ORIGINAL ARTICLE

A new experimentally validated formula to calculate the QT interval in the presence of left bundle branch block holds true in the clinical setting

Harilaos Bogossian M.D.^{1,2,*} | Gerrit Frommeyer M.D.^{3,*} | Ilias Ninios M.D.¹ | Eleni Pechlivanidou M.D.¹ | Fuad Hasan M.D.¹ | Quy Suu Nguyen M.D.¹ | Dejan Mijic M.D.¹ | Axel Kloppe M.D.¹ | Zana Karosiene M.D.¹ | Artak Margkarian M.D.¹ | Dirk Bandorski M.D.¹ | Dominik Schultes M.D.¹ | Damir Erkapic M.D.⁴ | Melchior Seyfarth M.D.^{2,5} | Bernd Lemke M.D.¹ | Lars Eckardt M.D.³ | Markus Zarse M.D.^{1,2}

¹Märkische Kliniken GmbH, Department of Cardiology and Angiology, Klinikum Lüdenschheid, Lüdenschheid, Germany

²Department of Cardiology, University Witten/Herdecke, Witten, Germany

³Division of Electrophysiology, Department of Cardiovascular Medicine, University of Münster, Münster, Germany

⁴Medical Clinic I, Department of Cardiology, Justus-Liebig University of Giessen, Giessen, Germany

⁵Department of Cardiology, Helios Klinikum Wuppertal, Wuppertal, Germany

Correspondence

Harilaos Bogossian, Department of Cardiology and Angiology, Märkische Kliniken GmbH, Lüdenschheid, Germany. Email: Harilaos.bogossian@klinikum-luedenschheid.de

Background: The evaluation of the QT interval in the presence of left bundle branch block (LBBB) is associated with the challenge to discriminate native QT interval from the prolongation due to the increase in QRS duration. The newest formula to evaluate QT interval in the presence of LBBB suggests: modified QT during LBBB = measured QT interval minus 50% of LBBB duration. The purpose of this study is therefore to validate the abovementioned formula in the clinical setting.

Methods: Validation in two separate groups of patients: Patients who alternated between narrow QRS and intermittent LBBB and patients with narrow QRS who developed LBBB after transcatheter aortic valve implantation (TAVI).

Results: The acquired mean native QTc intervals and those calculated by the presented formula displayed no significant differences ($p > .99$ and $p > .75$).

Conclusions: In this study we proved for the first time the validity and applicability of the experimentally acquired formula for the evaluation of the QT interval in the presence of LBBB in a clinical setting.

KEYWORDS

JT interval, left bundle branch block, long QT, QT formula, QT interval, QT prolongation

Cardiovascular and noncardiovascular drugs can prolongate ventricular repolarization resulting often in a significant prolongation of the QT interval (Woosley & Romero, 2013). This can increase the risk of arrhythmias such as polymorphic ventricular tachycardia of the torsade de pointes type. This risk is especially augmented when further risk factors like bradycardia or a reduced potassium concentration coincide (Shimizu et al., 1991).

Adjustments for heart rate are regularly used in the clinical setting for the analysis of the QT interval in narrow QRS complex (Luo et al.,

2004). Furthermore, modifications for gender can also be considered (Rautaharju et al., 2009) but are not regularly used. In large study populations, the importance of the amount of QT lengthening for cardiovascular risk stratification has been demonstrated (Nielsen et al., 2014; Priori et al., 2003).

In patients with dilated cardiomyopathy, the presence of a left bundle branch block (LBBB) independently increases all-cause mortality (Aleksova et al., 2014). In addition, LBBB induced a prolongation of the QT interval and thereby complicates precise interpretation of the measured values. Retrospective comparisons of patients with LBBB with healthy individuals have underlined that the JT interval may be

*Both authors contributed equally.

used for risk stratification in the presence of a significantly prolonged QT interval due to LBBB (Rautaharju et al., 2004).

