually had almost twice as many cases of RBBB than LBBB.[7]

We also note that the 99th and 97.5th percentile of QTc have lower values in the QTcRBK correction than the QTcBZT correction and in women compared with men. However, based on large population data, women on average have longer QTc. The explanation is most likely the age dependency of the QTc.[13,19] In older ages, QTc increases in men more than it does in women. Potential explanations include the decline in serum estrogen levels after menopause, which is a contributor to longer QTc in premenopausal women. Our population had a mean age of 74.1 years, likely due to the fact that LBBB affects an older population; therefore, we do not see the longer QTc in women of older age that might be present in younger women.

A novel contribution in the present study is the determination of the 99th and 97.5th percentile for JTc intervals. For those who choose to use the JTc interval to eliminate the QTc in LBBB, we recommend the use of percentile cutoffs to establish normative values.

We examined the prevalence of potential QTc prolongation in a large population of cases with LBBB. The distribution of QTc_{LBBB} for the larger QTc values varied considerably between formulae. It is not possible to determine which one is the "correct" value in the absence of a precise standard. It is however important to recognize the variability and appreciate the implications when selecting the optimal formulae. Using the first percentile of the QT distribution to define abnormal, we established guidance for defining a prolonged QT and JT in LBBB.

Limitations

There are several limitations of the study that need to be discussed. First, the population size with intermittent LBBB was small. This reflects the rarity of the condition as the cases represented all those identified from a very large data set. Second, the transient nature of intermittent LBBB complexes may not be representative of patients with persistent LBBB and there should be caution in extrapolating the results to all patients with LBBB. We chose intermittent LBBB because it was a population that was not subjected to conditions such as acute ischemia or transaortic valve replacement that may change ventricular repolarization due to alterations in myocardial blood flow or loading conditions of the heart. Furthermore, the possibility of some ECGs being tachycardia-dependent bundle branch block as opposed to typical LBBB must be considered. However, there was no major difference in heart rate during LBBB conduction (80.5 ± 22.7 bpm) compared with the intrinsic conduction (74.4 ± 15.6 bpm). Third, we propose a new formula for assessment of QT in LBBB. It performed well, but it was being tested in the population of intermittent LBBB from which it was derived. Given the small sample size, the newly derived formula (QTc_{LBBB}NEW) may be regarded as a proof of concept requiring validation in other studies. Fourth, in both the large population and the small population data sets, information regarding other medical conditions and medications, which may influence the intrinsic QT interval, could not be collected. Fifth, intermittent LBBB confronts the issue of QT memory or hysteresis.[20] In other settings, one waits a long time to ensure that the influence of the previous QTc has been dissipated. This approach is not possible in intermittent LBBB, which is transient, and intervals need to be captured within the time frame of the ECG recording of its presence. Sixth, the true relationship between the QT interval and heart rate is not linear.[13] We used a linear approach, for ease of comparison between different formulae. Seventh, one of the issues with the calculation of QTc, as we have often pointed out, is the absence of a "gold standard" for the QTc against which various approaches can be compared.[13,14] The method that we used to define the QTc formula was the one with the least correlation with heart rate.[13] The problems with the absence of an accepted standard is circumvented by our approach to compare different formulae with respect to their correlation between the QTc in LBBB and normal intraventricular conduction or their labelling of QT prolongation in the large LBBB population. A challenge in adopting many of these formulae in a clinical setting, including our newly proposed formula, is that the relative complexity limits quick calculation by the bedside. However, the priority for diagnostic accuracy should supersede mathematical convenience. In the future, the availability of computerized calculations may assist the clinician. A few other points should be mentioned. It should be noted that the results may not be applicable to patients with RBBB, as our population was exclusively diagnosed with LBBB. The validity of this new formula in patients with inherited long QT syndrome plus LBBB should be the subject of further research.

Conclusions

In patients with complete LBBB, assessing the QT interval is challenging and involves appropriate heart rate correction and QRS correction in LBBB. We propose a new formula derived from using constants from the linear relationship between QTc in intrinsic conduction to QTc in LBBB. We furthermore propose a modification of all other existing formulae to incorporate an optimal heart rate correction approach. Formulae based on JT duration require appropriate heart rate correction to provide a good estimation of the intrinsic QT interval in the absence of LBBB. This approach is consistent with the findings in pacing-induced LBBB.[10] Importantly, using a large database of persons with LBBB, we established criteria based on 99th and 97.5th percentiles of various formulae to identify prolonged QTc in LBBB. Lastly, we conclude that although commonly used in the clinical setting, the Bazett formula should not be used in combination with LBBB correction formulae, as there is a significant heart rate dependency and weak relationship with intrinsic QTc, resulting in potential overestimation of QTc prolongation.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.02.014.