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A New Formula for Estimating the True QT Interval in Left Bundle Branch Block

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A New QT Formula for LBBB. ***Introduction:*** **QT prolongation is an independent risk factor for cardiac mortality. Left bundle branch block (LBBB) is more common in patients as they age. Widening of the QRS in LBBB causes false QT prolongation and thus makes true QT assessment difficult. We aimed to develop a simple formula to achieve a good estimate of the QT interval in the presence of LBBB.**

Methods and Results: **To determine the effect of QRS duration on the QT interval, QRS and QT were measured in sinus rhythm and during right ventricular apical pacing in 62 patients (age 55 ± 11 years, 60% male) undergoing electrophysiology studies. A QT formula for LBBB (QT-LBBB) was derived based on the effect of increased QRS_{LBBB} on QT_{LBBB}. The predictive accuracy of the QT-LBBB formula was then tested in 22 patients (age 66 ± 13 years, 64% male) with intermittent LBBB with comparisons to prior QT formulae and JT index. On average, the net increase in QRS_{LBBB} constituted 92% of the net increase in QT_{LBBB}. A new formula, QT-LBBB = QT_{LBBB} – (0.86 * QRS_{LBBB} – 71), which takes the net increase in QRS_{LBBB} into account, best predicted the QT interval with heart rate corrected QTc in the test set of LBBB ECGs when compared to the baseline value and prior formulae.**

Conclusion: **The QT-LBBB formula developed in this study best estimates the true QT interval in the presence of LBBB. It is simple and therefore can be easily utilized in clinical practice.** *(J Cardiovasc Electrophysiol, Vol. 28, pp. 684-689, June 2017)*

acquired long-QT syndrome, JT index, left bundle branch block, QT formula, QT interval

Introduction

It has been well recognized that a prolonged QT interval, either inherited or acquired, is an independent risk factor of cardiac mortality.[1] A complete left bundle branch block (LBBB) features a wide QRS (>120 ms), widened or "slurred" R wave on leads I and V_6, and prominent QS or rS in lead V_1.[2] The prevalence of LBBB increases with aging[3] and the population of older adults continues to grow in developed and developing countries. A wide QRS due to LBBB causes a false QT prolongation and therefore prevents accurate QT estimates. The presence of multiple risk factors for developing acquired long-QT syndrome (ALQTS) makes cardiovascular care of elderly patients challenging—especially when considering the potentially life-threatening nature of ALQTS.

Since QT interval is a function of heart rate (HR),[4] HR corrected QT interval (QTc) is used to determine whether the QT interval is normal or prolonged. Among QT formulae, Bazett's formula is by far the most widely adopted in clinical practice, but it does not take LBBB into consideration. Only a few formulae, such as the Rautaharju formula (QTc_R), the Bogossian formula (QT_B), and the JT index (JTI),[5-7] for instance, are designed to include bundle branch blocks in their calculations, but none of them have been widely adopted in clinical practice.

To address this unmet need, we hypothesized that the false QT prolongation is mostly caused by the widened QRS in LBBB. Thus, developing a simple formula that can remove the net increase in the QRS duration (ΔQRS) may help achieve a good estimate of the true QT interval in the presence of LBBB.

Methods

Study Design

Upon approval by the ethics committee of the First Affiliated Hospital of Dalian Medical University, a retrospective study of electrocardiogram (ECG) was conducted. First, we used a study set of ECGs (simulated LBBB) to determine the effects of widened QRS duration on the QT interval in the presence of LBBB. Next, we developed a QT formula for LBBB (QT-LBBB) by removing ΔQRS, the net

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increase in QRS, for estimating the true QT in LBBB. The study set ECGs were chosen from 62 patients (age 55 ± 11 years, 60% male) who were undergoing electrophysiology studies and had 12-lead ECG tracings available during right ventricular apical pacing (RVAP). We then applied the QT-LBBB formula to a test set of ECGs of 22 patients (age 66 ± 13 years, 64% male) with intermittent LBBB to determine its accuracy in measuring the true QT interval. Those who developed LBBB with dynamic ST-T and QT changes due to acute myocardial infarction were excluded. Other than 4 study subjects in the study set who had reduced left ventricular ejection fraction (44%, 48%, 30%, and 30%), ventricular function was normal in all other patients.

