Effect of desflurane at less than 1 MAC on QT interval prolongation induced by tracheal intubation


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Background. Desflurane at more than 1 minimum alveolar concentration (MAC) has been shown to prolong the QT interval, but it is unclear whether this is the case at lower concentrations. The aim of this study was to determine whether desflurane concentrations of <1 MAC affect tracheal intubation-induced prolongation of the QT interval.

Methods. Forty-four subjects received either inspired desflurane at 1 MAC in oxygen 100% at a fresh gas flow rate of 6 litre min⁻¹ (desflurane group) or only oxygen 100% (control group) beginning at anaesthesia induction with propofol, before tracheal intubation. The QT intervals were corrected by Bazett's (QTcB) and Fridericia's (QTcF) formulae. The primary outcome was the QTcB immediately after tracheal intubation. Secondary outcomes were the interval from the peak to the end of the T wave (Tp–e), mean arterial pressure (MAP), heart rate (HR), and bispectral index (BIS) score.

Results. The QTc interval immediately after tracheal intubation did not differ between the control and the desflurane groups [QTcB, 451 (SD 23) vs 456 (27) ms, \(P = 0.56\); QTcF, 422 (24) vs 429 (22) ms, \(P = 0.31\), control vs desflurane group, respectively]. There was no difference in Tp–e or HR between the two groups in this study. However, MAP and the BIS score were significantly lower in the desflurane group until 1 min after tracheal intubation.

Conclusions. The administration of desflurane at an inspiratory concentration of 1 MAC during manually controlled ventilation after anaesthesia induction with propofol did not affect tracheal intubation-induced QTc prolongation.

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Volatile anaesthetics such as halothane, enflurane, isoflurane, and sevoflurane at clinically relevant doses prolong the QT interval.¹⁻⁵ Recently, desflurane has been reported to prolong the QTc interval [QT interval corrected for heart rate (HR)] in both adults and children when used as an inhalation induction agent or for the maintenance of anaesthesia.⁶⁻⁷ As tracheal intubation itself also prolongs the QTc interval by activating the sympathetic nervous system,⁸⁻⁹ the use of desflurane before tracheal intubation may further increase QTc prolongation after tracheal intubation. Previous studies have reported that desflurane at a concentration producing an adequate level of anaesthesia did not prevent the tracheal intubation-related increase in the QTc interval¹⁰ and that the QTc interval was not prolonged after tracheal intubation when the end-tidal desflurane concentration was maintained at 2 minimum alveolar concentration (MAC).¹¹ However, it is unknown whether desflurane at concentrations of <1 MAC affects indices of ventricular repolarization [QTc and transmural dispersion of repolarization (TDR)], which can be measured from the peak to the end of the T wave (Tp–e).¹²

The purpose of this study was to determine whether the administration of desflurane at <1 MAC after anaesthesia induction with propofol and fentanyl affects the QTc interval and Tp–e changes related to tracheal intubation.

Methods

This study protocol was approved by the Institutional Review Board of Soonchunhyang University Hospital, Bucheon, Republic of Korea. Fifty-one patients classified
as American Society of Anesthesiologists physical status I, who were undergoing elective laparoscopic cholecystectomy, were recruited and assessed for eligibility between January and May 2009. Patients with arrhythmias or conduction abnormalities, a QTc interval >440 ms, or electrolyte imbalances and those taking medications known to prolong the QT interval were excluded. Three patients were excluded based on these criteria, and four refused to participate. Thus, 44 patients were enrolled, after providing written informed consent. The mean age of the patients was 39.2 yr (range, 24–50), and 21 of the 44 patients were women. Among the enrolled patients, those who failed intubation on the first attempt (e.g. oesophageal intubation) or had a duration of intubation exceeding 1 min were excluded from the analysis.

Forty-four patients were randomized into two blocks displayed in a LabChart® software window on a computer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n = 22)</th>
<th>Desflurane group (n = 22)</th>
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</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>13/9</td>
<td>10/12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40.1 (25–50)</td>
<td>38.3 (24–50)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.3 (9.3)</td>
<td>166.4 (8.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.0 (7.9)</td>
<td>63.7 (11.4)</td>
</tr>
</tbody>
</table>

