The Effects of Propofol and Sevoflurane on the QT Interval and Transmural Dispersion of Repolarization in Children

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Prolongation of the QT interval is associated with torsades de pointes (TdP), especially in children or young adults with long QT syndromes. Susceptibility to TdP arises from increased transmural dispersion of repolarization (TDR) across the myocardial wall. Several anesthetic drugs prolong the QT interval, but their effect on TDR is unknown. TDR can be measured on the electrocardiograph (ECG) as the time interval between the peak and end of the T wave (Tp-e). We investigated the effects of propofol and sevoflurane on the corrected QT (QTc) and Tp-e intervals in 50 unpremedicated ASA physical status I–II children, aged 1–16 yr, who were randomized to receive propofol (group P) or sevoflurane (group S). Twelve-lead ECGs were recorded preoperatively and intraoperatively. Sevoflurane significantly prolonged the preoperative QTc; propofol did not. Neither anesthetic had any significant effect on the preoperative Tp-e. Sevoflurane increases the duration of myocardial repolarization in children to a larger extent than does propofol, but as the dispersion of repolarization appears unaffected, the risk of TdP is likely to be minimal with either anesthetic.

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Ventricular repolarization is represented on the surface 12-lead electrocardiogram (ECG) by the QT interval, measured from the start of the QRS complex to the end of the T wave. There are several formulae for correcting the QT interval for heart rate (QTc). Although there is debate regarding which is best, the most commonly used is Bazette's formula (1), $QTc = QT/\sqrt{RR}$. Using this formula, the accepted upper limit of normal for the duration of repolarization is 440 ms (2).

At a cellular level, repolarization is effected by the efflux of potassium (K^+) ions through a variety of K^+ channels during phases 2 and 3 of the electrical cardiac cycle. The slowly activating (*iKs*) and rapidly activating (*iKr*) delayed rectifier channels conduct most of the repolarizing current (3). The outward flow of current is partially countered by small inward fluxes of sodium (Na^+) ions through late activating *iNa* channels and the activity of the sodium-calcium exchanger pump. The net balance of current flow through these ion channels determines the duration of repolarization.

The cellular composition of the myocardium is not homogenous and its component cells repolarize at different rates. Midmyocardial (M) cells have a lower density of *iKs* channels and a greater density of *iNa* channels compared with adjacent regions (4,5). Consequently, these M cells repolarize more slowly than either the epicardium or the endocardium. Repolarization therefore occurs asynchronously across the myocardial wall, producing a physiological transmural dispersion of repolarization (TDR). The intrinsic differential time course of repolarization across the myocardial wall is responsible for the morphology of the ECG T wave (6,7). Epicardial cells repolarize first, and the peak of the T wave corresponds with the completion of epicardial repolarization. M cells, which repolarize last, determine the total duration of the action potential; the end of the T wave corresponds with the full recovery of these cells (7). It follows that the interval from the peak to the end of the T wave (Tp-e) may be used as a measure of TDR.

Reduction in *iK* channel function or increase in *iNa* channel conductance reduces the net outward flow of repolarizing current, prolonging action potential duration and the QTc. The M cell is characterized by the capacity for its action potential to lengthen disproportionately compared with other parts of the myocardial wall in response to various stimuli, producing an exaggeration of TDR (8). This is proarrhythmogenic, as it exaggerates a milieu in which afterdepolarizations can

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initiate re-entrant circuits between areas of myocardium in variable states of refractoriness.

Prolonged TDR is the substrate for torsades de pointes (TdP), a malignant polymorphic ventricular tachycardia responsible for the presenting symptoms of syncope, aborted cardiac arrest, or sudden death, which are characteristic of hereditary long QT syndromes (LQTS) (7,9–11). QT prolongation has been dogmatically synonymized with LQTS, although it is only one of the diagnostic criteria (12). In an elegant series of experiments on isolated canine heart preparations, it has been shown that TdP in all three phenotypes of congenital LQTS only occurs when TDR is increased; QT interval prolongation *per se* is not sufficient to predispose to TdP (9,11).

