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Assessment of QT interval in ventricular paced rhythm: Derivation of a novel formula

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ABSTRACT

Objective: The objective of the study was to determine the optimal formula to estimate QT interval adjusting for QRS prolongation during right ventricular (RV) pacing.

Methods: This observational study included individuals ($n = 43$) with a newly implanted permanent ventricular pacemaker, who had a narrow QRS complex before pacemaker insertion. QT interval with RV pacing was related to QT interval before pacemaker implantation. The validation cohort ($n = 442$) had permanent RV pacing in DDD mode.

Results: A new QTc formula was derived utilizing the constants from the relationship between the spline heart rate QT correction (QTcRBK) before and after pacing; specifically, $QTcRBK_{PACED} = QTcRBK \times 0.86$. The JT interval from paced complexes was highly heart rate (HR) dependent and was not accurate for QT assessment. Previous, QTc formula for paced complexes were not highly correlated with QT before pacing unless a robust HR correction is added. Formulae subtracting a fixed amount from QTc_{PACED} markedly overestimated QTc before pacing.

Conclusion: We proposed a new, simple formula for QT estimation in RV pacing. JT interval in paced complexes is highly HR dependent and is not accurate for QT assessment. The new spline approach for HR correction for the QT, once incorporated into some previously proposed formulae, blunts HR dependency and improves prediction of QT before pacing. $QTcRBK_{PACED}$*0.86 and $QTcRBK_{PACED}$ – (QRS*0.5) demonstrated the best balance of relatively strong correlation to QTc before pacing and accurate QTc prolongation identification. Abnormal QT for $QTcRBK_{PACED}$*0.86 as defined by the 97.5th and 99th percentile are 469 and 479 ms respectively.

Introduction

Evaluation of the QT interval on the surface ECG, a measure of ventricular repolarization, has proven to be of considerable value as a predictor of potentially fatal arrhythmias, in the presence of drug-induced cardiac toxicity and other risk factors for sudden death [1–4]. Accurate assessment of QT interval in patients with ventricular pacemakers has been a difficult task for a number of reasons. Ventricular pacing widens QRS duration, so that the QT interval encompasses a longer depolarization time. Ventricular pacing also alters the spatial-temporal pathways for depolarization that may impact repolarization. With these caveats, there have been several attempts at estimating the QT interval in the presence of ventricular pacing. These methods essentially either subtract a fixed amount [5–7], subtract a proportion of the QRS duration from the QT interval in order to adjust for the contribution of the pacing-induced increased QRS duration [8,9], or attempt to modify QT interval measurement [10]. The approach of subtracting 50 ms from the measured QT value has been supported by a small prospective observational study using the Bazett QT correction formula (QTcBZT) to adjust for heart rate dependency [5]. Frommeyer et al. used a formula developed from assessment of the native QT interval in patients with left bundle branch block [9] by subtracting 50% of the QRS duration and correcting for heart rate with QTcBZT [11]. This 'Bogossian' formula was reported to be a reliable tool for QT interval estimation in patients with heart failure and right ventricular pacing [9]. However, the investigators cautioned that a 25 ms overestimation of the QT interval should be expected with this formula [9]. A recent algorithm using the interval from the onset of the Q-wave to the peak of the T-wave (QTp) during ventricular pacing was advanced [10]. Unfortunately, the QTp is not readily available in most clinical settings.

The necessity to correct or adjust for the heart rate dependency of the QT interval has long been appreciated. Although the problems with the Bazett formula (QTcBZT) are recognized [12], it is in widespread usage to adjust for heart rate dependency of the QT interval. Whether this formula is useful in the setting of pacing is open to question. The diverse approaches and lack of specific guidelines in adjusting for QRS duration [13] produces inconsistent estimation of the QT interval in ventricular pacing, which is further compounded by variability of

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the QRS duration due to different pathways of depolarization, the impact of factors governing repolarization, and the continuing issue of optimally adjusting the QT interval for heart rate dependency. The existence of a number of different formulae suggests the absence of a single universally-accepted formula, as well as the need to assess each of these in a different data set, separate from the originally studied population.

The objectives of this study were (i) to compare the QT interval in patients before and after the insertion of ventricular pacemaker in order to develop a new formula for QT interval assessment in RV pacing and to compare it to previous approaches; (ii) to determine whether newer QT correction formulae improve the ability to estimate QTc in paced complexes.

Methods

Patient population

Comparison of QT Interval before and after pacemaker implantation

Individuals who had the new insertion of a ventricular pacemaker at Vancouver General Hospital between January 1, 2014 and May 31, 2018 were evaluated. The study, inclusive of anonymous data collection, was approved by our institution's clinical research ethics committee, and excluded collection of data on clinical variables and medications administered. The study included all patients with a new pacemaker implant within that time frame who fulfilled the entry criteria. Patient selection criteria required (i) 12-lead electrocardiograms (ECGs) on Muse™ version 9.0 SP6 (General Electric, Boston) before and within one week after pacemaker insertion; (ii) ECGs prior to implantation with a narrow QRS complex duration (<120 ms); (iii) ECGs post-implantation consistent with ventricular pacing. The exclusion criteria were: (i) ECGs prior to pacemaker insertion with wide QRS duration (≥120 ms) (ii) ECGs prior to or after pacemaker insertion with low T-wave amplitude such that the QT interval could not be measured.

Evaluation of formulae in a large 'validation' pacemaker population

The study population consisted of individuals who were identified in the ECG (Muse™) database with the diagnosis of electronic pacemaker in DDD mode at Vancouver General Hospital between January 1, 2008 and July 13, 2018. The exclusion criteria were: (i) ECGs with ventricular rates <35 bpm or >155 bpm, as the published heart rate correction formula best applies to heart rates between 35 and 155 bpm (exclusion of three patients), (ii) ECGs where the QT interval could not be measured (exclusion of three patients), (iii) ECGs where the Muse™ program marked as "poor quality" (exclusion of five patients). Patient age, gender, QRS duration, QT interval, and ventricular rate were collected. The study was approved by our IRB.

