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Clonidine and Lidocaine Inhibition of Isoflurane-induced Tachycardia in Humans

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Background: A rapid increase in isoflurane concentration can induce tachycardia and hypertension and increase plasma catecholamine concentrations. To investigate a possible mechanism, we measured hemodynamic responses to isoflurane administered *via* mask; we also administered clonidine for premedication, lidocaine topically to the nasal mucosa, or lidocaine intravenously to evaluate the effect of these drugs on the hemodynamic responses.

Methods: Forty ASA physical status 1 patients (aged 20–30 yr) scheduled for elective oral surgery participated in the study. Thirty patients were randomly allocated to one of three groups: a control group, a group receiving 3–4 $\mu\text{g} \cdot \text{kg}^{-1}$ of oral clonidine for premedication, and a group receiving 2 ml of 4% lidocaine spray to the nasal mucosa. Ten patients were assigned nonrandomly to a group receiving intravenous lidocaine continuously (0.4 $\text{mg} \cdot \text{kg}^{-1}$ bolus followed by 30 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) after the initial randomized experiments were done to test whether systemic lidocaine blunts the responses to inhaled isoflurane. Anesthesia was induced with thiamylal, after which inhalation of 1% isoflurane in 100% oxygen *via* mask was begun. The inspired concentration of isoflurane was increased by 1% every 5 min to a maximum of 4%. During normocapnia and without surgical stimulation, heart rate and systolic blood pressure were measured every minute for 20 min before and during isoflurane inhalation. Plasma catecholamine concentrations were measured before and at each isoflurane concentration.

Results: In the control and intravenous lidocaine groups, an increase in isoflurane concentration from 2% to 3% significantly increased systolic blood pressure (peak changes of 16 ± 5 and 15 ± 6 mmHg, respectively) and heart rate (peak changes of 23 ± 3 and 13 ± 4 beats $\cdot \text{min}^{-1}$, respectively). A change in concentration to 4%, however, did not significantly alter hemodynamics. Blood pressure and heart rate responses to a change to 3% isoflurane were significantly blunted in the

groups receiving clonidine (peak changes of 4 ± 4 mmHg and 8 ± 3 beats $\cdot \text{min}^{-1}$, respectively) or nasal lidocaine (peak changes of 2 ± 1 mmHg and 4 ± 2 beats $\cdot \text{min}^{-1}$, respectively) compared with the control group. In all groups, plasma epinephrine and norepinephrine concentrations increased after administration of 2% and 1% isoflurane, respectively. Plasma lidocaine concentrations were 0.3–1.3 $\mu\text{g} \cdot \text{kg}^{-1}$ in the nasal lidocaine group and 0.6–1.5 $\mu\text{g} \cdot \text{kg}^{-1}$ in the intravenous lidocaine group.

Conclusions: Stepwise increases in isoflurane concentration elicited hypertension and tachycardia as well as increments in plasma catecholamine concentrations during mask anesthesia. Nasal administration of lidocaine and clonidine premedication significantly blunted the circulatory responses to isoflurane. Intravenous lidocaine did not significantly weaken the responses to changes in isoflurane concentration. (Key words: Anesthetics, topical: lidocaine. Anesthetics, volatile: isoflurane. Heart: tachycardia. Nose: nasal mucosa. Sympathetic nervous system, α_2 -adrenergic agonists: clonidine. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

ISOFLURANE is associated with a significant increase in sympathetic nervous system activity and associated hemodynamic changes during anesthesia induction.^{1,2} At least three factors contribute to the tachycardia associated with isoflurane anesthesia: (1) decreased systemic vascular resistance,¹ (2) less depression of baroreflex function than that seen with other volatile anesthetics such as halothane or enflurane,³ and (3) depressed parasympathetic tone in comparison with sympathetic tone during isoflurane administration.⁴

