

# Postoperative QT Interval Prolongation in Patients Undergoing Noncardiac Surgery under General Anesthesia

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## ABSTRACT

**Background:** Abnormal cardiac repolarization, indicated by a prolongation of the QT interval, increases the risk for torsades de pointes, a potentially life-threatening arrhythmia. Many perioperatively administered drugs and conditions prolong the QT interval. Despite several reports of perioperative torsades de pointes, systematic evidence regarding perioperative QT interval prolongation is limited. **Methods:** Serial postoperative 12-lead electrocardiograms were obtained from 469 adult patients undergoing major noncardiac surgery under general anesthesia. Heart rate corrected QT-interval duration (Fridericia formula) was the primary outcome. All perioperatively administered drugs were recorded. Emphasis was placed on absolute QTc prolongation greater than 500 ms and relative increases of 30 and 60 ms.

**Results:** At the end of surgery, 80% of the patients (345 of 429) experienced a significant QTc interval prolongation ( $\Delta$ QTc  $23 \pm 26$  ms (mean and SD), 95% CI 20–25 ms,  $P$  less than 0.001). Approximately 51% (219 of 429) had a QTc greater than 440 ms, and 4% (16 of 429) a QTc greater

### What We Already Know about This Topic

- Many commonly used drugs in perioperative medicine can prolong QT interval, although a large study examining incidence of QT interval prolongation postoperatively has not been performed

### What This Article Tells Us That Is New

- In a prospective study of almost 500 noncardiac surgery patients, minor prolongation of QT interval was common, with a 4% incidence of marked prolongation (QTc > 500 msec), and there was one case of torsades de pointes with modest QT prolongation
- QT prolongation was associated with multiple drugs, including opioids, general anesthetic agents, antibiotic agents, and cardioactive drugs

than 500 ms. In 39% (166 of 429), the  $\Delta$ QTc was greater than 30 ms, in 8% (34 of 429) >60 ms, and in greater than 0.5% (2 of 429) >100 ms. No changes in  $\Delta$ QTc occurred at subsequent time points. One patient developed torsades de pointes with a  $\Delta$ QTc: 29 ms (0.4% incidence rate). Several drugs had a large effect on  $\Delta$ QTc: isoflurane, methadone, ketorolac, cefoxitin, zosyn, unasyn, epinephrine, ephedrine, and calcium. Postoperative body temperature had a weak negative correlation with  $\Delta$ QTc ( $r = -0.15$ ,  $P = 0.02$ ); serum magnesium, potassium, and calcium concentrations were not correlated.

**Conclusion:** Postoperative QT-interval prolongation is common. Several perioperatively administered drugs are associated with a substantial QT-interval prolongation. The exact cause and its clinical relevance are, however, unclear. Nevertheless, an association between postoperative QT prolongation and risk for torsades de pointes is likely.

**I**N the past 30 yr more than 40 cases of sometimes fatal perioperative torsades de pointes have been reported in the literature, six of them in the year 2011 alone.<sup>1–6</sup> Abnormal cardiac repolarization is a well-known cause for malignant tachyarrhythmias, such as torsades de pointes, which

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can result in sudden cardiac death.<sup>7</sup> Abnormal cardiac repolarization can be identified on the electrocardiogram as a prolonged QT interval (commonly, the heart rate-corrected QT interval [QTc] is reported).<sup>8</sup> Typically, a QTc interval less than 440 ms is considered normal. QT prolongation can either be inherited, (such as in the long QT syndrome), acquired, or a combination of the two. Acquired QT prolongation is often caused by drugs; well-known examples are antiarrhythmic drugs (sotalol, flecainide), cisapride, and droperidol.<sup>9,10</sup> Drug-induced QTc interval prolongation increases the risk for torsades de pointes and subsequent sudden cardiac death, and is often the result of drug-drug interaction or polypharmacy.<sup>11,12</sup>

Surgical patients under general anesthesia are simultaneously exposed to a multitude of mostly intravenously administered drugs, several of which are known to cause QTc prolongation. Typical drug classes include antibiotics, anti-nausea medications (ondansetron or droperidol), inhalational anesthetic agents, and antihistamines.<sup>13–15</sup> In addition, conditions conducive for QTc prolongation such as stress, hypothermia, and electrolyte disturbances, particularly hypokalemia and hypomagnesemia, are common during major surgery.