Electrocardiogram measurements

12-lead electrocardiograms were recorded digitally on Muse™ version 9.0 SP6 (General Electric, Boston) and had been previously confirmed by a reading cardiologist. The ECGs were viewed at 25 mm/s paper speed, digitally magnified, and in rhythm strip mode. Digital calipers were used to measure the RR interval and heart rate, and then calipers were used in the "march out" function of Muse™ to assess rhythm regularity. The QRS duration and QT interval (uncorrected) were measured. This was completed by one observer (JT) to reduce inter-individual variability. Problems with measurement were resolved by another observer (SWR) blinded to the first observer's measurement. All 12 leads were visually inspected for the lead where the QT interval was most readily measured, which were usually precordial leads V2 or V3. The QT interval was measured at this lead, and then compared to other leads to ensure that the longest QT interval of all leads was recorded as specified in guidelines [13].

The RR interval was measured as the distance between the peak of the R-wave and the peak of the following R-wave in the same lead. The QRS duration was determined as the interval between the initial QRS deflection and the J point, which was measured by digital calipers and duration was calculated by Muse™. The QT interval was determined by the threshold method which measures interval from the initial QRS depolarization to the end of the T wave where it returns to the isoelectric line. The threshold method was selected because it was less ambiguous in the presence of electronic pacemaker-associated changes in ST-T waves. If the end of the T-wave was ambiguous, the tangent method (drawing a tangent line from the steepest descending slope of the T-wave, where the end of the T-wave was determined as the point at which the slope intersects the isoelectric line) was utilized. Both methods have a high validity [14]. The peak of the T wave was defined visually and the interval from the onset of the Q wave to the peak of the T wave was defined as QT-peak (QTp).

Derivation of a new formula

In order to derive a new formula, a model with relative simple utility was selected. The new formula was derived from the mean of the ratio of the QTcRBK before pacemaker implant and QTcRBK in RV pacing in the population with new pacemaker implantations.

Models or formulae for assessment of QT interval in ventricular-paced ECGs

QTcBZT was chosen because it is the QTc in most widespread usage and has been used by others to adjust for heart rate in QT calculation in RV pacing [5]. The second QTc formula was the new spline formula (QTcRBK) that was developed from about 13,600 individuals in the National Health and Nutritional Survey (NHANES) US population study and was found to be relatively independent of heart rate and superior to other QTc formulae [15]. It has been found to be relatively independent of heart rate during acute rapid heart rate pacing [16].

We used the nomenclature for QTc abbreviations which specified the first three syllables of the first authors' name [17,18]. One formula incorporated the Framingham heart rate correction formula (QTcFRM) [6], and was maintained herein.

Each of the proposed adjustments for the paced QRS was referred to depending on the QTc adjustment studied. The following is a demonstration of nomenclature and abbreviations.

Table 1
Patient characteristics of the two cohorts.

Derivative cohort ($n = 43$)		
Sex	M = 58.1%; F = 41.9%	
Age	74.7 ± 12.1 years	
Days apart between ECGs	1.9 ± 2.1 days	
	Intrinsic	**Paced**
Heart rate	58.8 ± 16.4 bpm	72.7 ± 12.5 bpm
QRS duration	89.7 ± 11.6 ms	164.6 ± 20.6 ms
QT interval	433.1 ± 55.2 ms	461.6 ± 31.7 ms
QTcBZT	418.4 ± 28.5 ms	504.5 ± 33.2 ms
QTcRBK	410.5 ± 23.4 ms	478.7 ± 24.6 ms
Validation cohort ($n = 442$)		
Sex		M = 64.4%; F = 35.6%
Age		75.5 ± 13.2 years
Heart rate		75.9 ± 14.8 bpm
QRS duration		160.8 ± 27.7 ms
QT interval		456.5 ± 47.7 ms
QTcBZT		507.5 ± 41.2 ms
QTcRBK		479.5 ± 35.0 ms

1. **$QTcBZT_{RVPACED}$CHA**: QTc = QTc(BZT) – 50 ms proposed by Chakravarty et al. [5], abbreviated as $QTcBZT_{PACED}$ – 50.
2. **$QTcBZT_{RVPACED}$ROW**: QTc = QT – (QRS - 120 ms), followed by heart rate correction with QTc(BZT) proposed by Rowland and Moore [7], abbreviated as $QTcBZT_{PACED}$ – (QRS-120).
3. **$QTcFRM_{RVPACED}$CHI**: QTc = QTcFRM – 43 ms proposed by Chiladakis et al. [6], abbreviated as $QTcFRM_{PACED}$ – 43.
4. **$QTcBZT_{RVPACED}$BOG**: QTc = QT – (50% × QRS), followed by heart rate correction with QTcBZT proposed by Bogossian et al. [9,11], abbreviated as $QTcBZT_{PACED}$ – (QRS*0.5).
5. **QT_{PACED} SRI**: QT = 0.86 × QTp (ms) – 1.21 × heart rate (beats/min) + 205 (uncorrected for heart rate) proposed by Sriwattanakomen et al. [10], abbreviated as QT_{PACED}SRI.
6. **$QT_{RVPACED}$NEW**: QTc = QTcRBK × 0.86 abbreviated as $QTcRBK_{PACED}$*0.86