However, another factor that may produce tachycardia has recently been identified. Yli-Hankala *et al.*⁵ found that a rapid increase in end-tidal concentration of isoflurane from 1.3% to 2.6% caused sympathetic activation and induced hemodynamic responses, such as tachycardia and hypertension. Ishikawa *et al.*⁶ also reported that a sudden administration of 5% isoflurane elicited hyperdynamic circulation in normotensive and hypertensive patients. Stimulation of the nasal mucosa with 5% isoflurane increases expiratory time and decreases respiratory frequency,⁷ both of which are thought to be defensive airway reflexes. Defensive air-

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way reflexes are elicited by mechanical stimulation or chemical irritation of the airways and increase blood pressure and sympathetic efferent nerve activity.⁸ These reports indicate that the irritating effect of isoflurane on the airways could be another cause of tachycardia.

If isoflurane stimulation of airway receptors subsequently evokes adenosympathetic reflexes, one might expect that isoflurane-induced tachycardia could be modulated by intervention within the reflex arc. For example, if local anesthetics are applied to the airways, the reflex should diminish at the receptor level. Also, drugs such as oral clonidine, a centrally acting, α_2 agonist that suppresses sympathetic reflexes,⁹⁻¹¹ might weaken the reflex.

In the current study, we measured circulatory variables and plasma catecholamine concentrations to investigate whether isoflurane elicits sympathetic activity during isoflurane anesthesia administered *via* mask. Furthermore, we studied whether clonidine premedication or lidocaine applied topically to the nasal mucosa could weaken isoflurane-induced circulatory changes. To examine the central nervous system effect of topically administered lidocaine, we also investigated the influence of lidocaine injected intravenously on isoflurane-induced circulatory alterations.

Materials and Methods

Patient Selection and Study Groups

After obtaining approval from the Institutional Ethics Committee of Sapporo Medical University and informed consent from the patients, we studied 40 ASA physical status 1 patients, 20–30 yr old, scheduled for elective oral surgery under general anesthesia. Thirty patients were allocated to one of three groups with the use of a random-number table: a control group, a clonidine premedication group, and a nasal lidocaine group ($n = 10$, each). Ten patients were assigned nonrandomly to an intravenous lidocaine group, after the initial randomized experiments were done, to evaluate the possibility for systemic lidocaine to blunt the responses to changes in isoflurane. The control group, nasal lidocaine group, and intravenous lidocaine group patients received 2.5 mg of intramuscular midazolam 1 h before induction of anesthesia. The clonidine group patients received 3–4 $\mu\text{g} \cdot \text{kg}^{-1}$ (225 or 300 μg total, according to body weight) of oral clonidine 2 h before induction of anesthesia. No anticholinergic drugs were given. In the nasal lidocaine group, the nasal mucosa

was sprayed with 2 ml of 4% lidocaine 10–20 min before induction of anesthesia. In the intravenous lidocaine group, 0.4 $\text{mg} \cdot \text{kg}^{-1}$ of lidocaine was injected intravenously 5 min before induction of anesthesia, which was followed by a continuous infusion of lidocaine, 30 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, throughout the study period to produce approximately the same plasma lidocaine concentration as the group given lidocaine topically.

Study Procedures

In the operating room, the electrocardiogram (Multimonitor, San-Ei, Tokyo, Japan) and hemoglobin oxygen saturation (finger pulse oximetry: OX-1, Colin, Komaki, Japan) were monitored continuously. Heart rate (HR) and systolic blood pressure (SBP) were measured by an automatic oscillographic method (Jentow, Colin, Komaki, Japan) at every minute during the study period. Under local anesthesia, an 18-G catheter for intravenous fluid (lactated Ringer's solution, 3 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and drug administration was placed in one forearm, and a 20-G catheter for venous blood sampling was inserted in the other forearm. A 6-ml blood sample was drawn to determine baseline catecholamine concentrations.

