CME

High-Fidelity Analysis of Perioperative QTc Prolongation

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BACKGROUND: Prolongation of the QTc interval indicates abnormal cardiac repolarization. A recent study has shown that postoperative QTc prolongation is common. However, it is unknown whether QTc prolongation is an isolated postoperative phenomenon or occurs regularly during surgery, or whether the type of anesthesia influences its incidence.

METHODS: To answer this question, we conducted a prospective cohort study (n = 300), where QTc duration was continuously recorded by 12-lead Holter electrocardiogram from 30 minutes preoperatively to up to 60 minutes postoperatively. QTc prolongation was compared between adult patients with at least 1 cardiac risk factor undergoing general (n = 101) or spinal anesthesia (n = 99) for orthopedic surgery, or local anesthesia (n = 100). Primary outcome was intraoperative QTc increase (ΔQTc, as defined by the intraoperative-to-preoperative QTc duration difference). The incidence of long QTc episodes (QTc > 500 milliseconds for at least 15 minutes) was also determined.

RESULTS: Significant QTc prolongation (median; interquartile range [IQR]) occurred during general anesthesia (ΔQTc, +33 milliseconds; IQR, +22 to 46 milliseconds) and spinal anesthesia (ΔQTc, +22 milliseconds; IQR, +12 to 29 milliseconds), whereas no QTc prolongation was observed during local anesthesia (biopsy, n = 53: ΔQTc, +4 milliseconds; IQR, −4 to +7 milliseconds; coronary angiography, n = 47: ΔQTc, +6 milliseconds; IQR, −5 to +16 milliseconds). The incidence of long QTc episodes was significantly different between general anesthesia (n = 6/63, 9.5%), spinal anesthesia (n = 1/56, 1.8%), local anesthesia for biopsy (n = 0/46, 0%), and coronary angiography (n = 0/19, 0%; P = 0.045).

CONCLUSIONS: These results indicate that QTc prolongation is not an isolated postoperative phenomenon and is common during surgery under general and spinal anesthesia. (Anesth Analg 2016;122:439–48)

The QTc interval measures the heart rate–corrected duration of ventricular depolarization and repolarization on an electrocardiogram (ECG) tracing. Prolongation of the QTc duration is a sign of abnormal cardiac repolarization that has been associated with an increased risk for life-threatening arrhythmias, such as torsade de pointes.[1] Critical care patients with substantial QTc prolongation (>500 milliseconds lasting at least 15 minutes) have a 3 times greater likelihood of in-hospital mortality than intensive care patients without QTc prolongation.[2] QTc prolongation (>10 milliseconds) has been recently shown to precede approximately 90% of reported perioperative torsade de pointes episodes, of which 4% were fatal.[3] A number of factors may lead to perioperative QTc prolongation.[4–6] For example, several drugs,[4–7] including volatile anesthetics[8] and antiemetics,[9] can prolong the QTc interval. Tracheal intubation or extubation, or spinal puncture, may cause the release of catecholamines and subsequently prolong QTc duration.[5] During tracheal intubation, a strong correlation between QTc changes and changes in plasma noradrenalin concentration has been reported.[10] Patient factors,[11] such as age[12] or preexisting comorbidities,[13] as well as inherited long QT syndrome can also cause QTc prolongation.[14]

However, the knowledge about perioperative QTc prolongation during routine clinical care is sparse. We recently compared preoperative and postoperative QTc duration in patients under general anesthesia[15] and found an 80% prevalence of QTc prolongation in the postoperative period (17% preoperatively). Six percent of patients had a substantial QTc prolongation (QTc, >500 milliseconds).[16] However, it is unknown whether QTc prolongation is an isolated postoperative phenomenon or occurs regularly in the intraoperative period. Furthermore, it is unknown whether the type of anesthesia (i.e., general, spinal, and local anesthesia) influences the incidence of QTc prolongation. In this study, we

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hypothesized that the QTc prolongation also occurs intraoperatively and that the type of anesthesia influences perioperative QTc duration. To address this issue, we measured QTc duration among patients undergoing general, spinal, and local anesthesia by continuous, high-fidelity 12-lead Holter ECG in a prospective cohort study.

METHODS

Design and Setting

The study was approved by IRB of Washington University, St. Louis, MO, and written informed consent was obtained from each patient. Recruitment was from patients scheduled for elective surgery at Barnes Jewish Hospital, St. Louis, MO, from January to November 2013.

We conducted a prospective cohort study in 300 evaluable patients who underwent either general (n = 101) or spinal anesthesia (n = 99) for orthopedic surgery, or local anesthesia for biopsy/excision or diagnostic coronary angiography (n = 100). The perioperative treatment was at the discretion of the clinicians and was not influenced by study participation. Patients undergoing diagnostic coronary angiography in local anesthesia were managed with monitored anesthesia care and with minimal sedation, whereas those undergoing biopsy in local anesthesia were managed without monitored anesthesia care and with local anesthetic drugs only.

Study Population

Patients scheduled for orthopedic surgery under general anesthesia or spinal anesthesia were eligible if they were 45 years or older or had at least 1 cardiac risk factor (coronary artery disease, history of myocardial infarction, insulin dependency, congestive heart failure, chronic renal failure, or stroke). Patients scheduled for biopsy/excision or diagnostic coronary angiography with local anesthesia were eligible if they were 18 years or older. Patients were excluded if they were isolated for infection precautions, scheduled for thoracic surgery, or surgery in prone position, as were those having active atrial fibrillation, a QRS > 120 milliseconds, a pacemaker, or who were previously enrolled in the study. We included patients regardless of their home medication. We had no inclusion or exclusion criteria based on the potential QT prolonging medication. Patients were withdrawn from the study if validation of QTc measurements revealed intraoperative Holter ECG disconnection, a violation of inclusion criteria, a preoperative record duration of <5 minutes or a postoperative record duration of <10 minutes (Fig. 1).

