Received: 15 May 2024 | Revised: 26 July 2024 | Accepted: 14 August 2024

DOI: 10.1111/aas.14515

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Intraoperative QTc interval interpretation: Effects of anaesthesia, ECG, correction formulae, sex, and current limits

A Prospective Observational Study

Thomas Krönauer[1] | Lorenz L. Mihatsch[1,2,3] | Patrick Friederich[1,2]

[1]Department of Anaesthesiology, Intensive Care Medicine, Pain Therapy, München Klinik Bogenhausen, Munich, Germany

[2]TUM School of Medicine and Health, Technical University of Munich, Munich, Germany

[3]Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany

Correspondence
Thomas Krönauer, c/o Klinik für Anästhesiologie, Operative Intensivmedizin und Schmerztherapie, München Klinik Bogenhausen, Englschalkinger Str 77, 81925 München, Munich, Germany.
Email: thomas.kroenauer@uk-augsburg.de

Present address
Thomas Krönauer, Anesthesiology and Operative Intensive Care Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany.

Funding information
Departmental funding only

Abstract

Background: Severe QT interval prolongation requires monitoring QTc intervals during anaesthesia with recommended therapeutic interventions at a threshold of 500 ms. The need for 12-lead ECG and lack of standardisation limit such monitoring. We determined whether automated continuous intraoperative QTc monitoring with 5-lead ECG measures QTc intervals comparable to 12-lead ECG and whether the interpretation of QTc intervals depends on the correction formulae and the patient's sex. We compared intraoperative QTc times to QTc times from resting ECGs of a population from the same region, to substantiate the hypothesis that patients under general anaesthesia may need specific treatment thresholds.

Methods: In this prospective observational study, intraoperative QT/QTc intervals were automatically recorded using 12 and 5-lead ECG in 100 patients (44% males). QTc values were analysed for sex and formula-specific aspects after correction for heart rate according to Bazett, Fridericia, Hodges, Framingham, Charbit and QTcRAS, and compared to a regional community-based cohort. The level of significance was set to $\alpha = 0.05$.

Results: QT interval duration was not significantly different between 12-lead and 5-lead ECG (difference − 0.09 ms ± 8.5 ms, $p = 0.793$). The QTc interval duration significantly differed between the correction formulae ($p < 0.001$) and between sexes ($p < 0.001$). Mean intraoperative QTc duration was higher than in resting ECGs from a large community-based population with the same regional background (438 vs. 417 ms). The incidence of prolonged values >500 ms significantly depended on the correction formula ($p < 0.001$) and was up to tenfold higher in women versus men.

Conclusion: Intraoperative QTc interval measurement using a 5-lead ECG is valid. Correction formulae and gender influence the intraoperative QTc interval duration

Preliminary data for this study was presented online as a poster presentation at the virtual Euroanaesthesia meeting of the ESAIC, 17–19 December 2021.

and the incidence of pathologically prolonged values according to current limits. The consideration and definition of sex-specific normal limits for QTc times under general anaesthesia, therefore, warrant further investigation.

KEYWORDS
electrocardiogram, intraoperative monitoring, long QT syndrome, torsade de pointes, ventricular arrhythmia

Editorial Comment

In this study, corrected QT intervals were compared between a 5- and 12-lead ECG in a cohort undergoing general anaesthesia, and then compared with another cohort measured in an ambulatory setting. This identified that 5-lead ECG is sufficient to estimate QTc, and that prolonged QTc was very common under anaesthesia using commonly used heart rate adjustment formulas. This suggests that the reference range for QTc or adjustment formulas might need to be reconsidered for measurements during anaesthesia.

1 | INTRODUCTION

Congenital and acquired long QT syndromes predispose to ventricular arrhythmia, for example Torsade de Pointes and sudden cardiac death.[1,2] As QT prolongation and Torsade de Pointes may occur during perioperative care,[3–7] monitoring perioperative QTc interval prolongation has been repeatedly recommended.[3,5,7] However, such measurements have not become a clinical routine. This may be partly due to the need to record a 12-lead ECG for QTc interval determination,[8] including manual analysis of QTc intervals during ongoing surgery.[9] Both 12-lead ECG recording for QTc interval determination and manual analysis of QTc intervals are impractical in many perioperative settings.[10] However, the feasibility of a computer-based algorithm for automated intraoperative measurement of QTc intervals using 12-lead ECG has been demonstrated.[11] In addition, automated ECG monitoring with a reduction of leads is available[12,13] and may facilitate QTc interval measurement. Whether an intraoperative 5-lead ECG with automated monitoring of QTc intervals measures statistically identical values compared with the validated 12-lead ECG and is thus feasible has not been investigated so far.

There are several different correction formulae, for example Bazett, Fridericia, Hodges, Framingham, Charbit or QTcRAS, for correcting QT intervals for the patient's heart rate,[9,14–18] yielding QTc intervals. Although Bazett's formula is mostly used, some monitors allow switching to other formulae, for example Fridericia, Framingham and Hodges. Upper limits of normal for QTc interval duration between 430–450 ms and 450–460 ms have been suggested for men and women, respectively, irrespective of the correction formula used.[7,19,20] Various reasons for sex differences in cardiac repolarisation have been discussed.[21] A QTc interval duration >500 ms predicts short-term in-hospital mortality[22] and requires decisive diagnostic and therapeutic action.[23] This also appears to be the case for QTc interval prolongation during general anaesthesia to prevent the development of Torsade de Pointes.[3–5,7,24] However, intraoperative monitoring of the QTc interval has not been standardised so far. As different correction formulae[9,14–18] are likely to influence the incidence of prolonged QTc intervals, the choice of correction formula may influence the likelihood of diagnosing QTc interval prolongation with the need for recommended therapeutic intervention.

In addition, it has not been addressed whether normal values of QTc intervals defined outside the operating room in large cohorts of patients[18,25] without the influence of general anaesthetics, opioids and sedatives remain valid for patients during general anaesthesia. This may not be the case as many anaesthetic agents have complex pharmacological effects in addition to QTc interval prolongation,[26–28] including potentially relevant antiarrhythmic effects through suppression of sympathetic nervous system activity.[29]

Current practical limitations and lack of standardisation limit the recommended use of routine QTc interval determination during perioperative care. The aim of the current study was, therefore, threefold: Firstly, to compare automated QT interval measurements obtained by 12-lead ECG recordings to the intraoperatively commonly used 5-lead ECG. Secondly, to determine whether the incidence of prolonged QTc intervals during general anaesthesia depends on the correction formula used and on sex. Thirdly, to compare intraoperative QTc intervals from patients under general anaesthesia with QTc intervals from resting ECGs in a regional community-based study population,[18] to substantiate the hypothesis that current ECG normal limits for QTc intervals may be inappropriate in patients under general anaesthesia.