We therefore hypothesized that patients undergoing major surgery under general anesthesia may be particularly vulnerable for acquired QTc prolongation due to the simultaneous exposure to the previously mentioned risk factors. Previous research in the perioperative setting has exclusively focused on individual drugs and their effect on QTc prolongation. We investigated the cumulative effects of these drugs and conditions on acquired QTc prolongation in a cohort of patients undergoing major noncardiac surgery under general anesthesia from the Vitamins in Nitrous Oxide (VINO) trial.

## Materials and Methods

This study is an independent ancillary study to the VINO trial [NCT00655980]. All patients provided written informed consent and the study was approved by the Washington University School of Medicine Institutional Review Board (St. Louis, Missouri).

### Design of the Parent Trial

The VINO trial has enrolled 625 patients to study the hypothesis that patients with a common gene variant in the folate cycle (*MTHFR* C677T) develop a higher risk for perioperative myocardial infarction after nitrous oxide anesthesia. The trial had three arms: in the first arm ( $n = 250$ ), patients received 60% nitrous oxide during surgery and 1 mg vitamin B<sub>12</sub> (cyanocobalamin) and 5 mg folic acid IV immediately before and after surgery; patients in arm 2 ( $n = 250$ ) received 60% N<sub>2</sub>O but no B-vitamins, just a saline control, and patients in arm 3 ( $n = 125$ ) receive no nitrous oxide and no B-vitamins. The target patient population was adult patients with or at risk for coronary artery disease (defined as a

combination of at least three of six risk factors: history of stroke, diabetes, peripheral vascular disease, smoking, hypertension, or hyperlipidemia) undergoing major noncardiac surgery under general anesthesia. Exclusion criteria include contraindications against the use of nitrous oxide, folic acid, and cyanocobalamin (vitamin B<sub>12</sub>). Other than for the interventions listed previously, the perioperative and anesthetic regimen was at the discretion of the attending anesthesiologist.

### Study Population

The eligible study population for this ancillary study included all patients from the VINO trial who did not have atrial fibrillation and had analyzable baseline and follow-up electrocardiograms. Our goal was to have 500 evaluable patients for this ancillary study.

### Measurements

Per study protocol, we obtained serial 12-lead electrocardiograms on all study patients at the following time points: (1) at baseline (immediately before surgery); (2) within 30 min of arrival in the postanesthesia care unit; (3) on the morning of postoperative day 1 and 2 (although the parent study asked for an electrocardiogram on postoperative day 3, we excluded this time point for the ancillary study because fewer than 25% of the patients were still hospitalized and no electrocardiogram could be obtained).

To identify potential drug-induced QTc interval prolongation, we recorded all perioperatively administered drugs for all patients from the electronic patient record from preoperative holding to postoperative care unit, as well as all home medications. We did not retrieve medication data from nursing floors. In addition, serum electrolytes (K<sup>+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup>) and temperature on admission to the postoperative care unit were recorded.

To assess the incidence of postoperative arrhythmias, and torsades de pointes in particular, we queried the electronic clinical patient database where all abnormal electrocardiogram rhythms that occurred in the postoperative anesthesia care unit were recorded. As standard of care in the postoperative anesthesia care unit, all patients are monitored with a continuous three-lead electrocardiogram. In addition, we queried all reports from postoperative telemetry, which consisted of a continuous three-lead Holter electrocardiogram monitoring with audible alerts for patients deemed at high risk for cardiovascular complications by the care team. Approximately 52% (242 of 469) of our study population were on postoperative telemetry for greater than 48 h.