We recently introduced a formula that allows an estimation of the adjusted QT interval during LBBB: $QT_m = QT_b - 48.5\% \text{ of } QRS_b$ (Bogossian et al., 2014). This formula resulted from an analysis of QT intervals in patients with normal QRS during sinus rhythm and during right ventricular pacing. The aim of this study was to validate the cited formula in a cohort of patients with intermittent intrinsic LBBB and in a cohort of patients with normal QRS who developed LBBB after transcatheter aortic valve implantation (TAVI).

1 | METHODS

1.1 | Study patients and ECG analysis

ECGs of 15 patients with sinus rhythm (SR) intermittent intrinsic LBBB (group 1) and of 15 patients with normal QRS and new LBBB after TAVI (group 2) were retrospectively analyzed. ECG analysis was performed independently by two investigators who were blinded regarding all measurements.

The study conforms to the guiding principles of the Declaration of Helsinki. In addition, the Institutional Committee on Human Research at our Institution approved the study. Narrow QRS had to be shorter than 110 ms. The intrinsic QRS and QT/JT time (QT_i/JT_i) were measured in ECGs with narrow QRS as well as in ECGs with LBBB. The QT interval was measured in the lead presenting the longest interval according to the current recommendations (Rautaharju et al., 2009). This usually was V_2 or V_3 . As recommended, a tangent was used for precise determination of the QT interval (Postema et al., 2008).

The measured QT interval during narrow QRS was compared with the modified QT (QT_m) calculated by the recently introduced formula ($QT_m = QT_b - 48.5\% \text{ of } QRS_b$ Fig. 1). For simplification in clinical

Published Formula : $QT_m = QT_b - 48.5\% \cdot QRS_b$ Simplified Formula : $QT_m = QT_b - QRS_b/2$	
QT_m	=> „modified QT“ (estimated QT by using the Formula)
QT_b	=> QT duration in LBBB
QRS_b	=> QRS duration in LBBB

FIGURE 1 Simplified formula for determination of the QT interval in the presence of left bundle branch block (LBBB)

practice, the formula was modified to: $QT_m = QT_b - QRS_b/2$ (Fig. 2). Calculated values were adjusted using Bazett's formula.

1.2 | Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation. Data were entered into a computerized database (Microsoft Excel, Microsoft, Redmond, WA, USA) and tested for normal distribution using Shapiro-Wilk test. Student's *t*-test was used to determine differences between groups. Differences were considered significant in case of $p < .05$ (two sided).

2 | RESULTS

As described in the Methods section, ECG analysis was performed independently by two investigators who were blinded regarding all measurements. Mean values of these measurements were calculated and differed no more than 5 ± 2 ms between both investigators in all study groups. In patients with intermittent LBBB (group 1) during narrow QRS, the mean QRS duration was 91 ± 11 ms, whereas the JT interval measured 280 ± 29 ms. The mean QT interval was 370 ± 34 ms leading to a QT_c calculated with Bazett's formula of 407 ± 34 ms at a mean heart rate of 73 ± 11 bpm. During intrinsic

FIGURE 2 Example of determination of the QT interval and usage of the new formula in the precordial leads. In this example, the presence of the U wave in leads V_3 – V_5 complicates measurement of the QT Interval. According to the current AHA/ACC/HRS recommendations for the standardization and interpretation of the electrocardiogram (Rautaharju et al., 2009), it is recommended (as in this case performed) "if the T wave and U wave are superimposed or cannot be separated" that the QT should be measured in the leads not showing U waves. Therefore, we chose to measure in lead V_6 , leading to the longest QT interval. Also drawing a tangent to the steepest proportion of the down slope until it crosses the TP segment, the QT intervals in the leads V_3 – V_5 are shorter

LBBB the mean QRS duration was 143 ± 13 ms and the mean JT interval was 280 ± 30 ms. The mean QT interval measured 424 ± 35 ms leading to a QTc interval of 488 ± 39 ms at a mean heart rate of 81 ± 11 ms. The above-described formula led to a QTm interval of 354 ± 32 ms leading to a QTmc interval of 409 ± 32 ms ($p = .99$ as compared with QTc interval in the presence of narrow QRS, Table 1).

