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QT Interval Prolongation after Cardiac Surgery; An Interesting Biological Phenomenon or A Clinical Problem? Data from the Prolonqit Study

Mohammad Toma[1], **Peter Marstrand**[1], **Kristina Holmenlund**[1], **Saadia Umar**[1], **Michael Wanscher**[2], **Steen Pehrson**[1], **and Juliane Theilade**[1*]

[1]*The Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen, Denmark*

[2]*The Department of Cardiothoracic Anesthesiology, The Heart Centre, Rigshospitalet, Copenhagen, Denmark*

[*]**Corresponding author:** Juliane Theilade, MD, PhD, The Department of Cardiology, The Heart Centre, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark, Tel: +45 3545 6319; E-mail: julianetheilade@gmail.com

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Abstract

Objective: Intrinsic and extrinsic factors may combine to delay the cardiac repolarization measured as the QT interval in the 12-lead electrocardiogram (ECG). As the duration of the QT interval is widely applied as an–albeit imperfect–marker of risk for malignant arrhythmias we characterized the prevalence and consequences of iatrogenic QT prolongation in patients undergoing cardiac surgery.

Design/patients/setting: We prospectively included clinical data and ECGs from 259 patients admitted to the intensive care unit following cardiac surgery.

Main results: Prolonged QT interval is common in patients undergoing cardiac surgery; 18% of patients displayed a QTc interval longer than 500 ms in the immediate postoperative period. The majority of these patients also showed QTc prolongation before surgery, however, the QTc interval was additionally prolonged following surgery. Drugs that prolong the QT interval were commonly used. The number of these drugs used in combination correlated with the prolongation of the QTc interval. QTc duration was not prolonged in patients with reduced left ventricular ejection fraction or renal function or in patients with atrial or ventricular arrhythmias or death.

Conclusions: An increased QT interval is a common finding amongst cardiothoracic surgery patients and it correlates to the administration of drugs with QT prolonging effects in the immediate postoperative period. We could not prove a correlation between the observed QT prolongation and adverse outcomes. However, the high prevalence of ECG abnormalities corresponding to the use of certain drugs calls for caution if treatment is continued especially when intensive care and monitoring is terminated.

Keywords: Acquired long QT interval; Drug induced arrhythmia; Sudden cardiac death; cardiothoracic surgery; Intensive care

Introduction

Prolongation of the QT interval on the electrocardiogram has been associated with an increased risk of malignant arrhythmias, cardiac arrest and death [1]. Case series of torsades de pointes ventricular tachyarrhythmia suggest that the extent of QT interval prolongation may be used as a marker for a given drug's cardiotoxicity [2,3]. Furthermore, a recent large investigation based on prescription data showed an increased mortality among people taking azithromycin suggesting this antibiotic exerted deleterious pro-arrhythmic effect through its effect on cardiac electrical homeostasis [4]. We wanted to ascertain how common prolonged QTc interval (QT interval corrected by heart rate) is in post-cardiac surgery patients in one of the largest Heart Centers in Europe. We wanted to determine whether QT interval prolongation is a common finding among consecutive patients following cardiac surgery, whether this possibly observed QT interval prolongation is acquired and/or mainly seen in patients with cardiac or renal dysfunction. In addition, we sought to establish whether QT interval prolongation in this group would reflect the prevalence of atrial and ventricular arrhythmias and death.

Methods

The Prolonqit study population consisted of prospectively included patients undergoing cardiac surgery at the Copenhagen University Hospital (Rigshospitalet) during the period from May 21st to November 21st 2013. The study was planned as an evaluation of our daily practice and as such did not require formal approval by the local ethical committee but was approved by the Directors of the departments involved. Patients were identified and included within 24 hours of surgery. Clinical information was gathered through review of the patients' medical notes. Cardiovascular risk factors (such as hypertension, hypercholesterolemia, diabetes, previous stroke, smoking and peripheral arterial disease) were noted. In addition, left ventricular function, renal function and potassium levels at the time of ECG recording were registered. A postoperative ECG from the day of inclusion was analyzed for heart rate, RR, PQ, QRS and QT intervals. The QTc interval was calculated using the Bazzett's formula. At the time of ECG recording patients were awake. None of ECGs included had been recorded while the patients were paced. Two independent researchers recorded the RR and QT interval and in cases of divergent measures a consensus was reached. As the initial part of the data analysis preoperative ECGs were collected from digital archives for patients with a postoperative QTc interval exceeding 500 milliseconds (ms). The administration of QT interval prolonging drugs were noted