### Statistical Analysis

The primary outcome variable was the change in QTc (corrected QT interval) between baseline and the other time points ( $\Delta$ QTc). Electrocardiogram measurements were read and analyzed by hand by a single experienced anesthesiologist. QT-interval measurements are typically

**Table 1.** Patient Characteristics

Age (yr)	65 ± 10
Male n (%)	282 (60%)
Race	—
White	369 (78.7%)
Black	94 (20.0%)
Asian	2 (0.4%)

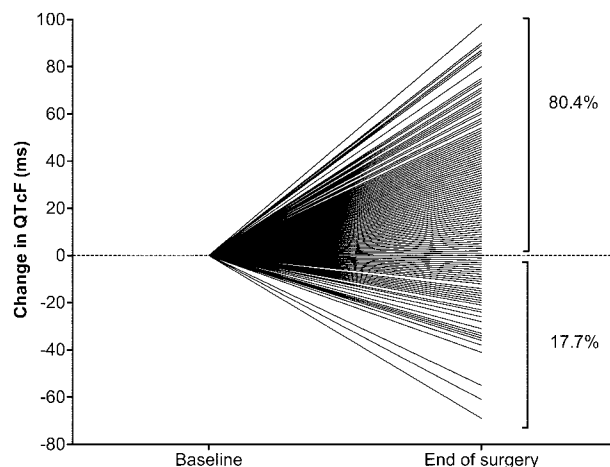
corrected for heart rate (our study used the Fridericia formula [ $QTcF = QT/\sqrt[3]{RR}$ ]; RR = interval between two QRS complexes). The Fridericia correction is the recommended approach (of the classic formulae).<sup>10,16,17</sup> Per Food and Drug Administration-endorsed International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E14 guideline,<sup>17</sup> we focused on identifying patients with an abnormal QTc greater than 440 ms and greater than 500 ms, and relative increases in  $\Delta QTc$  of greater than 30 ms and greater than 60 ms. In general, a QTc interval greater than 440 ms is considered abnormal. The change in QTcF between baseline and end of surgery was determined by a two-sided paired Student *t* test. The effects of drugs and other variables (*e.g.*, sex) was determined by comparing  $\Delta QTc$  between patients who received the drug *versus* those who did not by unpaired Student *t* test with unequal variances. The fraction of patients whose QTc was prolonged greater than 30 ms was tabulated for each drug. A one-tailed (for increasing the % > 30 ms) Fisher exact test was then performed. A *P* value corrected for multiple comparisons was then computed with the bootstrap method (500,000 samples). The effects of continuous variables, such as age, on  $\Delta QTc$  was determined by linear correlation using the Pearson correlation coefficient. Except, when indicated, all reported tests are two-sided and a *P* value less than 0.05 was considered statistically significant. IBM SPSS 20.0 (IBM, Armonk, NY) and SAS version 9.3 (SAS Institute Inc., Cary, NC) software packages were used for the statistical analysis.

## Results

### Postoperative QT Interval Prolongation

This study was performed in a subset of patients participating in the VINO trial (*n* = 469), and the main patient characteristics are described in table 1. At baseline, the mean QTc (Fridericia-corrected) was  $418 \pm 27$  ms; 17% (82 of 469) had a QTc greater than 440 ms, which is considered prolonged, and two patients had a QTc greater than 500 ms, which indicates a high likelihood of long QT syndrome. Because we were unable to obtain an electrocardiogram in 40 of 469 patients (8.5%) at the end of surgery, results are available only for 429 patients. The missing 40 patients had a virtually identical baseline QTc of  $418 \pm 25$  ms.

