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# The effect of sevoflurane or propofol with or without an anti-emetic dose of droperidol on the QTc interval and the transmural dispersion of repolarization

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## Abstract

**Purpose: Sevoflurane and droperidol but not propofol induce QTc interval prolongation, but there are several conflicting reports. We investigated the effects of sevoflurane and propofol with or without an anti-emetic dose of droperidol on the QTc interval and the transmural dispersion of repolarization for 2 hours, and the QT interval was adjusted for the patient's heart rate using 3 formulae.**

**Methods: One hundred two American Society of Anesthesiologists (ASA) physical status I-II patients, aged 20-70, were randomly allocated to one of four groups: Group 1 (n=25) receiving sevoflurane anesthesia without droperidol (1.25 mg), Group 2 (n=26) receiving sevoflurane anesthesia with droperidol, Group 3 (n=25) receiving propofol anesthesia without droperidol, or Group 4 (n=26) receiving propofol anesthesia with droperidol. RR intervals, QT intervals, and Tp-e intervals, which indicates the dispersion of ventricular repolarization (TDR), were measured. The QT interval was adjusted for the patient's heart rate using the formulae of Bazett, Fridericia, and Matsunaga.**

**Results: Sevoflurane significantly prolonged the QTc, but droperidol did not enhance sevoflurane-induced QTc prolongation in all the formulae. Conversely, propofol did not affect the QTc in all formulae. Tp-e intervals were not affected in any of the groups.**

**Conclusion: Although it significantly prolongs the QTc interval, sevoflurane, even with droperidol, does not seem to cause lethal arrhythmias associated with QT prolongation, because it does not induce Tp-e prolongation. Propofol is safer than sevoflurane in terms of arrhythmias associated with QT interval prolongation. Bazett's formula is reliable for detecting anesthetic-induced QT prolongation.**

**Key words: QTc interval, Tp-e interval, sevoflurane, droperidol, propofol**

## Introduction

Prolongation of the QT interval on an electrocardiogram (ECG) is associated with *torsade de pointes* (TdP), a malignant polymorphic ventricular tachyarrhythmia. It has been reported that sevoflurane inhibits not only HERG (human *ether-a-go-go-related gene*) currents (Ikr)[1] but also LQT1/minK currents (Iks) and Kv4.3 currents (Ito),[2,3] and induces significant QT interval prolongation.[1,4,5] Saussine et al. reported that TdP occurred during sevoflurane anesthesia in a child with congenital long QT syndrome.[6] however, there have been some con-

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flicting reports on sevoflurane-induced QT interval prolongation.[7–9] In contrast, propofol is generally believed to have no effect on the QT interval.[1,4,5] Droperidol is a butyrophenone antipsychotic drug and, at low doses (0.625-1.25 mg), droperidol has been widely used as an antiemetic drug. In 2001, the United State Food and Drug Administration (FDA) issued a "black box" warning regarding the use of droperidol and the potential for drug-induced QT interval prolongation and TdP, and recommended that ECG monitoring be continued for 2-3 h after droperidol administration. Although droperidol blocks the Ikr and causes an increase in action potential duration (APD), reports on QT interval prolongation are also conflicting,[10–14] probably because the observation times are so short (<30 min).

Recent studies have revealed that susceptibility to TdP arises from induction of early after depolarization and increased dispersion of ventricular repolarization, rather than QT interval prolongation *per se*.[5,15–19] Transmural dispersion of repolarization (TDR) across the myocardial wall can be measured on the ECG as the time interval from the peak to the end of the T wave (Tp-e).[20] Shah argues that Bazett's QTc interval prolongation alone is a poor surrogate marker for the risk of TdP.[21] Unlike the QTc interval, neither propofol nor sevoflurane have been reported to have any effect on the Tp-e interval.[5] Furthermore, the use of Bazett's formula is rooted deeply in medical practice, but this equation has been criticized because of its inaccuracy,[22] because it overcorrects the QT interval at fast heart rates and undercorrects the QT interval at slow rates, suggesting that the QTc would be prolonged if the heart rate increase and vice versa.