QT interval prolongation can also be drug-induced, resulting in an acquired LQTS that is almost exclusively caused by drugs that block *iKr* channels. However, not all QTc-prolonging drugs are torsadogenic and it is logical to hypothesize that those drugs that are associated with TdP are capable of increasing TDR through a preferential effect on M cell repolarization dynamics. Volatile anesthetics are *iKr* channel blockers; the QTc is prolonged in healthy patients undergoing anesthesia with halothane, enflurane, isoflurane, or sevoflurane (13–20). Of the IV induction anesthetics, thiopental prolongs the QTc (21,22), but there are conflicting accounts of the effect of propofol (19,23–26). However, no studies have investigated the effect of these anesthetic drugs on TDR, which is more relevant to the attendant risk of TdP.

Most patients with symptomatic QT prolongation are children and young adults with an inherited mutation in one of the genes encoding the constituent proteins of *iKs*, *iKr*, or *iNa* channels. There is little evidence to guide the rational selection of anesthetic drugs in these patients; the aim is clearly to avoid anything that may increase the already increased risk of TdP. Sevoflurane and propofol are two drugs widely used in pediatric anesthesia. We therefore undertook to study the effects of sevoflurane and propofol on QTc and Tp-e in children.

Methods

With the approval of the local research and ethics committees, we recruited 50 unpremedicated ASA physical status I–II children, aged between 1 and 16 yr, undergoing elective surgery under general anesthesia. Patients on medications known to prolong the QT interval were excluded. After obtaining written informed consent from parents and the written assent of older children where appropriate, enrolled patients were randomized to receive either propofol or sevoflurane at induction of anesthesia. Randomization schedules were devised using random number tables.

On arrival in the anesthetic room and before induction of anesthesia, ECG electrodes were sited at standardized locations for acquisition of a preoperative 12-lead ECG. An intraoperative ECG was taken 15 min after induction of anesthesia, using the same electrode positions. The patient's involvement in the study was then complete and conduct of anesthesia continued at the discretion of the supervising anesthesiologist. All ECGs were recorded in duplicate on a Hewlett Packard Pagewriter 100 (Philips Medical, Böblingen, Germany) at a paper speed of 50 mm/s. No identifying data or automated analysis were printed on the recorded traces. Each ECG was given a random number three-figure code to allow identification of paired preoperative and intraoperative traces after analysis.

Anesthesia was induced and maintained for 15 min with the drug allocated by randomization. In group S, children received sevoflurane 8% in oxygen for induction, followed by sevoflurane titrated to an end-tidal concentration of 3%, in oxygen and air. In group P, children received a target-controlled infusion of propofol, set to a target plasma concentration of 3 μg/mL. Infusion protocols were provided by Dr. N. S. Morton (University of Glasgow, personal communication) who ran sham infusions on a Paedfusor® containing a pediatric pharmacokinetic data set (27). As the infusion rates varied with weight, several protocols were available and the weight-appropriate one was selected on each occasion. After induction, the inspired oxygen concentration was reduced to 40%. The airway was maintained by face mask or by a laryngeal mask airway. In an attempt to minimize sympathetic stimulation, laryngoscopy was not permitted during the study period. No other drugs were administered and no local anesthetic blocks were conducted during the study period. Throughout the study period, all children breathed spontaneously and received routine monitoring, including capnography. End-tidal carbon dioxide values ranged between 34 mm Hg and 41 mm Hg.

Two authors (PDB and DGB) independently analyzed all the ECG traces in accordance with predetermined criteria. Both were blinded to the anesthetic used and to the status of the ECG recording (preoperative or intraoperative). Neither was involved in recruitment or randomization of patients, or in conduct of anesthesia or acquisition of ECG recordings, all of which was performed by SDW.

The QT interval, RR interval, and Tp-e interval were measured in leads II and V5. The QT interval was measured from the start of the QRS complex to the end of the T-wave and the Tp-e interval was measured from the peak of the T-wave to the end of the T-wave, defined as the point of return to the T-P baseline. If U waves were present, the end of the T wave was taken as the nadir of the curve between the T and U waves. The QT and Tp-e intervals were calculated for all

complete P-QRS-T cycles in each lead and averaged to give a mean QT interval and Tp-e interval for that lead. QT intervals were corrected according to the formula of Bazette (1), $QTc = QT/\sqrt{RR}$. Bland-Altman plots were used to compare the ECG data from the two independent reviewers. Where an interobserver difference of >10 ms in an RR interval or of >20 ms in a QT or Tp-e interval was found, the recordings, still coded, were reanalyzed and a consensus was reached if possible. Thus, for each lead in each trace, two values for the mean RR interval, the mean QTc interval, and the mean Tp-e interval were eventually obtained, one from each independent reviewer. Each pair of values was then averaged to give an overall mean value for use in further statistical analysis.