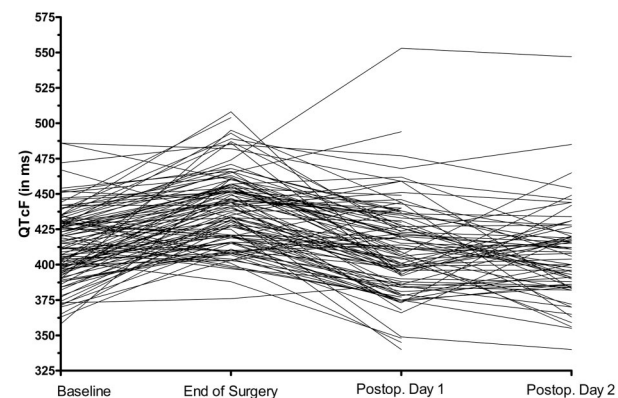
At the end of surgery, measured within 30 min of arrival in the postanesthesia care unit, 80% of the patients (345 of 429) experienced a significant prolongation of their respec-



**Fig. 1.** Relative change in QTc interval between baseline and end of surgery. Eighty percent of the patients experience a prolongation of their respective QTc interval. QTcF = corrected QTc interval (Fridericia formula).

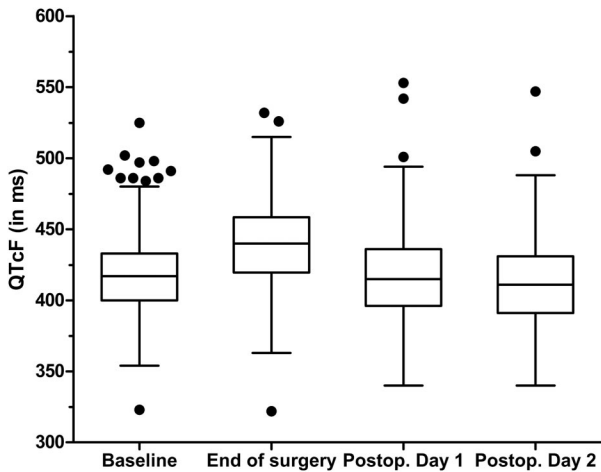
tive QTc interval. The average increase was  $23 \pm 26$  ms (mean  $\pm$  SD; 95% CI 20–25 ms, *P* value less than 0.001). Two percent (8 of 429) had no change in QTc and 18% (76 of 429) had a decrease in QTc interval length (fig. 1). Approximately 51% (219 of 429) had a QTc greater than 440 ms, and 4% (16 of 429) a QTc greater than 500 ms. In 39% of the patients (166 of 429), the QTc prolongation ( $\Delta QTcF$ ) was greater than 30 ms, in 8% (34/429) > 60 ms, and in 0.5% (2/429) > 100 ms.

On the subsequent time points, no QTc interval changes compared with baseline were detected: the mean QTc was  $417 \pm 30$  ms on postoperative day 1 and  $412 \pm 29$  ms on postoperative day 2 (fig. 2 and 3). To determine whether the observed QTc prolongation may have been influenced by a large change in heart rate, we compared the average heart rate at the four time points. The average heart rate increased steadily from baseline ( $70 \pm 13$ /min), to end of surgery ( $76 \pm 15$ /min) and postoperative day 1 ( $79 \pm 13$ /min) and 2 ( $81 \pm 13$ /min), whereas the only statistically significant QTc prolongation was at the end of surgery.



**Fig. 2.** Spaghetti plot of individual changes in QTcF interval. QTcF = corrected QTc interval (Fridericia formula).





**Fig. 3.** Box plots of postoperative changes in QTcF interval. QTcF = corrected QTc interval (Fridericia formula).

### Factors Influencing the QTc Interval Prolongation

To rule out that the trial intervention (B-vitamins) had an effect on postoperative QT interval prolongation, we measured the change in QT/QTc in both study arms. B-vitamin treatment had a small, statistically nonsignificant effect on QTcF: 4 ms (95% CI  $-1.1$ – $8.8$  ms,  $P = 0.13$ ). Because women are known to have a longer baseline QT interval and a larger risk for developing drug-induced long QT syndrome,<sup>18,19</sup> we next investigated sex-specific effects on postoperative QTc prolongation. In our study, women had a minimally larger, statistically nonsignificant increase in postoperative QTc prolongation (4 ms, 95% CI  $-1$ – $9$  ms,  $P = 0.11$ ).