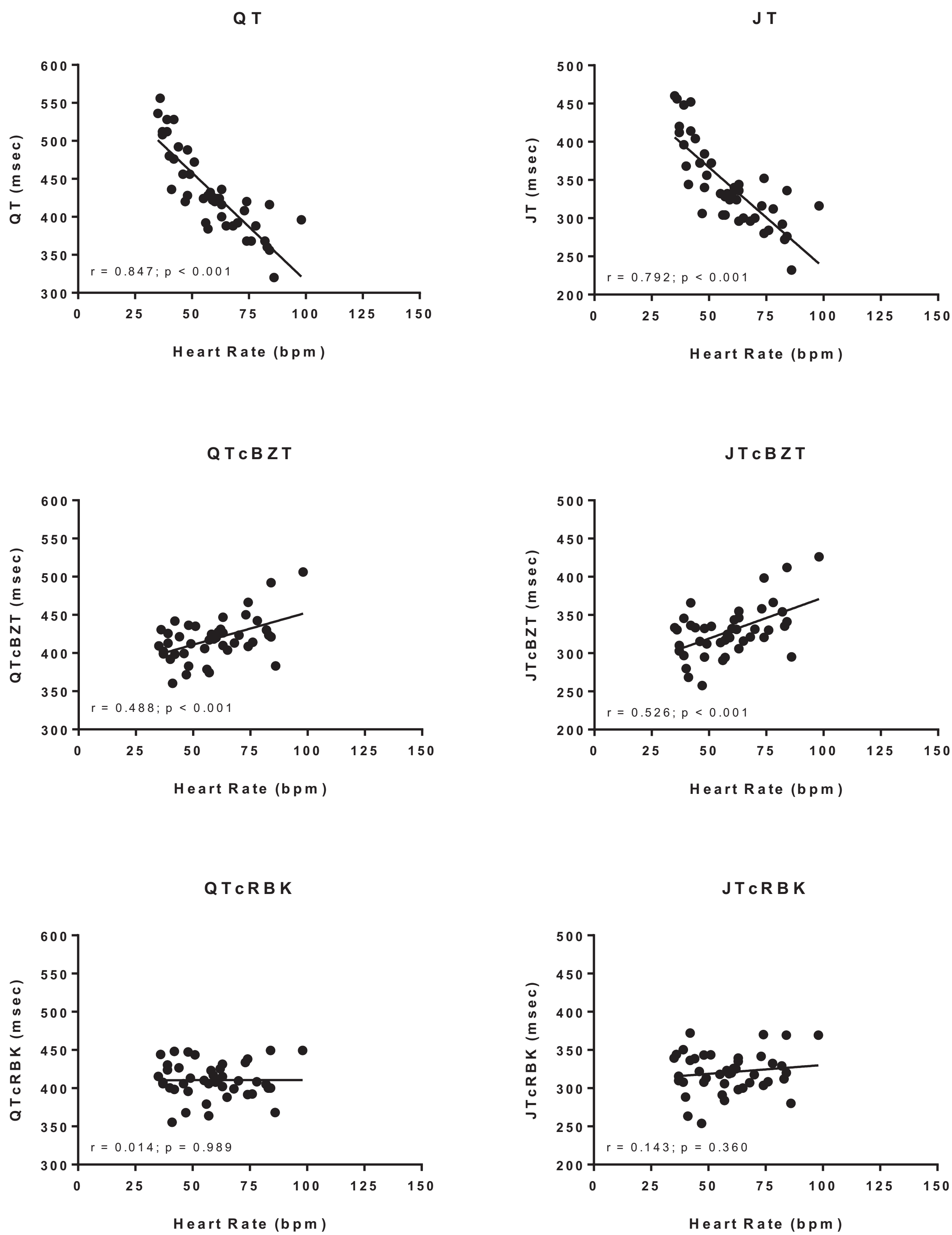

Fig. 1. Shows the relationship between heart rate and QT on the left panels or JT interval on the right panels in the ECG before pacemaker insertion. The upper panel is for the uncorrected QT (upper left) or JT (upper right). The QT corrected by Bazett formula is shown in the middle panels (QTcBZT middle left and JTcBZT middle right). The lower panel is the QT interval corrected by the spline formula (QTcRBK lower left and JTcRBK lower right).