2 | METHODS

In this prospective observational study, QT intervals, heart rates and QTc intervals (Bazett correction) were measured automatically and continuously during surgery in 100 adult patients (44% males) with standard monitoring (QT-algorithm of the CarescapeB850 monitor, GE Healthcare, Chicago, Illinois, USA) at *München Klinik Bogenhausen*, Munich, Germany. All patients were in sinus rhythm. A pilot study had shown no significant difference between automated and manually determined QTc values (unpublished data). In addition, the automatically measured QT intervals and the corresponding heart rate were

manually recorded every 15 min (to avoid ECG artefacts) with both 12-lead and 5-lead ECG[8,30] for further analysis. Depending on the duration of surgery, an average of 9 (range 3–30; random intercept models were used to correct for multiple measurements) measurements were performed per patient, yielding 900 pairs of 12-lead and 5-lead ECG recordings for further analysis. Correction of the QT interval for heart rate for these pairs was performed by applying the correction formulae according to Bazett,[14] Fridericia,[15] Hodges,[16] Framingham,[17] Charbit,[9] and QTcRAS.[18] Age, sex and ASA classification were determined at inclusion. This manuscript adheres to the STROBE guidelines.

2.1 | Ethics approval

Ethical approval (ref. 100007) was approved by the ethics committee of the Bayerische Landesärztekammer on August 31, 2010. Written informed consent was obtained from all patients prior to inclusion in the study.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were age ≥18 years and written informed consent to participation after indication for surgery under general anaesthesia. Patients with atrial fibrillation, bundle branch block or pacemaker carriers were excluded from the study.

2.3 | Statistical analysis

Data were analysed using R, version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical demographic variables were compared between sexes using chi-squared tests, and for continuous variables, the non-parametric Wilcoxon test was used. Means ± standard deviations (SD) of continuous variables were corrected for multiple measurements using random intercept models without co-variables.[31] Wald tests were used to test for significant differences between the groups. Bland-Altman plots adjusted for multiple measurements were used to analyse the agreement between the two methods: (1) 12-lead versus 5-lead ECG recordings and (2) QT intervals corrected by Bazett versus Fridericia. Wald tests were used to determine whether the difference between the two methods differed significantly from zero. Likelihood Ratio (LR) tests were used to test if the difference between the two methods was linearly dependent on the mean value of the two methods, that is whether the slope of a linear regression line was significantly different from zero. The mean QTc intervals resulting from the different correction formulae were compared using the LR test. The t-test was used to test the maximum intra-individual differences between QTc_{Bazett} and $QTc_{Fridericia}$. The incidence of prolonged QTc intervals, depending on the correction formula, was analysed using logistic regression models with random intercepts to account for repeated measurements. All Wald and LR tests were adjusted for multiple measurements. Normality assumptions were tested using QQ-plot analysis and analysis of residuals. All tests were conducted under two-sided hypotheses. The significance level was set to $\alpha = 0.05$. Bonferroni correction was used to correct for α-error accumulation due to multiple testing.

2.4 | Sample size calculation

A pilot study in perioperative patients found an average QTc time of 438 ± 25 ms (unpublished observation). We therefore considered an effect size of 20 ms difference between 12-lead and 5-lead ECG recordings to be clinically relevant. Using a two-sided hypothesis *t*-test, a significance level of $\alpha = 0.05$, and a power of $1-\beta = 0.9$, the required number of patients for the study was determined to be at least 35.

3 | RESULTS

The demographic characteristics of the study population are shown in Table 1. There were no significant differences in any of the categorical variables of these parameters between the male and female patients. The inclusion period was from February to November 2011. The final analysis was performed in 2023.

TABLE 1 Patient characteristics.

Sex	***n* patients (*n* measurements, range)**		
Men	44 (397; 3–22)	Women	56 (503; 3–30)
Age [years]	**Mean ± SD (Range)**		
Men	55.4 ± 14 (26–81)	Women	58.1 ± 15 (23–84)

	***n* Patients (*n* Measurements)**	
ASA	**Men**	**Women**
ASA 1	2 (19)	5 (39)
ASA 2	21 (197)	27 (274)
ASA 3	18 (156)	20 (163)
ASA 4	3 (25)	3 (23)
ASA 5	0 (0)	1 (7)

	***n* Patients (*n* Measurements)**	
Anaesthesia	**TIVA**	**BA**
Men	38 (352)	6 (45)
Women	51 (468)	5 (35)

	***n* patients (*n* patients, *n* measurements)**	
Surgery	**Intracranial**	**Other**
Men	38 (38 TIVA; 352)	6 (6 BA; 45)
Women	50 (48 TIVA–2 BA; 459)	6 (3 TIVA–3 BA; 44)

Note: Demographic patient characteristics.
Abbreviations: ASA, American Society of Anaesthesiology risk group; BA: balanced anaesthesia; TIVA, total intravenous anaesthesia.

3.1 | 12-lead ECG recording

Heart rates ranged from 37 to 112 min^{-1} ($n = 900$; Figure 1A), with mean values of 61 ± 14 min^{-1} and 62 ± 11 min^{-1} in male and female patients, respectively ($p = 0.742$). The range of the measured QT intervals was 330–584 ms (443 ± 47 ms; $n = 900$; Figure 1B), with mean QT durations of 436 ± 47 ms ($n = 397$) and 449 ± 46 ms ($n = 503$) in men and women, respectively ($p = 0.127$).

3.2 | 12-lead vs. 5-lead ECG recording

QT duration resulting from 12-lead and 5-lead ECG recordings ($n = 900$) was not significantly different (−0.09 ± 8.5 ms; $p = 0.793$, Figure 1C). The mean difference in QT interval duration between 12-lead and 5-lead ECG recordings was −0.27 ± 11.8 ms in male and 0.10 ± 6.1 ms in female patients, respectively. QT intervals obtained by 12-lead ECG recording correlated significantly with those obtained by 5-lead ECG recording (Pearson's correlation coefficient $r = 0.98$; $R^2 = 0.96$; $p < 0.001$). The Bland-Altman analysis revealed a regression line with a slope and y-intercept that did not significantly deviate from zero ($(QT_{12}–QT_5) = −0.0009 \times (QT_{12} + QT_5)/2 + 0.03$; $df_{slope} = 205.8$, $T_{slope} = −0.146$, $P_{slope} = 0.884$; $df_{intercept} = 203.2$, $T_{intercept} = 0.113$, $P_{intercept} = 0.910$; Figure 1D).

