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QT correction using Bazett's formula remains preferable in long QT syndrome type 1 and 2

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Abstract

Background: The heart rate (HR) corrected QT interval (QTc) is crucial for diagnosis and risk stratification in the long QT syndrome (LQTS). Although its use has been questioned in some contexts, Bazett's formula has been applied in most diagnostic and prognostic studies in LQTS patients. However, studies on which formula eliminates the inverse relation between QT and HR are lacking in LQTS patients.

We therefore determined which QT correction formula is most appropriate in LQTS patients including the effect of beta blocker therapy and an evaluation of the agreement of the formulae when applying specific QTc limits for diagnostic and prognostic purposes.

Methods: Automated measurements from routine 12-lead ECGs from 200 genetically confirmed LQTS patients from two Swedish regions were included (167 LQT1, 33 LQT2). QT correction was performed using the Bazett, Framingham, Fridericia, and Hodges formulae. Linear regression was used to compare the formulae in all patients, and before and after the initiation of beta blocking therapy in a subgroup (n = 44). Concordance analysis was performed for QTc ≥ 480 ms (diagnosis) and ≥500 ms (prognosis).

Results: The median age was 32 years (range 0.1–78), 123 (62%) were female and 52 (26%) were children ≤16 years. Bazett's formula was the only method resulting in a QTc without relation with HR. Initiation of beta blocking therapy did not alter the result. Concordance analyses showed clinically significant differences (Cohen's kappa 0.629–0.469) for diagnosis and prognosis in individual patients.

Conclusion: Bazett's formula remains preferable for diagnosis and prognosis in LQT1 and 2 patients.

KEYWORDS

Bazett's formula, corrected QT interval, long QT syndrome, LQTS, QT correction, QT interval

1 | INTRODUCTION

The congenital long QT syndrome (LQTS) is characterized by a prolongation of the QT interval on ECG and an increased risk of the typical polymorphic ventricular arrhythmia Torsades de Pointes (TdP) causing syncope or cardiac arrest. The degree of QT prolongation plays a role not only for diagnosis (Schwartz, 2006; Schwartz et al., 1993) but also has bearing on the prognosis (Priori et al., 2003). The evaluation of the QT interval therefore remains crucial.

The QT interval represents the time from the start of ventricular depolarization to the end of repolarization, corresponds to the time for mechanical systole, and varies with heart rate (HR) or, more specifically, a number of preceding diastolic intervals (Seethala et al., 2011). The HR dependence of the QT interval and need for correction was recognized already a century ago (Bazett, 1920; Fridericia, 1920). QT correction enables comparison of QT intervals at different HRs and at different time points within and between individuals. Using an ideal QT correction formula, no relationship would remain between HR (or RR interval) and the corrected QT interval (QTc). There are currently four different methods commonly used to calculate QTc, two exponential (Bazett and Fridericia) and two linear (Framingham and Hodges), with the common feature that QTc = QT at HR 60 beats per minute (bpm), that is, at a frequency of 1 Hz (Bazett, 1920; Fridericia, 1920; Hodges et al., 1983; Sagie et al., 1992).

Virtually, all studies on the LQTS have used Bazett's formula (QTcB). Therefore, most available prognostic information is based on QTcB (Liu et al., 2011; Priori et al., 2003). The applicability of Bazetts´s formula has, however, been questioned in several studies (Indik et al., 2006; Strohmer et al., 2007; Vandenberk et al., 2016), and present guidelines suggest the use of a linear formula (Rautaharju et al., 2009). We are not aware of any publication in LQTS patients focusing on whether QTcB (or QTcF, QTcFram, QTcH) eliminates the inverse relation between QT and HR. QTcB seems to have been generally applied in LQTS patients until recently when all four formulae were used for diagnostic purposes (Goldenberg et al., 2006; Vink et al., 2018).

This study was initiated to explore how the four most common correction formulae performed in patients with LQTS type 1 and 2, including the effect of initiating beta blockade, and the agreement between the formulae when applying specific clinically relevant QTc threshold values for diagnostic and prognostic purposes. Our hypothesis was that these correction formulae are not equally suitable in eliminating the influence of HR on the QT interval in patients with congenital LQTS.