Several drugs had a pronounced effect on postoperative QTc interval prolongation; table 2 lists the effects of each perioperatively administered medication on postoperative QTc interval duration. Due to the substantial differences in the number of patients who received each drug, the fraction of patients who developed a QTc prolongation greater than 30 ms is presented. Among home medications, 47% of patients who took angiotensin II receptor blockers had a QTc interval increase of greater than 30 ms. Among anesthesia drugs and analgesics, isoflurane (54%), methadone (53%), and ketorolac (58%) were associated with the most pronounced QTc prolongation. Several antibiotics were associated with a marked postoperative QTc interval prolongation: cefoxitin (65%), unasyn [ampicillin and sulbactam] (78%) and zosyn [piperacillin and tazobactam] (56%). Among the cardiovascular drugs, epinephrine had the strongest effect (80% of patients had a QTc prolongation greater than 30 ms); along with ephedrine (49%) and calcium (48%). Interestingly, hydralazine and metronidazole appear to be associated with a reduction in QTc interval. Only 17% and 27%, respectively, of patients receiving these drugs had a QTc prolongation longer than 30 ms.

Postoperative body temperature had a weak negative correlation with postoperative QTc interval prolongation (Pear-

son  $r = -0.15$ ,  $P = 0.02$ ); serum magnesium, potassium, and calcium concentrations were not correlated.

### Postoperative Torsades de Pointes and Ventricular Arrhythmias

For 243 of 469 patients (52%) postoperative telemetry data were available. One patient developed torsades de pointes on postoperative day 1; his QTcF was prolonged by 29 ms (from 439 ms to 468 ms). The observed incidence rate for postoperative torsades de pointes was 0.4% (1 of 242). Nonsustained monomorphic ventricular tachycardia (nontorsade;  $< 30$ -s duration) occurred in 11 of 242 patients (incidence rate: 5%); all were self-terminated. Ventricular tachycardia was not associated with QTcF prolongation: the mean change in QTcF compared with baseline at the time of the event was  $-12$  ms. Premature ventricular contractions occurred in 27 of 242 patients (incidence rate 11%). The mean change in QTcF at the time of the event was 15 ms, suggesting a moderate association with QTc interval prolongation.

### Discussion

The goal of the study was to investigate postoperative QTc interval prolongation in a large cohort of adult patients undergoing noncardiac surgery. Our study confirmed the hypothesis that most patients experience a marked QTc interval prolongation postoperatively. The average increase in QTc was 23 ms, but a large number of patients experienced a much longer QTc prolongation, with some patients exceeding an increase of 60 ms or an absolute QTc greater than 500 ms. Interestingly, the observed QTc prolongation was only present during the stay in the postoperative anesthesia care unit but not on the following postoperative days.

What is the likely cause for the observed QTc prolongation? We would like to point out that the granularity of our study design does not allow us to draw definitive conclusions. Despite having all administered drug data, patients in our study had serial electrocardiograms, but no continuous Holter electrocardiogram monitoring, which would have allowed for a much more detailed investigation of QTc interval dispersion. Given these constraints, we nevertheless believe the cause for the observed QTc interval prolongation is a combination of several influencing factors. Cardiac repolarization, as indicated by the duration of the QT/QTc interval, can be prolonged due to inherited or acquired factors or a combination thereof. In fact, approximately 5–20% of all patients who develop drug-induced torsades de pointes have subclinical (inherited) long QT syndrome.<sup>20,21</sup> Because most patients in our study experienced a QT interval prolongation and the prevalence of inherited long QT syndrome is low, it is very likely that the cause for the observed QTc interval prolongation was acquired. Given the clear evidence that several drugs were associated with a statistically significant QTc prolongation in our study, drug-induced QT prolongation appears to be a major contributor to the observed QTc prolongation. Because individual drugs mostly showed