In patients with an initially narrow QRS who presented LBBB after TAVI, the mean QRS duration before the TAVI procedure was 91 ± 9 ms and the mean JT interval was 267 ± 23 ms. The mean QT interval was 356 ± 27 ms leading to a calculated QTc interval of 388 ± 32 during narrow QRS. In the setting of LBBB, the mean QRS duration was 152 ± 13 ms and the mean JT interval was 268 ± 21 ms. The QT interval was 412 ± 28 ms leading to a QTc interval of 468 ± 33 ms. Usage of the new formula led to a QTm interval of 345 ± 24 ms and a QTmc interval of 382 ± 35 ($p = .75$ as compared with QTc interval in the presence of narrow QRS, Table 2).

3 | DISCUSSION

3.1 | Validation of the formula in the clinical setting

Patients with bundle branch block regularly present with a prolonged QTc interval. This may most likely be overestimated, as the prolongation in bundle branch block is mainly caused by a delay in depolarization and not in repolarization (Das, 1990). We recently introduced the formula $QTm = QTb - 48.5\% \text{ of } QRSb$ as a result of a proof-of-concept study (Bogossian et al., 2014). In this study, we induced a LBBB by right ventricular pacing. Therefore, the underlying mechanisms of an

intrinsic LBBB could not be taken into account. Furthermore, hearts were paced at a fixed rate. Therefore, variabilities induced by different heart rates could not be considered.

In this study, we validated the formula in patients with intermittent intrinsic LBBB with the advantage that the QT interval could be compared individually in the presence and absence of intrinsic LBBB. Heart rate variabilities were adjusted using Bazett's formula and the comparison to QTm values calculated with the above cited formula did not reveal significant differences.

These results underline the importance of the QRS duration for precise assessment of the real QT interval in the setting of LBBB.

In the Artherosclerosis Risk in Communities (ARIC) study a strong correlation of the QT interval with the duration of the QRS complex in the presence of a wide QRS complex was reported (Crow, Hannan, & Folsom, 2003). The potential overestimation of the QT interval in the presence of LBBB therefore should be corrected.

Possible reasons for physicians to only assess the QT interval in clinical practice instead of using a more precise formula may be feasibility reasons, as it is assumed to be more easily defined and its rate correction and automated ECG measurements are well established. On the other hand, the remaining problem of inaccurate measurement or interpretation of a prolonged QT interval has been comprehensively described by Viskin et al. (2005).

3.2 | Intermittent LBBB and LBBB after TAVI

Intermittent intrinsic LBBB is a regularly described clinical entity. It can be induced by different mechanisms such as coronary artery

TABLE 1 QT interval in patients with intermittent left bundle branch block (LBBB); mean values in bold

P	Narrow QRS						Left bundle branch block						
	HR (bpm)	QRS (ms)	JT (ms)	QT (ms)	QTc (ms)	Δ QTc	QTmc by formula (ms)	QTm by formula (ms)	HR (bpm)	QRS (ms)	JT (ms)	QT (ms)	QTc (ms)
1	63	95	305	400	410	45	455	415	72	170	330	500	548
2	81	105	290	395	459	0	459	373	91	135	305	440	542
3	76	82	338	420	473	−32	441	375	83	130	310	440	518
4	80	95	255	360	416	−6	410	355	80	145	285	430	497
5	58	95	325	420	413	2	415	390	68	160	310	470	500
6	65	85	305	390	406	−1	405	375	70	130	290	440	475
7	72	80	280	360	394	3	397	340	82	120	280	400	468
8	68	100	300	400	426	1	427	370	80	140	300	440	508
9	67	85	245	330	349	29	378	310	89	140	240	380	463
10	60	105	270	375	375	3	378	363	65	145	290	435	453
11	88	82	264	346	419	28	447	365	90	160	264	425	521
12	85	80	260	320	381	8	389	323	87	135	255	390	470
13	75	70	250	320	358	1	359	300	86	140	230	370	403
14	67	105	265	370	391	26	365	343	68	155	265	420	447
15	97	95	245	340	432	−16	416	310	108	140	240	380	510
Mean	73	91	280	370	407	5	409	352	81	143	280	424	488
SD	11	11	29	34	34	19	32	33	11	13	30	35	39

