# Endotracheal administration of lidocaine inhibits isoflurane-induced tachycardia

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**Purpose:** Rapid increase in inspired isoflurane concentration increases heart rate and arterial blood pressure. To investigate whether the responses to isoflurane were elicited from stimulation of lower airway and/or lungs, haemodynamic responses to isoflurane administered after tracheal intubation were measured with or without endotracheal or intravenous administration of lidocaine.

**Methods:** Seventy-two ASA physical status 1 patients, aged 21-50 yr, were randomly allocated to one of four groups. After tracheal intubation, anaesthesia was maintained with oxygen 100% and isoflurane 1.0% with controlled ventilation. After stabilization for 15 min, the isoflurane concentration was rapidly increased to 3.0% in three groups. An endotracheal lidocaine group received pretreatment with endotracheal 0.4 ml lidocaine 8% spray, an intravenous lidocaine group received pretreatment of 32 mg lidocaine *iv*, and an isoflurane 3% group received not pre- treatment. In a control group, inspired isoflurane concentration was maintained at 1.0%. Heart rate, systolic blood pressure and end-tidal isoflurane concentration were measured every minute for 10 min.

**Results:** The rapid increase in isoflurane concentration increased heart rate (25 ± 12% increase from baseline; $P < 0.05$) but the increase was reduced by endotracheal lidocaine (9 ± 9%), but not by intravenous lidocaine (22 ± 13%). The plasma concentration of lidocaine was lower in the endotracheal lidocaine group (0.4 ± 0.3 $\mu g \cdot ml^{-1}$) than in the *iv* lidocaine group (1.5 ± 0.2 $\mu g \cdot ml^{-1}$).

**Conclusion:** The isoflurane-induced tachycardia is reduced by pre-treatment with endotracheal lidocaine.

**Objectif :** Un accroissement rapide de la concentration d'isoflurane inspiré augmente la fréquence cardiaque et la tension artérielle. C'est afin d'évaluer si les réactions à l'isoflurane sont déclenchées par la stimulation des voies aériennes inférieures et/ou des poumons, que nous avons mesuré les réponses hémodynamiques à l'isoflurane, administré après l'intubation, avec ou sans administration endotrachéale ou intraveineuse de lidocaïne.

**Méthode :** Soixante-douze patients ASA, d'état physique I, âgés de 21 à 50 ans, ont été répartis au hasard en quatre groupes. Après l'intubation, l'anesthésie a été maintenue avec 100 % d'oxygène et de l'isoflurane 1,0 % sous ventilation contrôlée. Suivant une stabilisation de 15 min, la concentration d'isoflurane a été rapidement augmenté à 3,0 % dans trois groupes. Un groupe sous lidocaïne endotrachéale a reçu un prétraitement comprenant 0,4 ml de lidocaïne 8 % en pulvérisation endotrachéale, un groupe sous lidocaïne intraveineuse a reçu 32 mg de lidocaïne *iv* et un groupe sous isoflurane 3 % n'a reçu aucun prétraitement. Dans un groupe témoin, la concentration d'isoflurane inspiré a été maintenue à 1,0 %. La fréquence cardiaque, la tension artérielle systolique et la concentration d'isoflurane de fin d'expiration ont été mesurées à chaque minute pendant 10 min.

**Résultats :** L'accroissement rapide de la concentration d'isoflurane a augmenté la fréquence cardiaque (25 ± 12 % d'augmentation par rapport à la mesure de base; $P < 0,05$) mais cet accroissement a été réduit par la lidocaïne endotrachéale (9 ± 9 %), et non par la lidocaïne intraveineuse (22 ± 13 %). La concentration plasmatique de lidocaïne était plus faible dans le groupe de lidocaïne endotrachéale (0,4 ± 0,3 $\mu g \cdot ml^{-1}$) que dans le groupe de lidocaïne *iv* (1,5 ± 0,2 $\mu g \cdot ml^{-1}$).

**Conclusion :** La tachycardie induite par l'isoflurane est réduite par le prétraitement avec de la lidocaïne endotrachéale.

