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QTc interval on 24-hour holter monitor: To trust or not to trust?

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Abstract

Introduction: QT interval represents the ventricular depolarization and repolarization. Its accurate measurement is critical since prolonged QT can lead to sudden cardiac death. QT is affected by heart rate and is corrected to QTc via several formulae. QTc is commonly calculated on the ECG and not the 24-h Holter.

Methods: 100 patients presenting to our institution were evaluated by an ECG followed by a 24-h Holter. QTc measurement on both platforms using Bazett and Fridericia formulae was recorded and compared.

Results: Mean age was 14.09 years, with the majority being males. Mean heart rate was 125.87. In the ECG, the mean QTc interval via the Bazett formula was 0.40 s compared with 0.38 s using the Fridericia formula. The mean corrected QT via the Bazett formula was 0.45, 0.39, and 0.42 s for the shortest RR, the longest RR, and the average RR, respectively. In contrast to the Fridericia formula, the corrected QT interval was 0.40, 0.39, and 0.40 s for the shortest RR, the longest RR, and the average RR, respectively. Using the Bazett formula, the highest specificity was reached during the longest RR interval (92.2%), while the highest sensitivity was recorded during the shortest RR interval (40%). As for the Fridericia formula, sensitivity always reached 0%, while the highest specificity was reached during the average RR interval.

Conclusion: QTc measured during Holter ECG reached a high specificity regardless of RR interval using the Fridericia and during the longest and the average RR interval for the Bazett formula. The consistently low sensitivity reveals that Holter ECG should not be used to rule out prolonged QT.

KEYWORDS
conduction disturbances, event recorder, holter, pediatric electrophysiology, QT dispersion

1 | INTRODUCTION

The duration of the QT, or the ventricular repolarization, holds clinical significance whose true value has been historically approximated using the electrocardiogram (ECG). QT is measured from the beginning of the QRS complex to the end of the T wave. Accurate diagnosis of prolonged QT is critical to exclude life-threatening diseases such as ventricular fibrillation, which can lead to sudden cardiac death. Rate adaptation is an intrinsic property of QT where it is commonly affected by the heart rate (HR), which reflects on the RR interval. The faster the heart rate,

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the shorter the RR interval leading to a shorter QT interval and vice versa (Dickhuth et al., 1991; Luo et al., 2004). For this reason, many investigators have attempted to correct for the QT, namely QTc, to a value that might be predicted had the HR been around 60 beats per minute (Luo et al., 2004). Several large cohort studies have reported on a steady relationship between QTc and all-cause mortality and sudden cardiac death (Nielsen et al., 2014; Schouten et al., 1991).QTc measurement may either result in unnecessary treatment or preclude appropriate measures to be taken (Luo et al., 2004; Neyroud et al., 1998). Over 50 years ago, several formulae were developed to account for the dependence of QT on RR or heart rate. Assessment of QT and/or QTc is performed normally using the ECG, which only displays a limited number of beats. In this context, only a few studies attempted to assess QTc using the 24-hour Holter ECG (Charbit et al., 2006; Gueta et al., 2020; Linker et al., 1991; Merri et al., 1992; Viitasalo et al., 1996). In our study, we aimed at assessing the diagnostic performance of the QTc by the two most utilized formulae, Bazett and Fridericia, in 100 patients who underwent an ECG and a 24-h Holter recording.

2 | MATERIALS AND METHODS

2.1 | Equipment

This study aimed at comparing the QT interval between ECG and a 24-h Holter recording performed on the same set of pediatric patients presenting to the Children Heart Center (CHC) at the American University of Beirut Medical Center. Standard ECG was performed using a digital 12-lead ECG machine with a tape speed of 25 mm/s, and 10 mm/mV for amplitude. The ambulatory ECG recording was obtained using a portable Holter machine with leads I, II, and aVF (Medilog FD12PLUS; Schiller Manufacturing, Switzerland). The Holter monitor was applied for 24 h, and the ECGs were performed by skilled technicians while in a resting supine position.