TABLE 2 QT interval in patients with left bundle branch block (LBBB) after transcatheter aortic valve implantation (TAVI); mean values in bold

Patient	Narrow QRS						Left bundle branch block						
	HR (bpm)	QRS (ms)	JT (ms)	QT (ms)	QTc (ms)	Δ QTC	QTmc by formula (ms)	QTm by formula (ms)	HR (bpm)	QRS (ms)	JT (ms)	QT (ms)	QTc (ms)
1	70	100	300	400	432	4	436	378	80	165	295	460	531
2	72	95	225	320	351	-16	335	330	62	140	260	400	407
3	70	80	280	360	389	-22	367	345	68	170	260	430	458
4	48	90	280	370	338	-2	336	328	63	165	245	410	420
5	75	90	290	380	425	-14	411	365	76	150	290	440	495
6	68	105	265	370	394	17	411	375	72	170	290	460	504
7	78	80	250	330	376	-11	365	300	89	140	230	370	451
8	91	85	255	340	419	2	421	340	92	140	270	410	508
9	96	85	245	330	417	-15	402	340	84	140	270	410	485
10	60	100	280	380	380	-5	375	345	71	150	270	420	457
11	67	100	250	350	370	-9	361	313	80	155	235	390	450
12	71	75	285	360	392	-12	380	305	93	150	230	380	473
13	73	90	260	350	386	-5	381	350	71	140	280	420	457
14	70	100	260	360	389	-3	386	330	82	160	250	410	479
15	70	95	245	340	367	-4	363	300	88	140	230	370	448
Mean	72	91	267	356	388	6	382	345	78	152	268	412	468
SD	14	9	23	27	32	10	35	24	10	13	21	28	33

stenosis (Kershaw & Rogers, 2014), coronary vasospasm (Alhaji, 2013), or myocardial contusion (Pizzo et al., 2005). Mostly, intermittent LBBB appears or disappears depending on heart rate. In general, two entities of rate-dependent LBBB can occur. The first one is an acceleration-dependent block which occurs when the heart rate accelerates above a certain value. An acceleration of heart rate above the effective refractory period of the left bundle can be regarded as the underlying electrophysiological mechanism. In contrast, the deceleration-dependent block can occur when the heart rate slows down below a critical rate (Vereckei & Tenczer, 2003; Ott, 2001). In our study all group 1 patients displayed an acceleration-dependent block, underlining the necessity for rate correction as demonstrated in our article.

TAVI is associated with higher risk of new conduction disorders potentially requiring pacemaker implantation as compared with surgical aortic valve replacement. Among these disorders, LBBB is most frequently observed. The incidence of LBBB after TAVI varies among the implanted valve types and ranges about 31% (Schymik et al., 2015) in large cohorts including both the Medtronic CoreValve System and the Edwards SAPIEN Valve. The incidence of LBBB is significantly higher in registries that only include the Medtronic CoreValve System (Lenders et al., 2014).

3.3 | Limitations

The formula that was used in this study adjusts the QT interval by correcting the QRS duration in the presence of LBBB and thereby only addresses LBBB-induced changes in the depolarization period.

However, the repolarization period in the presence of LBBB may also follow different patterns than the repolarization period in the presence of normal conduction. These potential alterations cannot be addressed by the present formula. Nonetheless, the results of this study suggest that despite these limitations the employed formula still delivers a reliable correction of the QT interval in LBBB.

4 | CONCLUSION

In this study, the recently introduced formula was validated in patients with intermittent intrinsic LBBB and new LBBB after TAVI. No significant difference between measured QTc in the setting of narrow QRS and calculated QTmc using the above named formula in the presence of LBBB was observed. Only in the presence of extreme deviations in the QTc interval and/or the QRS duration, the formula might overestimate (or seldom underestimate) the true QTc interval. These results suggest that the formula which was developed in an artificial setting in a proof-of-concept study holds true in the clinical setting.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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