Study subjects served as self-controls for comparing the QRS duration and QT interval in sinus rhythm (SR) without LBBB and in the state of simulated LBBB (study set), or in SR with intermittent LBBB (test set). The clinical diagnoses of the study subjects were: atrioventricular nodal reentrant tachycardia (n = 20), atrioventricular reentrant tachycardia (n = 12), paroxysmal atrial fibrillation (n = 27), and atrial tachycardia (n = 3).

Furthermore, we compared the new QT-LBBB formula with several prior formulae designed for LBBB to determine which one could best predict the true QT interval in LBBB.

ECG Collection

Standard 12-lead ECGs, recorded by either MAC5500 or CardioLab (GE Healthcare, Little Chalfont, United Kingdom) at a paper speed of 25 mm/s and voltage of 10 mm/mV, were obtained from all subjects at SR and in the presence of LBBB (simulated or intermittent LBBB). In the study set, LBBB was created by RVAP, and ECG tracings were selected for a pacing cycle slightly faster than that of SR, but with full ventricular capture achieved (Fig. 1).

ECG Measurement and Parameters

The R-R interval, QRS duration, and QT interval were measured manually at baseline with normal QRS duration and in the presence of LBBB in each subject (Fig. 1). The ECG measurement was done by BHW and verified by a senior ECG investigator LZ. The measurements were performed in the same lead showing widest QRS duration in both SR with normal QRS duration (QRS ≤ 120 ms) and in the presence of complete LBBB. For QT measurement, the termination of the T wave was taken to be the point of maximal change in the slope as the T wave merges with the baseline.[2] QT and R-R cycle length were averaged from 2 to 3 consecutive beats. In the presence of sinus arrhythmia, the average R-R cycle length was obtained from consecutive beats over 10 seconds or from the HR. The U wave was

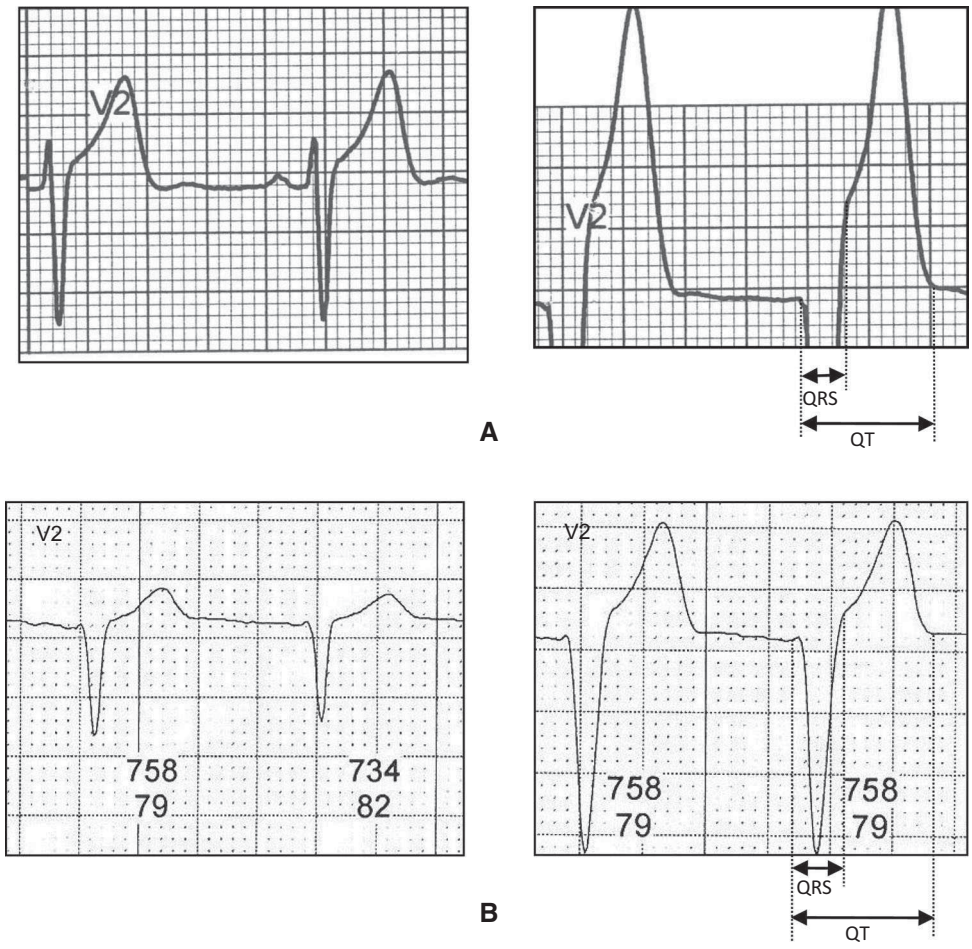

Figure 1. *Demonstration of QRS and QT measurement in the absence and presence of simulated or intermittent left bundle branch block (LBBB). Two ECG pairs with each from the same patient with the normal QRS under sinus rhythm and widened QRS by right ventricular apical pacing to achieve simulated LBBB (A) and intermittent LBBB (B), respectively. QRS duration and QT interval are taken in the same lead showing the widest QRS among 12 leads.*