2.2 | Patients and variables

This study was approved by our Institutional Review Board and had been performed in accordance with the ethical standards in the Declaration of Helsinki and its later amendments. The Institutional Review Board number is BIO-2018–0363. The medical records of patients younger than 21 years who presented to our institution, between January 2014 and January 2018, for evaluation of cardiac symptoms, were reviewed. Patients presented to the CHC for complaints of chest discomfort, chest pain, or palpitations. The value of focusing on the pediatric population lies in the uniqueness of their cardiovascular diseases, the presentations, and the management. Only patients with an ECG and a complete 24-h Holter performed were enrolled. EEGs were inspected visually, and those that have artifacts interfering with the quality of the ECG were excluded. The variables collected included the following: sex, age at presentation, heart rate during ECG or Holter readings, QT and

RR intervals in ECG and Holter, and shortest and longest RR in the Holter reading. Two validated formulas were used to report the corrected QT (QTc) intervals:

1. Bazett formula: $QTc = QT/(RR^{1/2})$
2. Fridericia formula: $QTc = QT/(RR^{1/3})$

QT was measured from the onset of the Q wave to the end of the T wave. The average of QTc in Holter readings during the shortest RR and longest RR intervals was also reported for each patient using both formulas. In this manuscript, age- and gender-specific cutoff values were used to maximize accuracy. In boys, the following cutoff values were used (453, 449, 448, and 449 msec) for ages 6 months, 12 months, 5 years, and 18 years, respectively. In girls, 448, 446, 442, and 457 msec were used for the same age intervals. The normal values for QT for both males and females in the different age groups were derived from a validated reference (Johnson & Ackerman, 2009; Rijnbeek et al., 2001).

2.3 | Statistical analysis

Intervals have been manually calculated by experienced cardiologists at the CHC. Lead II is the lead used by the cardiologists to calculate the QT interval. Means with standard deviations were calculated for continuous variables (age, heart rate, QT, RR, and QTc), and percentages were calculated for categorical variables (sex and QTc prolongation). To compare categorical variables, chi-square and Fisher's exact tests were used. The paired t test was used to compare QT between ECG and Holter readings. To assess sensitivity and specificity of Holter-derived QT intervals, receiver operating characteristic curve analysis was conducted and the area under the curve (AUC) was reported.

By including 70 patients, we would obtain a power of 80% with a 2-sided 5% level of significance to detect a significant difference in QT between ECG and Holter. p-value was considered significant if p-value was = <.05. All statistical analyses were conducted through SPSS software (version 24 IBM®; SPSS® Inc.).

3 | RESULTS

A total of 100 patients who fulfilled the eligibility criteria were enrolled in our study. All of these patients were younger than 21 years with a mean age of 14.09 years. The majority belonged to the age category between 13 and 21 years (68%), and the majority were males (52%). An ECG and a Holter were performed on all patients. The mean HR was 125.87. The mean RR interval in the ECGs was 0.7 s. In the ECG, the mean QTc interval via the Bazett formula was 0.40 s compared with 0.38 s using the Fridericia formula. During the Holter procedure, the shortest and longest RR intervals were recorded along with their averages for each patient. The corrected QT intervals using both formulae were calculated during the shortest RR, the longest RR, and the average RR for each patient. The median-corrected QT via the Bazett formula was 0.45, 0.39, and

TABLE 1 Demographic and clinical characteristics of the patients and their QT measurements