Measurements

Patients' demographics, medical history, and home medication were recorded. Time and type of anesthetic procedures (e.g., airway management), dose, type and timing of drugs, and vital parameters were captured through the electronic anesthesia chart for all cohorts, with the exception of the patients undergoing coronary angiography, for which a printout of the procedure protocol was used. A 12-lead Holter ECG monitor (DR 181 Digital Recorder™, NorthEast Monitoring Inc., Maynard, MA) was connected in the preoperative holding area, and each patient's ECG was continuously recorded from this point until up to 1 hour after arrival in the postoperative care unit. No chest leads were connected in patients who underwent coronary angiography. ECG data were analyzed using LX Analysis Pro software (NorthEast Monitoring Inc.), which derived an automatic beat-to-beat QT measurement for each minute on a 3-second strip recorded in 60-second intervals. Minutes of QT measurements were excluded if the respective 3-second strip showed no measurable QT interval. All computer-derived QT calipers were manually validated and corrected by the Fridericia method,[17,18] as recommended by the International Society for Computerized Electrocardiology.[19,20] Two investigators were trained to manually determine the QTc durations on the LX Analysis Pro software. Training was considered complete after an interobserver difference (minimum – maximum) of −5 to +2 milliseconds in 10 randomly chosen records was achieved. Each investigator, blinded to QT duration, cohort, and treatment, validated half of the ECG recordings that were recorded from 30 minutes preoperatively to up to 60 minutes postoperatively.

Outcomes

The primary outcome was the intraoperative-to-preoperative QTc duration difference expressed as ΔQTc. QTc duration of the preoperative, intraoperative, and postoperative periods was investigated for QTc prolongation within each cohort. The preoperative, baseline period began at the start of an ECG recording and ended either when the patient underwent spinal anesthesia or was brought into the operating room. The intraoperative period started on incision and stopped on incision closure, coinciding with the time of emergence. The postoperative period started on patient's arrival at the postoperative care unit and ended when the QTc recording was stopped. Prevalence of the main outcome ΔQTc and the perioperative QTc prolongation were reported in concordance with international recommendations.[19,20] Categories were defined as absent (ΔQTc ≤ 0 milliseconds), moderate (0 < ΔQTc ≤ 30 milliseconds), marked (30 < ΔQTc < 60 milliseconds), and substantial (ΔQTc ≥ 60 milliseconds) ΔQTc, as well as absent (QTc ≤ 450), moderate (QTc > 450 milliseconds), marked (QTc > 480 milliseconds), and substantial (QTc > 500 milliseconds) QTc prolongation.[19,20]

Incidence of long QTc (LQTc) episodes, defined as new QTc prolongation longer than 500 milliseconds for at least 15 minutes during anesthesia, were determined.[2,21] Only patients who had no QTc prolongation (≥450 milliseconds) before anesthesia were included. Incidence was calculated as the fraction of patients with new LQTc episodes during anesthesia while excluding those who had any preoperative QTc prolongation at baseline.

Statistical Analysis

Based on our previous data, QTc prolongation within a group was estimated to be 20 milliseconds with a SD of 25 milliseconds. The study was powered to detect statistically significant QTc prolongation with a 2-sided significance level of 0.017 (preoperative period versus intraoperative period versus postoperative period within a cohort: $\alpha = 0.05/3$; $\beta = 0.2$). This estimation would have required