based on entries in the digital chart; QT interval prolonging drugs administered were included if they had been administered within 24 hours of the ECG recording. We used the website www.qtdrugs.org for identification of drugs possibly contributing to any observed QTc interval prolongation. During the study period this website was revised twice with the inclusion of furosemide and other drugs as QT interval prolonging drugs; however, to secure comparability of data we did not implement revisions published after May 21st 2012. The occurrence of atrial and ventricular arrhythmias and deaths during hospitalization was recorded.

Statistical analyses

Continuous variables are presented as the median and 5th and 95th percentiles, while discrete variables are presented as percentages. First, the patients were classified into five groups according to the number of the QT interval prolonging drugs they received. Differences between these groups were analyzed using the ANOVA procedure. We also performed further analyses after dividing the patients into two large groups using a cut-off value, first for the number of QT interval prolonging drugs, then for the LVEF and lastly for the GFR. After each division, the two large groups of patients were tested for normal distribution visually with the quantile plot and statistically using the Shapiro-Wilk test. All the parameters showed normal distribution. Thereafter, the Student's t-test was used each time to analyze the differences between the two groups. A p value <0.05 was considered statistically significant. The analyses were performed with SAS statistical software (Cary, N.C., USA), version 9.1.3.

Results

The clinical characteristics of the 259 patients included in the Prolonqit study are shown in Table 1. In total, we had screened 278 patients but excluded 19 based on one of the following ECG findings; only ventricular paced ECGs available (14 patients), highly irregular cardiac rhythm prohibiting a meaningful measurement of the QT interval (four patients) and an incomplete 12 lead ECG recording (one patient). The majority of the patients were male (73%). The mean age was 68 ± 11 years; there were no differences in age between men and women. The mean body mass index was 27 kg/m^2.

Patient characteristics			**n (%)**
Demographic data	Patients included (hereof male)		259 (190 or 73%)
	Age ± SD [male/female], years	68 ± 11 [68 ± 11/68 ± 12]	
	BMI ± SD [male/female], kg/m^2	27 ± 4 [27 ± 4/26 ± 6]	
Risk factors for cardiovascular disease	Hypertension		170 (66)
	Hypercholesterolemia	170 (66)	
	Diabetes mellitus, on insulin	35 (14)	
	Smoker/ex-smoker	122 (47)/21 (8)	
	Extracardiac arteriopathy	18 (7)	
	Previous stroke	26 (10)	
	Alcohol overuse	48 (19)	
Clinical features	Left ventricular ejection fraction	>50	152 (59)
		31-50	62 (24)
		21-30	18 (7)
		<21	10 (4)
		Not reported	17 (7)
	Glomerular filtration rate ml/min/1.73 m^2	>85	72 (28)
		50-85	132 (51)
		<50	52 (20)
		Not reported	3 (1)
	New York Heart Association class	1	81 (31)
		2	86 (33)
		3	74 (29)
		4	8 (3)

		Not reported	10 (4)
	CCS class 4*	13 (5)	
	Recent myocardial infarction	65 (25)	
	Chronic obstructive pulmonary disease	40 (15)	
	Poor mobility	16 (6)	
Surgical conditions	Critical preoperative state		9 (3)
	Elective/urgent/emergency	207/43/9	
	Number of procedures 1/2/3	190/73/6	
	Active endocarditis	4 (2)	
Postoperative findings	O_2 saturation ± SD		97 ± 7
	Potassium ± SD	4.2 ± 0.5	
Number of QT prolonging drugs administered	Average		1.37
	1	117 (45)	
	2	30 (12)	
	3	12 (5)	
	4	3 (1)	
QTc duration ± SD, ms	All [male/female]		462 ± 43 [458 ± 43/472 ± 41]
QTc 481-500 ms (%)	All [male/female]		22 (9) [15(8)/7(10)]
QTc >500 ms (%)	All [male/female]		47(18) [30(16)/17(25)]

*CCS class = Canadian cardiovascular society angina classification
Class 4 is angina at any level of exertion including rest

Table 1: Clinical characteristics of patients included in the Prolonqit study.

