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Editorial

QT-Interval Assessment in Left Bundle Branch Block: Deciphering Normal Within Abnormal

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See article by Tang and Rabkin, pages 855–865 of this issue.

The electrocardiographic QT interval spans ventricular depolarization and repolarization and extreme values are associated with an increased risk of malignant ventricular arrhythmias.[1,2] A pathologic delay in ventricular repolarization leads to abnormal QT prolongation and susceptibility to syncope and sudden death secondary to torsades de pointes. Proper identification of individuals with pathologic QT prolongation, which may be secondary to genetic mutations, medications, and/or electrolyte abnormalities, is critical to preventing potentially catastrophic cardiac events.[3]

The QT interval is also influenced by a variety of physiological factors, including age, sex, and heart rate.[4] The prominent impact of heart rate on the QT interval requires that a correction factor be applied to its absolute value to facilitate its interpretation. Prior QT correction methods have attempted to fit the QT-heart rate relationship as a function of a mathematical formula; examples include Bazett, Framingham, and Fredericia.[5] The Bazett QT-interval correction is the most widely used correction method in clinical practice and adjusts the QT through its division by the square root of the R-R interval. Evaluation of QTc values measured from the general population has led to upper limits of normal for males and females being proposed that variably correspond to 2 (95^{th} percentile) and 3 (99^{th} percentile) standard deviations above the mean.[6]

Although engrained in clinical practice, none of the correction factors serve as a perfect model for the QT-heart rate relationship, as all under- or overcorrect at certain heart rate ranges. Recent work by Rabkin et al.[7]took an alternative approach to QT-heart rate correction and leveraged the use of splines, which are mathematical functions defined piecewise by polynomials. In contrast to the traditional approach of attempting to fit a biological relationship with a predefined mathematical formula, the behaviour of a spline is instead defined by the data itself, which often lends itself to a much higher fidelity fit. This is particularly useful when fitting a relationship that changes according to range, as observed for the QT interval along the range of heart rates. Using electrocardiogram (ECG) data derived from a large population-based cohort, Rabkin et al. developed a spline function that eliminated evidence of the QT-heart rate relationship, suggesting that they had succeeded in effectively modelling its intricate behaviour and pointing to the potential of the method to provide an ideal correction, though a further large-scale validation study would be desirable.

Although extensive investigations have been devoted to QT-heart rate adjustment in the context of sinus rhythm and a normal QRS interval, there is relatively little to guide practitioners for QT-interval assessment in pathologic states, such as conduction system disease and atrial fibrillation. QT prolongation secondary to QRS prolongation per se is not anticipated to impact the risk of torsades; however, it remains unclear how to appropriately adjust for such a change. On first blush, excluding the QRS and focusing on the JT interval seems attractive; however, such an approach is suboptimal given that repolarization initiates before the completion of depolarization, which is further exaggerated in conduction system disease. A series of approaches have been proposed for assessing the QT interval in the context of left bundle branch block (LBBB) that have generally aimed to predict the QT interval when the QRS was normal.[8-12] Development of these methodologies required the availability of within-subject comparative measures during a narrow QRS, examples being individuals with normal QRS values who undergo right ventricular apical pacing during an invasive electrophysiology study and those with new-onset LBBB and a recent ECG with a normal QRS value. These efforts have led to the development of a series of formulae to correct the QT with LBBB; however, the relatively small size of the derivation cohorts has led to lingering uncertainty regarding their validity and generalizability and none, to date, has gained widespread acceptance in clinical practice.

In this issue of the *Canadian Journal of Cardiology*, Tang and Rabkin[13] evaluated 17 individuals possessing intermittent LBBB recorded on a single ECG, to derive a linear regression equation that predicts the QT interval in the absence of

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LBBB. Their derived formula, $QTc_{LBBB}New = 0.945*QTcRabkin(RBK)_{LBBB} - 26$, includes the LBBB QT value after adjustment for heart rate using their spline-based correction formula. When compared with the other 5 equations previously proposed for QT adjustment in the context of LBBB[8-12] using these same 17 individuals, their formula provided the highest degree of correlation for the QT interval in the absence of LBBB ($r = 0.794$; range of other 5 formulae: 0.611-0.788); however, this finding should be viewed with caution given that their equation was derived using this dataset.