Statistical analysis was conducted with Analyze-It software (Analyze-It Software Ltd., Leeds, England). Using previously published data (28), interpretation of an effect in either direction, and the criterion for significance (α) set at 0.05, it was calculated that a sample size of 21 per group would detect a difference of 10 ms in Tp-e between the intraoperative means of the two groups with a power of 80%. Within-group and between group comparisons of preoperative and intraoperative ECG indices were performed using paired and unpaired Student's *t*-test respectively.

Results

Fifty patients were recruited to the study (17 female, 33 male). Twenty-two were randomized to group P (six females) and 28 to group S (11 females). Two patients from group P were excluded from the final analysis. No venous access was obtainable in one, and the cannula was accidentally pulled out during the study period in another; the preoperative ECGs from both these patients were included in the interobserver comparison. In both cases anesthesia was continued with sevoflurane. One patient in group S was too uncooperative to obtain a preoperative ECG, but the intraoperative ECG parameters was included in the comparison between groups S and P.

Table 1 illustrates the demographic characteristics and baseline ECG parameters of the two groups. There were no significant differences between groups S and P with respect to any of these variables.

There was very close agreement in measured RR intervals in both leads between the reviewers (lead II mean bias −1.5 ms; mean error −2.1% to +1.4%; lead V5 mean bias −1.2%; mean error −1.9% to +1.4%). The interobserver bias (95% limits of agreement) for the measurement of QTc was −0.7 ms (−20.1 to + 19.1 ms) in lead II and + 1.9 ms (−16 to + 19.8 ms) in lead V5. For the measurement of Tp-e, the values were −1.6 ms (−15.3 to + 12.0 ms) in lead II and −1.6 ms (−15.9 to + 12.7 ms) in lead V5. These figures indicate that, between the reviewers, the difference in measured QTc interval averaged only one small ECG square either way; for Tp-e measurements, the difference was less than this.

Table 2 shows the results of the within-group analyses of preoperative and intraoperative ECG recordings in groups P and S. Propofol, at a predicted plasma concentration of 3 μg/mL, increased the QTc interval by a mean of 8 ms in lead II and 5 ms in lead V5; neither of which difference achieved statistical significance. The Tp-e interval altered by small, statistically insignificant margins of −0.6 ms and +2.6 ms in leads II and V5, respectively. Sevoflurane markedly prolonged the QTc in both leads II and V5, by a highly statistically significant margin of more than 30 ms. After 15 min of sevoflurane anesthesia, the absolute QTc exceeded the upper limit of normal in both leads. However, as with propofol, the Tp-e interval altered by only small, statistically insignificant margins of −0.2 ms and +2.7 ms in leads II and V5, respectively.

Table 3 shows the results of the between-group analysis of intraoperative ECG recordings in groups P and S. The effect of sevoflurane on the QTc was significantly greater than that of propofol at the concentrations used in this study, but there was no difference between the groups with respect to the effect on Tp-e.

Discussion

Prolongation of the QTc is associated with a risk of TdP. This arrhythmia results in a precipitous decrease in cardiac output. TdP usually occurs in short, self-limiting bursts but may degenerate into ventricular fibrillation. This accounts for the clinical manifestations of the arrhythmia: syncope, aborted cardiac arrest, and sudden death. The association of QTc prolongation with the risk of TdP does not imply causality and the long-held hypothesis that it is the prolonged repolarization that predisposes to the arrhythmia is flawed for several reasons. First, up to 40% of patients with congenital QT prolongation are asymptomatic at the time of diagnosis (29). Second, not all drugs that are capable of prolonging the QT interval are torsadogenic (30). Third, 6% of patients with symptomatic LQTS have a QTc interval that is not absolutely prolonged (31).