Patients displayed a significant amount of cardiovascular risk factors and co-morbidities (Table 1). Hypertension and hypercholesterolemia were each noted in 66%, 14% had diabetes and were treated with insulin, more than half were active or former smokers, 10% had reported to have previously had a cerebral stroke and 19% had reported high alcohol intake. (The alcohol intake was not specifically recorded for all patients but was generally considered high when exceeding seven or 14 units of alcohol for men and women, respectively, with 1 unit corresponding to a 33 cc regular beer). Cardiac function as assessed by preoperative echocardiography was abnormal in 35% and renal function was affected in 72% (Table 1). With regards to the subjective classification of dyspnea patients were almost equally distributed in New York Heart Association classes 1, 2 and 3. We noted that 16% of patients had reported to be diagnosed with chronic obstructive pulmonary disease. In addition, 25% had recently suffered a myocardial infarction. In fact, 5% were classified as being in class 4 by the Canadian Cardiovascular Society angina classification meaning that they were not pain free even during rest prior to the surgical procedure.

With regards to the surgical intervention the majority (73%) of patients underwent a single procedure such as either coronary artery bypass grafting or surgery on cardiac valves, whereas 28% underwent a double procedure such as for instance coronary artery bypass grafting combined with valvular surgery. Perioperatively patients were routinely implanted with a temporary, epicardial pacemaker. In the postoperative period patients were well controlled with respect to oxygen saturation and potassium levels (Table 1). The administration of drugs with the potential to prolong the QT interval was common; 63% of patients received at least one QT interval prolonging drug (on average 1.4 QT interval prolonging drugs per patient). This translates to almost half of the patients receiving 1 QT interval prolonging drug, 12% receiving 2 QT interval prolonging drugs and 5% receiving 3 QT interval prolonging drugs and 1% of patient receiving 4 QT interval prolonging drugs within the time period defined above.

We show, that QT interval prolongation is common among patients undergoing cardiothoracic surgery (Table 1); 69 patients (27%) displayed a QTc interval longer than 480 ms. In addition, the QTc interval prolongation observed among our patients was acquired. We employed two strategies to prove this. First, after the termination of the study and in the initial part of data analysis, we selected the 47 patients with a QTc interval longer than 500 ms and in 28 cases a preoperative ECG was available (Table 2a).

Preoperative QTc duration, ms	Postoperative QTc duration, ms	δQTc* duration, ms	Gender
406	537	131	female
409	524	115	female
412	511	99	female
418	505	87	female
421	505	84	female
422	525	103	female
433	550	117	female
438	509	71	male
447	512	65	female
448	516	68	male
452	518	66	male
458	505	47	female
460	510	50	male
466	518	52	male
469	541	72	male
473	535	62	female
473	551	78	male
474	508	34	male
474	530	56	male
477	596	119	male
483	519	36	male
485	508	23	male
508	551	43	male
531	512	-19	male
540	574	34	male
543	560	17	male
550	520	-30	male
655	533	-122	female

*δQTc=difference in corrected QT interval duration postoperatively and preoperatively.

QTc was calculated using the Bazzett's formula.

Table 2a: Pre- and post-operative QTc interval duration for patients with the most prolonged QTc intervals measured (>500 ms).

In fact, only 12 of the 28 ECGs were with QTc intervals within the accepted normal limits (shorter than 450 ms for men and 460 ms for women). However, in all but two cases the preoperative QTc interval was shorter than postoperatively during recovery in the cardiothoracic intensive care unit. Overall, the QT interval increased 51 ± 54 ms for this group (39 ± 40 ms versus 71 ± 69 ms for men and women, respectively). Subsequently, we registered the administration of QT interval prolonging drugs on the day before and on the day of the ECG recording. Our results show, that QT interval prolongation in cardiothoracic surgery patients is associated to the combined effects of disease and treatment. The QT interval prolongation correlated to the number of QT interval prolonging drugs administered in the early recovery phase following cardiac surgery (Table 2b).