excluded from QT measurement. The JT interval was obtained by subtracting the QRS duration from the QT interval. The QRS duration and QT interval at SR and in the presence of LBBB were expressed as QRS_{SR}, QRS_{LBBB}, QT_{SR}, and QT_{LBBB}, respectively.

For QT comparisons between groups, Bazett's formula was applied since the HR was in the physiologic range of 60–100 beats per minute in all the ECG tracings analyzed.

Developing a QT-LBBB Formula

As we hypothesized, the major contributor of the QT lengthening was the ΔQRS, a net increase in QRS duration caused by LBBB:

$$\Delta QRS = QRS_{LBBB} - QRS_{SR}$$

In reality, QRS_{SR} is not readily available in most patients with LBBB. The alternative approach to obtain the ΔQRS is to utilize a linear model based on the data distribution in the study set:

ΔQRS = a * QRS_{LBBB} – b, in which a and b are the constants in the model based on our hypothesis that ΔQRS has a linear relationship with QRS_{LBBB}. If so, removing ΔQRS from QT_{LBBB} may achieve a QT estimate that is likely much closer to the true QT interval in the presence of LBBB:

$$\text{QT-LBBB} = QT_{LBBB} - \Delta QRS$$

Since ΔQRS = a * QRS_{LBBB} – b, it can also be expressed as:

$$\text{QT-LBBB} = QT_{LBBB} - (a * QRS_{LBBB} - b)$$

Next, we tested this new formula in the test set ECGs with comparisons to 2 prior QT formulae and JTI, a JT index, to determine which one best predicts the true QT in the presence of LBBB:

(1) Rautaharju[5]: $QT_R = QT_{LBBB} - 155 * (RR_{LBBB} - 1) - 0.93 * (QRS_{LBBB} - 139) + k$, (k is – 22 ms for man, and – 34 ms for woman)
(2) Bogossian[6]: $QT_B = QT_{LBBB} - 48.5\% * QRS_{LBBB}$
(3) JT index[7]: JTI = JT * (HR + 100) / 518, (it indicates a delayed ventricular repolarization if JTI ≥ 112)

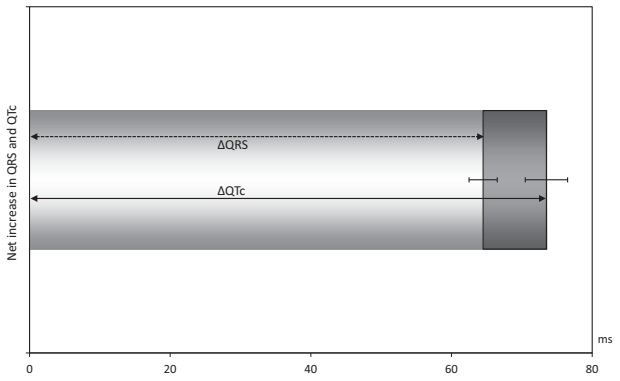

Figure 2. *The role that widened QRS played in the net increase in heart rate corrected QT interval (QTc) in the presence of LBBB. ΔQRS is the difference between QRS at LBBB and QRS at sinus rhythm (SR). ΔQTc is the difference between QTc at LBBB and QTc at SR. Among all study subjects with LBBB from both study and test sets, the net increase in QRS duration contributes 92% of the extra time in QTc.*