2 | METHODS

2.1 | Subjects

We performed a two-center observational cohort study including 200 LQTS patients, adults and children. DNA analysis had confirmed the diagnosis in all patients. The Gothenburg cohort included all patients with a diagnosis of the LQTS type 1 and 2 from the cardiogenetic clinic, between 2013 and 2017, with at least one available technically satisfactory ECG during sinus rhythm. These 89 patients had a confirmed pathogenic variant in KCNQ1 (LQT1, $n = 69$, 78%) or KCNH2 (LQT2, $n = 20$, 22%). The Umeå cohort was recruited from the LQTS Family Clinic at the Centre for Cardiovascular Genetics at Umeå University Hospital. It consisted of 111 patients: 98 (88%) had a confirmed pathogenic variant in KCNQ1 (LQT1) and 13 (12%) in KCNH2 (LQT2). They constitute the majority (91%) of the patients in a previous study comparing the identification of LQTS patients from automatic or manual measurement of the QTcB from 12-lead ECG or from Frank leads (Diamant et al., 2010).

2.2 | Electrocardiographic recordings

From each subject at the Gothenburg center, the first available and technically satisfactory 12-lead routine ECG (50 mm/s paper speed, 10 mm/mV amplitude, and 500 Hz sampling rate) was retrieved from our digital ECG system, but in some patients from referring hospitals. When possible, we also collected the first ECG after initiation of beta blocker therapy. HR and QT intervals were determined automatically in 82 patients. In 7 patients, the QT interval was measured manually using the tangent method in lead II. All ECGs were inspected for rhythm and quality, as well as to confirm that the annotation points for the automatic QT measurements were correctly positioned. Incorrect automatic measurements were measured manually (Goldenberg, et al., 2006). ECGs with missing leads or too much noise were excluded, as were ECGs with a ventricular paced rhythm, arrhythmias (atrial fibrillation/flutter), or conduction disorders as well as ECGs from “specific clinical events,” such as intoxication and myocardial infarction.

In the Umeå cohort, a 12-lead ECG was recorded on a Mac 5000 (GE Medical System, Information Technologies) with the same paper speed, amplification, and sampling rate, and HR and QT was automatically determined by the 12 SL algorithm of the equipment (Diamant et al., 2010).

2.3 | QT correction

QTc in ms was calculated as follows, with RR in s and HR in bpm.

1. Bazett: $QTcB = QT/RR^{1/2}$.
2. Fridericia: $QTcF = QT/RR^{1/3}$.
3. Framingham: QTcFram = QT+0.154*(1−RR).
4. Hodges: QTcH = QT+1.75*(HR-60).

2.4 | QTc/HR relationship

We analyzed and presented the QTc/HR relationship and not the QTc/RR relationship for two reasons: (1) the automatically

measured HR during the ECG recording was used and not a single QT/RR interval, and (2) in the clinical context, HR is the more common of the two. Scatterplots were used for illustrating the relation between QT and QTc on one hand with HR on the other. Linear regression was calculated for the individual QTc/HR pairs for each correction formula, and the slopes, regression coefficients, and *p*-values were used in the comparisons between the four formulae; the smaller the slope and the correlation coefficient (Spearman's r_s) and the closer the *p*-value to 1, the better the method. This is a commonly applied approach used to evaluate any remaining HR influence on the QTc (Dogan et al., 2005; Goldenberg, et al., 2006; Indik et al., 2006; Phan et al., 2015; Strohmer et al., 2007; Vandenberk et al., 2016).

2.5 | Analytical protocol

First, the performance of the correction formulae was compared in all LQT1 and LQT2 patients. Secondly, we made the same comparison before and after initiation of beta blocker therapy in a subgroup of the Gothenburg cohort ($n = 44$). Finally, with QTcB as the reference, we studied the concordance (agreement) for (1) a QTc ≥ 480 ms, which is the 3-point threshold value in the Schwartz' diagnostic scoring system (Schwartz et al., 1993), and (2) a QTc ≥ 500 ms, which is the threshold value for high-risk patients (Goldenberg et al., 2008; Priori et al., 2003).