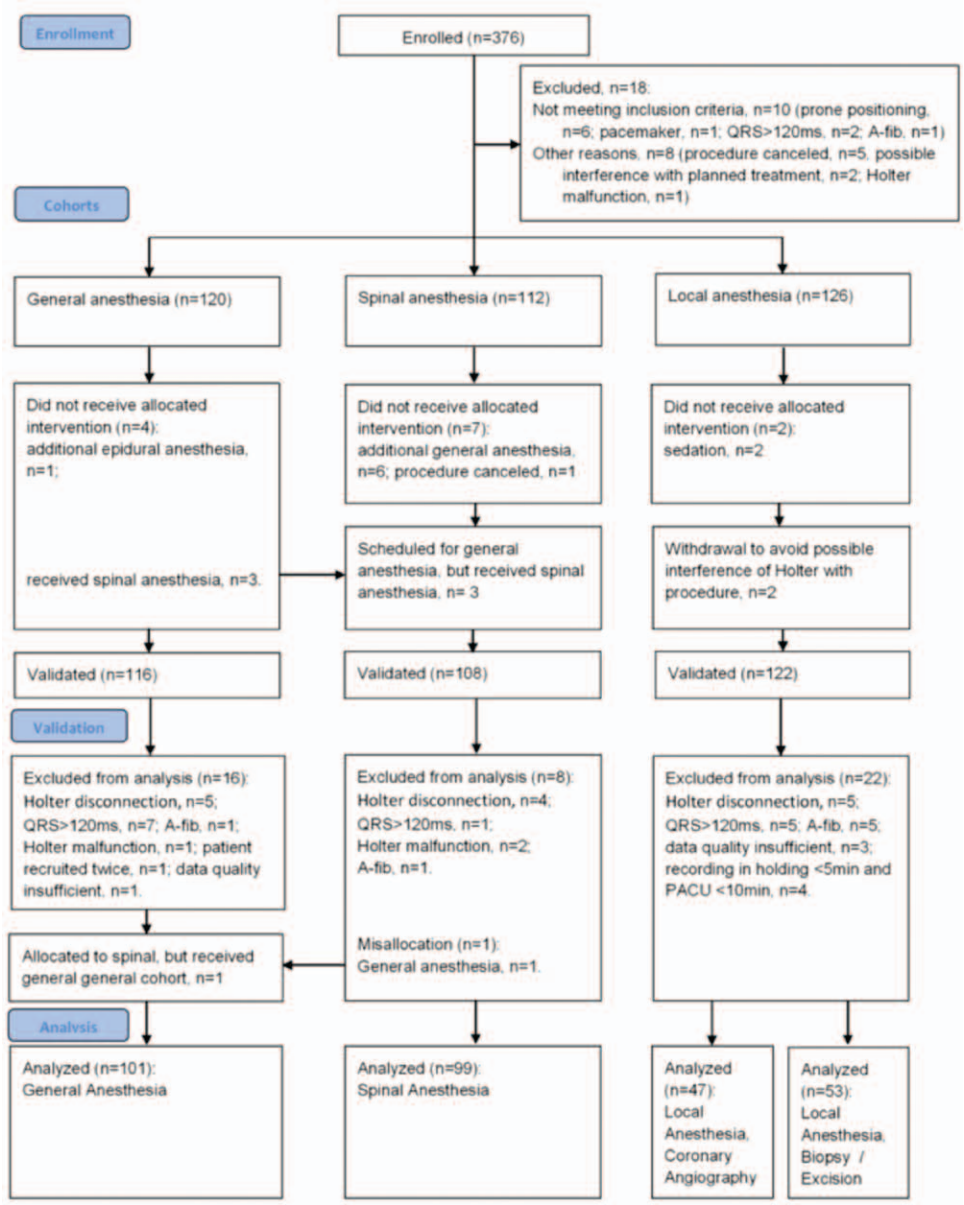

Figure 1. Flow diagram of cohort assignment and analysis. The flow diagram shows the process of enrollment, assignment to cohorts, validation, and analysis of the study population. Patients assigned to the local anesthesia cohort were scheduled for either biopsy/excision or coronary angiography. They were separated based on this parameter and were analyzed as independent strata. PACU = postanesthesia care unit.

a total sample size of 99 patients. Because the magnitude of the difference between groups was unknown, we powered the study to determine intraoperative QTc with a 95% confidence interval (CI) of 6 milliseconds total width, which required a sample size of 246 patients.

Because of skewness, data are presented as median and interquartile range. Minute-by-minute QTc measurements of each patient were averaged to calculate the patient's mean for the investigated periods. Nonparametric tests and adjustments for multiple pairwise post hoc comparisons were applied to analyze for differences in QTc duration within and between cohorts (IBM® SPSS® version 22, IBM, Armonk, NY) and JMP® Pro version 11, SAS Institute Inc., Cary, NC) as follows. ΔQTc was compared among cohorts using a robust 1-way analysis of variance (Welch F) and the Games-Howell post hoc correction method. Kruskal-Wallis test and post hoc pairwise comparisons of all possible pairs with adjusted *P* values were used to compare ordinal ΔQTc categories between groups. Within each cohort, continuous QTc duration and ordinal QTc duration categories were compared using Friedman test and post hoc pairwise comparisons of all possible pairs with adjusted *P* values for 3 consecutive periods and Wilcoxon test for 2 consecutive periods. To avoid inflation of the familywise error rate, *P* values from pairwise comparisons were adjusted by multiplying the *P* value with the number of comparisons. Fisher exact test was used to compare the incidence of LQTc episodes between cohorts. For general versus spinal anesthesia, relative risk (RR) and 95 % CI of incidence of LQTc episodes were calculated using the formulae of Morris and Gardner.[22] Graphs were designed with GraphPad Prism® version 6.04 (La Jolla, CA).

RESULTS

In 300 patients, 57,665 minutes of ECG recordings were reviewed, and 7563 minutes of ECG recordings (13.1%)

Table 1. Baseline Patient Characteristics

	General anesthesia (*n* = 101)	Spinal anesthesia (*n* = 99)	Local anesthesia (*n* = 100)	
			Biopsy (*n* = 53)	Angiography (*n* = 47)
Patient characteristics				
Female, *n* (%)	63 (62)	57 (58)	28 (53)	21 (45)
Black, *n* (%)	13 (13)	12 (12)	5 (9)	12 (26)
Age, median (IQR)	67 (61–76)	66 (61–74)	54 (36–65)	60 (55–65)
BMI, median (IQR)	27.5 (24.3–32.4)	30.4 (26.8–35.6)	26.0 (23.3–31.3)	28.0 (24.8–34.6)
QTc, median (IQR), ms	430 (413–446)	438 (425–450)	421 (408–434)	448 (422–475)
Morbidity				
ASA classification, *n* (%)				
I	4 (4)	4 (4)	16 (30)	0
II	37 (37)	52 (53)	30 (57)	10 (21)
III	59 (58)	43 (43)	7 (13)	37 (79)
IV	1 (1)	0	0	0
RCRI, *n* (%)				
I	67 (66)	80 (81)	42 (79)	19 (41)
II	26 (26)	17 (17)	8 (15)	17 (37)
III	8 (8)	2 (2)	3 (6)	7 (15)
IV	0	0	0	3 (7)
CAD	22 (22)	12 (12)	4 (8)	15 (32)
CHF	1 (1)	0	1 (2)	4 (8.5)
Hypertension	71 (70)	69 (70)	39 (83)	26 (49)
History of arrhythmia	7 (7)	11 (11)	2 (4)	1 (2)
History of LQTS	0	0	0	0
Diabetes mellitus	19 (19)	14 (14)	10 (19)	19 (40)
Hepatic dysfunction	3 (3)	2 (2)	1 (2)	1 (2)
Chronic renal failure	9 (9)	4 (4)	0	7 (15)
QT drugs, *n* (%)				
0	55 (54)	45 (46)	35 (66)	16 (34)
1	26 (26)	36 (36)	10 (19)	14 (30)
2	18 (18)	14 (14)	3 (6)	13 (28)
≥3	2 (2)	4 (4)	5 (9)	4 (8)