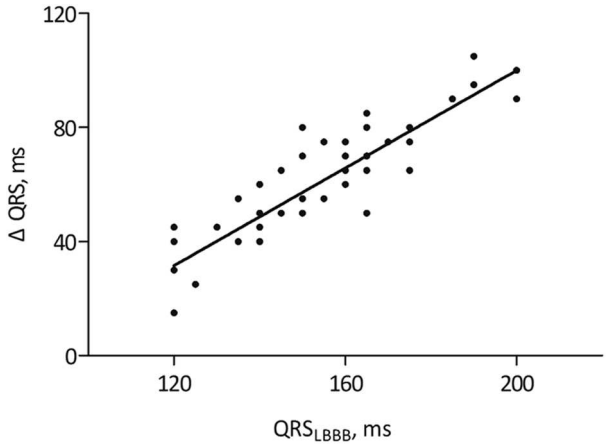

Figure 3. *A linear relationship between ΔQRS and QRS duration in the presence of LBBB. Since QRS at LBBB (QRS_{LBBB}) > QRS at sinus rhythm (QRS_{SR}), ΔQRS is the difference between QRS_{LBBB} and QRS_{SR}. The data distribution of ΔQRS and QRS_{LBBB} from study set ECGs reveals a linear relationship: $\Delta QRS = 0.86 * QRS_{LBBB} - 71$ ($R^2 = 0.801$, $P < 0.001$).*

Statistical Analysis

Continuous variables showing normal distributions were presented as mean ± SD, and paired *t* tests were used for group comparisons. The correlation between ΔQRS and QRS_{LBBB} was determined by linear regression analysis. Sensitivity and specificity plus Bland–Altman analysis were applied to determine which formula best predicted the true QT interval in the presence of LBBB. The statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA) and $P < 0.05$ (2-tailed) was considered statistically significant.

Results

The Role of Widened QRS in the False QT Prolongation of LBBB

Figure 1A and B illustrate the changes of QRS_{LBBB} and QT_{LBBB} in patients with simulated LBBB by RVAP and with intermittent LBBB, respectively. Table 1 demonstrates that QTc_{LBBB} is markedly prolonged. With a mean $QTc_{LBBB} > 500$ ms, the vast majority of LBBB subjects could have met the diagnostic criteria for long-QT syndrome.[8] However, the net increase in QRS_{LBBB} constitutes 92% of the extra time in QTc_{LBBB} (Fig. 2).

A Linear QT Formula

Since QRS duration is a fixed time period regardless of HR changes and ΔQRS is the primary contributor of artificially prolonged QT in the presence of LBBB, removing ΔQRS is essential to achieve the estimate of the true QT interval. Figure 3 reveals a linear relationship between ΔQRS and pacing-QRS in the presence of simulated LBBB: $\Delta QRS = 0.86 * QRS_{LBBB} - 71$ ($P < 0.001$, $R^2 = 0.801$) in the data of the study set ECGs. As such, a new formula to estimate the true QT interval in simulated LBBB is derived: $\text{QT-LBBB} = QT_{LBBB} - (0.86 * QRS_{LBBB} - 71)$.

The QT Predictive Accuracy

Although ΔQRS contributed 92% of QTc prolongation in LBBB, the remaining 8% of the net QT increase

TABLE 1

Changes of QRS Duration and QT Interval Caused by Both Simulated and Intermittent LBBB

	Study Set ECGs		Test Set ECGs	
	Baseline	**Simulated LBBB**	**Baseline**	**Intermittent LBBB**
LQTS (%)†	10% (6/62)	92% (57/62)	23% (5/22)	86% (19/22)
HR, bpm	72 ± 10	79 ± 10	74 ± 14	79 ± 20
QRS*, ms	94 ± 9	156 ± 20	92 ± 10	152 ± 16
QTc*, ms	444 ± 21	516 ± 32	441 ± 34	510 ± 39
JTc, ms	350 ± 23	360 ± 27	350 ± 31	359 ± 33

†QTc values met the diagnosis of LQTS[8]: QTc ≥ 470 ms for male; QTc ≥ 480 ms for female.
*P < 0.001 baseline versus LBBB in each group. JTc: HR-corrected JT interval by Bazett's.

TABLE 2

Baseline and Estimated QTc Derived by 3 Formulae in the Test Set ECGs

	QTc, ms	**P Value**
QTc_{SR}	441 ± 34	0.758
QTc-E†	443 ± 32	
QTc-LBBB	443 ± 29	0.663
QTc_R	445 ± 24	0.575
QTc_B	427 ± 32	<0.0001

QTc_{SR}: $QTc_{\_Bazett}$ for baseline QT interval with narrow QRS (QRSD ≤ 120 ms).
QTc-E: $QTc_{\_Bazett}$ for QT interval with ΔQRS removed from wide QRS of LBBB.
QTc-LBBB: $QTc_{\_Bazett}$ for the new linear formula derived QT-LBBB.
QTc_R: HR-corrected QT_R using Rautaharju formula.[5]
QTc_B: HR-corrected QT_B using Bazett's formula.[6]
†Used for group comparisons.