None of the patients was premedicated. On arrival in the operating theatre, each patient was monitored using a three-lead ECG, pulse oximetry, non-invasive arterial pressure measurement (Solar 8000, GE, Milwaukee, WI, USA), and a bispectral index monitor (BIS; BIS® A-2000, Aspect Medical Systems, Newton, MA, USA). After 10 min of stabilization, the pre-induction values for the mean arterial pressure (MAP), HR, and BIS score were recorded. General anaesthesia was then induced with fentanyl 2 μg kg⁻¹, followed 2 min later with a bolus injection of propofol 2 mg kg⁻¹. Immediately after loss of consciousness, a bolus of rocuronium 0.6 mg kg⁻¹ was administered to facilitate tracheal intubation and manually controlled ventilation via a facemask was begun, while maintaining the end-tidal carbon dioxide concentration between 4.7 and 5.3 kPa with oxygen 100% at a flow rate of 6 litre min⁻¹. In the desflurane group, an inspired concentration of 6 vol% desflurane was delivered to the patients at loss of consciousness. No volatile anaesthetic was given to the control patients. Controlled ventilation was continued until tracheal intubation at 2 min after loss of consciousness. After tracheal intubation, anaesthesia was maintained with 6 vol% desflurane in a mixture of oxygen 60% and air in both groups. A semi-closed circuit with a fresh gas flow rate of 4 litre min⁻¹ was used in both groups. All patients remained untouched for 10 min after tracheal intubation to prevent possible ECG artifacts, without adjustment of the desflurane concentration. Induction of anaesthesia and tracheal intubation were performed by two of the authors (P.S.Y. and J.H.C.), who were unaware of the group allocation.

**QT and Tp–e interval measurements**

Data from a continuous ECG via lead II were collected using LabChart® software (Version 6, AD Instruments, Colorado Springs, CO, USA) and a data acquisition system (PowerLab; AD Instruments). For each patient, the data were saved in a separate file and coded using the enrolment number. The ECG recordings were acquired by one author (C.W.S.), who was unaware of the group allocation. QT and the Tp–e interval were measured in the pre-induction period, immediately before laryngoscopy, immediately after tracheal intubation, and 1, 5, and 10 min after tracheal intubation. At each time point, the ECG curves from three consecutive beats were averaged and displayed in a LabChart® software window on a computer monitor. The baseline and peak of the T wave were determined automatically. If acceptable, the automatically measured QT interval and Tp–e values were used for statistical analysis. If the automatic measurement did not correctly detect the earliest onset of the QRS complex or the end of the T wave, the QT intervals and Tp–e were measured manually, using the cursor from the earliest onset of the QRS complex to the latest end of the T wave, where its terminal limb joined the baseline. The QT interval was corrected for HR using Bazett’s formula (QTcB = QT/√RR) or Fridericia’s formula (QTcF = QT/√RR). The QTc interval and Tp–e interval were measured by one author (L.J.S.), who was unaware of the group allocation.

MAP, HR, BIS score, and end-tidal desflurane concentration were measured in the pre-induction period, immediately before laryngoscopy, immediately after tracheal intubation, and at 1, 5, and 10 min after tracheal intubation.

The primary endpoint was the QTcB interval immediately after tracheal intubation. Secondary endpoints were changes in the QTcF, Tp–e interval, MAP, HR, and the BIS score, and the incidence of awareness. A BIS score more than 60 after the first minute of tracheal intubation was regarded as an arousal response, and this information was recorded. Cough and laryngospasm were recorded as adverse events related to desflurane before laryngoscopy. Before being discharged from the PACU, all patients were asked whether they could remember what had happened during the induction of anaesthesia.
Table 2 Comparison of QTc (ms) between the groups according to HR correction formula. Data are expressed as means (sd). P-values are for between-group comparisons. Pre-induction, before induction; Laryngoscopy, immediately before laryngoscopy; Intubation, immediately after tracheal intubation; 1, 5, and 10 min, 1, 5, and 10 min after tracheal intubation, respectively. *P<0.001, compared with pre-induction