History of arrhythmia includes the diagnosis of intermittent atrial fibrillation or flutter, premature beats, supraventricular tachycardia, and history of electric ablation. QT drugs are drugs that may increase the risk of torsade de pointes, listed at crediblemeds.org (accessed March 4, 2014).

ASA = American Society of Anesthesiologists; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; IQR = interquartile range; LQTS = long QT syndrome; QTc = average of minute-by-minute QT duration corrected for heart rate by the Fridericia method from the start of an electrocardiogram recording to either when the patient underwent spinal anesthesia or was brought into the operating room; RCRI = revised cardiac risk index.

were excluded because no QT interval could be identified (Supplemental Digital Content, Supplemental Table 1, recorded and validated QTc data, http://links.lww.com/AA/B264).

The baseline cohort characteristics differed among cohorts. The local anesthesia cohorts were stratified for patients undergoing biopsy/excision and for patients undergoing coronary angiography. The proportion of patients with coronary artery disease, ASA physical status III, and Lee Revised Cardiac Risk Index II to III in the general anesthesia cohort was higher than in the spinal anesthesia cohort. Patients who underwent biopsy or excision under local anesthesia were younger and had less morbidity than those of the other cohorts.

Patients who underwent diagnostic coronary angiography under local anesthesia had more morbidity than those in the other cohorts (Table 1). Cohort-specific, perioperative data are presented in Table 2. Exemplary patient-level data are presented in the Supplemental Digital Content (Supplemental Figure 1, QTc records of 4 patients from the general anesthesia cohort; Supplemental Figure 2, QTc records of 4 patients from the spinal anesthesia cohort; and Supplemental Figure 3, QTc records of 4 patients from the local anesthesia cohort, http://links.lww.com/AA/B264).

General Anesthesia

Median (interquartile range) QTc duration increased from 427 (412–442) milliseconds before induction and airway management to 445 (429–468) milliseconds after induction and airway management (Fig. 2A). ΔQTc was 33 (22–46) milliseconds (Fig. 3), substantial (ΔQTc ≥ 60 milliseconds) in 10% and marked (30 < ΔQTc < 60 milliseconds) in 54% of patients (Fig. 4). Substantial QTc prolongation was observed only in the general anesthesia cohort. Of all cohorts, the intraoperative QTc prolongation in patients under general anesthesia was the most pronounced. Within the general anesthesia cohort, QTc prolongation was less pronounced postoperatively, but was still present compared with the baseline QTc duration (Fig. 5). The prevalence of a marked or substantial QTc prolongation was 5% preoperatively, 27% intraoperatively, and 14% postoperatively (Friedman test: $P < 0.001$; Fig. 6A).

Spinal Anesthesia

QTc duration was 438 (425–453) milliseconds before spinal anesthesia and 439 (429–461) milliseconds after spinal anesthesia, and after the start of sedation, the QTc duration was prolonged, reaching 450 (433–473) milliseconds (Fig. 2B). The ΔQTc was 22 (12–29) milliseconds (Fig. 3) and marked

Table 2. Perioperative Variables

	General anesthesia	Spinal anesthesia	Local anesthesia biopsy	Local anesthesia angiography
Perioperative data				
Procedure	Orthopedic leg surgery	Orthopedic leg surgery	Biopsy or excision	Diagnostic PTCA
Duration of procedure (min), median (IQR)	89 (63–133)	94 (81–122)	27 (20–34)	25 (16–35)
Patients (*n*)	101	99	53	47
Inhaled anesthetics (*n*)				
Desflurane	75	1	0	0
Isoflurane	7	0	0	0
Sevoflurane	45	1	0	0
N_2O	41	2	0	0
IV drugs (*n*)				
Cardiovascular drugs				
β-Blockers	22	6	0	0
Dexmedetomidine	0	17	1	0
Neostigmine	66	0	0	0
Nitroglycerine	0	1	0	0
Succinylcholine	28	0	0	0
Sympathomimetics	38	69	0	0
Vagolytics	71	16	1	0
Electrolytes				
Calcium gluconate	18	4	0	0
Magnesium sulfate	2	0	0	0
Antihistaminic drugs				
Diphenhydramine	4	8	0	0
Famotidine	6	3	0	0
Antiemetic/neuroleptic drugs				
Droperidol	2	1	0	0
Haloperidol	1	0	0	0
Ondansetron	89	46	0	0
Antibiotic drugs				
Cephalosporins	86	86	0	0
Macrolides	37	97	0	0
β-Lactams	4	9	0	0
Miscellaneous drugs				
Acetaminophen	81	88	0	0
Ketamine	0	9	0	0
Ketorolac	27	76	0	0
Lidocaine IV	92	26	0	0
Propofol	99	94	0	0
Rocuronium	54	0	0	0
Tranexamic acid	20	82	0	0
Vecuronium	23	0	0	0
Opioids				
Hydromorphone	75	20	0	0
Fentanyl	100	71	1	47
Meperidine	1	1	0	0
Methadone	1	0	0	0
Morphine	1	2	0	0
Oxycodone	6	32	0	0
Spinal drugs (*n*)				
Bupivacaine	0	86	0	0
Lidocaine	0	6	0	0
Tetracaine	0	7	0	0

The absolute count of administered drugs is shown for each cohort. Drugs not listed as QT drugs at crediblemeds.org (accessed March 4, 2014) or that were given to <5% of patients are not shown.