TABLE 3

The Predictive Accuracy of QTc-LBBB, QTc_R, QTc_B, and JTI in Identifying Delayed Ventricular Repolarization†

	QTc-LBBB	**QTc_R**	**QTc_B**	**JTI**
Sensitivity	88%	73%	54%	27%
Specificity	98%	84%	98%	100%

†Delayed ventricular repolarization is defined by: (1) QTc ≥ 450 ms for male and QTc ≥ 460 ms for female; or (2) JTI ≥ 112. QTc-E is used as the reference to determine the predictive accuracy.

(Fig. 2) may be attributed to the altered repolarization sequence caused by the LBBB itself. Taking the effect of LBBB on ventricular repolarization into consideration, we used the estimated QTc (QTc-E) in LBBB with ΔQRS removal as the reference level to determine the predictive accuracy of QT formulae (Tables 2 and 3). Table 2 shows that the QTc values are highly agreeable between QTcSR and QTc-E, followed by QTc derived from the QT-LBBB formula and QTc_R estimated by the Rautaharju formula. In contrast, the Bogossian formula overcorrects the QTc and makes it too short (427 ± 32 ms vs. 444 ± 26 ms, P < 0.0001). Table 3 demonstrates that the QTc derived from the QT-LBBB formula best predicts the true QT interval in the presence of LBBB. Further evaluation using Bland–Altman curves revealed that the 95% confidence interval is narrower in the QT-LBBB formula than that of the Rautaharju formula (Fig. 4A and B), implying that QT-LBBB is superior.

Although HR-adjusted JT interval does not change much before and after developing LBBB (Table 1), Table 3 shows that JT index is the least sensitive in identifying delayed repolarization in the presence of LBBB. The sensitivity of the JT index in predicting delayed repolarization decreases with an increasing QRSD (Table 4).