**Table 2.** Factors Influencing Postoperative QTc Interval Prolongation

Drug	Given/Used			% of Those on Drug with Increase > 30 ms			
	Mean Change in QTc (ms)	SD	n (%)	P Value for Student t Test	% with Increase > 30 ms	P Value Fisher Exact Test (1-tail)	Bootstrap P Value Corrected for Multiple Comparison
<b>Chronic medications</b>							
Clopidogrel	25.6	26.2	88	0.2301	43	0.2150	0.9999
Heparin	24.1	24.6	15	0.8366	40	0.5720	1.0000
Warfarin	18.4	23.9	36	0.3048	39	0.5658	1.0000
β-blocker	21.9	27.0	221	0.5665	41	0.1918	0.9998
ACE-Inhibitor	23.9	28.8	158	0.4260	44	0.0731	0.9371
Statin	22.5	26.8	234	0.9203	39	0.4582	1.0000
Angiotensin-R blocker	29.8	19.7	57	0.0196	47	0.0989	0.9823
Nitrate	24.3	26.8	36	0.6863	39	0.5772	1.0000
Digoxin	20.8	24.3	12	0.7932	42	0.5359	1.0000
Calcium channel blocker	21.5	26.0	125	0.5333	38	0.5877	1.0000
Diuretic	24.5	25.0	150	0.2580	41	0.3241	1.0000
<b>Perioperative medications</b>							
<i>Anesthetics and anesthesia-related drugs</i>							
Midazolam	22.7	25.5	361	0.6941	39	0.4154	1.0000
N <sub>2</sub> O	23.3	25.4	351	0.2158	40	0.1722	0.9996
Sevoflurane	22.3	28.7	141	0.8883	39	0.5039	1.0000
Desflurane	22.2	23.9	268	0.7017	38	0.7442	1.0000
Isoflurane	29.7	26.5	26	0.1417	54	0.0779	0.9513
Etomidate	24.8	30.4	36	0.5893	44	0.2849	1.0000
Propofol	22.4	25.2	388	0.7582	39	0.5885	1.0000
Dexmedetomidine	25.3	22.5	3	0.8502	33	0.7706	1.0000
Rocuronium	21.5	23.1	201	0.4227	35	0.9260	1.0000
Succinylcholine	22.1	21.3	114	0.8388	40	0.3764	1.0000
Vecuronium	23.4	29.1	174	0.5695	43	0.2608	1.0000
Neostigmine	22.2	25.5	282	0.6861	37	0.8796	1.0000
<i>Antihistamines and H<sub>2</sub>-blockers</i>							
Famotidine	25.1	20.7	41	0.5066	34	0.7861	1.0000
Cimetidine	26.4	8.7	8	0.6704	38	0.6586	1.0000
Dimenhydrinate	31.8	26.9	8	0.3075	38	0.6586	1.0000
Diphenhydramine	24.4	17.2	8	0.8381	38	0.6586	1.0000
<i>Analgesics</i>							
Fentanyl	22.9	25.5	390	0.3956	40	0.1065	0.9866
Morphine	24.2	24.2	109	0.4278	40	0.3802	1.0000
Hydromorphone	18.8	23.3	170	0.0161	35	0.9303	1.0000
Methadone	30.7	28.8	15	0.2098	53	0.1794	0.9997
Meperidine	24.4	22.7	13	0.7922	31	0.8101	1.0000
Ketorolac	28.0	28.0	26	0.2645	58	0.0340	0.7045
Acetaminophen	20.2	27.3	11	0.7603	36	0.6746	1.0000
<i>Antiemetics</i>							
Ondansetron	23.0	25.5	299	0.5786	38	0.6030	1.0000
Droperdol	23.2	26.5	13	0.9205	38	0.6123	1.0000
<i>Antibiotics</i>							
Cefazolin	21.5	25.4	306	0.2111	36	0.9579	1.0000
Cefoxitin	33.3	21.2	17	0.0788	65	0.0245	0.6110
Ciprofloxacin	28.8	27.3	12	0.3906	42	0.5253	1.0000
Metronidazole	17.3	22.4	15	0.4276	27	0.8959	1.0000
Vancomycin	19.9	28.8	83	0.2936	33	0.9217	1.0000
Zosyn	30.8	24.6	9	0.3324	56	0.2378	1.0000
Clindamycin	21.4	17.9	13	0.8713	46	0.3861	1.0000
Unasyn	36.0	13.7	9	0.1131	78	0.0195	0.4950
<i>Cardiovascular drugs</i>							
Calcium	26.8	25.8	58	0.1738	48	0.0723	0.9358