Number of QT drugs	0	1	2	3	4	p-value
Number of patients	97	117	30	12	3	
Prolonged >500 ms (%)	20 (21)	11 (9)	10 (33)	4 (33)	2 (66)	
QTc duration±SD, ms	464 ± 43	454 ± 39	483 ± 47	456 ± 42	519 ± 41	0.009

Table 2b: QTc duration in patients grouped depending on the number of QTc interval prolonging drugs administered.

Number of QT drugs	<2	≥2	p-value
Number of patients	214	45	
QTc duration ± SD, ms	458 ± 41	480 ± 47	0.002

Table 2c: QT duration in patients grouped according to the administration of <2 og ≥ 2 drugs with QTc interval prolonging effects, respectively.

Table 2d shows the 'top 5' used QT interval prolonging drugs in the immediate postoperative period. The most commonly used QT interval prolonging drug were ondansetron, followed by (in declining order) droperidol, amiodarone, ciprofloxacin and fluconazole. However, antibiotics such as ciprofloxacin and fluconazole were not used routinely, and patients receiving these drugs likely have been considered sicker than the average patients (e.g. suspected/confirmed sepsis), which may contribute to the ECG changes observed.

Top 5 QT drugs, n	
Ondansetron	130
Droperidol	27
Amiodarone	24
Ciprofloxacin	15
Fluconazole	7

Table 2d: The five most commonly administered QT drugs. In total, 203 (92%) of 222 QT prolonging drugs administered are on this list.

QT interval prolongation was not observed more commonly among patients with reduced left ventricular ejection fraction or renal dysfunction was not confirmed (Table 3); no significant prolongation of the QTc interval duration was observed when comparing patients with severe impairment of either left ventricular ejection fraction or glomerular filtration rate with patients without either severe left ventricular dysfunction or renal dysfunction.

QT interval prolongation did not correlate to the development of atrial and/or ventricular tachyarrhythmia or death (Table 4). In summary, four patients died before discharge, ten patients developed malignant arrhythmias (either non-sustained ventricular tachycardia or ventricular tachycardia/fibrillation) and 143 developed atrial fibrillation according to the chart. However, there was no statistical correlation between these events and the duration of the QTc interval measured in the immediate postoperative phase.

Cardiac function	LVEF >30%	LVEF <30%	p-value
QTc interval ± SD	461 ± 42	478 ± 43	0.6
Renal function	**GFR >50 ml/min/1.73 m^2**	**GFR <50 ml/min/1.73 m^2**	
QTc interval ± SD	465 ± 35	461 ± 46	0.5

Table 3: Comparison of the QTc duration after introducing a cut-off value for left ventricular ejection fraction (30%) and glomerular filtration rate (50 ml/min/1.73 m^2), respectively.

	Yes	No	p-value
Atrial fibrillation	468±45	456±39	0.09
Ventricular tachycardia	455±58	462±42	0.58
Death	473±44	461±44	0.54

Table 4: QTc duration in patients that developed atrial or ventricular arrhythmias or died. Values are given as mean ± standard deviation (ms).