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ISOFLURANE is associated with an increase in sympathetic activity, leading to tachycardia during induction of anaesthesia.[1] Although several causes of tachycardia have been reported such as decrease of systemic vascular resistance,[1] less depression of baroreflex function than that seen with other volatile anaesthetics (e.g. halothane and enflurane),[2] or greater depression of parasympathetic than sympathetic tone,[3] the precise mechanism(s) are unknown. Recently, airway reflexes have been regarded as another cause of the tachycardia.[4–7] Mechanical stimulation or chemical irritation of the airways elicited these reflexes and increased sympathetic activity.[8] Nishino *et al.*[6] found that stimulation of the nasal mucosa with isoflurane 5% increased laryngeal wall tension and expiratory time. In addition, Tanaka *et al.*[7] reported that lidocaine spray to the nasal mucosa blunted the increase of arterial blood pressure and heart rate when isoflurane was inhaled by mask. These reports indicate that responses to isoflurane may be elicited from stimulation of the upper airway. However, even if the upper airway is bypassed by tracheal intubation, a rapid increase of isoflurane increases blood pressure and heart rate[4] suggesting that the site(s) stimulated may lie in the lower airway and/or lungs.

Consequently, we investigated whether lidocaine administered through the endotracheal tube diminished the haemodynamic responses to isoflurane. If isoflurane evokes adreno-sympathetic reflexes, isoflurane-induced tachycardia may be modulated by intervention within the reflex arc with local anaesthetics. In addition, to examine the systemic anaesthetic effect of topical lidocaine we studied the effect of lidocaine administered intravenously.

## Methods

After local ethics approval and informed consent, 72 ASA physical status 1 patients, aged 21 - 50 yr, scheduled to undergo surgery, were assigned to one of the following four groups with permuted block design: isoflurane 1.0%, isoflurane 3.0%, endotracheal lidocaine, and intravenous lidocaine groups. Atropine sulfate (0.5 mg) and midazolam (0.8 $mg \cdot kg^{-1}$) *im* were given 30 min before induction of anaesthesia. After preoxygeneration for three minutes, anaesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopental and 0.15 $mg \cdot kg^{-1}$ vecuronium was used to facilitate tracheal intubation. Anaesthesia was maintained with oxygen 100% and isoflurane with controlled ventilation (tidal volume; 10 $ml \cdot kg^{-1}$, frequency; 8 - 10·$min^{-1}$, I - E ratio; 1 : 2) with a semi-closed circuit system at a fresh gas flow of 6 $L \cdot min^{-1}$. An inspired isoflurane concentration of 1.0 %, $P_{ET}CO_2$ 35 - 40 mmHg and $sPO_2$ 99% were maintained. After both heart rate and blood pressure had been stable for 15 min (baseline), the inspired isoflurane concentration was rapidly increased to 3.0%. Heart rate, systolic blood pressure (by an automatic oscillographic method) and end-tidal concentration of isoflurane were then measured every minute for 10 min. In the endotracheal lidocaine group, 0.4 ml lidocaine 8% was manually sprayed via the nozzle set at about 10 cm upstream from the distal end of an endotracheal tube at the beginning of inspiration five minutes before the rapid increase in concentration of isoflurane. In the intravenous lidocaine group, 32 mg lidocaine *iv* were administered five minutes before the rapid increase in inspired isoflurane. In the isoflurane 1.0% group, the 1.0% inspired concentration was maintained. In six patients from each of the endotracheal and the intravenous lidocaine groups, plasma lidocaine concentrations were measured by a standard fluorescence polarization immunoassay (sensitivity: $\geq 0.1\ \mu g \cdot ml^{-1}$, variability: < 2.5%) in a sample drawn five minutes after lidocaine administration. Inspired and expired concentration of isoflurane, $P_{ET}CO_2$, $V_{1.0}$ (volume expired during the first second / expiratory tidal volume), compliance (expiratory tidal volume / (plateau pressure - end expiratory pressure)), and $sPO_2$ were monitored continuously using the Capnomac Ultima™ (Datex: Helsinki, Finland).

TABLE Demographic Data

| | *Isoflurane 1.0% (n = 18)* | *Isoflurane 3.0% (n = 18)* | *Intratracheal Lidocaine (n = 18)* | *Intravenous Lidocaine (n = 18)* |
|---|---|---|---|---|
| Age (yr) | 42 ± 11 | 39 ± 10 | 40 ± 11 | 41 ± 14 |
| Weight (kg) | 59 ± 7 | 53 ± 7 | 57 ± 11 | 58 ± 7 |
| Height (cm) | 161 ± 9 | 161 ± 6 | 161 ± 10 | 160 ± 7 |
| Sex (M/F) | 9/9 | 10/8 | 7/11 | 7/11 |

Mean ± SD.