An alternative hypothesis has been gathering momentum over the last decade. Elegant experiments using drugs to target ion channels involved in repolarization dynamics have generated models that mimic the genetic defects that result in the three phenotypes of LQTS. Using these models, it has been demonstrated that QTc prolongation *per se* does not predispose to TdP but exaggeration of physiological TDR does (6,9,11). Further work, correlating the time course of monophasic action potentials from epicardium, endocardium, and M cells

Table 1. Patient Demographics and Baseline Electrocardiograph (ECG) Variables

	Group P (n = 22)	Group S (n = 28)	Total	Difference (95% CI)	P value
Male/Female	16/6	17/11	33/17	–	–
Age group (yr)					
1–2	2	1	3	–	–
2–5	5	7	12	–	–
5–13	13	19	32	–	–
>13	2	1	3	–	–
Age (mo)	92.5 (50.8)	90.7 (49.3)	–	−1.8 (−27.6 to 31.3)	0.90
Weight (kg)	31.3 (15.1)	28.5 (15.5)	–	2.8 (−6.3 to 11.8)	0.55
ECG Variables (msec)					
QTc lead II	423 (27)	413 (28)	–	−10 (−27 to 6)	0.22
QTc lead V5	436 (28)	423 (26)	–	−13 (−29 to 3)	0.11
Tp-e lead II	75 (12.3)	70.8 (9.7)	–	−4.2 (−10.7 to 2.2)	0.19
Tp-e lead V5	79.9 (14.9)	77.1 (12.3)	–	−2.8 (−10.9 to 5.2)	0.48

Values are mean (SD) unless otherwise indicated.
QTc = corrected QT interval (ms); Tp-e = $T_{peak\text{-}end}$ interval (ms).

Table 2. Comparison of Preoperative and Intraoperative QTc and Tp-e in Groups P and S

	Preop	Intraop	Difference (95% CI)	P value
Group P-QTc				
Lead II	423 (27)	432 (20)	8 (0 to 17)	0.06
Lead V5	436 (28)	442 (22)	5 (−3 to 13)	0.18
Group P-Tp-e				
Lead II	75.0 (12.3)	74.4 (8.4)	−0.6 (−5.7 to 4.5)	0.81
Lead V5	79.9 (14.9)	82.5 (9.9)	2.6 (−4.0 to 9.2)	0.42
Group S-QTc				
Lead II	413 (28)	449 (22)	36 (26 to 46)	<0.0001
Lead V5	423 (26)	456 (17)	33 (24 to 43)	<0.0001
Group S-Tp-e				
Lead II	70.8 (9.7)	70.6 (11.6)	−0.2 (−5.4 to 5.0)	0.94
Lead V5	77.1 (12.3)	79.8 (15.8)	2.7 (−2.3 to 7.6)	0.28

Values are mean (SD) unless otherwise indicated.
Preop = preoperative value; Intraop = intraoperative value; CI = confidence interval; QTc = corrected QT interval (ms); Tp-e = $T_{peak\text{-}end}$ interval (ms).
Group P: n = 20; Group S: n = 27.
Paired Student t-tests, two-tailed P <0.05 for significance.

Table 3. Comparison of the Effects of Sevoflurane and Propofol on Intraoperative QTc and Tp-e Intervals

	Group P (n = 20)	Group S (n = 28)	Difference (95% CI)	P value
Intraop QTc				
Lead II	432 (20)	449 (22)	17 (5 to 29)	0.02
Lead V5	442 (22)	456 (17)	14 (3 to 26)	0.01
Intraop Tp-e				
Lead II	74.4 (8.4)	70.4 (11.4)	−4.0 (−10.1 to 2.0)	0.19
Lead V5	82.5 (9.9)	79.4 (15.6)	−3.1 (−11.1 to 4.9)	0.44

Values are mean (SD) unless otherwise indicated.
Preop = preoperative value; Intraop = intraoperative value; CI = confidence interval; QTc = corrected QT interval (ms); Tp-e = $T_{peak\text{-}end}$ interval (ms).
Paired Student t-tests, two-tailed $P < 0.05$ for significance.

with the surface ECG, has accounted for the morphology of the T wave, both in healthy models and in those with LQTS 1, 2, and 3 (7). The observation that conclusion of epicardial repolarization coincides with the peak of the T wave and completion of M cell repolarization coincides with the end of the T wave led to the proposition of the Tp-e interval as a surface ECG marker of TDR. Although the validity of this variable is still being investigated, the evidence is encouraging. Lubinski et al. (32) have contributed to the clinical validation of Tp-e as a marker of TDR by showing it to be prolonged in LQTS patients. In assessing the risk of arrhythmias in LQT1 and LQT2, Tp-e appears to be a useful index of TDR (33,34). Tp-e is increased in premature neonates receiving the torsadogenic drug cisapride (28). Further studies of the correlation between TDR and surface ECG T wave morphology in humans are required to validate Tp-e.