In this study, we recorded ECG monitoring under sevoflurane or propofol anesthesia, with or without droperidol (1.25 mg), for 2 hours and measured the QTc intervals using three different QTc formulae, Bazett's, Fridericia's, and Matsunaga's. The TDR was simultaneously calculated using the Tp-e interval.

## Methods

After obtaining institutional approval (H070128) form Kansai Medical University (Osaka, Japan) Human Subjects Review Committee and written informed consent, we enrolled 102 patients classified as ASA physical status I or II. We recruited patients, aged between 20 and 70 y, undergoing various kinds of elective surgery such as abdominal, gynecological, urological, and otorhinolaryngological surgery, with an expected duration of more than 2 h. Patients on medications known to prolong the QT interval and/or with an abnormal QTc prolongation (>450 ms by Bazett's formula) were excluded. The patients were randomly allocated to one of four groups: Group 1 (n=25) receiving sevoflurane anesthesia without droperidol, Group 2 (n=26) receiving sevoflurane anesthesia with droperidol, Group 3 (n=25) receiving propofol anesthesia without droperidol, or Group 4 (n=26) receiving propofol anesthesia with droperidol. An epidural catheter was inserted before anesthesia induction at the doctor's discretion. In all patients, the II lead was recorded throughout the operation. ECG signals were networked to a sever storage system and the ECG recordings were retrieved after the operation. In Group 1 and Group 2, anesthesia was induced with 2 mg/kg propofol, 100 $\mu$g fentanyl, with or without 1.25 mg droperidol, and intubation was carried out after administration of 0.1 mg/kg vecuronium. Anesthesia was maintained with 1.5-2.5% sevoflurane with $O_2$ and air and intermittent fentanyl administration and/or epidural anesthesia. In Group 3 and Group 4, anesthesia was induced with TCI (target control infusion) of propofol at a target concentration of 4 $\mu$g/ml, 100 $\mu$g fentanyl with or without 1.25 mg droperidol, and intubation was carried out after administration of 0.1 mg/kg vecuronium. Anesthesia was maintained with 2.5-3.5 $\mu$g/ml TCI propofol with $O_2$ and air and intermittent fentanyl administration and/or epidural anesthesia. The RR interval, the QT interval (from the onset of QRS complexes to the end of the T wave), and the Tp-e interval were manually measured by two investigators. The QT interval was adjusted for the patient's heart rate using the formulae of Bazett ($QTc=QT/(RR/1000)^{1/2}$), Matsunaga ($QTc=\log 600x\ QT/\log RR$, and Fridericia, ($QTc=QT/(RR/1000)^{1/3}$), where a unit of the RR interval is given as ms.[23]

The results are presented as the mean ±SD. Age and the QTc and Tp-e intervals at the same time points (before, 30 min, 1 h, and 2 h after sevoflurane or propofol administration) among groups were composed using one-way analysis of

variance followed by the Bonferroni correction applied for multiple comparisons. The changes in the QTc and Tp-e intervals within groups were analyzed by one-way analysis of variance for repeated measures followed by the Bonferroni *post hoc* test. A p value of less than 0.05 was considered significant.

## Results

The four study groups were similar with respect to age and gender (Table 1). The QTc interval in each group before drug administration was not significantly different. There were no significant differences in heart rates before and during anesthesia among the four groups. No critical arrhythmias occurred and no electrolyte abnormalities were observed in any of the group. When corrected using Bazett's and Fridericia's formulae, the QTc interval was significantly prolonged by sevoflurane alone only after 2 h (Figure 1b); however, when corrected using Matsunaga's formula, the QTc interval was already significantly prolonged 30 min after sevoflurane administration and this prolongation continued at least for 2 h, but sevoflurane-induced QTc prolongation did not progress with time (Figure 1c). Sevoflurane with droperidol also significantly prolonged the QTc interval corrected using all three formulae (Figure 1a, b, c); however, droperidol did not enhance sevoflurane-induced QTc prolongation. Conversely, propofol did not affect the QTc (Figure 1a, b, c), but when droperidol was added to propofol anesthesia, the QTc interval was significantly prolonged only 2 h after propofol administration when corrected using Matsunaga's formula but not when using Bazett's and Fridericia's formulae (Figure 1c). The Tp-e intervals were not affected in any of the groups (Figure 1d).