2.6 | Statistical analysis

Descriptive data are presented as median and interquartile range or numbers and percentages. Linear correlation analysis was performed, and the Spearman correlation coefficients were calculated. Mann–Whitney and the chi-square test were used for between group comparisons and Wilcoxon for within-group comparisons. In the concordance analysis, we used Cohen's kappa (with 95% confidence interval), which takes into account the differences between the observed agreement and the agreement expected from chance alone on a 5-step scale from poor (<0.20) to very good (0.81–1.0) (Kwiecien et al., 2011). A $p < .05$ was considered significant.

3 | RESULTS

3.1 | Subjects

A total of 200 LQTS patients, 167 LQT1 (83%) and 33 LQT2 (17%), were included in the study. Table 1 shows baseline clinical and ECG characteristics. The median age was 31.5 years and ranged from 0.1 to 77.5 years, 123 (62%) were female and 52 (26%) were children <16 years. Sex and age distribution were similar in LQT1 and LQT2 patients. HR did not differ between LQT1 and 2, but QT and QTc were numerically but not significantly longer in the LQT1 group. The number on beta blocking therapy at the time of the first available ECG was 70 (36%) in the whole cohort (5 missing data).

3.2 | Comparison of correction formulae

The scatterplots for the QTc/HR relationship for all four correction formulae in the whole cohort of 200 LQTS patients are shown in Figure 1. Table 2 shows the slopes (*k*) and the correlation coefficients (r_s) for all patients and separated for LQT1 and 2; the lower the slope (*k*) and the correlation coefficient (r_s), and the closer the

TABLE 1 Clinical and ECG characteristics of the study cohort

	All LQT 1 + 2 ($n = 200$)	LQT1 ($n = 167$)	LQT2 ($n = 33$)
Female sex	123 (62%)	102 (61%)	21 (64%)
Children <16 years	52 (26%)	43 (26%)	9 (27%)
Age at ECG (years)	31 (15–47) [0.1–78]	32 (15–46) [0.1–78]	30 (15–49) [0.1–74]
Beta blockers[a]	70 (36%)	55 (34%)	15 (47%)
HR (bpm)	67 (57–77)	67 (59–77)	66 (56–76)
RR (s)	0.900 (0.780–1.050)	0.900 (0.780–1.020)	0.910 (0.790–1.080)
QT (ms)	440 (410–480)	441 (412–480)	432 (394–482)
QTcB (ms)	469 (442 –488)	469 (446–489)	453 (432–480)
QTcF (ms)	459 (434–480)	460 (437–481)	456 (422–473)
QTcFram (ms)	456 (432–479)	458 (434–480)	455 (423–473)
QTcH (ms)	455 (435–478)	455 (435–478)	453 (419–476)

Note: Data are presented as median (Q1-Q3) and [full range for age] or numbers (%).

Abbreviations: ECG, electrocardiogram; LQTS, long QT syndrome; QTc, rate corrected QT interval using the correction formulae: B, Bazett, F, Fridericia, Fram, Framingham, H, Hodges.

[a]5 missing.