(continued)

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Table 2. Continued

Drug	Given/Used			P Value for Student t Test	% of Those on Drug with Increase > 30 ms		
	Mean Change in QTc (ms)	SD	n (%)		% with Increase > 30 ms	P Value Fisher Exact Test (1-tail)	Bootstrap P Value Corrected for Multiple Comparison
Potassium	22.8	27.1	16	0.9640	38	0.6343	1.0000
Metoprolol	21.6	24.2	38	0.8075	42	0.3869	1.0000
Hydralazine	12.1	22.4	12	0.1548	17	0.9773	1.0000
Labetalol	24.5	24.9	36	0.5572	47	0.1787	0.9997
Glycopyrrolate	23.1	25.4	323	0.3957	38	0.6348	1.0000
Epinephrine	55.2	32.7	5	0.0042	80	0.0762	0.9468
Ephedrine	28.0	27.3	138	0.0022	49	0.0015	0.0468
Phenylephrine	22.6	25.0	274	0.9576	39	0.3811	1.0000
<i>Other</i>							
Metoclopramide	29.7	17.8	28	0.1290	43	0.3902	1.0000
Albuterol	23.9	20.3	27	0.7712	37	0.6458	1.0000
Lidocaine	21.9	26.0	355	0.2404	37	0.8986	1.0000
Protamine	22.5	24.5	42	0.9943	31	0.8959	1.0000
Dexamethasone	26.3	25.6	78	0.1551	43	0.1965	0.9999
Nonpharmaceutical drugs							
Sex-female	25.0	25.5	164	0.1172	43	—	—
B-vitamins	24.7	26.6	189	0.1225	46	—	—

ACE = angiotensin-converting enzyme; N<sub>2</sub>O = nitrous oxide.

a median QTc-prolonging effect of less than 10 ms and the average observed postoperative QTc interval prolongation was 23 ms, drug-drug interactions and cumulative effect of several drugs were likely contributing to the postoperative QTc interval prolongation.

However, surgical stress—a concept difficult to quantify and measure—may also have been an important contributor. The observed large effects of epinephrine on QTc interval duration would be consistent with this notion; however, the median heart rate was only slightly increased in the postoperative period and showed no correlation with the QTc interval prolongation. Moreover, it cannot be ruled out that the stress during anesthesia emergence resulting from extubation, neuromuscular reversal, and pain had a marked effect on postoperative QTc interval.

Our study identified several drugs that had a pronounced effect on the QTc interval. Many of them, such as several antibiotics and methadone, have long been known to affect QTc duration. What was surprising was that neither ondansetron nor droperidol were associated with postoperative QTc interval prolongation. Both drugs have been shown to cause QTc interval prolongation in the perioperative setting,<sup>13,22</sup> and droperidol even received a black box warning from the Food and Drug Administration. However, other studies have found no or little effect of droperidol on QTc interval duration,<sup>23,24</sup> so the overall strength of evidence is unclear. It should also be pointed out that when corrected for multiple comparisons, nearly all *P* values became nonsignificant. This part of the analysis should be interpreted with caution and as exploratory.