3.3 | QT correction formula and QTc duration during general anaesthesia

QTc intervals calculated using different correction formulae ($n = 900$) differed significantly (LR test: $\chi^2 = 236.31$, $df = 5$, $p < 0.001$). QTc intervals ranged from 357 to 535 ms for Bazett to 381–561 ms for Hodges. The mean values of QTc intervals ranged from 438 ± 29 ms (QTcRAS) to 445 ± 33 ms (Hodges),(Table 2). Analysis of intraoperatively determined QTc intervals regressed on QT intervals demonstrated systematic differences between the formulae, with all slopes being significantly different from zero. Consequently, the incidence of values above the current limits of normal (>440 ms: $\chi^2 = 93.47$, $df = 5$, $p < 0.001$; >500 ms: $\chi^2 = 46.74$, $df = 5$, $p < 0.001$) depended significantly on the correction formula (Figure 2A,B). Bazett yielded the lowest incidence of prolonged QTc intervals >440 ms as well as >500 ms at heart rates below 50 min^{-1}

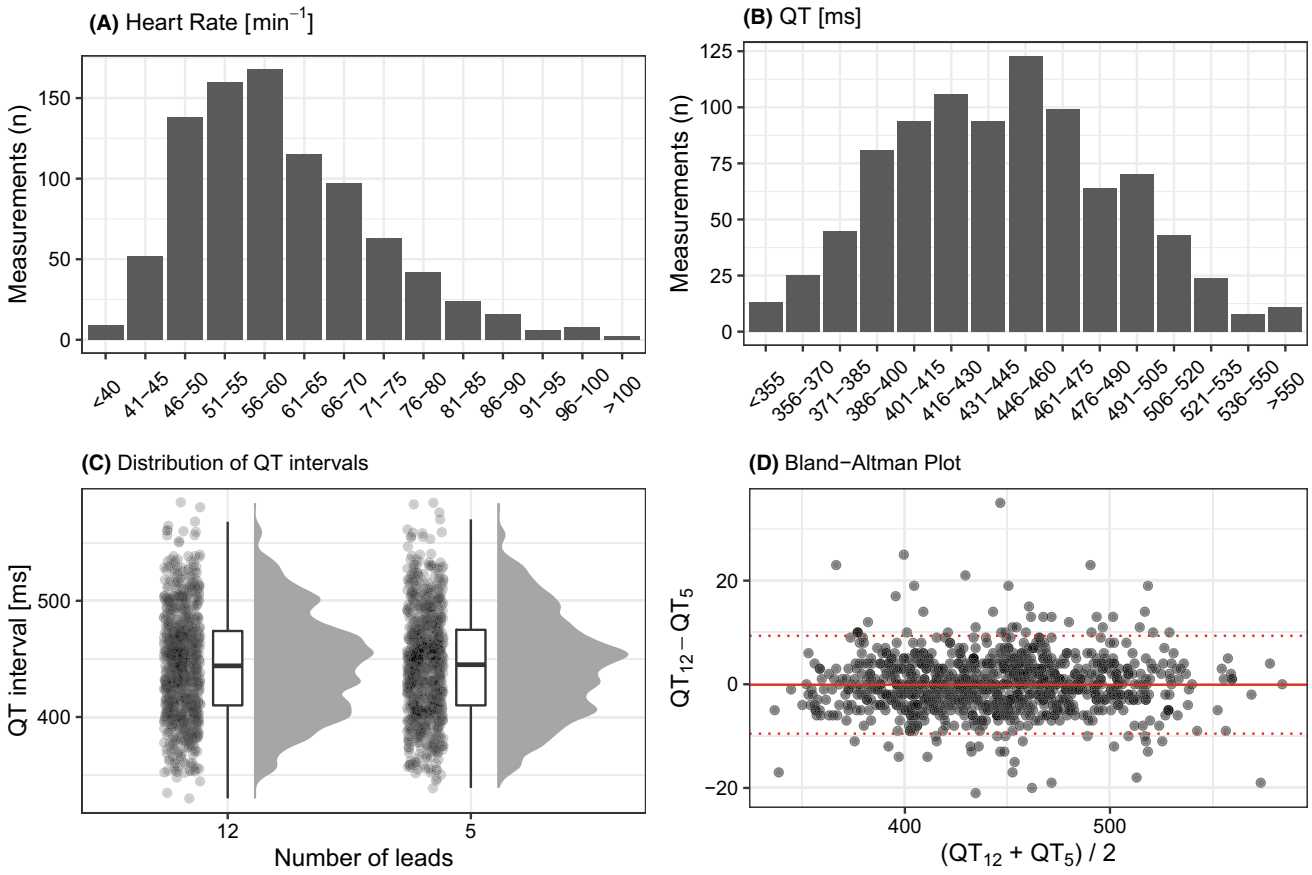

FIGURE 1 Distribution of heart rates and QT intervals. Distribution of measured intraoperative heart rates, QT intervals and comparison of 12-lead and 5-lead ECG measurements. (A) histogram of heart rates, (B) histogram QT intervals, (C) distribution (left sub-column), boxplot (middle sub-column) and empirical density (right sub-column) of intraoperative QT intervals measured by 12-lead (left) and 5-lead (right) ECG, (D) Bland-Altman analysis of intraoperative QT intervals measured by 12-lead and 5-lead ECG.

TABLE 2 Summary of QTc values and incidence of prolonged QTc intervals.

QTc [ms]	Bazett	Framingham	Fridericia	Hodges	Charbit	QTcRAS
All patients						
Mean ± SD	440 ± 29	440 ± 30	442 ± 30	445 ± 33	443 ± 31	438 ± 29
Range	357–535	361–541	372–538	381–561	374–555	364–544
Men						
Mean ± SD	430 ± 24	430 ± 26	432 ± 26	437 ± 30	434 ± 28	432 ± 25
Range	357–516	361–541	372–538	381–561	374–555	364–544
Women						
Mean ± SD	448 ± 30	448 ± 31	449 ± 31	452 ± 34	451 ± 32	444 ± 30
Range	377–535	381–523	384–521	386–549	378–532	372–515
Incidence of prolonged QTc interval [%]						
Men	**Bazett**	**Framingham**	**Fridericia**	**Hodges**	**Charbit**	**QTcRAS**
>430 ms	46	48	51	53	54	53
>450 ms	17	20	22	30	21	26
>500 ms	1	1	1	2	1	2
Women						
>430 ms	70	66	68	70	63	70
>450 ms	46	46	47	51	41	49
>500 ms	5	5	7	10	3	7

Note: The distribution of QTc interval duration and the incidence of prolonged QTc intervals obtained every 15 min during general anaesthesia were calculated for both genders using different correction formulae.

and the highest incidence of prolonged QTc intervals at heart rates above 70 min^{-1} (Figure 2A,B).