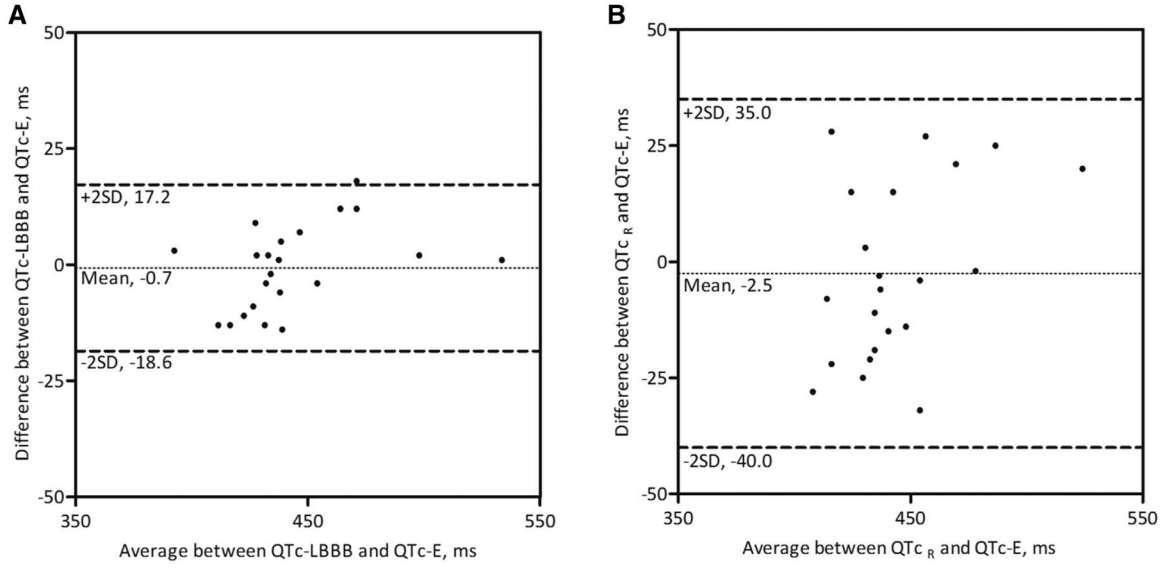

Figure 4. *Bland–Altman analyses between QTc-E and QTc using different formulae. QTc-E: $QTc_{\_Bazett}$ for QT interval with ΔQRS removed from wide QRS of LBBB. QTc-LBBB: heart rate corrected QT interval using the new formula and Bazett's formula. QTc_R: heart rate corrected QT interval using Rautaharju formula. QTc-E was used as a reference to determine how close to the truth when a QT formula is applied for estimating QT in the presence of LBBB. Bland–Altman analyses for comparing QTc-LBBB and QTc-E (A), as well as QTc_R and QTc-E (B) in the study set. The 95% CI of the difference between QTc-E and QTc-LBBB is narrower in (A) than that using QTc_R in (B), implying the QT estimate derived from QT-LBBB formula is closer to the true QT value in the presence of LBBB.*

TABLE 4
The Predictive Accuracy of JT Index in Identifying Delayed Ventricular Repolarization in Patients With Narrow and Wide QRS

QRSD, ms	No of Patients	Sensitivity	Specificity
≤ 120	84	50%	98%
121–174	71	30%	100%
≥ 175	13	0	100%

Discussion

This study demonstrates that ΔQRS, a net increase in QRS, is the primary contributor to a falsely prolonged QT interval in patients with LBBB (Figs. 1 and 2, Table 1). This finding is consistent with prior studies.[6,9] On average, a widened QRS contributed 62 ms to the QT interval in LBBB (Fig. 2), making QTc greater than 500 ms in most patients with LBBB in our study cohort (Table 1). A falsely prolonged QT is the main reason that clinicians simply ignore QT prolongation in their patients with LBBB. As such, those with a true QT prolongation and bearing high risks of arrhythmic sudden death are left unprotected only because of the presence of LBBB. In this study, we developed a simple formula $QT\text{-}LBBB = QT_{LBBB} - (0.86 * QRS_{LBBB} - 71)$ based on the linear relationship between ΔQRS and QRS_{LBBB} in study set ECGs. Furthermore, we tested the QT predictive accuracy in test set ECGs. It is proven that applying the QT-LBBB formula can remove the effects of ΔQRS and therefore provide a reliable prediction of the true QT interval in LBBB. This approach, if adopted in clinical practice, will address the unmet need of identifying high-risk patients with true ALQTS from those with artificial QT prolongation due to LBBB.