IQR = interquartile range; PTCA = percutaneous transluminal coronary angioplasty.

in 21% of patients (Fig. 4). The ΔQTc was less pronounced in the spinal anesthesia cohort than in the general anesthesia cohort, but QTc prolongation persisted postoperatively without decline (Fig. 5). The prevalence of a marked or substantial QTc prolongation was 3% preoperatively and increased to 19% intraoperatively, and this increase persisted postoperatively at 21% (Friedman test: $P < 0.001$; Fig. 6B).

Local Anesthesia Cohort

No significant QTc prolongation was observed in patients who underwent biopsy or excision (4 [−4 to 7] milliseconds) and in patients who underwent diagnostic coronary angiography (6 [−5 to 16] milliseconds; Fig. 3). Patients who underwent biopsy or excision in local anesthesia showed no ΔQTc > 30 milliseconds (Fig. 4) and no perioperative QTc prolongation. Patients who underwent diagnostic coronary

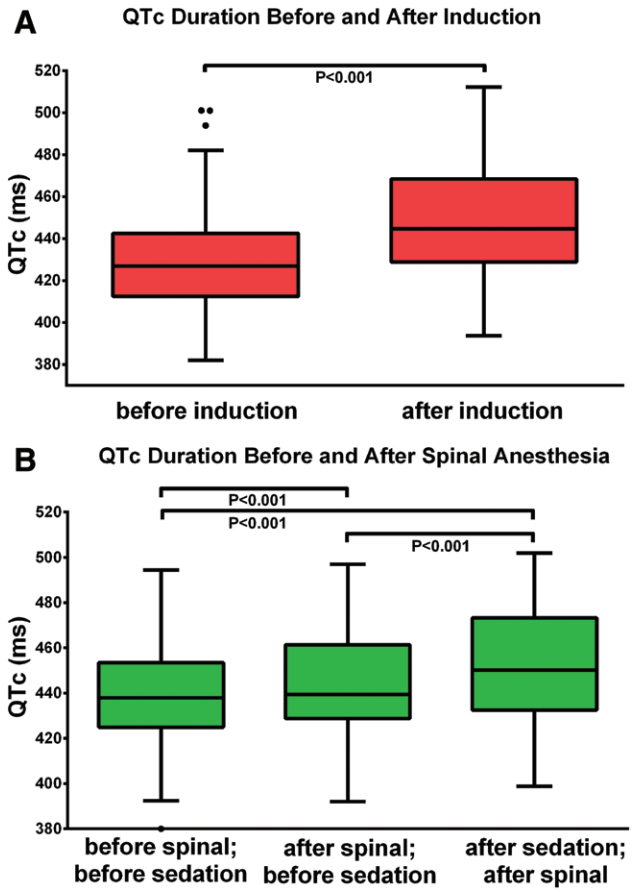

Figure 2. Induction with airway management and spinal anesthesia. A, The QTc duration before induction with airway management and after induction with airway management in patients of the general anesthesia cohort (n = 99). Wilcoxon test (P < 0.001) was used. B, The QTc duration before spinal puncture, after spinal puncture, and after start of sedation in patients of the spinal anesthesia cohort (n = 91). Friedman test (P < 0.001) and post hoc pairwise comparisons of all 3 pairs were used. P values of pairwise comparisons were adjusted by multiplying the P value with the number of comparisons (adjusted $P = P \times 3$). Adjusted P values of pairwise comparisons are shown.

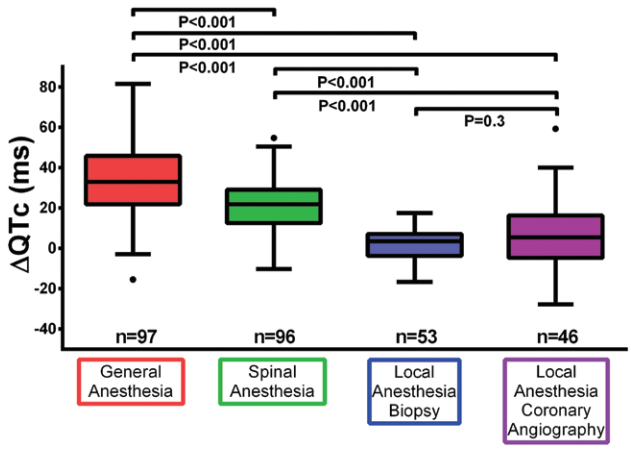

Figure 3. ΔQTc by anesthesia type. ΔQTc, the intraoperative-to-preoperative QTc duration difference, varied among cohorts (Welch F = 86.4; P < 0.001) and was associated (effect size η = 0.63) with the type of anesthesia. Robust 1-way analysis of variance (Welch F) and the Games-Howell post hoc correction method were used.