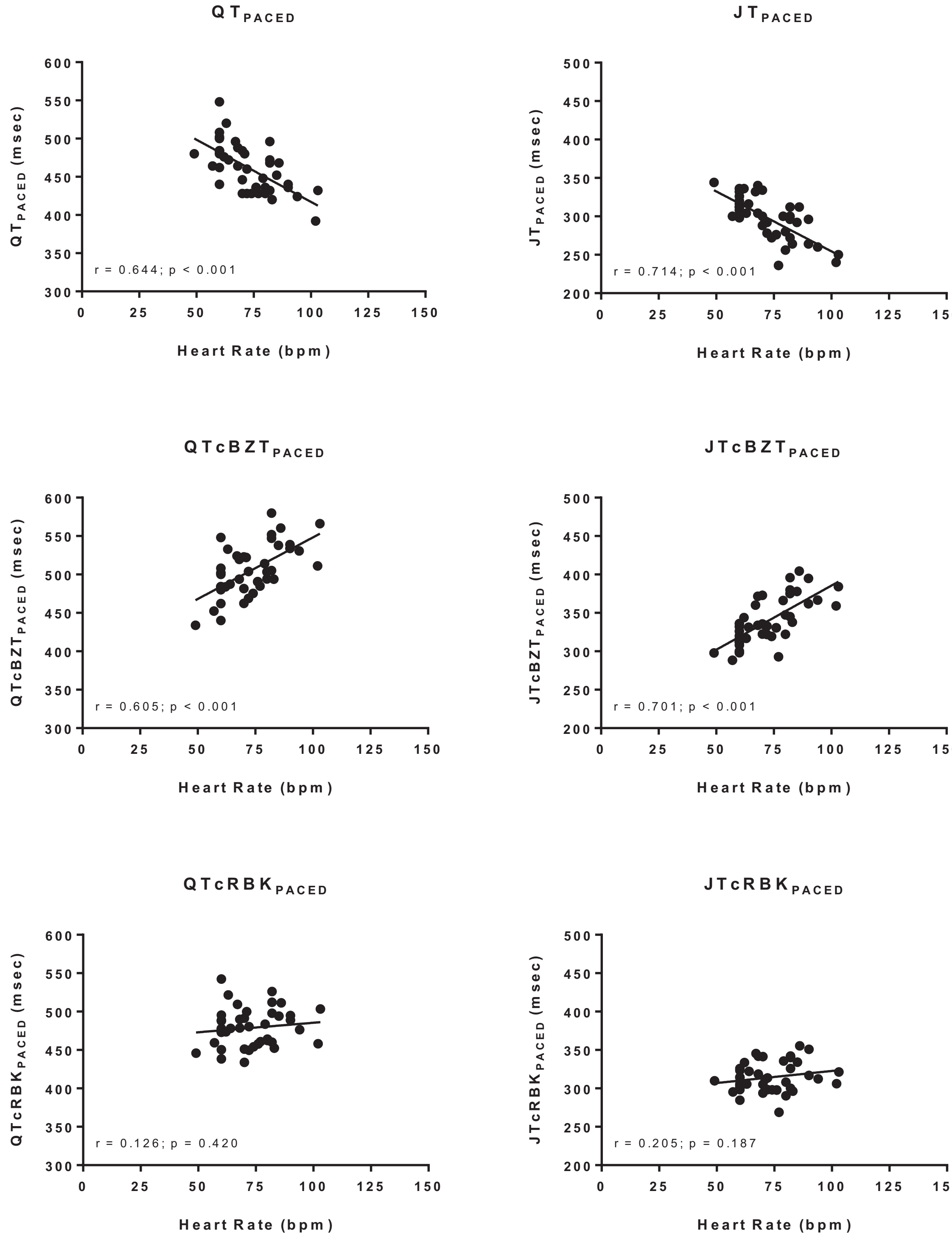

Fig. 2. Shows the relationship between heart rate and QT or JT interval in paced rhythm as well as for the different QTc formulae.

This QTc formula was derived from the mean of the ratio (0.86) between QTcRBK before pacemaker implant and QTcRBK in RV pacing in the population with new pacemaker implantations.

Statistical analysis

Data are presented as the mean and one SD. Data analysis used correlation analysis. The two-tailed McNemar's Test was used to exam for significant differences between the various approaches in the identification of QTc prolongation. The 5% level of significance ($p < 0.05$) was selected as representing a statistically significant difference.

Results

The study population consists of 43 patients (mean age 74.7 ± 12.1 (SD), 58.1% male) (Table 1). The heart rate-QT relationship prior to right ventricular pacing demonstrated the well-described and highly significant ($p < 0.001$) inverse relationship between QT interval and heart rate (Fig. 1). Heart rate adjustment by the Bazett formula produced only a partial correction for the effect of heart rate, as there was a significant ($p < 0.001$) positive relationship. In contrast, the spline formula (QTcRBK) adjusted completely for the effect of heart rate as there was no significant relationship between QTc and heart rate ($p = 0.989$). The JT interval was significantly related to heart rate ($p < 0.001$). In contrast, the JT interval after QTc correction (QTcRBK) no longer had a significant relationship to heart rate ($p = 0.360$).

During ventricular pacing, there was a highly significant ($p < 0.001$) inverse linear relationship between QT interval and heart rate (Fig. 2). While the QTcBZT provided an adjustment for the impact of heart rate, the residual positive association between QTcBZT and ventricular rate was evident. In contrast, QTcRBK was not associated with a significant relationship to heart rate ($p = 0.420$). There was a significant inverse relationship between JT and heart rate even after correction by the Bazett approach. In contrast, JTc after adjustment for the spline formula $JTcRBK_{PACED}$ did not demonstrate a significant relationship to heart rate ($p = 0.187$).

To assess the relationship between the predicted QTc in patients with pacemakers and the measured QTc before pacemaker insertion, linear correlations analyses were performed. Formulae that used the spline heart rate correction had a stronger correlation with their respective QTc before pacemaker implantation compared to formulae corrected by the QTcBZT, while $QTcFRM_{PACED}$ – 43 ($r = 0.480$) and $QTcRBK_{PACED}$ – (QRS*0.5) ($r = 0.473$) had strong relationships (Fig. 3). Using the interval from the onset of the Q-wave to the peak of the T-wave (QTp) and the Bazett heart rate correction, the $QTcBZT_{PACED}$SRI formula did not demonstrate a statistically significant relationship with QT before pacemaker implantation with either QTcBZT ($p = 0.171$) or QT interval without any correction ($p = 0.101$).

Table 2
Number of QTc prolongation cases identified in derivative pacemaker group.