3.4 | Bazett correction versus Fridericia correction

Analysis of intraoperative QTc intervals calculated with the two most commonly used correction formulae (Bazett and Fridericia) showed similar mean values over all heart rates (Bazett: 440 ± 29 ms vs. Fridericia: 442 ± 30 ms, $n = 900$). Bland-Altman analysis of all measurements (Figure 3A, $n = 900$) revealed mean differences that were not significantly different from zero (−1.1 ± 14.3 ms, $T = -0.839$, $df = 98.96$, $p = 0.403$). Analysing groups with heart rates of 50–70 min^{-1} (Figure 3B, $n = 582$), below 50 min^{-1} (Figure 3C, $n = 157$) and above 70 min^{-1} (Figure 3D, $n = 161$) demonstrated heart rate dependence of the difference between Bazett and Fridericia corrections. At heart rates of 50–70 min^{-1} the mean difference was the smallest (−2.2 ± 7.7 ms, $T = -2.94$ $df = 83.5$, $p = 0.004$, Figure 3B). For heart rates lower than 50 min^{-1} the mean difference was negative (−19.5 ± 4.6 ms, $T = -31.16$, $df = 38.02$, $p < 0.001$, Figure 3C), and thus QTc_{Bazett} intervals were shorter than $QTc_{Friedericia}$ intervals. At heart rates above 70 min^{-1}, the mean difference was positive (18.3 ± 7.0 ms, $T = 18.46$, $df = 37.61$, $p < 0.001$, Figure 3D) and QTc_{Bazett} intervals were significantly longer than $QTc_{Friedericia}$ intervals. Bland-Altman analysis yielded regression lines with slopes significantly different from zero only for QTc intervals at heart rates above 70 min^{-1} ($(QTc_{Bazett}-QTc_{Fridericia}) = 0.082 \times (QTc_{Bazett} + QTc_{Fridericia})/2-17.7$, $T = 2.7$, $df = 86.87$; $p = 0.008$, Figure 3D). The intra-individual differences in maximum and minimum QTc interval duration were not significantly different between QTc_{Bazett} intervals and $QTc_{Friedericia}$ intervals (25 ± 11 vs. 23 ± 11 ms, $p = 0.207$, $n = 100$).

3.5 | QTc intervals in male and female patients

The QTc interval duration was sex-specific, with mean values ranging from 430 ± 23 ms (Bazett) to 437 ± 30 ms (Hodges) in male patients ($n = 397$) and from 444 ± 30 ms (QTcRAS) to 452 ± 34 ms (Hodges) in female patients ($n = 503$), respectively (Table 2). The incidence of QTc intervals >430 ms ranged from 46% to 54% in males, and the incidence of QTc intervals >450 ms ranged from 41% to 51% in female patients (Table 2). QTc intervals longer than 500 ms were present in 1%–2% and 3%–10% of the male and female patients, respectively (Table 2). The sex-dependent difference in QTc_{Bazett} intervals remained highly significant when comparing only one type of surgery (brain surgery) performed with one type of anaesthesia (total intravenous anaesthesia, $n = 38$ men versus $n = 48$ women, $T = 3.746$, $df = 83.9$; $p < 0.001$).

4 | DISCUSSION

The results of our study demonstrate that automated intraoperative recording of QTc interval duration using 5-lead ECG monitoring is