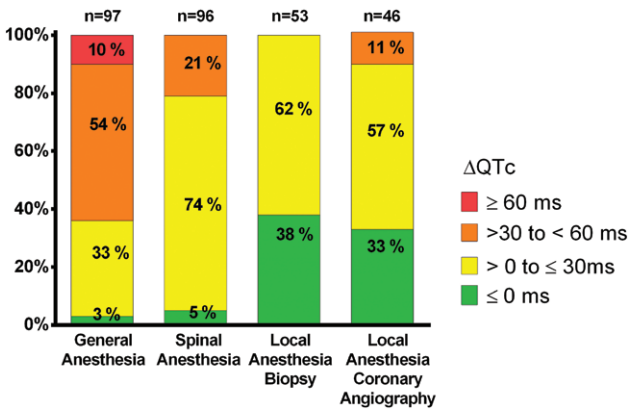

Figure 4. Prevalence of moderate, marked, and substantial ΔQTc by anesthesia type. The prevalence of absent (ΔQTc ≤ 0 milliseconds), moderate (0 < ΔQTc ≤ 30 milliseconds), marked (30 < ΔQTc < 60 milliseconds), and substantial (ΔQTc ≥ 60 milliseconds) ΔQTc varied among the cohorts (P < 0.001). Pairwise comparisons (adjusted P): general anesthesia with spinal anesthesia (P < 0.001), general anesthesia with local anesthesia for biopsy (P < 0.001), general anesthesia with local anesthesia for coronary angiography (P < 0.001), spinal anesthesia with local anesthesia for biopsy (P < 0.001), spinal anesthesia with local anesthesia for coronary angiography (P = 0.02), and local anesthesia for biopsy with local anesthesia for coronary angiography (P = 1). Kruskal-Wallis test and post hoc pairwise comparisons of all 6 pairs of cohorts were used. P values of pairwise comparisons were adjusted by multiplying the P value with the number of comparisons (adjusted $P = P \times 6$).

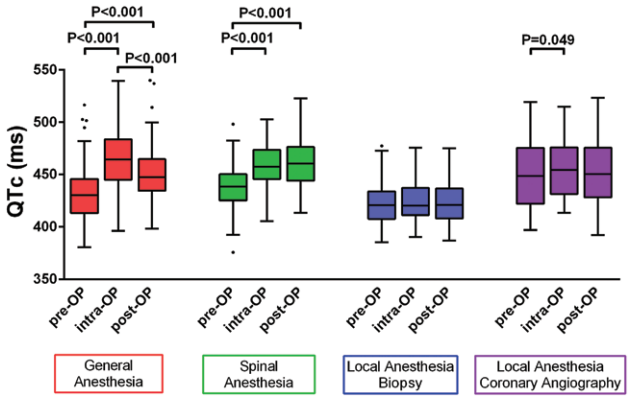

Figure 5. Perioperative QTc prolongation. The median (interquartile range) QTc duration in the preoperative (pre-OP), intraoperative (intra-OP), and postoperative (post-OP) periods was 430 (413–446), 464 (445–483), and 447 (434–465) milliseconds in the general anesthesia cohort (red); 438 (425–450), 457 (446–473), and 461 (444–476) milliseconds in the spinal anesthesia cohort (green); 421 (408–434), 420 (411–437), and 421 (408–437) milliseconds in the local anesthesia cohort stratified for biopsy (blue); 448 (422–475), 454 (431–476), and 450 (428–475) milliseconds in the local anesthesia cohort stratified for coronary angiography (purple), respectively. Significant, adjusted P values of pairwise comparisons are shown. Friedman test and post hoc pairwise comparisons of all 3 pairs in each cohort were used. Within each cohort, P values of pairwise comparisons were adjusted by multiplying the P value with the number of comparisons (adjusted $P = P \times 3$).

angiography under local anesthesia had a marginally significant intraoperative QTc prolongation compared with preoperative QTc duration (adjusted P = 0.049; Fig. 5). The postoperative QTc duration did not differ from that in the preoperative or the intraoperative period, and prevalence of marked or substantial perioperative QTc prolongation was