After preoxygenation for 3 min and obtaining SBP and HR (0-min values), anesthesia was induced with thiamylal 3 $\text{mg} \cdot \text{kg}^{-1}$, after which mask inhalation of 1% isoflurane in 100% oxygen was begun. We used a modified Jackson-Rees anesthetic circuit system at a fresh gas flow of 8 $\text{L} \cdot \text{min}^{-1}$. A soft catheter was inserted about 2 cm into the right nostril just after the induction of anesthesia. Through this catheter, end-tidal carbon dioxide tension as well as inspired and end-tidal isoflurane concentration was continuously monitored with a precalibrated infrared carbon dioxide and anesthetic agent analyzer (5250 RGM, Ohmeda, Salt Lake City, UT).

The initial inspired isoflurane concentration was 1%; this inspired concentration was increased by 1% every 5 min to a maximum concentration of 4%. All patients' lungs were ventilated *via* mask to maintain an end-tidal carbon dioxide tension of 35–40 mmHg and a hemoglobin oxygen saturation (by pulse oximetry) greater than 99%. SBP and HR were measured at every minute for 20 min after the start of isoflurane administration. Blood samples were drawn to determine the concentrations of plasma catecholamines 3 min after each increase in the isoflurane concentration. In the lidocaine groups, another 2 ml of blood (total, 8 ml) was drawn to determine the plasma lidocaine concen-

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Table 1. Demographic Data

	Control (n = 10)	Clonidine (n = 10)	Nasal Lidocaine (n = 10)	Intravenous Lidocaine (n = 10)
Age (yr)	24 ± 1	22 ± 1	25 ± 2	24 ± 1
Weight (kg)	51 ± 2	55 ± 3	58 ± 2	56 ± 3
Height (cm)	161 ± 3	162 ± 2	162 ± 2	164 ± 2
Sex (M/F)	3/7	1/9	3/7	5/5

There were no significant intergroup differences by the ANOVA and chi-square test.

tration at the same time blood was drawn for catecholamine testing. Blood samples were collected in prechilled vacuum glass tubes containing ethylenediamine tetraacetic acid and immediately placed on ice. The samples were centrifuged at 0°C, and the plasma was stored at -20°C; all plasma samples were analyzed within 48 h. Plasma catecholamine concentrations were measured by high-performance liquid chromatography. The detection limit for both epinephrine and norepinephrine was 0.01 ng · ml⁻¹. Plasma lidocaine concentrations were measured by a standard fluorescence polarization immunoassay. The coefficients of variation for measurements of epinephrine, norepinephrine, and lidocaine were approximately 3%, 1%, and 2%, respectively.

Data Analysis

Statistical analysis was performed on a personal computer using Stat View II software (Abacus Concepts, Berkeley, CA). The chi-square test was applied to compare differences in sex among the four groups. Plasma lidocaine concentrations were analyzed by one-way repeated measure analysis of variance and an unpaired Student's *t* test. Other results were analyzed by one-way analysis of variance (between the groups) and repeated-measures analysis of variance (within the group). *Post hoc* comparisons were done using Fisher's protected least significant difference test.¹² The significance level was set at *P* ≤ 0.05. Data are reported as mean ± standard error of the mean.

Results

Demographic data are presented in table 1. The four groups did not differ significantly with respect to sex, age, height, or weight. In no patient was there an abnormal electrocardiogram, laryngospasm, cough, or a

hemoglobin oxygen saturation of less than 99% during the study period. End-tidal concentrations of isoflurane were not significantly different among the four groups. They were 0.59% ± 0.03% at 5 min, 1.25% ± 0.03% at 10 min, 1.91% ± 0.04% at 15 min, and 2.61% ± 0.06% at 20 min.

Plasma lidocaine concentrations in the nasal and intravenous lidocaine groups are shown in table 2. In the intravenous lidocaine group, lidocaine was administered with the intent to produce the same plasma concentrations as in the nasal lidocaine group. The total dose of lidocaine injected intravenously was 64.4 ± 3.5 mg in the intravenous lidocaine group. Plasma lidocaine concentrations in the intravenous lidocaine group (0.6–1.5 µg · ml⁻¹) were, however, significantly greater than those in the nasal lidocaine group (0.3–1.3 µg · ml⁻¹) except at 8 min (2% isoflurane).