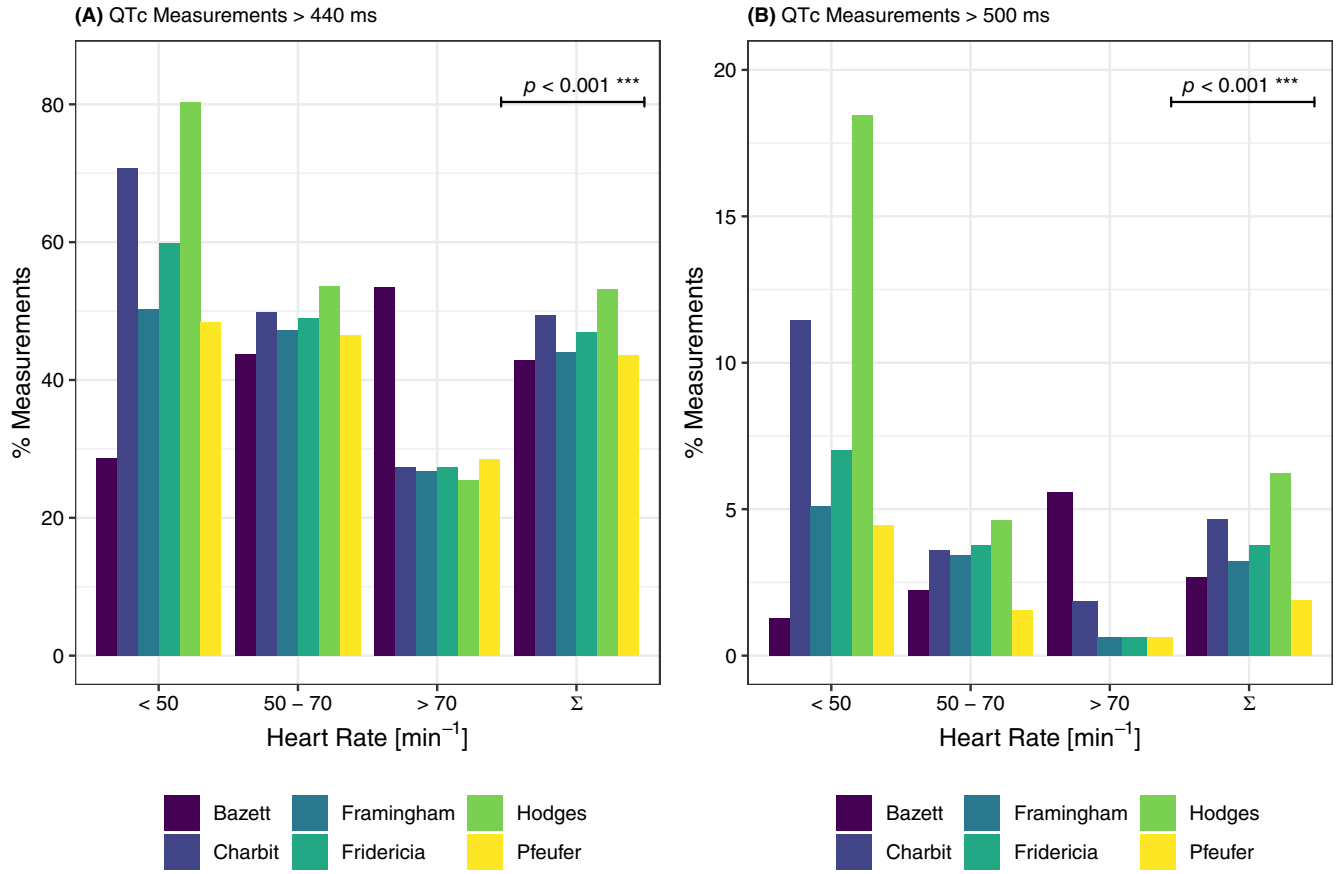

FIGURE 2 Incidence of prolonged QTc values. The percentage of intraoperative QTc measurements longer than 440 ms (A) and 500 ms (B) with regard to heart rate groups. Correction formulae are colour-coded. Σ = Sum of all heart rate groups. The number of QTc measurements >440 ms and >500 ms are significantly different between the correction formulae.

feasible under general anaesthesia and may substitute the recommended 12-lead ECG monitoring.[8] This is not surprising, as reduced lead ECG analysis of multiple cardiac abnormalities, such as wide-QRS-complex tachycardia and acute myocardial infarction, has been shown to be as useful as standard 12-lead ECG analysis outside the operation theatre.[12] The loss of information from leads V1-V4 and V6 in the 5-channel ECG compared with the 12-channel ECG did not show any effect in our study either. The QT interval is, by definition, the longest QT interval in any lead, and manual measurement is traditionally recommended in lead II and V5.[19] As both 12-lead and 5-lead ECGs contain information from limb and precordial leads, a non-significant difference was expected. Nevertheless, this is the first study to compare automated intraoperative QT and QTc intervals recorded with standard 12-lead ECG and 5-lead ECG and hence validates the intraoperative feasibility of automated 5-lead ECG monitoring of the QTc interval. Although QTc interval measurement has also been described with reduced lead ECG using a different algorithm with a new electrode position,[12,13] to our knowledge, intraoperative QT/QTc interval measurement with 3-lead ECG has never been validated. Since 3-lead ECG lacks information from the precordial leads, we reason that the QT/QTc interval may be underestimated in some patients. Since the recommendation of manual QTc analysis for borderline values[9] more than 15 years ago, mainly due to technical progress and improved validity, the authors in 2024 see the advantages of automated measurement.

Our study shows that all commonly used correction formulae have a different effect on the incidence of pathologically prolonged QTc intervals during general anaesthesia. Given the known mathematical definitions of the correction formulae, the fact that there are differences between QTc values obtained with different correction formulae (given QT duration, heart rate/RR interval variable) is not primarily surprising. However, it is important to understand that a QTc value depends on two variables (QT interval and heart rate/RR interval). In the present study, these two variables were automatically collected together in an intraoperative patient population and analysed using the correction formulae mentioned above.

Such intraoperative measurements of QTc intervals have not been standardised so far. This is important not only for reasons of comparability. Our data show that the choice of correction formula may influence therapeutic decisions. As current recommendations consider a QTc interval >500 ms as an important therapeutic threshold,[3–5,23,24,32] the likelihood of an intervention will be influenced by the underlying correction formula. As correction formulae differentially over- and under-correct QT intervals at heart rates significantly higher and lower