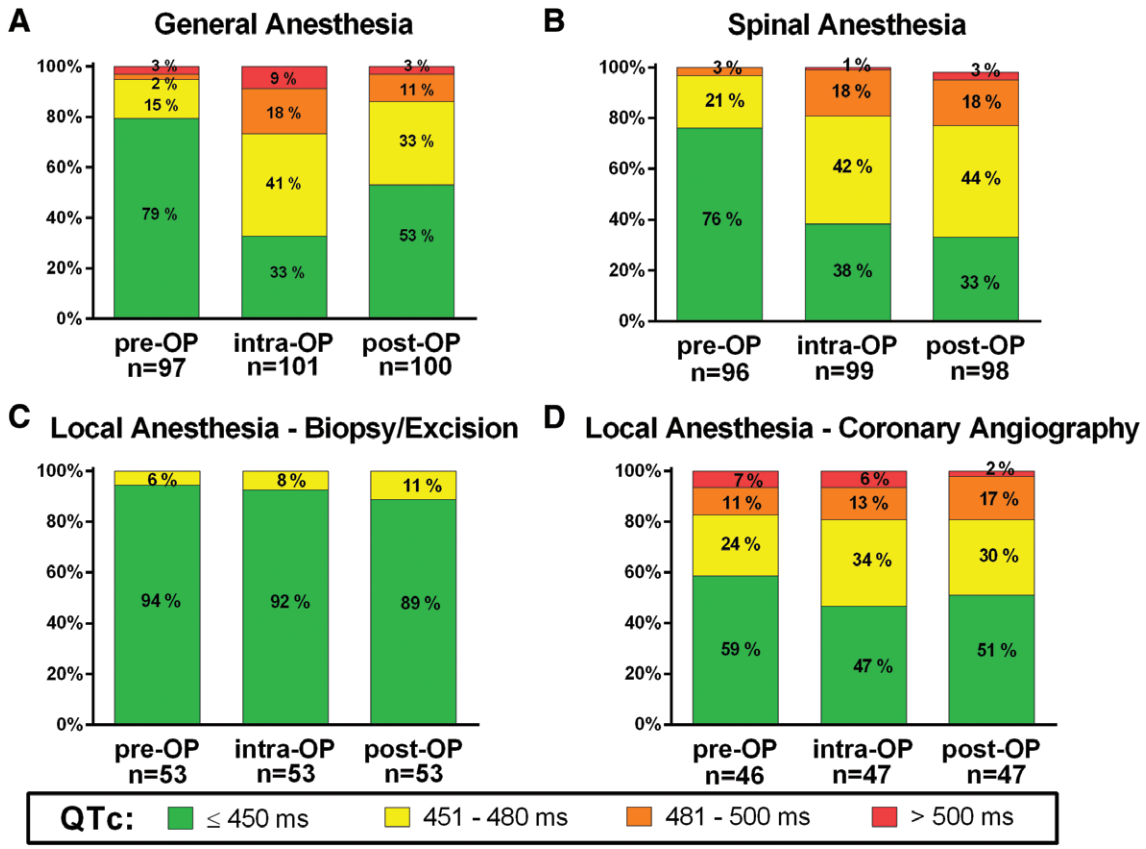

Figure 6. Incidence of perioperative QTc prolongation. The percentage of patients who had absent (QTc ≤ 450 milliseconds), moderate (QTc > 450 milliseconds), marked (QTc > 480 milliseconds), and substantial (QTc > 500 milliseconds) QTc prolongation during the preoperative (pre-OP), intraoperative (intra-OP), and postoperative (post-OP) periods is shown in each bar. Within each cohort, Friedman test was used, and if significant, post hoc pairwise comparisons of the 3 pairs (pre-OP versus intra-OP, pre-OP versus post-OP, and intra-OP versus post-OP) were performed. *P* values of pairwise comparisons were adjusted by multiplying the *P* value with the number of comparisons (adjusted $P = P \times 3$): A, Friedman test: $P < 0.001$; pre-OP versus intra-OP: adjusted $P < 0.001$; pre-OP versus post-OP: adjusted $P = 0.007$; and intra-OP versus post-OP: adjusted $P = 0.003$. B, Friedman test: $P < 0.001$; pre-OP versus intra-OP: adjusted $P < 0.001$; pre-OP versus post-OP: adjusted $P < 0.001$; intra-OP versus post-OP: adjusted $P = 1$. C, Friedman test: $P = 0.1$. D, Friedman test: $P = 0.4$.

Table 3. Incidence of Long QTc Episodes During Anesthesia Care

	General anesthesia	Spinal anesthesia	Local anesthesia biopsy	Local anesthesia angiography	Total
Incidence					
Crude, *n*/total (95% CI)	6/63 (2–11)	1/56 (0–3)	0/46 (0–7)	0/19 (0–16)	7/184 (2–12)
Incidence per 100 patients	9.5	1.8	0.0	0.0	3.8
Incidence per 100 anesthesia care hours	3.6	0.7	0.0	0.0	1.8
Relative risk					
General anesthesia/spinal anesthesia			5.3 (0.7–43.0)		

A long QTc episode was defined as a prolongation of QTc > 500 milliseconds for at least 15 minutes or longer. The period of anesthesia care started when patients either received spinal anesthesia or were brought to the OR (whichever happened first) and ended when patients arrived at the postoperative care unit. All patients with a QTc prolongation (≥450 milliseconds) at any time before anesthesia care were excluded (*n*/total=116/300) from the analysis of incidence. Fisher exact test: $P = 0.045$.

CI = confidence interval.

unchanged at 18% preoperatively, 19% intraoperatively, and 19% postoperatively (Friedman test: $P = 0.4$; Fig. 5D).

Incidence of LQTc Episodes

There was a significant difference in the incidence of LQTc episodes among cohorts (Fisher exact test: $P = 0.045$). There was a nonsignificant trend of a higher RR for the incidence of LQTc episodes in the general anesthesia cohort in comparison with the spinal anesthesia cohort (RR = 5.3; 95% CI, 0.7–43.0, $P = 0.12$; Table 3). In the local anesthesia cohort, no patient with absent QTc prolongation at baseline had an LQTc episode.

DISCUSSION

This study resulted in several novel observations: We found that QTc prolongation is not an isolated postoperative phenomenon and commonly occurs early during general and spinal anesthesia. Perioperative QTc prolongation occurred within minutes after anesthesia induction or spinal anesthesia and further increased during surgery. QTc prolongation

was most pronounced under general anesthesia, where more patients had LQTc episodes than under spinal or local anesthesia. After surgery, QTc duration decreased in the general anesthesia cohort, but persisted in the spinal anesthesia cohort.

Several steps were taken to determine accurate QTc duration. First, continuous high-fidelity Holter ECG recording ensured reliable capture of perioperative QTc duration. Second, we undertook extensive data validation to minimize measurement bias. Third, QT duration was determined using the recommended standardized 12-lead ECG approach, which prevents underestimation of QTc duration. Fourth, we chose the Fridericia method[17] for heart rate correction of the QT interval duration, because this is the most validated method for perioperative patients.[18] Finally, we used ΔQTc as the primary outcome, which controls for the confounding effect of baseline QTc duration.