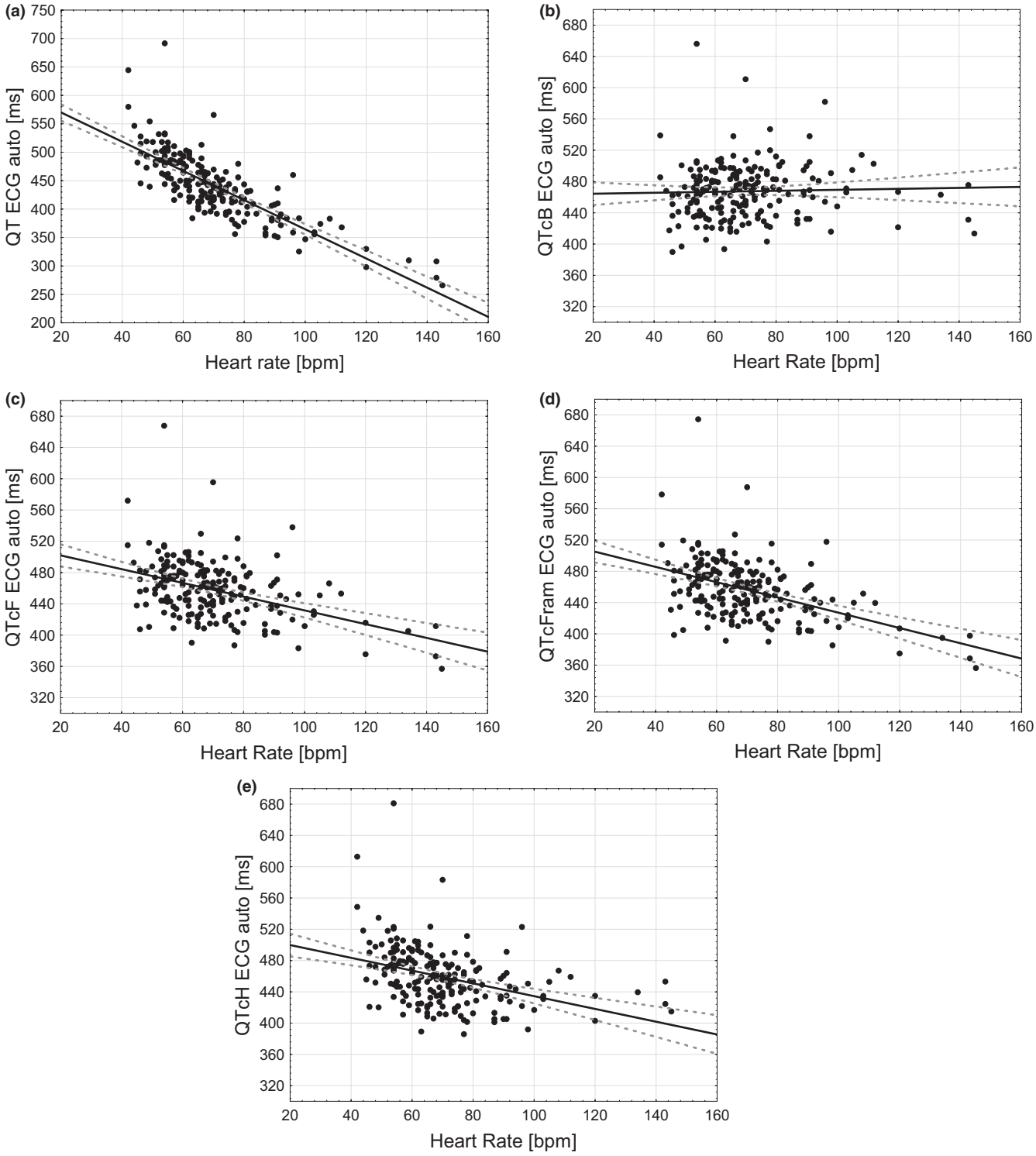

FIGURE 1 QT/HR (panel a) and QTc/HR relationships applying Bazett's (QTcB, panel b), Fridericia's (QTcF, panel c), Framingham's (QTcFram, panel d), and Hodges' (QTcH, panel e) formulae. Bazett's formula was the only method resulting in a QTc without relation with heart rate. See Table 2 for comparison of slope values (k), Spearman's regression coefficients (r_s), and *p*-values

p-value to 1.0, the better the method. QTcB shows no significant correlation with HR, while there is a significant relation between QTcF, QTcFram, and QTcH on the one hand and HR on the other. The results were similar when the subgroup of children <16 years ($n = 52$, 30 females) was analyzed separately; Figure S1, panels a-e.