The effects on QTc of several commonly used anesthetics have been investigated in healthy adults and children. Sevoflurane, isoflurane, and thiopental have

been reported to prolong QTc, but the clinical significance of this has been unclear; it is usually concluded that anesthesiologists should be aware of a potential increased risk of TdP with these drugs. Very few of these studies have examined the effect of a single drug in unpremedicated patients and in the absence of confounding adrenergic stimulation from airway manipulation or surgery. None have investigated the effect of anesthetics on TDR. The aim of this study was to investigate the effect of propofol and sevoflurane on QTc and on Tp-e as a marker of TDR.

Our finding that propofol 3 μg/mL does not prolong the QTc to a significant extent is consistent with several studies (19,25,26) but contradicts others (23,24). This may now be of only academic interest because the insignificant prolongation of Tp-e by propofol 3 μg/mL suggests that propofol is not torsadogenic. However, a plasma propofol concentration of 3 μg/mL is insufficient on its own for surgical anesthesia and larger plasma concentrations may result in greater prolongation of the Tp-e interval. At present, it is unknown whether there is a dose-response relationship between plasma propofol concentration and the Tp-e interval.

Our finding that sevoflurane at an end-tidal concentration of 3% significantly prolongs the QTc is in keeping with previous studies in adults and children that have consistently shown a marked propensity for sevoflurane to prolong the QTc (16–20). This is a predictable side effect. In guinea pig cardiac myocytes, sevoflurane inhibits *iKr* channels, which contribute significantly to the repolarizing current in phase 3 of the cardiac cycle action potential in many species (35). Mutations in *iKr* channel proteins cause LQTS 2 and 6 in humans (36,37), and most drug-induced LQTS is caused by *iKr* channel blockade. However, sevoflurane had no significant effect on the Tp-e interval in this study, suggesting that it does not increase the risk of TdP despite its propensity to prolong the QTc. One hypothesis for the failure of sevoflurane to prolong the Tp-e interval is the possibility that sevoflurane has an equal effect on repolarization in epicardial, endocardial, and M cells, such that there is prolongation in the overall duration of repolarization (reflected in QTc prolongation) but no increase in TDR.

Our finding that sevoflurane does not prolong Tp-e provides the link to explain the discrepancy between the drug's ability to dramatically prolong QTc and the apparent absence of TdP associated with extensive sevoflurane usage around the world. We are unaware of any reports that attribute an intraoperative or postoperative complication to cardiac repolarization abnormalities after sevoflurane anesthesia in pediatric patients. Interestingly, thiopental, which also prolongs QTc but appears not to be torsadogenic, reduced TDR in an *in vivo* animal model (38). Conversely, although there are contradictory reports on the ability of halothane to prolong QTc (13–15,39,40), it exaggerates TDR in dogs (41) and was the anesthetic in use in three case reports of perioperative TdP in patients with previously undiagnosed LQTS (42–44). All these observations are compatible with the evolving hypothesis that it is possible to have a prolonged QT interval without exaggerated TDR; the risk of TdP in these instances is very small, whereas increased TDR increases the risk of arrhythmias even if the absolute QT interval is normal.

QTc is conventionally measured in lead II. The best lead for measuring Tp-e has not been defined, but it has been suggested that precordial lead values may best reflect true TDR (38). We examined interobserver variability in all 12 leads (data not shown) and found it to be least in leads I, II, and V5. Hence, we thought that leads II and V5 were the most appropriate from which to report our results.

The normal range (and hence the upper limit of normal) for Tp-e has not been defined. We found a mean (SD) Tp-e of 72.2 (10.9) ms in our sample of 49 preoperative ECG traces from healthy children. This is similar to the value of 65 (11) ms in the premature neonatal population on which we based our power calculations. In the absence of information from healthy children on what would constitute a clinically significant change in Tp-e, we chose to look for the smallest ECG difference we could reliably detect, which was half of one small ECG square. At a paper speed of 50 mm/s, this equates to 10 ms. Had we chosen to look for a bigger difference, we would have run the risk of a type II error if subsequent research were to find a small difference to be clinically important. As it happens, even with adequate power to detect a small change in Tp-e, we found it to be essentially unchanged from the preoperative value after the administration of either propofol or sevoflurane.