The results are expressed as mean ± SD in the text and tables, and as mean ± SEM in the figures. Group differences were analyzed by contingency table analysis or by one-way analysis of variance and Fisher's protected least significant difference test as post hoc comparisons for multiple comparison at a significance level of 0.05. The analyses were performed using Stat View II 4.0 software (Abacus Concepts, Berkeley, CA).

## Results

### *Demographic data*

There were no group differences with respect to age, body weight, height or sex (Table). No patient exhibited an abnormal ECG, hypotension, laryngospasm, $sPO_2$ < 99% or other complication during the study.

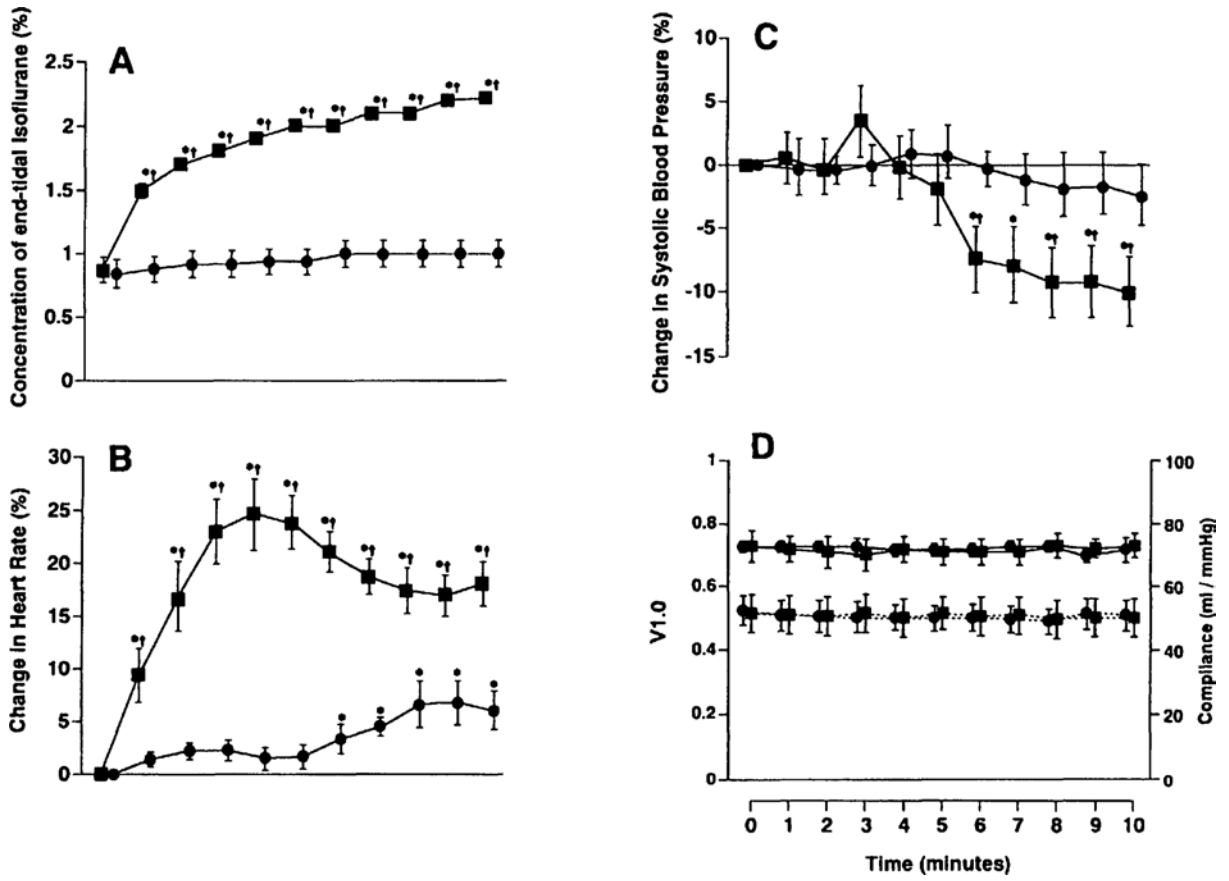


FIGURE 1 Concentration of end-tidal isoflurane (A), changes in heart rate (B), changes in systolic blood pressure (C), $V_{1.0}$ and lung compliance (dashed line) (D) from the respective baselines in the isoflurane 1.0% (●) and isoflurane 3.0% (■) groups.
Mean ± SEM. * $P < 0.05$ compared with baseline within the group;
† $P < 0.05$ compared with the isoflurane 1.0% group.