	N	Mean (SD)
Age	100	14.09 (4.27)
Age category (years)	100	
1–3	2	(2%)
4–5	2	(2%)
6–8	6	(6%)
9–12	22	(22%)
13–16	35	(35%)
17–21	33	(33%)
Gender	100	
Male (%)	52	(52%)
HR	100	125.87 (18.38)
ECG (sec)		
RR	100	0.70 (0.19)
QT	100	0.33 (0.04)
QT corrected (Bazett)	100	0.40 (0.04)
QT corrected (Fridericia)	100	0.38 (0.04)
Holter (sec)		
RR		
Shortest	100	0.49 (0.11)
Longest	100	1.05 (0.28)
Average	100	0.77 (0.14)
QT		
Shortest	100	0.31 (0.04)
Longest	100	0.38 (0.05)
Average	100	0.35 (0.03)
QT corrected (Bazett)		
Shortest	100	0.45 (0.47)
Longest	100	0.39 (0.07)
Average	100	0.42 (0.04)
QT corrected (Fridericia)		
Shortest	100	0.40 (0.44)
Longest	100	0.39 (0.54)
Average	100	0.40 (0.03)

0.42 s for the shortest RR, the longest RR, and the average RR, respectively. In contrast to the Fridericia formula, the corrected QT interval was 0.40, 0.39, and 0.40 s for the shortest RR, the longest RR, and the average RR, respectively (Table 1).

Mean RR was calculated in both the ECG reading and the Holter recording (longest, shortest, and average RR). Mean QTc was calculated via the two formulae and compared among all the different RR measurements and the ECG reading. QTc from both formulae reached highest measurements when calculated using the shortest RR. In addition, QT readings were higher when calculated from the Holter than when calculated from the ECG reading in most instances. In the Bazett formula, the comparison of QTc from the ECG and the three different RR measurements (shortest, longest, and average) reached statistical significance (p-value < .001, .008, and .018, respectively). As for the QTc calculated using the Fridericia formula, the comparison between QTc from the ECG and the RR measurements reached statistical significance in all but the longest RR measurements (Table 2).

The prolongation of QTc from both formulae using ECG was measured against that from the three different Holter readings. 40% of QTc that were prolonged by the Bazett formula in ECG were also prolonged by the Holter recording using the shortest RR compared with none using the Fridericia formula. All QTc that were prolonged by Bazett and Fridericia formulae in ECG were not prolonged using the longest RR. 90% of QTc prolonged by the Bazett formula via ECG were not prolonged in the shortest RR from the Holter machine compared with 100% using the Fridericiaformula. None of these comparisons reached statistical significance (Table 3).

Diagnostic studies were performed to assess the diagnostic performance of Holter in accurately reporting QT prolongation compared with the standard method, ECG. Using the Bazett formula, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 40%, 50%, 9.1%, and 88%, respectively, during the shortest RR interval. During the longest RR interval, the sensitivity, specificity, PPV, and NPV were 0%, 92.2%, 0%, and 89.2%, respectively. If the average of the RR intervals is used, the sensitivity, specificity, PPV, and NPV reach 1%, 87.8%, 8.3%, and 89.7%, respectively. If the Fridericia formula is used, the sensitivity and PPV were 0% for all RR intervals. However, the specificity for the shortest RR, the longest RR, and the average RR were 90.8%, 96.9%, and 93.8%, respectively. The NPV for the shortest RR, the

TABLE 2 Comparison of RR, QT, and QTc among ECG and Holter readings using Bazett and Fridericia formulae

	ECG	24-h Holter					
		Shortest RR		Longest RR		Average RR	
Measurement (s)	Mean (SD)	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
RR	0.704 (0.188)	0.499 (0.112)	<0.001*	1.045 (0.278)	<0.001*	0.772 (0.142)	0.001*
QT	0.339 (0.048)	0.318 (0.045)	<0.001*	0.389 (0.055)	<0.001*	0.354 (0.039)	0.001*
QTc (Bazett)	0.409 (0.044)	0.453 (0.047)	<0.001*	0.390 (0.067)	0.008*	0.422 (0.036)	0.018*
QTc (Fridericia)	0.384 (0.039)	0.402 (0.044)	<0.001*	0.388 (0.053)	0.430	0.396 (0.034)	0.006*

Note: *P < 0.05.