3.3 | QTc formulae before and after initiation of beta blockade

In a subgroup of 44 individuals (34 women, 77%, 36 LQT1, 82%) in the Gothenburg cohort, ECGs were available before and after the

TABLE 2 QT correction applying 4 formulae

		QTcB			QTcF			QTcFram			QTcH		
LQTS type	***n***	***k***	r_s	***p***	***k***	r_s	***p***	***k***	r_s	***p***	***k***	r_s	***p***
1	167	0.14	−.11	NS	−0.83	−.35	***	−0.95	−.39	***	−0.84	−.44	***
2	33	−0.14	−.01	NS	−0.99	−.47	**	−1.03	−.49	**	−0.73	−.58	***
1 & 2	200	0.06	.10	NS	−0.88	−.37	***	−0.98	−.41	***	−0.82	−.46	***

Abbreviations: H, Hodges' formulae; k, slope; LQTS, long QT syndrome; QTc, QT interval corrected using B = Bazett's, *F* = Fridericia's, Fram = Framingham's; r_s, Spearman's regression coefficient.

**$p < .01$,

***$p < .001$.

initiation of beta blocking therapy (Table S1). Propranolol was the most common betablocker (43%) followed by metoprolol (25%). The median interval was 474 days between the two ECGs with a wide variation between 9 days and 21 years. We applied the same analyses as above and found the same result: Only with Bazett's formula, there was no relation between QTc and HR (Figure 2).

3.4 | Diagnosis and risk stratification based on QTc—a concordance analysis

According to the Schwartz diagnostic criteria, a QTcB ≥ 480 ms implies 3 points where ≥3.5 points indicate a high probability of LQTS (Schwartz, 2006). Using QTcB ≥ 480 ms as the reference, the Cohen's kappa values for ≥480 ms for QTcF, QTcFram, and QTcH were 0.629, 0.588, and 0.487, respectively. Using QTcB ≥ 500 ms as the reference, indicating a high risk for events (Goldenberg et al., 2008; Priori et al., 2003), the corresponding kappa values for a QTc ≥ 500 ms for QTcF, QTcFram, and QTcH, were 0.647, 0.612, and 0.469, respectively. Using the 5-level categorization, 0.41–0.60 is "moderate" and 0.61–0.80 "good" agreement (Kwiecien et al., 2011). For both diagnostic and prognostic purposes, the best agreement was between QTcB and QTcF and the worst between QTcB and QTcH in this cohort. Table S2 shows the number of patients with QTc exceeding these threshold values and the 95% confidence intervals for the kappa values. The confidence intervals for the kappa values of the 6 comparisons overlapped.

4 | DISCUSSION

We compared the suitability of the four most common QT correction formulae (Bazett, Fridericia, Framingham and Hodges) in 200 patients of all ages with genetically confirmed LQTS type 1 and 2. Bazett's correction formula was the only method resulting in a QTc without relation with HR. The initiation of beta blocking therapy did not alter this result. When a QTcB ≥ 480 ms was used as reference for diagnostic and a QTcB ≥ 500 ms for prognostic purposes, there was a disagreement between the formulae that was not negligible in the individual patient. With the Bazett formula, we identified 67 patients with a QTc ≥ 480 ms out of which 17–22 would be missed using the other formulae. For a QTcB ≥ 500 ms, the difference was less due to a small number of patients. HR correction of the QT interval with Bazett's formula remains preferable in the LQTS context, at least for LQT1 and 2.

Earlier studies outside the LQTS context have shown a strong correlation between QTcB and HR which has raised doubts about the applicability of Bazett's formula. Thus, Strohmer identified the Fridericia formula as the most accurate for correcting the QT interval in a population of middle-aged patients in an atherosclerosis prevention program (Strohmer et al., 2007). Vandenberk concluded that Fridericia and Framingham were the best methods in an unselected hospital cohort (Vandenberk et al., 2016). In addition, Indik et al. (2006) observed that both Bazett and Fridericia introduced errors in the assessment of drug effects on the QT interval.