*End-tidal isoflurane concentration*

After the rapid increase in inspired isoflurane concentration, the end-tidal concentration increased (Figure 1A). The concentrations, which were not different among the three isoflurane 3.0% groups, increased rapidly for three to four minutes, and then almost reached a plateau (Figure 2A).

*Heart rate*

Baselines heart rates were not different among the four groups; 90 ± 12, 91 ± 15, 95 ± 12, and 92 ± 9 bpm in the isoflurane 1.0%, isoflurane 3.0%, endotracheal lidocaine, and intravenous lidocaine groups, respectively. Immediately after the rapid increase of the inspired concentration of isoflurane, heart rate increased rapidly (Figure 1B). The increases continued for four minutes, but then gradually abated. Heart rate increased rapidly in the intravenous lidocaine group, and did not differ from that in the isoflurane 3.0% group at any time (Figure 2B). Heart rate in the endotracheal group was less than that in the isoflurane 3.0% and intravenous lidocaine groups ($P < 0.05$).

*Systolic blood pressure*

Baseline systolic blood pressures were not different among the four groups: 112 ± 10, 109 ± 10, 111 ± 10, and 104 ± 14 mmHg in the isoflurane 1.0%, isoflurane 3.0%, endotracheal lidocaine, and intravenous lidocaine groups, respectively. After the rapid increase in the inspired isoflurane concentration, systolic blood pressure was stable for four to five minutes in the isoflurane 3.0% and intravenous lidocaine groups. Subsequently, systolic blood pressure in the two groups decreased from baseline. In the endotracheal lidocaine group, immediately after the rapid increase of the inspired isoflurane concentration, systolic blood pressure decreased (Fig 2C).

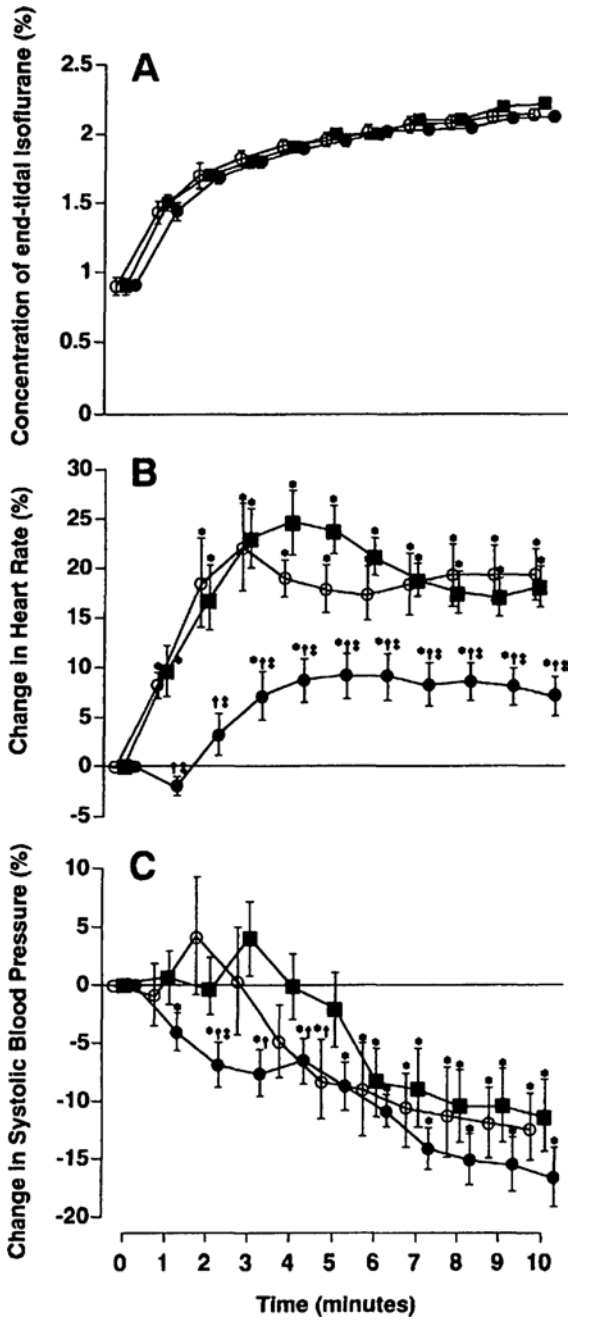


FIGURE 2 Concentration of end-tidal isoflurane (A), changes in heart rate (B), and changes in systolic blood pressure (C) from the respective baselines in the three groups inspired isoflurane 3%. Isoflurane 3.0% group;■, endotracheal lidocaine group;●, intravenous lidocaine group;○. Data are expressed as means ± SEM. * $P < 0.05$ compared with baseline within the group; ‡ $P < 0.05$ compared with the isoflurane 3.0% group; † $P < 0.05$ compared with the intravenous lidocaine group.