## Discussion

The new findings of this study were that, in

**Table 1** Baseline Characteristics of the Study Population

| | Sevoflurane (n=25) | Sevo+Dro (n=26) | Propofol (n=25) | Propo+Dro (n=26) |
|---|---|---|---|---|
| Age | 53.4±12.6 | 56.3±13.2 | 50.9±10.4 | 55.4±13.4 |
| Gender | male=12, female=13 | male=11, female=15 | male=11, female=14 | male=12, female=14 |
| Epidural Anesthesia | 13 | 14 | 12 | 9 |
| Type of Surgery | General Surgery (13), Gynecology (1), Urology (3), Otorhinolaryngology (5), Orthopedics (3) | General Surgery (15), Gynecology (5), Urology (2), Otorhinolaryngology (4), | General Surgery (12), Gynecology (4), Urology (4), Otorhinolaryngology (3), Orthopedics (2) | General Surgery (12), Gynecology (5), Urology (3), Otorhinolaryngology (2), Orthopedics (4) |

Sevo : sevoflurane, Dro : droperidol, Propo : propofol

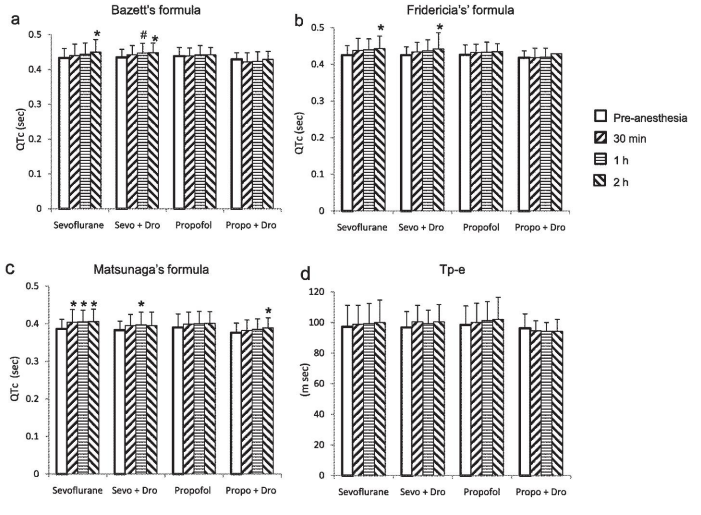


**Fig. 1** shows the QTc intervals (a-c) or Tp-e intervals (d) before anesthesia, 30 minutes, 1 hour, and 2 hours after sevoflurane alone, sevoflurane with droperidol, propofol alone, and propofol with droperidol administration. QT intervals are adjusted for heart rate with Bazett's formula (a), Fridericia's formula (b), and Matsnaga's formula (c). Sevo : Sevoflurane, Dro : Droperidol $^{*}P<0.05$ vs. Pre-anesthesia, $^{\#}P<0.05$ vs. Propo+Dro (1 h)

ordinary clinical settings in various kinds of surgery, sevoflurane significantly prolonged the QTc interval but did not affect the Tp-e interval. Conversely, propofol did not affect either the QTc or the Tp-e interval. Droperidol, at an antiemetic dose, neither prolonged QTc interval nor enhanced the sevoflurane-induced QTc prolongation. Of the correction formulae used to normalize the QT interval for heart rate (QTc), Matsunaga's formula seems more sensitive at detecting sevoflurane-induced QTc interval prolongation.

Some investigators advocate that Matsunaga's and/or Fridericia's formulae would better predict the net repolarization delay.[23] In the present study, of the correction formulae used to normalize the QT interval for heart rate, Matsunaga's formula seemed more sensitive at detecting sevoflurane-induced QTc interval prolongation. In general, a QTc interval of $>450$ ms is regarded as abnormal, and in individual patients an absolute QTc interval of $>500$ ms or an increase of 60 ms from baseline is regarded as indicating an increased risk of TdP.[24] If we used Bazett's formula, several patients were already categorized into an abnormal QTc interval group ($>450$ ms) before drug administration (20/102) but not Matsunaga's (1/102) and Fridericia's (6/102). We suggest this is becouse that the patients were anxious in the operation room before anesthetic induction and their heart rates were rather high, and the QT interval was overcorrected for heart