There are several weaknesses in this study. First, we did not study children with LQTS, which inevitably makes speculative our conclusions regarding the effects of propofol and sevoflurane on dispersion of repolarization in such patients. For this reason, we must emphasize caution in the extrapolation of our findings to these patients. Second, we did not adjust the concentration of sevoflurane to reflect age-related changes in minimum alveolar concentration values. A follow-up study to investigate the age-response and dose-response characteristics of Tp-e during sevoflurane anesthesia is planned and will address this deficiency. Finally, the randomization of only 22 patients to group P and the subsequent exclusion of 2 patients resulted in the between-group comparison being slightly underpowered. Given the insignificant changes in Tp-e within groups, it is highly unlikely that this has caused a type II error. The power of the paired tests still exceeded 80%.

Summary

In conclusion, neither sevoflurane nor propofol exaggerate physiological TDR as measured by the Tp-e interval. These results suggest that neither anesthetic is torsadogenic, irrespective of its effect on QTc. We speculate that both drugs could be used in patients with or at risk of LQTS without increasing the risk of TdP. Further corroborative studies are needed to confirm these results; their value will be increased by comprehensively validating the Tp-e interval measurement as a surface marker of TDR in humans.

References

1. Bazette HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–70.
2. Davignon A, Rautahaju P, Boiselle E, et al. Normal ECG standards for infants and children. Pediatr Cardiol 1979;1:123–31.
3. Tristani-Firouzi M, Chen J, Mitcheson JS, Sanguinetti MC. Molecular biology of K(+) channels and their role in cardiac arrhythmias. Am J Med 2001;110:50–9.
4. Liu DW, Antzelevitch C. Characteristics of the delayed rectifier current (IKr and IKs) in canine ventricular epicardial, midmyocardial, and endocardial myocytes. A weaker IKs contributes to the longer action potential of the M cell. Circ Res 1995;76: 351–65.
5. Zygmunt AC, Eddlestone GT, Thomas GP, et al. Larger late sodium conductance in M cells contributes to electrical heterogeneity in canine ventricle. Am J Physiol 2001;28:H689–97.
6. Antzelevitch C, Shimizu W, Yan GX, Sicouri S. Cellular basis for QT dispersion. J Electrocardiol 1998;30 Suppl:168–75.
7. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928–36.
8. Antzelevitch C, Shimizu W, Yan GX, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. J Cardiovasc Electrophysiol 1999;10: 1124–52.
9. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade des pointes in LQT2 and LQT3 models of the long-QT syndrome. Circulation 1997;96:2038–47.
10. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. J Am Coll Cardiol 2000;35: 778–86.
11. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. Circulation 1998;98:2314–22.
12. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. Circulation 1993; 88:782–4.
13. Schmeling WT, Warltier DC, McDonald DJ, et al. Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. Anesth Analg 1991;72:137–44.
14. Michaloudis D, Fraidakis O, Lefaki T, et al. Anaesthesia and the QT interval in humans: the effects of isoflurane and halothane. Anaesthesia 1996;51:219–24.
15. Michaloudis D, Fraidakis O, Lefaki T, et al. Anaesthesia and the QT interval in humans: effects of halothane and isoflurane in premedicated children. Eur J Anaesthesiol 1998;15:623–8.
16. Kuenszberg E, Loeckinger A, Kleinsasser A, et al. Sevoflurane progressively prolongs the QT interval in unpremedicated female adults. Eur J Anaesthesiol 2000;17:662–4.
17. Loeckinger A, Kleinsasser A, Maier S, et al. Sustained prolongation of the QTc interval after anesthesia with sevoflurane in infants during the first 6 months of life. Anesthesiology 2003; 98:639–42.
18. Kleinsasser A, Loeckinger A, Lindner KH, et al. Reversing sevoflurane-associated Q-Tc prolongation by changing to propofol. Anaesthesia 2001;56:248–50.