<table>
<thead>
<tr>
<th>Time point</th>
<th>Bazett’s formula QTc (ms) P-value</th>
<th>Fridericia’s formula QTc (ms) P-value</th>
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<tbody>
<tr>
<td></td>
<td>Control group (n=20) Desflurane group (n=20)</td>
<td>Control group (n=20) Desflurane group (n=20)</td>
</tr>
<tr>
<td>Pre-induction</td>
<td>402 (19) 402 (25) 0.98</td>
<td>402 (17) 402 (15) 0.39</td>
</tr>
<tr>
<td>Laryngoscopy</td>
<td>404 (24) 404 (29) 0.58</td>
<td>402 (20) 403 (21)* 0.90</td>
</tr>
<tr>
<td>Intubation</td>
<td>451 (23)* 456 (27)* 0.56</td>
<td>422 (24)* 429 (22)* 0.31</td>
</tr>
<tr>
<td>1 min</td>
<td>425 (23)* 436 (19)* 0.13</td>
<td>398 (24) 410 (20)* 0.10</td>
</tr>
<tr>
<td>5 min</td>
<td>428 (25)* 425 (25)* 0.69</td>
<td>406 (24) 404 (19)* 0.76</td>
</tr>
<tr>
<td>10 min</td>
<td>426 (28)* 425 (34) 0.91</td>
<td>409 (25) 408 (23)* 0.88</td>
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Table 3 Comparison of Tp–e (ms) between the groups. Data are expressed as means (sd). Pre-induction, before induction; Laryngoscopy, immediately before laryngoscopy; Intubation, immediately after trachal intubation; 1, 5, and 10 min, 1, 5, and 10 min after tracheal intubation, respectively. *P<0.012, compared with pre-induction

<table>
<thead>
<tr>
<th>Time point</th>
<th>Tp–e (ms) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (n=20) Desflurane group (n=20)</td>
</tr>
<tr>
<td>Pre-induction</td>
<td>72.5 (11.0) 73.0 (10.5) 0.89</td>
</tr>
<tr>
<td>Laryngoscopy</td>
<td>75.6 (13.6) 73.2 (13.0) 0.56</td>
</tr>
<tr>
<td>Intubation</td>
<td>73.2 (14.9) 74.9 (12.4) 0.71</td>
</tr>
<tr>
<td>1 min</td>
<td>70.2 (14.4) 71.3 (12.6) 0.81</td>
</tr>
<tr>
<td>5 min</td>
<td>68.3 (10.9) 67.6 (7.60) 0.83</td>
</tr>
<tr>
<td>10 min</td>
<td>68.8 (12.8) 66.9 (7.20)* 0.57</td>
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Statistical analyses

On the basis of our pilot study, a mean difference of 20 (sd 21) ms in the QTcB interval immediately after tracheal intubation between the groups was considered to be clinically significant. We calculated that the sample size required to detect this difference at an alpha level of 0.05 was 19 patients in each group, with 80% power. Thus, we enrolled 44 patients to compensate for possible drop-outs.

Statistical analyses were performed using SPSS software (SPSS 14.0 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were compared between the groups using Student’s t-test. Changes over time within the groups were evaluated using repeated-measures ANOVA, and where multiple comparisons were made, a post hoc Bonferroni correction was applied. Categorical data were analysed with a χ² test or Fisher’s exact test, as appropriate. Continuous variables are presented as means (sd) or 95% CIs. P-values of <0.05 were deemed to be statistically significant.

Results

Of the 44 enrolled patients, four were excluded from the analysis. Two patients from the desflurane group were excluded, one because of the loss of ECG data from 1 min after tracheal intubation and the other because of oesophageal intubation. Two patients from the control group were excluded: one because of a poor-quality ECG curve and the other because of an intubation time exceeding 1 min. Thus, 20 patients in each group completed the study.

Changes in QTc and Tp–e intervals

There was no significant difference in the QTc interval between the two groups at any time point during the study, regardless of the method of correction for HR (Table 2). In the desflurane group, the QTcB interval was significantly prolonged during the 5 min post-tracheal intubation period (P<0.001; Table 2), and the QTcF interval was significantly prolonged from immediately before laryngoscopy until 10 min after tracheal intubation, compared with the pre-induction values (P<0.001; Table 2). In the control group, the QTcB interval increased significantly immediately after tracheal intubation, and this was maintained for 10 min, compared with the pre-induction values (P<0.001; Table 2). Compared with the pre-induction values, the QTcF interval was significantly increased only immediately after tracheal intubation in the control group (P<0.001; Table 2). The Tp–e interval during the study period was not significantly different between the two groups. However, the Tp–e interval decreased significantly in the desflurane group during the course of the study (P=0.012; Table 3) but did not change significantly in the control group.