**Table 2** QTc intervals after sevoflurane or propofol with or without droperidol administration adjusted by Bazett's, Fridericia's, or Matsunaga's formula

| QTc (Bazett's formula) | | | | |
|---|---|---|---|---|
| | Sevoflurane (n=25) | Sevo+Dro (n=23) | Propofol (n=25) | Propo+Dro (n=23) |
| Pre-anesthesia | 0.433±0.027 (sec) | 0.435±0.023 | 0.438±0.025 | 0.429±0.019 |
| 30 min | 0.440±0.033 | 0.442±0.027 | 0.439±0.023 | 0.422±0.026 |
| 1 h | 0.444±0.032 | 0.447±0.028# | 0.442±0.027 | 0.423±0.028 |
| 2 h | 0.450±0.036* | 0.448±0.028* | 0.442±0.021 | 0.429±0.023 |
| QTc (Fridericia's formula) | | | | |
| | Sevoflurane (n=25) | Sevo+Dro (n=23) | Propofol (n=25) | Propo+Dro (n=23) |
| Pre-anesthesia | 0.425±0.026 (sec) | 0.425±0.023 | 0.426±0.027 | 0.418±0.019 |
| 30 min | 0.438±0.033 | 0.434±0.026 | 0.432±0.023 | 0.418±0.026 |
| 1 h | 0.440±0.030 | 0.437±0.030 | 0.433±0.028 | 0.420±0.024 |
| 2 h | 0.443±0.034* | 0.442±0.044* | 0.435±0.021 | 0.429±0.023 |
| | | | | *P<0.05 vs. Pre-anesthesia, #P<0.05 vs. Propo+Dro (1 h) |
| QTc (Matsunaga's formula) | | | | |
| | Sevoflurane | Sevo+Dro | Propofol | Propo+Dro |
| Pre-anesthesia | 0.386±0.026 (sec) | 0.383±0.024 | 0.390±0.036 | 0.376±0.026 |
| 30 min | 0.404±0.034* | 0.395±0.030 | 0.399±0.032 | 0.382±0.028 |
| 1 h | 0.405±0.031* | 0.397±0.034* | 0.400±0.033 | 0.385±0.028 |
| 2 h | 0.406±0.033* | 0.395±0.036 | 0.401±0.031 | 0.389±0.027* |
| | | | | *P<0.05 vs. Pre-anesthesia |
| Tp-e (msec) | | | | |
| | Sevoflurane | Sevo+Dro | Propofol | Propo+Dro |
| Pre-anesthesia | 97.2±14.0 | 96.7±10.5 | 98.4±12.5 | 96.2±9.4 |
| 30 min | 98.8±12.4 | 100.4±10.8 | 100.0±12.6 | 94.6±6.5 |
| 1 h | 99.2±13.2 | 99.2±8.8 | 101.2±12.4 | 94.2±5.8 |
| 2 h | 100±14.7 | 100.4±11.2 | 102.0±14.4 | 94.2±7.8 |

rate using Bazett's formula, and conversely the QT interval was undercorrected using Bazett's formula during the operation when the anesthetic depth was sufficient and the heart rate was low.

Recent studies have shown that the QTc interval alone is not a reliable indicator of TdP, and intramyocardial dispersion of repolarization appears to play a more important role both in electrical stability of the ventricles and arrthymogenesis.[5,15–19] In fact, Tanabe et al. reported that epinephrine significantly increased the Tp-e in both LQT 1 and LQT2 syndrome patients but not in control normal patients.[19] Therefore, in addition to QTc interval measurements, we investigated the Tp-e interval changes and demonstrated that neither propofol nor sevoflurane and droperidol affected the Tp-e interval, i. e., TDR ; however, since the Tp-e interval does not seem to be an established and absolutely reliable method of detecting the TDR, further studies will be required.