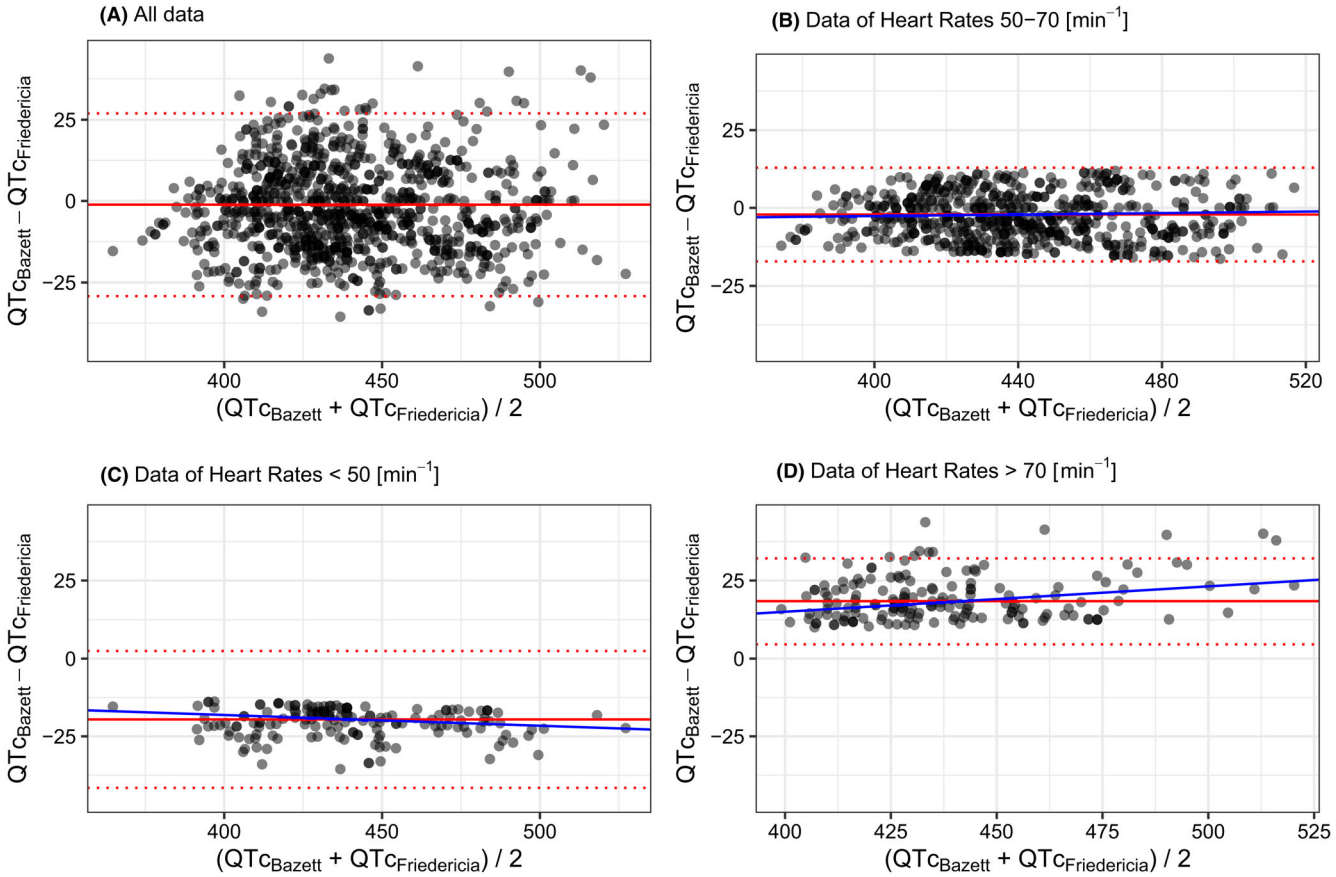

FIGURE 3 Comparison of Bazett vs. Fridericia. Bland-Altman analysis comparing QTc intervals resulting from the Bazett and Fridericia correction for different groups of heart rates. Red lines show the mean, and red dashed lines 2SD show the differences between QTc_{Bazett} and $QTc_{Friedericia}$. Regression lines of the mean differences regressed on mean QTc values are shown in blue. (A) all heart rates (B) heart rates between 50 and 70 min^{-1}. The slope of the blue regression line is not significantly different from zero ($T = 0.683$, $df = 361.2$, $p = 0.495$), (C) heart rates <50 min^{-1}. The Slope of the blue regression line is not significantly different from zero ($T = -1.85$, $df = 55.5$, $p = 0.069$), (D) heart rates >70 min^{-1}. The slope of the blue regression line is significantly different from zero ($T = 2.7$, $df = 86.9$, $p = 0.008$).

than 60 min^{-1}, the number of pathologically prolonged QTc intervals requiring intervention will also be influenced by the intrinsic characteristics of the patient population with extremes ranging from endurance athletes[33] to neonates.[34] In addition, the incidence of pathologically prolonged QTc intervals during heart rate-modifying perioperative interventions, such as beta-blocker treatment or thoracic epidural anaesthesia, will depend on the correction formula.

This is particularly evident when using Bazett's formula. This formula is the only one with a positive correlation between heart rate and the resulting QTc intervals. Therefore, compared to all other correction formulae, QTc intervals according to Bazett, will have a shorter duration at low heart rates and a longer duration at higher heart rates. This is important because Bazett's formula still remains the most widely used correction formula despite repeated recommendations otherwise.[20,35,36]

It is noteworthy that regardless of the correction formula used, a high percentage of the QTc intervals recorded intraoperatively (41%–54%) are above the current sex-specific limits of normal of 430–450 and 450–460 ms in male and female patients, respectively. Up to 10% of values are above the diagnostically and therapeutically important clinical threshold of 500 ms.[3–5,7,23,24,32] Comparing the intraoperative QTc intervals obtained in our study with identical correction formulae (QTcRAS) to those obtained in a large community-based study population with the same regional background,[18] it is noteworthy that the mean duration of the QTc intervals during general anaesthesia is 21 ms longer (Figure 4A). There is also a quantitative difference of 20–40 ms when comparing the QTc intervals obtained in our study using the formulae of Bazett and Fridericia with those of another large cohort of ambulatory patients, outside the operation theatre[25] (Figure 4A). This difference persists even after correction for sex (Figure 4B,C) and is consistent with other studies describing a similar QTc prolongation during the intra- and post-operative period in the context of general and regional anaesthesia.[4,37]

It has long been known that both general anaesthetics and sedatives prolong the QTc interval.[26,27] This may be further modified by the type of surgery[4,6,38] and type of anaesthesia.[37] Given the fact that cardiac arrhythmias, T-wave alternans or short-long-short QT intervals were not observed in any patient during our study, it may be hypothesised that therapeutically relevant thresholds of QTc intervals during general anaesthesia differ from those in a population without general