Before pacemaker insertion	# of cases	After pacemaker insertion	# of cases	p-Value[a]
QTcBZT	3	$QTcBZT_{PACED}$SRI	23	<0.001*
		$QTcBZT_{PACED}$ – (QRS–120)	19	<0.001*
		$QTcBZT_{PACED}$ – 50	18	0.001*
		$QTcBZT_{PACED}$ – (QRS*0.5)	7	0.289
		$QTcBZT_{PACED}$*0.86	10	0.065
QTcRBK	0	$QTcRBK_{PACED}$SRI	7	0.016*
		$QTcRBK_{PACED}$ – (QRS–120)	10	0.002*
		$QTcRBK_{PACED}$ – 50	7	0.016*
		$QTcRBK_{PACED}$ – (QRS* 0.5)	0	–
		$QTcRBK_{PACED}$*0.86	1	1.000
QTcFRM	2	$QTcFRM_{PACED}$ – 43	13	0.001*

[a] McNemar's Test, 2-tailed exact sig.
* P<0.05

During ventricular pacing, all formulae showed a statistically significant increase in identified QTc prolongation cases, except $QTcBZT_{PACED}$ – (QRS*0.5) ($p = 0.289$), $QTcBZT_{PACED}$*0.86 ($p = 0.065$), $QTcRBK_{PACED}$ – (QRS*0.5) (no difference; exact same proportion), and $QTcRBK_{PACED}$*0.86 ($p = 1.000$) (Table 2). In contrast, the other formulae overestimated the number of cases with QT prolongation; sometimes markedly. $QTcBZT_{PACED}$SRI (23 cases, $p < 0.001$), $QTcBZT_{PACED}$ – (QRS-120) (19 cases, $p < 0.001$), and $QTcBZT_{PACED}$ – 50 (18 cases, $p = 0.001$) performed the worst, identifying over six times more cases of QTc prolongation compared to conduction before pacemaker implant (QTcBZT) (three cases). When ventricular pacing QT correction formulae were paired with the Bazett heart rate correction, all formulae identified more cases of QTc prolongation than measured before pacemaker

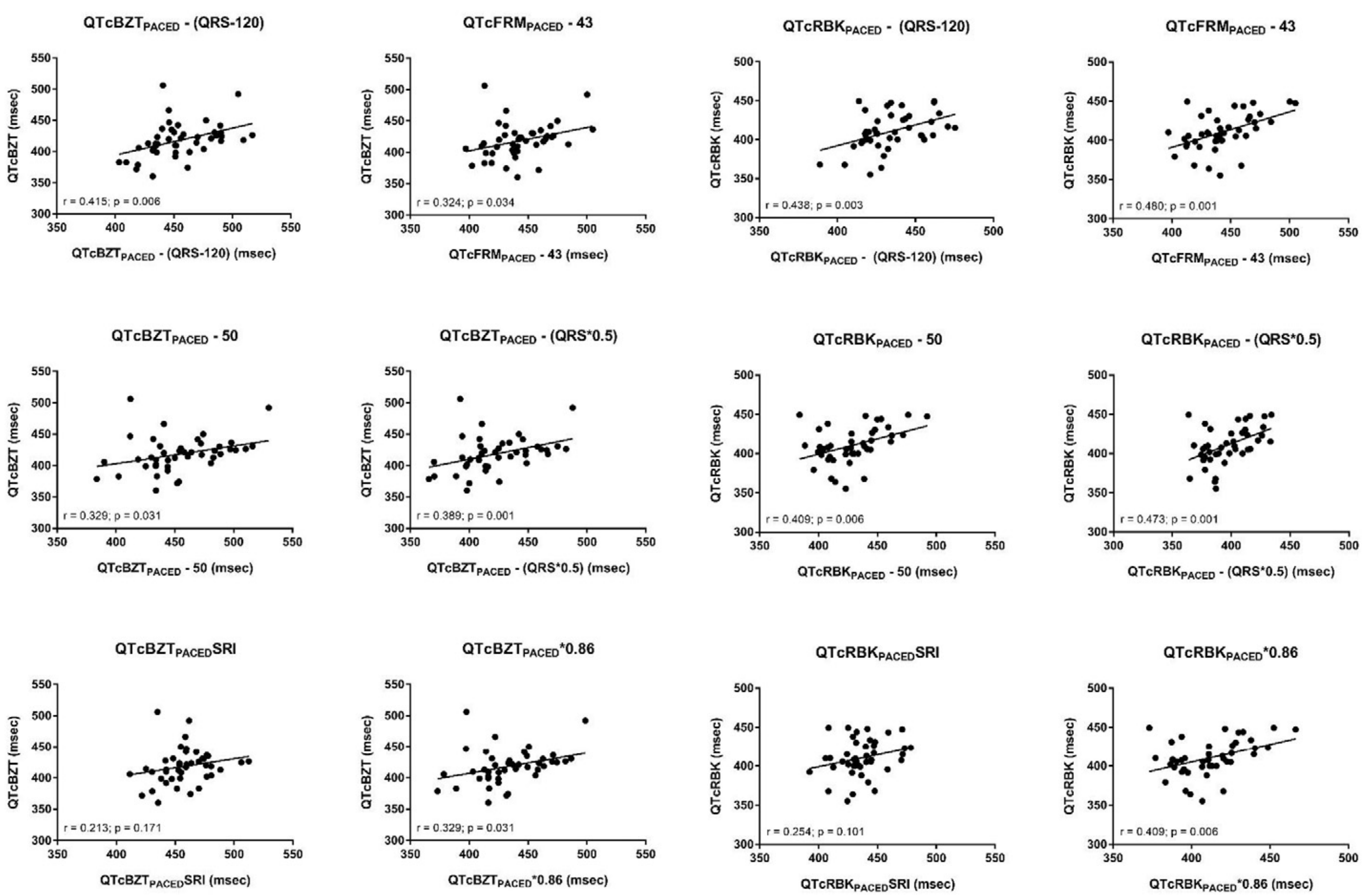

Fig. 3. Shows the relationship between the QT interval in the absence and in the presence of RV pacing for the different formulae as abbreviated in the text.