19. Kleinsasser A, Kuenszberg E, Loeckinger A, et al. Sevoflurane, but not propofol, significantly prolongs the Q-T interval. Anesth Analg 2000;90:25–7.
20. Gallagher JD, Weindling SN, Anderson G, Fillinger MP. Effects of sevoflurane on QT interval in a patient with congenital long QT syndrome. Anesthesiology 1998;89:1569–73.
21. McConachie I, Keaveny JP, Healy TE, et al. Effect of anaesthesia on the QT interval. Br J Anaesth 1989;63:558–60.
22. Saarnivaara L, Lindgren L. Prolongation of QT interval during induction of anaesthesia. Acta Anaesthesiol Scand 1983;27: 126–30.
23. Saarnivaara L, Klemola UM, Lindgren L, et al. QT interval of the ECG, heart rate and arterial pressure using propofol, methohexital or midazolam for induction of anaesthesia. Acta Anaesthesiol Scand 1990;34:276–81.
24. Saarnivaara L, Hiller A, Oikkonen M. QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. Acta Anaesthesiol Scand 1993;37:419–23.
25. Michaloudis DG, Kanakoudis FS, Petrou AM, et al. The effects of midazolam or propofol followed by suxamethonium on the QT interval in humans. Eur J Anaesthesiol 1996;13:364–8.
26. Paventi S, Santevecchi A, Ranieri R. Effects of sevoflurane versus propofol on QT interval. Minerva Anestesiol 2001;67: 637–40.
27. Absalom A, Amutike D, Lal A, et al. Accuracy of the "Paedfusor" in children undergoing cardiac surgery or catheterization. Br J Anaesth 2003;91:507–13.
28. Benatar A, Cools F, Decraene T, et al. The T wave as a marker of dispersion of ventricular repolarization in premature infants before and while on treatment with the I(Kr) channel blocker cisapride. Cardiol Young 2002;12:32–6.
29. Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. Mayo Clin Proc 1998;73:250–69.
30. www.torsades.org.
31. Garson A Jr, Dick M II, Fournier A, et al. The long QT syndrome in children: an international study of 287 patients. Circulation 1993;87:1866–72.
32. Lubinski A, Lewicka-Nowak E, Kempa M, et al. New insight into repolarization abnormalities in patients with congenital long QT syndrome: the increased transmural dispersion of repolarization. Pacing Clin Electrophysiol 1998;21:172–5.
33. Tanabe Y, Inagaki M, Kurita T, et al. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. J Am Coll Cardiol 2001;37:911–9.
34. Shimizu W, Tanabe Y, Aiba T, et al. Differential effects of beta-blockade on dispersion of repolarization in the absence and presence of sympathetic stimulation between the LQT1 and LQT2 forms of congenital long QT syndrome. J Am Coll Cardiol 2002;39:1984–91.
35. Park WK, Pancrazio JJ, Suh CK, Lynch C III. Myocardial depressant effects of sevoflurane: mechanical and electrophysiologic actions *in vitro*. Anesthesiology 1996;84:1166–76.
36. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803.
37. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999;97:175–87.
38. Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. Basic Res Cardiol 2001;96:517–27.
39. Gallagher JD. Effects of halothane and quinidine on intracardiac conduction and QTc interval in pentobarbital-anesthetized dogs. Anesth Analg 1992;75:688–95.

40. Lindgren L. ECG changes during halothane and enflurane anaesthesia for ENT surgery in children. Br J Anaesth 1981;53: 653–62.
41. Weissenburger J, Nesterenko VV, Antzelevitch C. Transmural heterogeneity of ventricular repolarization under baseline and long QT conditions in the canine heart *in vivo*: torsades de pointes develops with halothane but not pentobarbital anesthesia. J Cardiovasc Electrophysiol 2000;11:290–304.
42. Adu-Gyamfi Y, Said A, Chowdhary UM, et al. Anaesthetic-induced ventricular tachyarrhythmia in Jervell and Lange-Nielsen syndrome. Can J Anaesth 1991;38:345–6.
43. Holland JJ. Cardiac arrest under anaesthesia in a child with previously undiagnosed Jervell and Lange-Nielsen syndrome. Anaesthesia 1993;48:149–51.
44. Wig J, Bali IM, Singh RG, et al. Prolonged Q-T interval syndrome: sudden cardiac arrest during anaesthesia. Anaesthesia 1979;34:37–40.