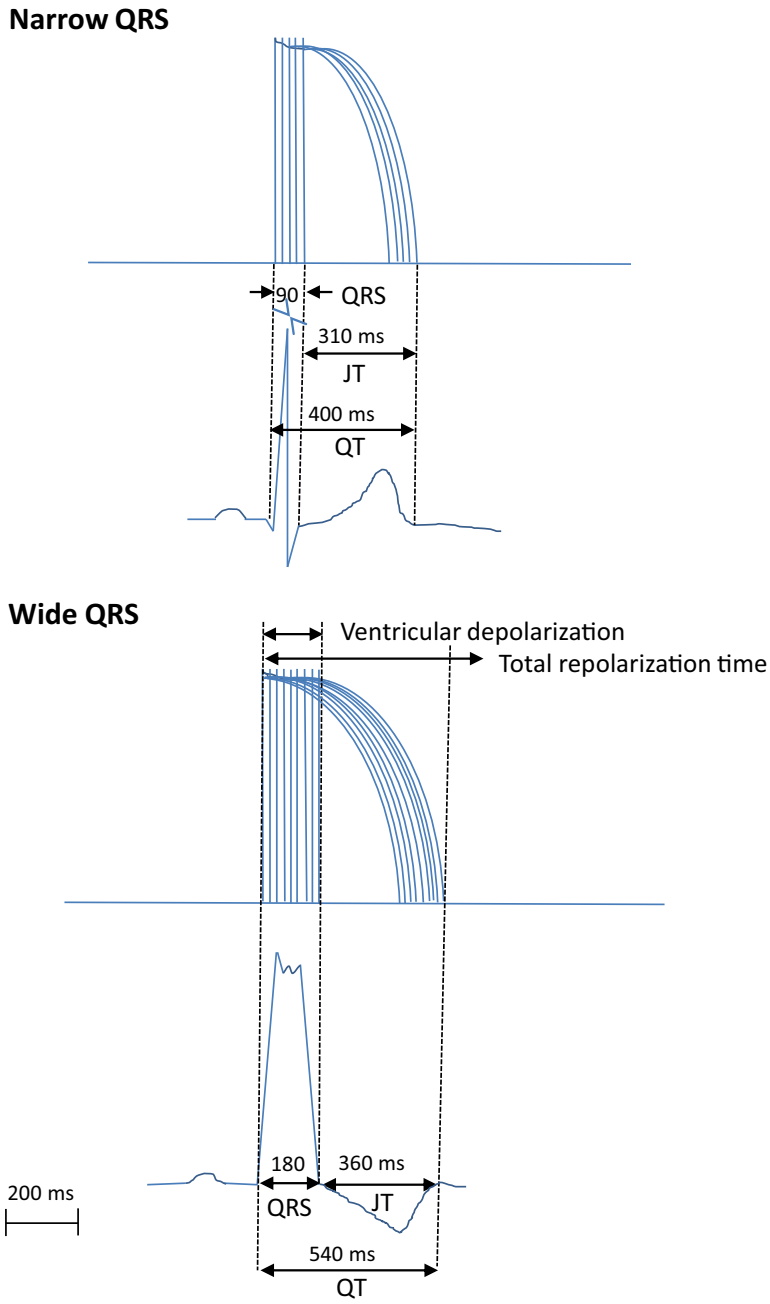

Figure 5. *JT interval underestimates the total repolarization time in the presence of wide QRS. This diagram demonstrates that repolarization starts immediately after the depolarization of the first ventricular cardiomyocyte. The top panel demonstrates that under normal condition, ventricular depolarization is very brief, thus QRS is narrow (QRSD ≤ 120 ms). As such, JT interval can reflect ventricular repolarization on large. In the lower panel, a significant portion of repolarization is elapsed along with delayed ventricular conduction showing as a wide QRS (QRSD > 120 ms). Therefore, JT can underestimate the total time of repolarization in the presence of wide QRS. [Color figure can be viewed at wileyonlinelibrary.com]*

Previously, Bogossian and Banker[6,10] used right ventricular (RV) pacing to achieve simulated LBBB for QT formula studies. Our study confirms that this method is indeed useful. There are no significant differences in QRS and QT measures between simulated LBBB by pacing and intermittent LBBB (Table 1). Unlike most of the prior studies, we tested the QT-LBBB formula derived from simulated LBBB in patients with intermittent LBBB and found that LBBB-related ECG measurements in both conditions are highly comparable with no statistical differences shown (Table 1).

The Bogossian formula[6] was designed to remove the net increase in the QT interval caused by LBBB from measurements of the QT in patients with LBBB. However, we found it actually overcorrected the QT interval, making QT shorter than it should be.

On the other hand, we found that the Rautaharju formula can provide a good QT estimate (Table 2), though it is much more complicated. Further analysis by Bland–Altman curves revealed that QT-LBBB formula developed in this study is better than the Rautaharju formula for measuring the true QT interval in LBBB.

The JT interval has been used to measure repolarization time in the presence of a wide QRS such as intraventricular conduction delay (IVCD).[9] Unfortunately, in clinical practice, most physicians are unfamiliar with the JT interval in terms of its normal value, gender differences, and changes under various pathologic conditions. Our study finds that JT index is the least sensitive in detecting LBBB subjects with a true QT prolongation when compared to the QT formulae tested. The sensitivity of JT index in identifying patients with delayed ventricular repolarization decreases dramatically with increasing QRSD. Table 4 reveals that the JT index loses its predictive power completely when the QRSD $\geq$ 175 ms. This is because ventricular repolarization starts long before the J point in the presence of a wide QRS (Fig. 5). Using the JT interval can artificially shorten the repolarization time and, therefore, it is ineffective in predicting delayed repolarization in patients with a very wide QRS.

Strengths and Limitations

Stimulated LBBB was applied to develop a QT formula for LBBB in a previous study.[6] Our investigation used intermittent LBBB in patients with their baseline ECG results available for self-control and for comparisons with prior formulae. Moreover, the new QT formula is easily applicable to HR-corrected formulae including Bazett's. Nonetheless, the QT-LBBB formula is developed and tested in small sample studies. Larger sample size-based validation is warranted in the future.

Conclusion

A new QT formula for LBBB was developed: QT-LBBB $= QT_{LBBB} - (0.86 * QRS_{LBBB} - 71)$. This formula best estimates the true QT interval in the presence of LBBB. It is simple and therefore can be easily utilized in clinical settings to protect patients from potentially deadly arrhythmias. The JT index, on the other hand, failed to identify delayed repolarization in patients with a very wide QRS duration.

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