Changes in MAP and HR

MAP decreased significantly immediately before laryngoscopy in both groups, compared with the pre-induction values (P<0.001; Fig. 1). In the desflurane group, MAP was decreased significantly at 5 and 10 min after tracheal intubation, compared with the pre-induction values (P<0.001), whereas MAP after tracheal intubation was not significantly different from the pre-induction value in the control group. MAP was increased significantly in the control group compared with the desflurane group at all post-intubation time points (P<0.05). HR was significantly increased compared with pre-induction values, until 1 and 5 min post-intubation in the desflurane and control groups, respectively (P<0.001; Fig. 2). There was no difference in HR between the groups during the study period.
**Fig 1** Changes in MAP. The MAP was measured before induction (Pre-induction), immediately before laryngoscopy (Laryngoscopy), immediately after tracheal intubation (Intubation), and at 1, 5, and 10 min after tracheal intubation. *P<0.001, compared with pre-induction. *P<0.05, compared with the desflurane group. Error bars indicate 95% CI.

**Fig 2** Changes in HR. The HR was measured before induction (Pre-induction), immediately before laryngoscopy (Laryngoscopy), immediately after tracheal intubation (Intubation), and at 1, 5, and 10 min after tracheal intubation. *P<0.001, compared with pre-induction. Error bars indicate 95% CI.
Changes in the BIS, end-tidal desflurane concentration, and incidence of awareness

BIS values were significantly higher in the control group than in the desflurane group, immediately (P=0.011) and 1 min (P=0.032) after tracheal intubation (Fig. 3). Compared with the value immediately before laryngoscopy, BIS values were significantly increased immediately (P=0.005) and 1 min (P=0.033) after tracheal intubation in the control group, but did not increase significantly in the desflurane group. The number of patients with arousal responses during the first minute after tracheal intubation was significantly higher in the control group (n=9) than in the desflurane group (n=2; P=0.031). No patient reported recall while at the PACU. The end-tidal desflurane concentrations immediately before laryngoscopy were 4.3 (0.7) and 0 vol% in the desflurane and control groups, respectively. End-tidal desflurane concentrations were significantly higher in the desflurane group than in the control group until 1 min after tracheal intubation (P<0.001; Fig. 4). There were no adverse events in either group.

Discussion

This study demonstrated that desflurane at <1 MAC [4.3 (0.7) vol%], delivered by manually controlled ventilation after anaesthesia induction with propofol and fentanyl until tracheal intubation, did not influence the QTc prolongation induced by tracheal intubation, regardless of the HR correction formula applied. In addition, the QTc prolongation did not accompany Tp–e prolongation.

Several studies investigating the effects of desflurane on the QTc interval have confirmed that desflurane at 1 MAC consistently prolonged the QTc interval.6 7 10 11 These previous studies examined the effect of desflurane at a steady state of end-tidal concentration and did not evaluate the combined sympathetic nervous activation related to tracheal intubation. Furthermore, none of these studies explored the effect of desflurane on TDR. The aim of the present study was to investigate the effects of desflurane at <1 MAC on QTc prolongation and the Tp–e interval, as related to tracheal intubation. Our results indicate that desflurane administered at <1 MAC before tracheal intubation did not affect the tracheal intubation-induced prolongation of either the QTc or Tp–e interval. Assuming that increased TDR is a reliable indicator of risk of torsades de pointes (TdP), these results suggest that desflurane at <1 MAC, administered after induction of anaesthesia with propofol and fentanyl, probably does not induce TdP after tracheal intubation in healthy adults. As the desflurane concentrations in this study were those most commonly used during the major portion of anaesthesia, our study indicates that at clinically relevant doses, desflurane does not have proarrhythmic properties and can be safely used during induction.

A few studies have examined the effect of desflurane, administered during the induction of anaesthesia, on tracheal intubation-related QTc prolongation. Owczuk and colleagues10 found that inhalation induction of anaesthesia...
with desflurane, starting at a concentration of 6 vol%, significantly prolonged the QTcB interval within the first minute after achieving adequate anaesthesia. Similarly, Silay and colleagues\textsuperscript{11} reported that inhalation induction with desflurane (inspired concentration, 18\%) significantly prolonged the QTcB interval, from 1 min after induction of anaesthesia to 3 min after the administration of vecuronium. The present finding that desflurane did not prolong the QTcB interval during the second minute after induction of anaesthesia is inconsistent with the previous studies.\textsuperscript{10,11} A reason for this discrepancy may be the lower end-tidal concentration of desflurane (0.7 MAC after 2 min of inhalation) in the current study. Here, desflurane was used at an inspiratory concentration of 6 vol\% to avoid airway irritation and sympathetic nervous activation, because desflurane produces sympathetic stimulation and increases the HR at concentrations $>$1 MAC.\textsuperscript{14,15}