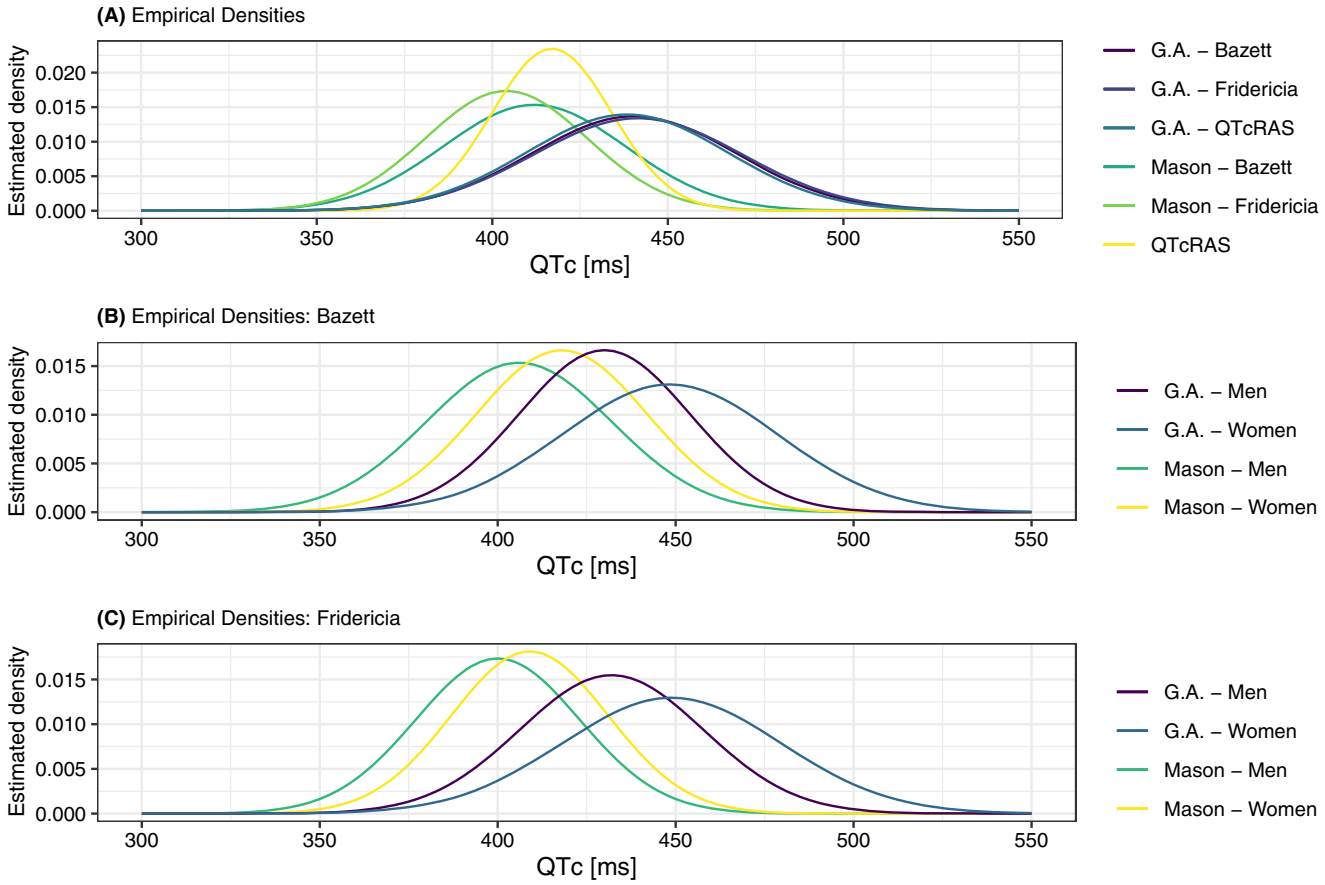

FIGURE 4 Comparison of resting ECG versus general anaesthesia. Comparison of the distribution of QTc values from our study during general anaesthesia (G. A.) with published QTc values from resting ECG data (Mason and QTcRAS) assuming normal distributions depending on the correction formula used as well as on sex. (A) all QTc values, (B) QTc_{Bazett} depending on sex, (C) $QTc_{Fridericia}$ depending on sex.

anaesthesia or sedation. In addition to QTc interval prolongation, the pharmacological effect of general anaesthetic agents[26–28] may influence the risk of developing Torsade de Pointes during general anaesthesia. As relevant suppression of sympathetic nervous system activity has been extensively described for general anaesthetic agents[29] and is also an established strategy for reducing the risk for Torsade de Pointes in Long QT syndrome,[39] an adjustment of current recommendations for therapeutic intervention during general anaesthesia may be worth considering. The perioperative case reports of a Torsade de Pointes have regularly been associated with a significant prolongation of the QTc interval. There are numerous cut-off values for the QTc interval, with treatment recommended above 500 ms. However, our data show that in general anaesthesia, a QTc prolongation outside of 2 standard deviations above the mean value starts between 478 (Bazett) and 507 ms (Hodges) in men, and between 504 ms (QTcRAS) and 520 ms (Hodges) in women, and thus, markedly depends on sex and the correction formula used (Table 2). Therefore, the treatment limit during anaesthesia may be higher. In addition, the incidence of prolongation above 500 ms in our study was dependent on sex and the correction formula used. If current recommendations are followed, this could lead to unnecessary overtreatment in general anaesthesia due to the lack of limits for men and women. QTc prolongation is associated with an increased risk of developing Torsade de Pointes tachycardia. In this respect, gender-specific thresholds for intervention would be necessary and clinically relevant. On the other hand, specific limit values for each correction formula could be confusing. Standardisation is needed, and the Fridericia correction seems to be preferred in the current literature.

The small number of reports on perioperative Torsade de Pointes[5] despite a high incidence of prolonged QTc intervals during general anaesthesia (this study),[4,6,37] together with more than 300 million operations per year worldwide,[40] supports this hypothesis.

Our study is limited in that it was not designed to demonstrate the interaction of various influences on intraoperative QTc intervals, such as age, genetic background, sex, type of surgery, anaesthetic management and concomitant diseases and medications. This would require large numbers of patients to allow multivariate analysis.[18,25] Such data have not been available to date. Unfortunately, a resting ECG was not available to be used as a possible baseline QTc value before the patients were admitted to the hospital, nor was it required for most patients in our cohort according to recommendations for perioperative anaesthesia assessment. Therefore, we chose the

community-based cohort of the KORA study[18] with identical regional background for comparison. If QTc measurements before induction of anaesthesia may be used as baseline remains an important outstanding question to further studies since premedication, stress and an increased sympathetic tone might already impact the duration of the QTc interval.[29]

Nevertheless, our results provide evidence that intraoperative monitoring of QTc intervals and therapeutic recommendations based on intraoperative QTc intervals require further evaluation and standardisation regarding correction formulae and normal limits. Applying the current limit for treatment of 500 ms may lead to overtreatment in patients under general anaesthesia. However, further studies are needed to confirm this.

5 | CONCLUSION

In conclusion, the results of our study demonstrate that intraoperative monitoring of QTc intervals with 5-lead ECG recording during surgery is feasible and allows valid continuous intraoperative measurements of QTc intervals. Furthermore, our results show a much higher incidence of prolonged QTc intervals and a different distribution of values in patients under general anaesthesia than in a standard population. Our study shows that this prolongation of the QTc time under general anaesthesia, as demonstrated in other studies, occurs regardless of sex and the correction formula used. However, common correction formulae and gender differentially influence the incidence of prolonged QTc intervals during perioperative care. Further studies are needed to recommend a preferred correction formula and sex-specific QTc thresholds for interventions under general anaesthesia.