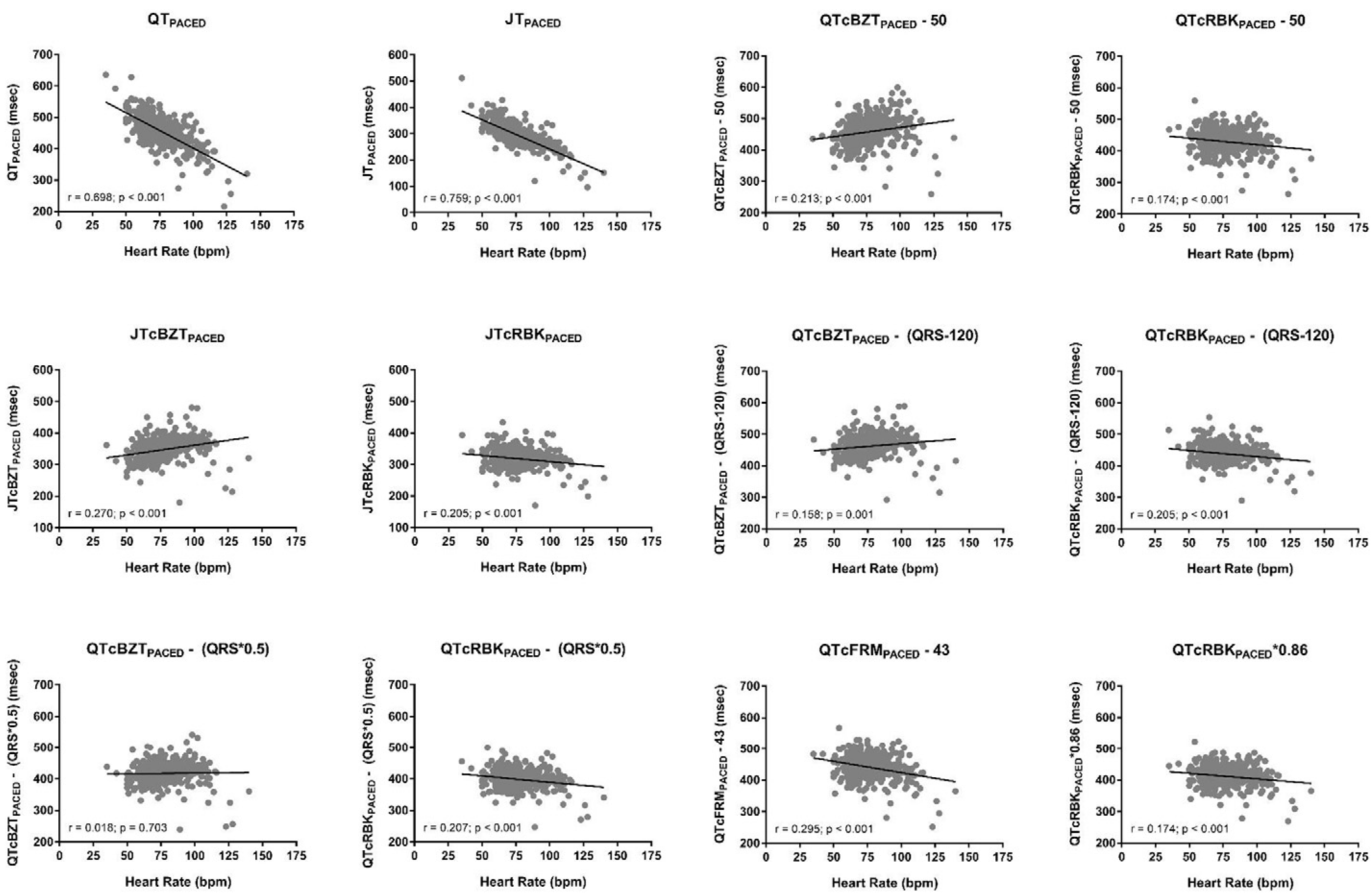

Fig. 4. Shows the relationship between heart rate and QT or JT in the validation cohort ($n = 442$) of pacing for the different formulae as abbreviated in the text.

implantation. When combined with the spline heart rate correction formula, $QTcRBK_{PACED}$ – (QRS*0.5) performed the best, identifying the same number of QTc prolongation cases as before pacemaker implant (QTcRBK) (zero cases), closely followed by $QTcRBK_{PACED}$*0.86 ($p = 1.000$).

Evaluation of formulae in the validation pacemaker population

A population of 442 unique individuals (mean age 75.5 ± 13.2 years (SD), 64% male) with permanent RV pacing were evaluated (Table 1). There was a significant inverse relationship between QT interval and heart rate (slope = −2.26 ± 0.11) (Fig. 4). There was also a significant inverse association between JT and heart rate. Adjustment for the heart rate by applying the QTcBZT ($r = 0.270$, $p < 0.001$) or QTcRBK ($r = 0.205$, $p < 0.001$) blunted the relationship, but both remained statistically significant. When combining ventricular pacing correction formulae with either Bazett, Framingham, or spline heart rate correction, all formulae demonstrated statistically significant heart rate dependency, except $QTcBZT_{PACED}$ – (QRS*0.5). $QTcRBK_{PACED}$ – (QRS*0.5) and $QTcRBK_{PACED}$*0.86 demonstrated a small but significant heart rate