For the diagnostic purpose, Bazett is currently the recommended formula when calculating the Schwartz score (Schwartz, 2006). Our results show that 3 points would not have been reached in 8%–11% of LQT1 and 2 mutation carriers if the three other formulae had been applied instead of Bazett's. Furthermore, in a study of a large LQT3 family, Bazetts´s formula was shown to be at least as good as other QT correction formulae for identifying gene carriers (Brouwer et al., 2003). Recently, Vink et al. showed that the QT interval was influenced by age, sex, the correction formula, and the method for defining the end of the T wave and, therefore, suggested the use of a web-based QT calculator (Vink et al., 2018). We have, however, not been able to identify any report on how well the different formulae eliminates the inverse QT/HR relation in LQTS patients which is the point of correcting the QT interval for HR.

From the prognostic perspective, Priori et al. found a correlation between LQTS type and QTcB as well as a correlation between the QTcB and the likelihood of cardiac events. They used QTcB 500 ms as cutoff point for categorical risk stratification (Priori et al., 2003), which also was applied in a review by Goldenberg et al. (2008). Subsequently, Barsheshet et al. identified Bazetts's formula as the best predictor of life-threatening events in LQT1 patients (Barsheshet et al., 2011). When we compared the four correction formulae with regard to 500 ms as threshold value, we found a level of disagreement, which is not negligible for risk prediction in the individual patient. Although different diagnostic thresholds for different QTc formulae have been presented recently by Vink et al. (2018), as discussed above, the available prognostic information is based on QTcB (Priori et al., 2003). In the clinical setting and for the individual patient, a diagnosis of LQTS also warrants risk assessment, and our