Tracheal intubation-induced QTc prolongation has been confirmed by many investigators\textsuperscript{8,16,17} and was also observed in the present study. Different concentrations of desflurane appear to differentially modify the tracheal intubation-induced prolongation. In this study, desflurane at $<$1 MAC did not affect the QTc prolongation induced by tracheal intubation, and the percentage increase in QTcB from immediately before laryngoscopy to immediately after tracheal intubation was 11.5\%. Previous studies have reported increases of about 5\% at 1 MAC of desflurane and $<$1\% for desflurane at 2 MAC.\textsuperscript{10,11} In addition to these previous results, the current study adds evidence that the effect of desflurane on the QTc interval after tracheal intubation depends on the end-tidal concentration before tracheal intubation and that increasing concentrations of desflurane suppress, rather than increase, the QTc prolongation related to tracheal intubation.

It has been proposed that prolongation of the QTc interval is a poor predictive factor for TdP. The Tp–e interval, a secondary outcome variable in the current study, has been suggested to be a more reliable indicator of the occurrence of TdP.\textsuperscript{18,19} Studies on sevoflurane in children have confirmed that sevoflurane does not increase TDR; thus, malignant arrhythmias associated with sevoflurane seem unlikely to occur.\textsuperscript{20–22} The results here are consistent with those sevoflurane studies,\textsuperscript{20–22} in that TDR did not increase when desflurane was administered. However, because this study had limited power to detect differences in Tp–e, a further study on the effects of desflurane on TDR is needed.

Both Bazett’s and Fridericia’s formulae were used to correct the QT interval. The Bazett correction is the one typically reported by computerized ECG machines and in the medical literature. The QTcB interval provided by this formula represents the QT interval normalized for a HR of 60 beats min$^{-1}$. Thus, the QTcB interval may be an overestimate in tachycardia and an underestimate in bradycardia. Because Bazett’s formula might have overestimated the QT interval during the post-intubation period because of a faster HR, the QTc interval was also corrected using Fridericia’s formula, which is less sensitive to HR changes.\textsuperscript{23,24} The difference between the two methods

![Fig 4 Changes in mean end-tidal desflurane concentration. The end-tidal desflurane concentration was measured before induction (Pre-induction), immediately before laryngoscopy (Laryngoscopy), immediately after tracheal intubation (Intubation), and at 1, 5, and 10 min after tracheal intubation. *P<0.001, compared with the control group. Error bars indicate 95\% CI.](image)
resulted in the control group having a prolonged QTc interval during 5 min post-tracheal intubation, although the QTcF interval was prolonged only immediately after tracheal intubation. This result suggests that QTcB might have overestimated the QTc interval at increased HRs in the present study. Given that tracheal intubation increases the HR, this bias might have implicated tracheal intubation in the prolongation of cardiac repolarization. A previous study reported that Bazett’s formula did not eliminate the dependence of QTc on HR in patients who received β2-adrenergic agonists.25 Thus, the possibility that an overestimate of the QTc interval with Bazett’s formula should be considered, especially when the HR increases.

Deepening anaesthesia to prevent arterial pressure or arousal response to tracheal intubation is another purpose of administering a volatile agent during the induction of anaesthesia, although some regimens omit the use of inhaled agents.26 The blunted arterial pressure and arousal response (BIS > 60) in this study support the use of desflurane to achieve stable anaesthesia during the induction period, although it is not clear whether BIS monitoring reduces the incidence of awareness during anaesthesia.27 28

This study has some limitations. Desflurane was not the sole agent used for anaesthesia induction in the present study, and the results might have been influenced by the combined use of propofol, fentanyl, and rocuronium. However, it has been reported that neither propofol nor the combination of propofol 1.5 mg kg⁻¹ and fentanyl 2 µg kg⁻¹ has an effect on the QTc interval.29 Although rocuronium may have mild vagolytic activity at the dose of 0.6 mg kg⁻¹ (2 × ED₉⁵),30 this does not seem to have been an issue, because the HR increased in this study. Moreover, this study was performed in healthy adults with normal QTc intervals; thus, the results may not be applicable to patients with long QT syndrome.

In conclusion, the administration of desflurane at an inspired concentration of 6 vol% by manually controlled ventilation, from after loss of consciousness induced by the bolus administration of fentanyl and propofol until immediately before laryngoscopy and tracheal intubation, did not increase the tracheal intubation-induced QTc prolongation and did not prolong the Tp–e interval. These findings indicate that in normal adults, desflurane at clinically relevant concentrations can be used safely without concern for arrhythmias, while blunting the arterial pressure and arousal response related to tracheal intubation.

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