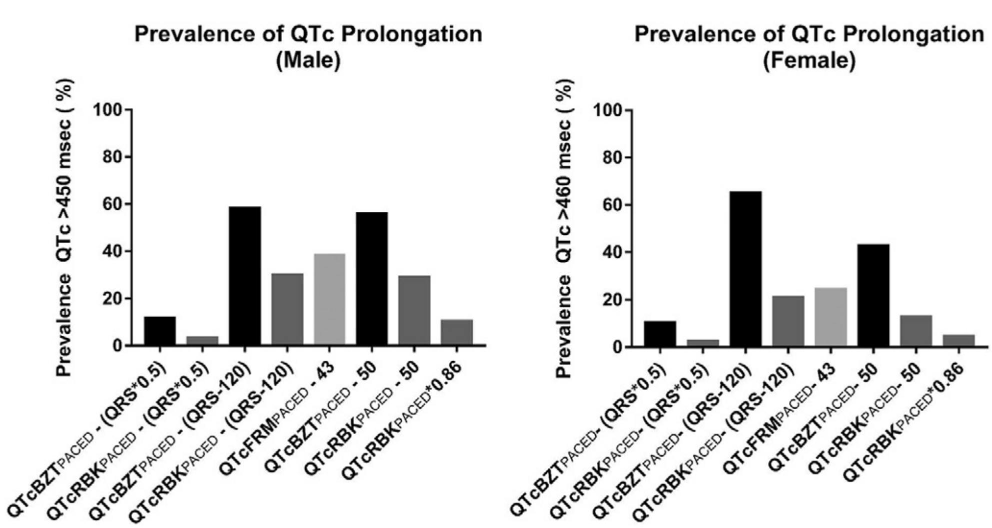

Fig. 5. Shows the proportion of men with a QTc over 450 ms and women with a QTc over 460 s across the heart rate spectrum for the different formulae as abbreviated in the text.

Table 3
The 97.5th and 99th percentile for QT interval using different correction formulae in patients with RV pacing.

Paced formulae	Men		Women	
	99th percentile (ms)	97.5th percentile (ms)	99th percentile (ms)	97.5th percentile (ms)
QTcBZT	604.51	595.629	630.936	587.817
QTcRBK	556.546	545.533	557.262	544.623
JTcBZT	414.282	399.599	466.785	437.954
JTcRBK	390.804	374.171	397.801	393.119
QTcBZT − (QRS*0.5)	488.501	474.056	524.252	500.405
QTcRBK − (QRS*0.5)	463.584	450.502	474.696	457.893
QTcBZT − (QRS-120)	524.604	516.387	583.385	552.184
QTcRBK − (QRS-120)	510.804	494.171	517.801	513.119
QTcFRM − 43	514.319	504.891	520.228	511.952
QTcBZT − 50	554.51	545.629	580.936	537.817
QTcRBK − 50	506.546	495.533	507.262	494.623
QTcRBK*0.86	478.63	469.158	479.245	468.376

relationship with a slope of -0.40 ± 0.09 and -0.36 ± 0.10 respectively, in contrast to the smaller pacemaker insertion sample. Sriwattanakomen et al.'s formula was not assessed in this population as it required QT_p, which was not available.

Ventricular pacing formulae combined with a heart rate correction were assessed for the number of identified QTc prolongation cases. In both males and females, heart rate correction with the Bazett formula identified more cases of QTc prolongation compared to the spline formula when applied to the same ventricular pacing correction formula (Fig. 5). $QTcBZT_{PACED}$ − (QRS-120) (58.1% for male, 65.0% for female) and $QTcBZT_{PACED}$ − 50 (55.8% for male, 42.7% for female) identified the most cases of QTc prolongation. $QTcRBK_{PACED}$ − (QRS*0.5) (3.2% for male, 2.5% for female) and $QTcRBK_{PACED}$*0.86 (10.3% for male, 4.5% for female) identified the least cases of QTc prolongation.

The distribution of QTc and JTc intervals as corrected by Bazett and spline formula for male and female were examined and the 97.5th and 99th percentile values were calculated (Table 3). Abnormal QT for $QTcRBK_{PACED}$*0.86 as defined by the 97.5th and 99th percentile is 469 and 479 ms respectively. For men, the 99th percentile and 97.5th percentile of $JTcRBK_{PACED}$ was 390.8 ms and 374.2 ms respectively. For the female sample, the 99th percentile and 97.5th percentile of $JTcRBK_{PACED}$ was 397.8 and 393.1 ms respectively.

Discussion

We derived and validated a new formula to calculate the QT interval and correct for QRS prolongation during ventricular pacing that performs better than previous methods. This study contributes novel data to identify an approach to optimally define the underlying QT interval in patients with ventricular pacemakers. Several approaches have been previously suggested but rarely have they been analyzed and compared, especially when combined with different heart rate correction formulae. We proposed a new approach or formula to address this issue. Importantly, our comparative analyses demonstrated wide discrepancies in proposed estimates of the QT interval before and after ventricular pacing. The new formula developed here is proposed as the optimal method to estimate the QTc in patients with right ventricular pacing because it demonstrated the best balance of relatively strong correlation to QTc before pacemaker implant with a reasonable and accurate identification of QTc prolongation.

The JTc interval has been examined as a more accurate measure of ventricular repolarization in the setting of a prolonged QRS duration [19]. In our patient sample before and after pacemaker insertion, there was a highly significant relationship between JT and heart rate. This finding supports the contention that the JT interval alone cannot be used to estimate QT as JT is significantly impacted by the underlying heart rate. JTc as corrected by the Bazett formula (JTcBZT) was slightly better but also demonstrated a meaningful heart rate dependency. In contrast, JTc as corrected by the spline formula (JTcRBK) was found to be independent of heart rate.

The relationship between the estimated QTc before compared to after pacemaker insertion and the actual QTc before pacemaker insertion was investigated with correlation analyses. None of the formulae demonstrated a high correlation with QT interval before pacemaker implant. Formulae that subtracted a fix amount from the QT [5–7] did not perform well overall. Attempts to change the nature of the QT interval by measuring the Q wave to the peak of the T wave (QT_p) demonstrated similar performance [10]. The utilization of the QTcBZT to correct for the impact of heart rate on QT interval [5] increased the inaccuracies of estimating the QTc before pacemaker implant.

We compared the number of identified QTc prolongation cases in persons before and after pacemaker insertion. All formulae significantly overestimated the cases of QTc prolongation, except our newly proposed formula and the Bogossian formula (Table 1). Of these formulae, our heart rate modification, specifically $QTcRBK_{PACED}$ − (QRS*0.5), was the only formula that identified the same number of QTc prolongation cases after pacing compared to before pacing.