*$V_{1.0}$ and compliance*

There were no changes in $V_{1.0}$ and compliance in the isoflurane 1.0% or in any of the three groups in which isoflurane concentration increased rapidly during the study (Figure 1D).

*Lidocaine concentration*

The sample plasma lidocaine concentration was 0.4 ± 0.3 $\mu g \cdot ml^{-1}$ in the endotracheal group and 1.5 ± 0.2 $\mu g \cdot ml^{-1}$ in the intravenous group ($P < 0.05$).

## Discussion

The present study confirmed the increase in heart rate during rapid increase in isoflurane concentration in patients whose tracheas were intubated. The effect of isoflurane was decreased by endotracheal but not by intravenous administration of lidocaine. The higher plasma lidocaine concentration after intravenous than that after endotracheal administration did not influence isoflurane-induced haemodynamic changes. Although 3 - 6 $\mu g \cdot ml^{-1}$ plasma lidocaine concentration may have as much of an anaesthetic effect as nitrous oxide,[9] plasma lidocaine concentration was much less than 3 $\mu g \cdot ml^{-1}$ in this study. Therefore, it is unlikely that the systemic anaesthetic effect of lidocaine can exclusively explain the inhibitory effects observed in the endotracheal lidocaine administration. These results suggest the possible existence of a site or sites within the lower airway and/or lungs which are stimulated by isoflurane. There are rich sensory afferent nerve endings and receptors such as pulmonary stretch receptors, rapidly adapting irritant receptors, and c-fiber receptors in lower airway and lungs.[10, 11] Some of these may be the source of the tachycardia caused by isoflurane.

Isoflurane also produces laryngospasm and breath-holding in pediatric patients during induction of anaesthesia by face mask.[12] However, in this study with isoflurane administration via an endotracheal tube, both $V_{1.0}$ and compliance did not change after the rapid increase in isoflurane concentration. In a study by Nishino *et al.*[6] nasal insufflation of isoflurane 5% was associated with prolongation of expiratory time during spontaneous ventilation and increase of laryngeal wall tension but not of tracheal wall tension. Therefore, the lower airway does not appear to be constricted by isoflurane stimulation.

More recently, several studies with another irritating vapor, desflurane, have been reported. Weiskopf *et al.*[13] postulated the existence of tracheopulmonary receptors, which, in part, were responsible for the increases in heart rate and blood pressure resulting from increases in pulmonary but not systemic desflurane concentration. During induction of desflurane anaesthesia by face mask, 1.5 $mg \cdot kg^{-1}$ lidocaine *iv* did not attenuate the cardiovascular or catecholamine responses[14] and nebu-

lized ldnocaine (3 $mg \cdot kg^{-1}$) did not prevent airway irritation such as laryngospasm, breath-holding and coughing or the haemodynamic changes.[15] The epipharynx and nose seem to be more sensitive to mucosal irritation than the lower respiratory tract regarding cardiovascular responses.[8] Therefore, the discrepancy between these and our results might be because of different administration methods of volatile anaesthetics via face mask or via an endotracheal tube. In addition, desflurane can cause greater transient cardio-vascular stimulation than isoflurane.[16]

Patients included in this study were young ASA physical status 1 and had no history of cardiovascular disease. Elderly patients with cardiovascular disease may not show the same cardiac responses.[1] Ishikawa *et al.*[5] reported that the haemodynamic responses to sudden increased inhaled isoflurane were more pronounced in hypertensive than in normotensive patients. It may be interesting to investigate changes of response to isoflurane with lidocaine administered endotracheally in such patients.

In conclusion, the present study confirmed the increase in heart rate during rapid increase in isoflurane concentration in intubated patients. In addition, we found that the effect of isoflurane was decreased by endotracheal administration of lidocaine. We believe that part of the isoflurane-induced tachycardia may be caused via receptors in the lower airway and/or lungs.

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