It is important to emphasize that QTc interval prolongation is only an intermediate outcome measure that is associated with, but does not cause, torsades de pointes. Torsades

de pointes is a unique, potentially catastrophic tachyarrhythmia that is caused by an abnormal cardiac repolarization and thought to be triggered by a premature ventricular contraction.<sup>9,11</sup> The occurrence of torsades de pointes is probabilistic and correlated with the duration of the QT/QTc interval.<sup>25</sup> Each 10-ms increase in QTc interval duration exponentially increases the risk for developing torsades de pointes by 5–7%.<sup>26,27</sup> Data from congenital long QT-syndrome show that a QTc interval duration of greater than 500 ms increases the risk for torsades de pointes twofold to threefold.<sup>28</sup> Perioperative torsades de pointes is a rare event and as of the year 2011, 37 cases have been reported in the literature. The fact that one of our study patients, who had a QTc interval prolongation from 439 ms to 468 ms (29 ms), developed torsades de pointes may be a mere coincidence or an indicator that perioperative torsades de pointes is more common than previously assumed and substantially underreported. The fact that in contrast to other tachyarrhythmias such as ventricular tachycardia or ventricular fibrillation most instances of torsades de pointes are self-limited may contribute to underreporting.

In a recent scientific statement from the American Heart Association and the American College of Cardiology titled “Prevention of Torsades de Pointes in Hospital Settings” the authors raise several important points.<sup>25</sup> First, they convincingly point out that hospitalized patients are at higher risk for torsades de pointes. One of the major causes for the increased risk is polypharmacy or drug-drug interactions, which was also shown in a recent report from an intensive care unit setting.<sup>12</sup> Consistent with this observation is recent evidence from a well-conducted prospective study in the intensive care unit that found a high incidence of QT interval prolongation

and torsades de pointes.<sup>29</sup> Second, the scientific statement points out that increased vigilance, particularly for high-risk patients, can potentially identify patients at increased risk for QT prolongation and torsades de pointes as classic premonitory signs often precede the initiation of torsades de pointes (e.g., short-long-short sequence of R-R intervals).

The magnitude of the observed postoperative QTc prolongation in our study was substantial (23 ms). In comparison, during new drug development the current international guidelines target drug-induced QTc interval prolongations of 5 ms in so-called thorough QT studies. Drugs that prolong the QTc interval by greater than 5 ms are often removed from further development.<sup>16,17,30</sup>

This study had several potential limitations. First, the study was an ancillary study to a clinical trial and we cannot rule out that the study intervention (B-vitamins and nitrous oxide) had measurable effects on the findings, despite being statistically nonsignificant in the statistical analysis. Second, in our study patients had serial 12-lead electrocardiograms but not a continuous Holter electrocardiogram monitoring, which would have allowed us to determine the full range of QTc interval dispersion, particularly during surgery. Using a spot electrocardiogram on arrival in the postanesthesia care unit is somewhat random and drugs that were given shortly before the electrocardiogram measurement or clinical events may have had a larger effect on the observed change in QTc interval. Furthermore, this study setup limited our ability to measure the effects of short-acting drugs including anesthetic agents, whose short half-life would have eliminated most drug effects on QTc by the time the patient arrived in the postanesthesia care unit. It is therefore impossible to draw any conclusions regarding the effects of short-acting intraoperatively administered drugs on QTc interval prolongation. Third, our sample size was robust enough to determine the overall effects on QTc interval duration, but too small to allow for a robust multivariate analysis of all administered drugs. With more than 60 drugs and several additional covariates, a multivariate analysis would have probably resulted in many false-negative results and become inconclusive.

In summary, our study shows that postoperative QTc interval prolongation is common. Several perioperatively administered drugs are associated with a substantial QT-interval prolongation. Drug-drug interactions appear to be a major contributing factor to postoperative QTc prolongation. The exact cause of postoperative QTc prolongation and its clinical relevance, however, are unclear. Nevertheless, an association between postoperative QTc prolongation and risk for torsades de pointes is likely. It therefore seems prudent to increase the vigilance for perioperative QTc prolongation. Inexpensive measures may include the assessment of the preoperative baseline QTc interval duration, the display of the QTc interval duration on vital sign monitors, and the avoidance of potentially dangerous drug-drug interactions.

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