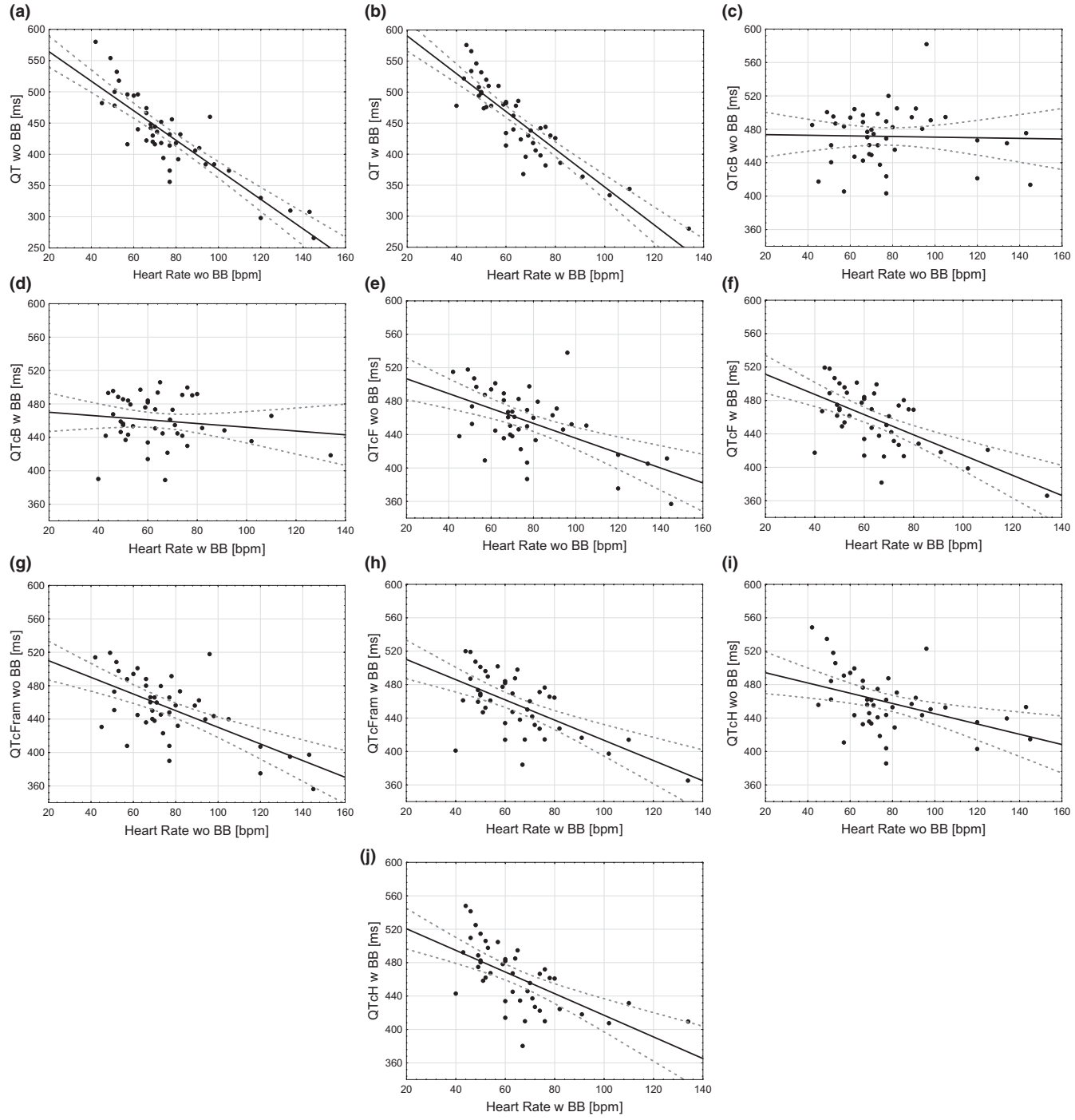

FIGURE 2 QT/HR (panels a,b) and QTc/HR relationships applying Bazett's (QTcB, panels c,d), Fridericia's (QTcF, panels e,f), Framingham's (QTcFram, panels g,h), and Hodges' (QTcH, panels i,j) formulae before and after betablockade. Bazett's formula was the only method resulting in a QTc without relation with heart rate

results corroborate the use of QTcB for both purposes, at least in LQT1 and 2.

4.1 | Methodological aspects and limitations

From a physiological and pathophysiological point of view, previous work implies that an individualized corrected QT interval based on the QT/HR relation at different HRs obtained from Holter recordings might provide the most correct picture including in LQTS patients (Malik et al., 2008; Robyns et al., 2017). This method requires an elaborate analysis and has not yet gained general acceptance and proven to be clinically useful. Furthermore, the QT interval at a certain HR may differ depending on whether HR is increasing or decreasing (Malik et al., 2008; Rosen & Bergfeldt, 2015). Preferably, and for studies on ventricular repolarization at rest, an

electrocardiographic recording should be preceded by ≥3 min of supine rest (Seed et al., 1987). Since many ECGs in this study were obtained as part of clinical routine, we cannot guarantee that this principle was followed in all recording procedures. Another limitation is that only a single ECG per patient was used, as in most previous studies. Goldenberg et al. pointed out variability between serial ECGs during follow-up and that repeated ECGs should be used to improve risk stratification (Goldenberg, et al., 2006). Presently, the method applied in this study is the most established for testing the ability of different formulae to eliminate the QT/HR relation (Dogan et al., 2005; Goldenberg, et al., 2006; Indik et al., 2006; Phan et al., 2015; Strohmer et al., 2007; Vandenberk et al., 2016; Vink et al., 2018). Although most of the LQTS patients in two large regions of Sweden were included in the present study, the number of participants was limited. Nevertheless, the results seem robust according to the statistical analyses. The number of children was limited, but the result was similar when this subgroup was analyzed separately; only Bazett's formula eliminated the inverse relation between QT and HR. Our result corroborates the result of Phan et al. who studied infants and young children and found support for the continued use of Bazett's formula (Phan et al., 2015).

4.2 | Conclusion

In a cohort of LQTS patients type 1 and 2, only Bazett´s formula eliminated the inverse relation between QT and HR, irrespective of the presence of beta blockers. Our results corroborate the continued use of QTcB for both diagnostic and prognostic purposes in the LQTS context.

CONFLICT OF INTEREST

The authors have no conflicts to disclose.

ETHICAL APPROVAL

The study was performed in accordance with the principles of the Helsinki declaration and approved by the regional ethics committees.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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