TABLE 3 Comparison of prolonged QTc utilizing Bazett and Fridericia formulae

		QTc on Holter								
		Shortest RR			Longest RR			Average RR		
QTc on ECG		Prolonged	Not prolonged	p-value	Prolonged	Not prolonged	p-value	Prolonged	Not prolonged	p-value
Bazett	Prolonged	4 (40.0)	6 (60.0)	1	0 (0.0)	10 (100.0)	0.741	1 (10.0)	9 (90.0)	1
	Not prolonged	45 (50.0)	45 (50.0)		7 (7.8)	83 (92.2)		11 (12.2)	79 (87.8)	
Fridericia	Prolonged	0 (0.0)	2 (100.0)	1	0 (0.0)	2 (100.0)	1	0 (0.0)	2 (100.0)	1
	Not prolonged	9 (9.2)	89 (90.8)		3 (3.1)	95 (96.9)		6 (6.1)	92 (93.9)	

longest RR, and the average RR was 97.8%, 97.9%, and 97.8%, respectively, (Tables 4 and 5).

A receiver operating characteristic (ROC) curve was created for QTc obtained from the Bazett formula. QTc for the shortest, the longest, and the average RR showed very low area under the curve (0.463, 0.573, and 0.597, respectively), indicating a low sensitivity and specificity for Holter to diagnose QT prolongation (Figure 1).

4 | DISCUSSION

QT interval represents the depolarization and repolarization of the right and left ventricles, and it is known to be dependent on the heart rate. Its accuracy at different heartbeats has been historically challenged (Smulyan, 2018. It has been previously shown that the first portion of the QT interval (ending at the peak T wave) is the part that is mostly affected by the cycle length (Merri et al., 1992; Christiansen et al., 1996). For this reason, many investigators have attempted to correct for the QT. Left undiagnosed, prolonged QTc can provoke torsades de point, which is a dangerous underlying heart condition that can lead to sudden cardiac death (Indik et al., 2006). Because of the catastrophic implications of undiagnosed prolonged QT interval, correcting QT to QTc and obtaining an accurate recording of QTc are critical. For example, the Romano–Ward long QT syndrome (LQTS) is an autosomal dominant disease that affects the cardiac channels making the heart susceptible to arrhythmias. This disease has high mortality if left untreated or undiagnosed. Other conditions that may affect QT are arrhythmias, medication use, body temperature, electrolyte disturbances, and other diseases (Luo et al., 2004; Neyroud et al., 1998). Four commonly used formulas were created that take into consideration the complex relationship between RR and QT. The Bazett formula is the most used formula, and it divides the QT by the square root of RR. Despite that, the Bazett formula is known to overcorrect the QT at higher heart rates and undercorrect at lower ones. However, Brouwer et al concluded that the effect of the phenomenon does not seem to affect its diagnostic performance (Brouwer et al., 2003). The second most used formula is the Fridericia, which uses the cube of the RR instead. Other formula corrections such as Framingham and Hodges adjust for age, gender, and other variables but are less widely utilized (Malik et al., 2002; Rautaharju et al., 2009). Several authors have compared the QTc from the four formulas in order to assess its accuracy (Merri et al., 1992; Dickhuth et al., 1991; Linker et al., 1991; Luo et al., 2004; Neyroud et al., 1998; Viitasalo et al., 1996). Brouwer et al compared all four formulae in patients with LQTS. He reported that the differences between QTc from the formulae were only marginal and not statistically significant during an ECG. He also concluded that the Bazett formula was as good as the other formulae to diagnose prolonged QT in patients with LQTS. In addition, he revealed that using the Bazett formula at the lowest heart rate (or longest RR) during a 24-h Holter provided a clear distinction between carriers and non-carriers of the mutant gene, with specificity and sensitivity above 90% (Brouwer et al., 2003).