After assessment of their novel formula as a predictor of the QT interval in the absence of LBBB, the authors subsequently evaluated the QT-heart rate relationship in their 17 patients after the 6 LBBB QT correction formulae were applied. Consistent with their prior findings in individuals with a normal QRS complex, incorporation of their spline correction formula into their LBBB QT correction formula eliminated the impact of heart rate on QT. The Rautaharju et al.[10] formula, which also includes a correction factor for heart rate, exhibited minimal association with heart rate after its application, whereas the adjusted QT values generated from the remaining 4 formulae, which do not contain QT-heart rate correction factors, perhaps not surprisingly continued to exhibit prominent distortion with heart rate.

The performance of the 6 formulae was subsequently evaluated in a cohort of 2610 individuals (average age 75 years and 47% male) with LBBB on ECG. The derived QT values from the 4 formulae without heart rate correction factors were adjusted using both the Bazett and the Rabkin spline correction methods. The proportion of individuals with QTc prolongation, defined as > 450 and > 460 in males and females, respectively, demonstrated a wide range, extending to $> 20\%$ among males using the Bazett corrected Yankelson[12] adjusted QT interval to $< 1\%$ among females using the Rabkin corrected Bogossian[8] adjusted QT interval. Heart rate adjustment using the Rabkin spline correction formula was invariably associated with a lower proportion of individuals with QT prolongation relative to the Bazett correction method.

Tang and Rabkin should be congratulated for tackling this important clinical question and for leveraging use of their new spline QT-heart rate correction formula for this endeavour. Appropriate interpretation of the QT interval in LBBB is of critical importance that extends beyond facilitating an LQTS diagnosis, particularly given that elderly patients with LBBB are often exposed to QT-prolonging drugs. In addition to undesired off-target QT prolongation, a significant proportion of patients with LBBB have atrial and ventricular arrhythmias that may benefit from potassium channel blockade. Proper interpretation of the QT interval in LBBB not only allows for identification of at-risk patients, but also helps ensure that patients are not unnecessarily deprived of efficacious therapies.

Although the study constitutes an important attempt to improve our assessment of the QT interval in the context of LBBB, it should be noted that the primary equation generated from this study ($QTc_{LBBB}New = 0.945*QTcRBK_{LBBB} - 26$) was gleaned from 17 patients. Although patients with intermittent LBBB on a single ECG tracing are rare, and hence a large cohort typical of epidemiologic studies may not be feasible, the small sample size of this derivation cohort inevitably leads to some uncertainty regarding the validity of the novel formula, particularly given the lack of a validation cohort. In addition, although their formula yielded the highest degree of correlation with the QT interval in the absence of LBBB among the 6 formulae evaluated, this result should be viewed with caution owing to the formula having been calibrated on this dataset.

Although the newly derived Tang/Rabkin QT-correction formula for LBBB will require further validation, the current investigation serves to further emphasize the value of their previously reported spline QT-heart rate correction method. These findings provide further support for considering widespread adoption of their spline correction method in preference to the Bazett correction formula, which remains the primary clinical standard despite its often cited limitations.[5]

Although it is reasonable to assume that creating agreement with QT values present before the onset of LBBB serves as an ideal correction method, it should be noted that abnormal depolarization may impact repolarization, a concept that is illustrated by T-wave memory.[14] Beyond a correction formula to fit with the QT interval in the absence of LBBB, definitively concluding an upper limit of safety for the QT interval in LBBB may require a prospective cohort of individuals followed for arrhythmic outcomes. In this context, corrected QT values generated by each formula could be compared for their ability to identify individuals at risk for arrhythmic events.

In summary, Tang and Rabkin have developed a novel approach to QT-interval assessment in the context of LBBB. Although their new formula appears promising, further evaluation will be necessary before definitive conclusions can be drawn regarding its merit. Ultimately, delineation of the range of safe QT values in the setting of LBBB may require a study that combines evaluation of the proposed correction formulae with a prospective cohort of individuals with LBBB followed for arrhythmic outcomes.

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Disclosures

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