Discussion

QT interval prolongation may occur as a congenital trait or be acquired; the prevalence of the inherited long QT syndrome is estimated to 1:2.500 whereas the frequency of acquired QT syndrome has not been reported in population-based studies [5]. In this study, we show that QT interval prolongation is common in the cardiothoracic intensive care unit among unselected prospectively studied patients following cardiac surgery. In fact, 18% of patients displayed a QTc interval longer than 500 ms in the immediate postoperative period. Similar results have been published previously; in 18% of 900 patients admitted to dedicated cardiology beds the QT duration was >500 ms [6]. In addition, it was shown that QT interval prolongation among medical patients was common (22% of 537 patients) and related to the use of QT interval prolonging drugs, hypokalemia and liver disease [7]. Additional factors such as age, gender, congestive heart failure and bradycardia may contribute to prolong the QT duration [8,9]. We document that the QT interval prolongation observed among patients having undergone cardiac surgery is acquired/enhanced in the postoperative period. Based on our data, the combined effects of the surgical trauma and the medications administered are associated with prolongation of the QT interval. However, we were not able to correlate the observed QT interval prolongation to cardiac or renal dysfunction or to increased mortality. Also, Pasquier et al. did not demonstrate increased risk of death among patients with QT interval prolongation [7]. In contrast, others have documented that QT interval prolongation in consecutively monitored patients was associated with an increased risk of cardiac arrest and death [6]. A study from the Stanford University including 537 acutely ill medical, surgical and trauma patients monitored by an automated QTc interval analysis software documented QTc interval prolongation in 24% of patients and linked the observed QT interval prolongation to in-hospital cardiac arrests [9]. In a report by Letsas et al. 6 of 21 patients with a QTc interval longer than 500 ms developed malignant arrhythmias [3]. Methodological variations may in part account for diverging conclusions; the 259 patients included in the Prolonqit study were included consecutively during the 6-month study period whereas the 21 patients studied by Letsas et al. were selected due to significant QT interval prolongation during a 33-month period. In addition, our small sample size may have obscured any clear signal that QT interval prolongation is associated with arrhythmic death following cardiothoracic surgery. In addition it is clear that any given drug's effect on QT duration does not automatically translate to an increased risk of cardiac arrhythmias; amiodarone often produces significant QT interval prolongation but is rarely pro-arrhythmic, whereas a drug such as haloperidol exerts only a minor effect on QT duration but has a significant pro-arrhythmic potential. These differences may reflect additional effects of the individual drugs. For instance amiodarone affects a number of cardiac ion channels with presumed counteracting effects on its QT interval prolongating properties [8-11]. Furthermore, the routine perioperative use of temporary cardiac pacemakers set at 80 beats per minute in our patients may have hindered the development of torsades de pointes in a number of patients as temporary pacing is in fact an empirical treatment option for suppression of ventricular tachyarrhythmias in patients with QT prolongation.

At present, physicians appreciate the existence of the syndrome of acquired or iatrogenic QT interval prolongation. The fact, that 2-3% of prescription drugs have the ability to prolong the QT interval, implies that we need to understand the consequences of this phenomenon [12]. Currently, conclusions from clinical studies are conflicting as discussed above. In epidemiological studies estimating the risk of death in persons taking QT interval prolonging drugs, event rates are very low compared to the number of persons studied and a direct comparison of risk between different drugs is difficult to ascertain. However, one study did show that two specific antidepressants – citalopram and nortriptyline – were associated with an increased rate of cardiac arrest [13], but this association may in part be due to the widespread use of these specific drugs in comparison to other drugs investigated for whom no increase in risk could be proved. It is also possible that malignant arrhythmias following pharmacologically induced QT interval prolongation require a particular susceptibility; approximately 50% of cardiac arrest survivors (in whom the cardiac arrest was considered to be due to acquired QT interval prolongation) developed recurrent malignant arrhythmias during a 10-year follow-up period despite no identifiable triggers at recurrence [14]. A joint report from the Societies of Psychiatry and Cardiology in Denmark have suggested a stepwise approach when prescribing QT interval prolonging drugs to psychiatric patients; suggestions include screening for symptoms and risk factors for QT interval prolongation, avoidance of polypharmacy as well as repeated ECG screening which seems time-consuming and challenging to implement [15]. We found that 63% of consecutively included patients undergoing cardiac surgery were administered QT interval prolonging drugs (or on average 1.4 drugs/patient) in the immediate postoperative period. The period of time during the postoperative phase where the QT interval is prolonged may determine the number of arrhythmic events. This susceptible period may be short for surgical patients generally recovering rapidly.

In addition, the use of QT interval prolonging drugs is probably biased; the sickest patients will receive more medications when compared to uncomplicated patients and the underlying multitude of diseases battled as well as the medications prescribed may combine to affect cardiac repolarization. Furthermore, patients in whom QT interval prolongation is succeeded by malignant arrhythmias are apparently frailer than patients not displaying malignant arrhythmias when assessing the prevalence of for example reduced left ventricular function and renal dysfunction [3,6,7,9]. As such, risk factors for QT interval prolongation were abundant among the few patients that did develop malignant tachyarrhythmias (data not shown), even though our data did not find a statistical association between the QT interval duration and arrhythmias and/or death.

Conclusions

We conclude that QT interval prolongation is common among cardiothoracic surgery patients and correlates to the administration of drugs with QT interval prolonging effects in the immediate postoperative period. We could not prove a correlation between the observed QT interval prolongation and adverse outcomes; however, the high prevalence of ECG abnormalities corresponding to the use of certain drugs calls for caution if treatment is prolonged especially when intensive care and monitoring is terminated.

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