TABLE 4 Performance characteristic of Holter compared with ECG in diagnosis of prolonged QTc using the Bazett formula

Holter	N	TP	TN	FP	FN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	PPV	NPV
Shortest RR	100	4	45	45	6	40.0% (13.7–72.6%)	50.0% (39.4–60.6%)	0.8(0.36–1.76)	1.20(0.36–1.76)	8.1%	88%
Longest RR	100	0	83	7	10	0.0% (0.0 –34.4%)	92.2% (84.1–96.5%)	0	1.08(1.07–1.08)	0%	89.2%
Average RR	100	1	79	11	9	1% (0.5–45.8%)	87.8% (78.7–93.4%)	0.82 (0.12–5.69)	1.02 (0.83–1.26)	8.3%	89.7%

TABLE 5 Performance characteristic of Holter compared with ECG in diagnosis of prolonged QTc using the Fridericia formula

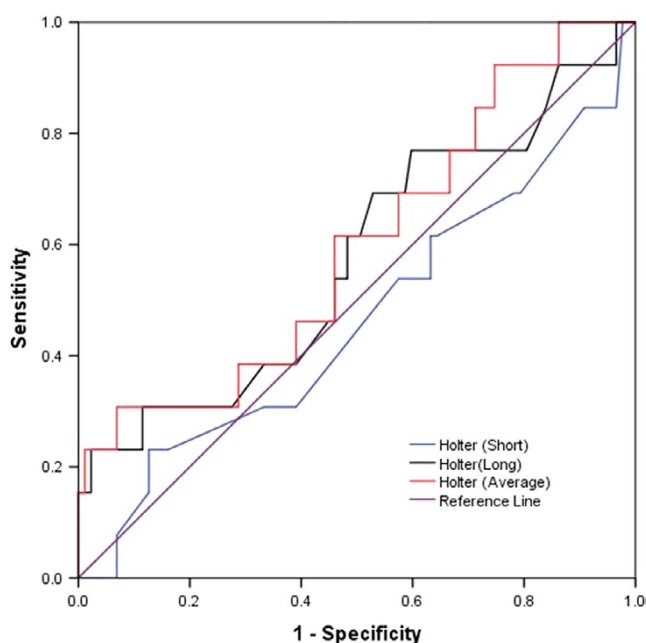| Holter	N	TP	TN	FP	FN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	PPV	NPV
Shortest RR	100	0	89	9	2	0.0% (0.0 –80.2%)	90.8% (82.8–95.4%)	0	1.10 (1.09–1.10)	0%	97.8%
Longest RR	100	0	95	4	2	0.0% (0.0 –80.2%)	96.9% (90.6–99.2%)	0	1.03 (1.03–1.03)	0%	97.9%
Average RR	100	1	93	5	1	0.0% (0.0 –80.2%)	93.8% (86.6–97.4%)	0	1.07 (1.06–1.07)	0%	97.8%

FIGURE 1 Receiver operating characteristic curve of the QTc from the Bazett formula compared between ECG and Holter

In the recent years, research has shown that even QTc exhibits diurnal variations within the same individual (Charbit et al., 2006; Christiansen et al., 1996). The relationship between QT and heart rate is so complex that normal limits of QT using correction formulae may vary among different individuals. Also, the QTc of normal subjects has been shown to demonstrate diurnal variation (longer during sleep and during REM sleep in particular), and the QTc is significantly longer in winter months than in summer months. More research is needed that is geared toward understanding this phenomenon (Indik et al., 2006).