In our large pacemaker population sample, we demonstrated a significant QT-heart rate dependency. $QTcBZT_{PACED}$ − (QRS*0.5) did not demonstrate heart rate dependency. However, this was in contrast to the results of our small pacemaker population sample and previous literature, which demonstrated that QTcBZT has a significant positive relationship with heart rate. $QTcRBK_{PACED}$*0.86 and $QTcRBK_{PACED}$ − (QRS*0.5) had a small but significant heart rate relationship. It is unclear why $QTcBZT_{PACED}$ − (QRS*0.5) showed minimal heart rate dependency and it may have occurred by chance.

This 'Bogossian' formula was reported to be a reliable tool for QT interval estimation in patients with heart failure and right ventricular pacing [9]. However, the investigators cautioned that a 25 ms overestimation of the QT interval should be expected with this formula [9].

The prevalence of QTc prolongation was assessed in the validation population sample. All formulae, except our newly proposed formula and the Bogossian formula identified QTc prolongation in over 20% of cases in both sexes. With the caveat that there is no precise independent method to assess underlying QT interval at the same time as ventricular pacing, the prevalence of QT prolongation as identified by these formulae are significantly higher than expected from data of non-pacemaker patients. Our definition of QTc prolongation was that of the AHA 2009 guidelines for ECG measurements, which derived its values from 2% and 5% upper limits of non-pacemaker females and males respectively [10]. Only $QTcRBK_{PACED}$ − (QRS*0.5) (3.2%) for males and $QTcRBK_{PACED}$ − (QRS*0.5) (2.5%), $QTcRBK_{PACED}$*0.86 (4.5%) for females identified <5% of subjects with QTc prolongation.

A major contribution of this work is the establishment of new 99th percentile and 97.5th percentile cut-offs for male and females using both the JTcBZT and JTcRBK heart rate correction formulae. Similar data is available for the new formula.

Considering the results of the derivative pacemaker insertion sample and the validation cohort, $QTcRBK_{PACED}$ − (QRS*0.5) and $QTcRBK_{PACED}$*0.86 had the best balance of a relatively strong correlation to QTc before pacemaker implant and accurate QTc prolongation identification, with $QTcRBK_{PACED}$ − (QRS*0.5) performing slightly better in both domains. However, there is a small inverse heart rate dependent relationship with both formulae. All other formulae demonstrated either a weak correlation to QTc before pacemaker implant, significant overestimation of QTc prolongation, or a combination of both.

There are several limitations of the study that warrant discussion. We studied patients before and after pacemaker insertion. While the sample size of 43 patients is not large, it exceeds the numbers evaluated in many of the previous studies that developed proposals for QT adjustments in patients with permanent pacemakers. The relatively small sample size was due to our selection criteria that required 12 lead ECG before and shortly after pacemaker insertion. Most 12 lead ECGs were done in the Pacemaker clinic follow up visit at a longer time period after pacemaker implantation, and were excluded from consideration. Second, we cannot exclude that the derivative cohort may have had changes to their management during the time period between ECGs. As the mean days between the ECG recordings were <2 days, the risk of this confounder is low. Third, measurements of QT interval were made at paper speed of 25 mm/s which may constrain the accuracy of QT measurement accuracy. Fourth, correlation analysis only demonstrates the relationship, and not the predictive ability of the various formulae in estimating QTc before pacemaker implant. To improve the reliability with assessment of QTc before pacemaker implant, we also compared the number of QTc prolongation cases identified before and after pacemaker insertion, as well as in the large pacemaker population sample, to assess accuracy of QTc estimation before pacemaker implant. However, this approach might be influenced by formulae that underestimate QTc, which will trend towards identifying less QTc prolongation cases and as a result appear to accurately match the low number of cases identified in the QTc before pacemaker implant. Fifth, it is unlikely that the pacemaker lead was in the exact same place in the right ventricle for all patients. This variability may explain, in part, the modest correlation of QTc before and after pacemaker insertion as some patients may have had different relationships depending on the precise location of the tip of the RV pacing electrode. Lastly, although the QT interval is an important marker on the surface ECG of the repolarization process, as depolarization of the heart occurs as a wave of activation some regions of the heart will be repolarizing as others are depolarizing. These processes occurring at the same time may explain why approaches of simply subtracting the QRS or a fixed value from the QT interval are poor approaches to estimate the QTc before pacemaker insertion and why even our best approach did not provide a 'perfect' correlation of QTc before with QTc after pacemaker insertion.

Conclusion

We proposed a new formula that significantly predicts the QT interval in patients without pacing from their QT interval after RV pacing. The precision of the correlation is not high but is better than previous approaches that subtracted a fix amount from the QT. In addition, we showed that approaches that do not consider optimal heart rate corrections are intrinsically flawed. Our data demonstrated that the new spline approach for heart rate correction for the QT interval can be incorporated into a number of the previously proposed formulae and blunt heart rate dependency. $QTcRBK_{PACED}*0.86$ as well as a similar formula $QTcRBK_{PACED} - (QRS*0.5)$ demonstrated the best balance of relatively strong correlation to QTc before pacemaker implant and accurate QTc prolongation identification, but with a small inverse heart rate dependency. Other formulae should be used with caution due to significant overestimation of the proportion of QTc prolongation. The commonly used JT interval from RV paced complexes is highly heart rate dependent and is not accurate for assessment of underlying Interval. Incorporation of the spline heart rate correction formulae into the JT interval improves the estimate of the QT interval from paced complexes.

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Declaration of Competing Interest

The authors declare no conflicts of interest with this work.

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