It is generally agreed that sevoflurane inhibits Ikr, Iks, and Ito and prolongs the QT interval.[1–5] In the present study, we confirmed that sevoflurane significantly prolonged the QTc interval but, in contrast to previous reports,[4,5] which showed that sevoflurane-induced QTc (Bazett's formula) interval prolongation occurred within 30 min after sevoflurane exposure, only the QTc interval (Bazett's formula) 2 h after sevoflurane exposure was significantly prolonged. This result may be due to insufficient statistical power, because we found a small, but not statistically significant, increase in the QTc interval both 30 minutes and 1 hour after sevoflurane exposure. Conversely, the QTc interval corrected using Matsunaga's formula was significantly prolonged within 30 minutes and this prolongation lasted for at least 2 h, suggesting that this formula should be more sensitive than Bazett's and Fridericia's formulae for detecting sevoflurane-induced QT interval prolongation. On the other hand, it is generally agreed that propofol has no effects on the QT interval[1,4,5] and we also confirmed this result. Stuth et al. reported that droperidol led to a significant increase in the QTc interval that was still present at 15 min but had resolved within 30 min after the intravenous bolus injection.[25] Also almost all reports observed the ECG for a maximum of 10 min after droperidol administration.[13,14,25] However, as serious cardiac adverse events or death have occurred later than 20 min after droperidol administration in at least 4 out of the 10 cases,[10] the FDA recommend that ECG monitoring be continued for 2-3 h after drug administration. In the present study, we confirmed that droperidol neither induced QT interval prolongation nor enhanced sevoflurane-induced QTc interval prolongation later than 30 minutes after its administration. Although sevoflurane with and without droperidol significantly prolongs the QTc interval, sevoflurane, even with droperidol, does not seem to cause lethal arrhythmias, because droperidol does not enhance sevoflurane-induced QTc prolongation and sevoflurane does not affect the TDR. However, patients who are susceptible to QT interval prolongation and increased dispersion of ventricular repolarization, e.g., patients with congenital long QT syndrome, or medicated with drugs known to prolong the QT interval, such as anti-arrhythmics, psychotherapeutics, and antihistamines, with hypokalemia should be monitored carefully by the ECG for a long time when under sevoflurane anesthesia. In fact, we previously demonstrated that sevoflurane caused greater QTc interval prolongation in elderly patients than in younger patients .[26] Propofol seems safer than sevoflurane in terms of arrhythmias associated with QT interval prolongation, but as it was reported that the QT interval was markedly prolonged even by propofol in a patient with acute myocardial infarction,[27] careful observation of the ECG should also be made after propofol administration, especially when droperidol is co-administered.

Several potential limitations of our study should be considered. First, because we conducted the study in ordinary clinical settings to measure the QT interval for 2 h, the anesthetic methods (e.g., with or without epidural anesthesia) and anesthetic concentrations were not strictly regulated, and the type of surgery was not limited ; paradoxically, we think that this is why our results are important because they may be applied to various types of anesthesia and surgery in the ordinary clinical setting. Furthermore, the QTc interval is not likely to be greatly prolonged by stress and pain *per se* as long as the patient does not have LQT1 syndrome, in which Iks is blocked, because $\beta$-adrenergic stimulation by stress and pain activates not only $Ca^{2+}$ channels but also Iks channels,[28] suggesting that the net cation flux through the cardiac cell membranes may not be changed greatly in phase 2

and 3. On the other hand, Ikr is exclusively inhibited by almost all drugs which are related to drug-induced QT prolongation ; however, both fentanyl at the doses we used and ropivacaine administered epidurally were unlikely to affect the QTc and Tp-e intervals directly, because their expected plasma concentrations seem too low to block the IKr. Second, propofol was used for anesthetic induction in all groups, but its effect did not influence the results because the effect is very short.

In conclusion, sevoflurane significantly prolonged the QTc interval, but droperidol did not enhance sevoflurane-induced QTc prolongation. Propofol did not affect the QTc interval at all. Neither sevoflurane nor droperidol prolonged the Tp-e. Of the three formulae we investigated, although Matsunaga's formula seemed the most sensitive to detect sevoflurane-induced QTc interval prolongation, Bazett's and Fridericia's formulae were also sensitive. We anesthesiologists should be aware of the QTc interval changes by anesthetics and/or anesthesia-related drugs.

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