There are several plausible explanations for our findings. The architecture of QTc duration is highly complex, and ventricular repolarization can be perturbed perioperatively in many ways.[14] Interaction among sympathetic and parasympathetic activity, hormonal influences, hemodynamics, electrolytes, temperature, and structural cardiovascular disease (e.g., atherosclerosis, cardiomyopathy) influence QTc duration in daily life.[13,14,17,23] Anesthesia may perturb the electrophysiologic balance predominantly through drugs, which are well known to cause QTc prolongation.[4,5,8] Anesthetic drugs cause QTc prolongation via cardiac ion channel block or sympathetic stimulation. In the general anesthesia cohort, patients received desflurane or sevoflurane, and both drugs may have caused QTc prolongation. Since the pioneering report of Schmeling et al.,[24] volatile anesthetics have been found to prolong QTc duration.[8,12,25,26] Drug–drug interactions with volatile anesthetic and other drugs administered intraoperatively may have triggered the pronounced QTc prolongation in the general anesthesia cohort.[4,5,11] Postoperative QTc prolongation was less pronounced than intraoperative in the general anesthesia cohort. Our findings of postoperative QTc prolongation >450 milliseconds in 47% of patients, of which 3% had a substantial QTc prolongation >500 milliseconds, confirm the results of our previous study where we found a postoperative QTc prolongation >440 milliseconds in 51% of patients, of which 4% had a substantial QTc prolongation >500 milliseconds.[16] It is still unclear whether and when QTc prolongation normalizes in patients after surgery. However, our previous study indicated that QTc duration returned to baseline on postoperative day 1.[16]

Although patients in the spinal anesthesia cohort were not exposed to inhaled anesthetics, they developed QTc prolongation. What are plausible mechanisms of QTc prolongation under spinal anesthesia? Spinal anesthesia causes temporary deafferentation of the sensory nerve signals sent from the surgical site to the sympathetic and central nerve system and causes imbalance of the lumbar and thoracic sympathetic activity.[4,5,27] Seminal work by Owczuk et al.[27] has shown that this imbalance may cause QTc prolongation because of increased sympathetic activity of unblocked thoracic segments. This indirect action on cardiac repolarization during lumbar block may explain why QTc prolongation occurred after spinal puncture and persisted after surgery. In addition, hemodynamic changes (e.g., hypotension) concomitant with spinal anesthesia may also have triggered an increased sympathetic activity of unblocked thoracic nerves and indirectly contributed to QTc prolongation. On the contrary, local anesthesia omits stimulating nerve signals sent from the surgical site but does not disturb the balanced activity among sympathetic ganglions, as spinal anesthesia does. Also, in our study, patients under local anesthesia were not exposed to systemic anesthetic agents such asinhaled anesthetics. This might explain why we did not observe QTc prolongation in the local anesthesia cohort. In addition to anesthetic drugs, patients under general and spinal anesthesia, but not those under local anesthesia, were also exposed to a long list of analgesic, sedative, antibiotic, cardiovascular, antiemetic, and miscellaneous drugs. For example, 88% of patients in the general anesthesia cohort and 46% in the spinal anesthesia cohort were treated with ondansetron, which has been shown to prolong QTc.[9] These drugs, as well as other drugs and their complex drug–drug interactions, may have directly and indirectly prolonged cardiac repolarization.

Although perioperative QTc prolongation appears common, the relationship with triggers for torsade de pointes is unclear and hotly debated.[28] The risk for torsade de pointes is not simply a function of QTc prolongation but depends on the mechanism of QTc prolongation and the patient.[14,29,30] Lacking more specific ECG indices to predict malignant arrhythmias, to date however, QTc prolongation is still the best-validated predictor for torsade de pointes available at the bedside.[28] Therefore, regulatory agencies enforce warnings, or even the abandonment of drugs, based on a drug-induced QTc-prolongation above 10 milliseconds in an effort to minimize population-wide risk of sudden cardiac death.[31] These stringent safety measures are justifiable for QTc-prolonging drugs that have been shown to increase risk for sudden cardiac death in the general population.[14] However, the upper limit for safe, drug-induced QTc prolongation in the perioperative population is unknown and frequently discussed.[29] In addition, the individual risk for life-threatening arrhythmias is further influenced by the congenital, chronic, and acute conditions of a patient.[28] For example, a 10-millisecond QTc prolongation may bear more risk for TdP in a woman with diabetes mellitus than in a healthy man.[14]

A limitation of this study is the difference in the distribution of patient characteristics among the 3 cohorts. Patients were allocated to the cohorts by indication and not at random. This led to a higher proportion of patients with coronary artery disease, ASA physical status III, and Lee Revised Cardiac Risk Index II to III in the general anesthesia cohort than the spinal anesthesia cohort, and may have confounded the more pronounced QTc prolongation in the general anesthesia cohort.[13,14] Another limitation of this study is the exclusion of patients with atrial fibrillation and bundle branch block. Although this was done to avoid unreliable measurement of QTc duration, excluding those patients with structural heart disease may have led to selection bias and underestimation of perioperative QTc prolongation. In addition, the sample size limited the identification of

individual effects on QTc duration and prolongation. This study has limited clinical impact. We thoroughly quantified the phenomenon of perioperative QTc prolongation associated with different types of anesthesia, but the design of this study did not allow us to determine distinct causes or clinical consequences of QTc prolongation.

In conclusion, our results indicate that QTc prolongation is not an isolated postoperative phenomenon, but, rather, is common during surgery under general and spinal anesthesia. The incidence of LQTc episodes may be more likely with general anesthesia than with regional anesthesia. Future studies are needed that determine the origin of perioperative QTc prolongation and the associated risk for torsade de pointes.[28]

DISCLOSURES

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