AUTHOR CONTRIBUTIONS

PF designed and conceptualised the study. TK acquired the data. TK, LLM and PF analysed and interpreted the data. TK drafted the first version of the manuscript. LLM and PF edited and commented on the manuscript. All authors contributed to writing the manuscript and read and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

We thank all participants in this study. All authors declare no conflict of interest. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

Departmental funding only.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Thomas Krönauer https://orcid.org/0009-0009-9068-1463

REFERENCES

1. Schwartz PJ, Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and Torsades de pointes. *J Am Coll Cardiol*. 2016; 67(13):1639-1650.
2. Lahrouchi N, Tadros R, Crotti L, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation*. 2020;142(4):324-338.
3. Kies SJ, Pabelick CM, Hurley H a, White RD, Ackerman MJ. Anesthesia for patients with congenital long QT syndrome. *Anesthesiology*. 2005;102(1):204-210.
4. Nagele P, Pal S, Brown F, Blood J, Miller JP, Johnston J. Postoperative QT interval prolongation in patients undergoing noncardiac surgery under general anesthesia. *Anesthesiology*. 2012;117(2):321-328.
5. Johnston J, Pal S, Nagele P. Perioperative torsade de pointes: a systematic review of published case reports. *Anesth Analg*. 2013;117(3): 559-564.
6. Joyce DD, Bos JM, Haugaa KH, et al. Frequency and cause of transient QT prolongation after surgery. *Am J Cardiol*. 2015;116(10): 1605-1609.
7. O'Hare M, Maldonado Y, Munro J, Ackerman MJ, Ramakrishna H, Sorajja D. Perioperative management of patients with congenital or acquired disorders of the QT interval. *Br J Anaesth*. 2018;120(4): 629-644.
8. Hnatkova K, Gang Y, Batchvarov VN, Malik M. Precision of QT interval measurement by advanced electrocardiographic equipment. *Pacing Clin Electrophysiol*. 2006;29(11):1277-1284.
9. Charbit B, Samain E, Merckx P, Funck-Brentano C. QT interval measurement. *Anesthesiology*. 2006;104(2):255-260.
10. Viskin S, Rosovski U, Sands AJ, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. *Hear Rhythm*. 2005;2(6):569-574.
11. Anton D, Friederich P. Automated perioperative QT monitoring in a patient with long QT syndrome 2. *Br J Anaesth*. 2010;105(5): 701-702.
12. Drew BJ, Pelter MM, Brodnick DE, Yadav AV, Dempel D, Adams MG. Comparison of a new reduced lead set ECG with the standard ECG for diagnosing cardiac arrhythmias and myocardial ischemia. *J Electrocardiol*. 2002;35(4):13-21.
13. Martínez JP, Laguna P, Olmos S, Pahlm O, Pettersson J, Sörnmo L. Assessment of QT-measurement accuracy using the 12-lead electrocardiogram derived from EASI leads. *J Electrocardiol*. 2007;40(2): 172-179.
14. Bazett H. An analysis of the time-relations of electrocardiograms. *Heart*. 1920;7:353-370.
15. Fridericia L. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand*. 1920;53(1): 341-342.
16. Hodges M, Salerno D, Erlien D, Bazett's QT. correction reviewed. Evidence that a linear QT correction for heart rate is better. *J Am Coll Cardiol*. 1983;1:694.
17. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham heart study). *Am J Cardiol*. 1992;70(7):797-801.
18. Pfeufer A, Jalilzadeh S, Perz S, et al. Common variants in myocardial ion channel genes modify the QT interval in the general population: results from the KORA study. *Circ Res*. 2005;96(6):693-701.
19. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol*. 2006;17(3):333-336.
20. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval. *Circulation*. 2009;119(10):241-250.
21. Smetana P, Malik M. Sex differences in cardiac autonomic regulation and in repolarisation electrocardiography. *Pflugers Arch*. 2013;465(5): 699-717.

22. Gibbs C, Thalamus J, Kristoffersen DT, et al. QT prolongation predicts short-term mortality independent of comorbidity. *Europace*. 2019; 21(8):1254-1260.
23. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings. *J Am Coll Cardiol*. 2010;55(9):934-947.
24. Kaye AD, Volpi-Abadie J, Bensler JM, Kaye AM, Diaz JH. QT interval abnormalities: risk factors and perioperative management in long QT syndromes and Torsades de pointes. *J Anesth*. 2013;27(4):575-587.
25. Mason JW, Ramseth DJ, Chanter DO, Moon TE, Goodman DB, Mendzelevski B. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. *J Electrocardiol*. 2007;40(3):228-234.
26. Saarnivaara L, Lindgren L. Prolongation of QT interval during induction of anaesthesia. *Acta Anaesthesiol Scand*. 1983;27(2):126-130.
27. Schmeling WT, Warltier DC, McDonald DJ, Madsen KE, Atlee JL, Kampine JP. Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. *Anesth Analg*. 1991;72(2):137-144.
28. Kleinsasser A, Kuenszberg E, Loeckinger A, et al. Sevoflurane, but not propofol, significantly prolongs the QT interval. *Anesth Analg*. 2000; 90(1):25-27.
29. Neukirchen M, Kienbaum P, Warner DS, Warner MA. Sympathetic nervous system. *Anesthesiology*. 2008;109(6):1113-1131.
30. Xue JQ. Robust QT interval estimation—from algorithm to validation. *Ann Noninvasive Electrocardiol*. 2009;14(Suppl 1):35-41.
31. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1):1-48.
32. Booker PD, Whyte SD, Ladusans EJ. Long QT syndrome and anaesthesia. *Br J Anaesth*. 2003;90(3):349-366.
33. Pickham D, Hsu D, Soofi M, et al. Optimizing QT interval measurement for the preparticipation screening of young athletes. *Med Sci Sports Exerc*. 2016;48(9):1745-1750.
34. Stramba-Badiale M, Karnad DR, Goulene KM, et al. For neonatal ECG screening there is no reason to relinquish old Bazett's correction. *Eur Heart J*. 2018;39(31):2888-2895.
35. ICH Harmonised Tripartite Guideline E 14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non antiarrhythmic drugs. 2005.
36. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc*. 2016;5(6): e003264.
37. Duma A, Pal S, Helsten D, Stein PK, Miller JP, Nagele P. High-fidelity analysis of perioperative QTc prolongation. *Anesth Analg*. 2016; 122(2):439-448.
38. Capparelli FJ, Abello M, Maskin LP, et al. QTc prolongation after brain surgery. *Neurol Res*. 2013;35(2):159-162.
39. Dusi V, Pugliese L, De Ferrari GM, et al. Left cardiac sympathetic denervation for long QT syndrome. *J Am Coll Cardiol Clin Electrophysiol*. 2022;8(3):281-294.
40. Weiser TG, Haynes AB, Molina G, et al. Size and distribution of the global volume of surgery in 2012. *Bull World Health Organ*. 2016; 94(3):201-209.

How to cite this article: Krönauer T, Mihatsch LL, Friederich P. Intraoperative QTc interval interpretation: Effects of anaesthesia, ECG, correction formulae, sex, and current limits. *Acta Anaesthesiol Scand*. 2024;68(10):1369-1378. doi:10.1111/aas.14515