As such, some authors attempted to examine the cardiac rhythm under prolonged intervals, such as a 24-hour Holter recording. This provides a continuous flow of information in attempts to increase the yield. However, there are well-known downfalls to assessing QT on the 24-hour Holter ECG due to the presence of signal filtering and recording methods (Lutfullin et al., 2013). This was further asserted in research regarding patients with genetically confirmed long QT syndrome whose ECG recording revealed normal QTc at times (Merri et al., 1992; Charbit et al., 2006; Christiansen et al., 1996; Gueta et al., 2020; Linker et al., 1991; Neyroud et al., 1998; Viitasalo et al., 1996). Neyroud et al reported on the diagnostic performance of QTc in both ECG and ambulatory 24-h Holter in patients with genotypical Romano–Ward LQTS and normal patients. The rate of dependence of QT on HR differed between day and night where it increased at night and was relatively stable throughout the day. With genetic test as their reference method, prolonged QTc by ECG had a 76% sensitivity and 84% sensitivity. On the contrary, Holter ECG had 88% sensitivity and 96% specificity in predicting long QT syndrome (Neyroud et al., 1998). Similarly, Merri et al reported similar findings when they compared QTc using the Bazett formula between participants without a cardiac disease and individuals with LQTS from both an ECG and a 24-hour Holter recording (Merri et al., 1992). Lutfullin et al assessed QTc by ECG and Holter and concluded that the ECG QTc interval correlated with that on Holter-only autonomic nervous system on the heart's electrophysiology (Indik et al., 2006; Lutfullin et al., 2013).

One study that compared QTc in ECG and Holter belonging to the same patients reported that Holter recordings underestimated QTc in lead V_1 and overestimated that in lead V_5. The authors concluded that despite the differences, QTc measurement remained similar but not sufficiently enough to warrant the use of Holter instead of ECG (Christiansen et al., 1996). Despite having a high correlation between ECG and Holter, the agreement between the two methods was low;

results that were replicated in other studies (Christiansen et al., 1996; Morganroth et al., 1991). Morganroth et al used a similar methodology and reported that in individuals without QTc prolongation on ECG, 55% of them had QTc prolongation on 24-h Holter recording with a wide variability throughout the day (Morganroth et al., 1991).

Proper representation of the slowly moving components of the ECG strip, such as the P and T waves, is crucial to ensure accurate measurement. Artifacts, such as those resulting from electrode placement, can have diverse effects on different intervals. There is, knowingly, less distortion in the ECG than there is in the ambulatory Holter recording. These distortions come in the form of T-wave and S-wave amplitudes, ST segments, and others. On the contrary, the Holter machine does not have the same frequency response as does the ECG. Also as such, accurate reproducibility, and measurement of the ST wave, for example, is affected (Rautaharju et al., 2009). More studies are needed to address and compare the S- and T-wave morphologies between ECG and Holter.

This is the first regional study to calculate correct QT in the same set of patients using two formulae obtained from two sources: ECG and 24-h Holter monitoring. In our study, we demonstrated that, if comparing using the Bazett formula, Holter recording exhibits high specificity to predict true prolonged QTc only during the longest RR intervals or low heart rates. On the contrary, the Fridericia formula had a high specificity regardless of RR interval. While sensitivity was 0% using the Fridericia formula, it approached 40% using the Bazett formula during the shortest RR intervals or increased heart rates. If we were to only utilize the Bazett formula, a simultaneously high specificity and sensitivity cannot be achieved.

This study has a few limitations. First, all the Holter recordings were performed using the same machine from a single manufacturer. The frequency characteristics may differ among different machines from different manufacturers around the globe. Another inherent limitation is the comparison between the 12-lead ECG and the two leads, namely V_1 and V_5, in the Holter recording. The assessment of QT interval is known to be affected by lead placement, which may be placed along different planes between the ECG and the Holter. Based on our study, we advise caution in utilizing the Holter recording as a diagnostic or screening tool for prolonged QT interval. Without obvious prolongation evident on the strip, it is common to have false positives or false negatives. This caution has been raised by other authors who devised similar methodologies. Research regarding QTc in Holter records with much larger sample sizes is also needed. Comparing QTc from Holter monitor with more accurate standardized methods such as a genetically confirmed LQTS may present higher accuracy than the one presented in our study.

5 | CONCLUSION

Holter ECG possesses low sensitivity to rule out prolonged QTc. The higher specificity is not sufficient to warrant the exclusive use of Holter ECG in diagnosing prolonged QT. Extensive future research is needed that incorporates the individual's clinical, pharmacological,

and biochemical variables into a patient-specific algorithm to produce a reliable QTc. Caution is to be advised when using Holter recording solely for QTc interpretation.

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