Table 3 shows HR changes for the four groups before (0 min) and 5 min after the administration of each isoflurane concentration. HR in the clonidine group before isoflurane administration was significantly less (*P* ≤ 0.05) than in the other three groups. In the control and intravenous lidocaine groups, HR increased significantly after 1% isoflurane administration. No significant difference was observed between the control and intravenous lidocaine groups. The HR response after 1% isoflurane administration was blunted in the clonidine and nasal lidocaine groups. HR in the clonidine group increased significantly from 0 min after 2% isoflurane but HR in the nasal lidocaine group did not significantly increase until 4% isoflurane administration. HR in the nasal lidocaine group was significantly less than that in the control (at 3% and 4% isoflurane) and intravenous lidocaine groups (at 2% and 3% isoflurane).

Table 4 shows SBP changes for the four groups before (0 min) and 5 min after each concentration of isoflurane administration. SBP in the control group decreased

Table 2. Plasma Lidocaine Levels (µg/ml) in the Nasal and Intravenous (IV) Lidocaine Groups

	Isoflurane Concentration			
	1%	2%	3%	4%
Nasal lidocaine	0.5 ± 0.1*	0.7 ± 0.4	0.6 ± 0.1*	0.8 ± 0.1*
IV lidocaine	1.0 ± 0.3	0.9 ± 0.2	1.1 ± 0.1	1.1 ± 0.2

Values are mean ± SEM. Blood samples were drawn 3 min after each increase in isoflurane.

* *P* ≤ 0.05 versus the IV lidocaine group.

Table 3. Effect of Increasing Isoflurane Concentration on Heart Rate (beats/min)

Time (min)	0	5	10	15	20
Isoflurane concentration (%)	0	1	2	3	4
Control	75 ± 3	69 ± 2	85 ± 2§	103 ± 5§	106 ± 6§
Clonidine	64 ± 4*†‡	59 ± 3*†‡	66 ± 3*†‡	73 ± 4*†§	78 ± 5*†§
Nasal lidocaine	79 ± 4	73 ± 2	78 ± 3‡	82 ± 4‡	91 ± 4*§
IV lidocaine	76 ± 4	75 ± 3	90 ± 5§	100 ± 6	100 ± 6§

Values are mean ± SEM.

* $P \leq 0.05$ versus the control group.

† $P \leq 0.05$ versus the nasal lidocaine group.

‡ $P \leq 0.05$ versus the intravenous (IV) lidocaine group.

§ $P \leq 0.05$ versus time 0 (awake) in the group.

only at 5 min. In the remaining three groups, however, SBP decreased significantly from 0 min throughout isoflurane administration except at 15 min in the intravenous lidocaine group. No significant difference was observed between the control and intravenous lidocaine groups. However, SBP in the clonidine group was significantly less than that in the control and intravenous lidocaine groups at 2% and 3% isoflurane administration. SBP in the nasal lidocaine group was also less than that in the intravenous lidocaine group at 2% and 3% isoflurane.

Figures 1 and 2 show detailed changes in HR and SBP from baseline after each increase in isoflurane concentration for the four groups. HR increased significantly during 2% isoflurane administration in all groups but only in the control and intravenous lidocaine groups during 3% isoflurane administration. Maximum increases in HR in the control group were 16 ± 2 and 23 ± 3 beats \cdot min⁻¹ during 2% and 3% isoflurane, respectively. Maximum increases in the clonidine group

were 10 ± 4 and 8 ± 3 beats \cdot min⁻¹ and in the nasal lidocaine group were 6 ± 1 and 4 ± 4 beats \cdot min⁻¹, respectively. The increase in HR in the control group was significantly greater than that in the nasal lidocaine group ($P < 0.005$) and the clonidine group ($P < 0.02$) during 2% (at 10 min) and 3% isoflurane (at 12, 13, and 15 min). The increase in HR in the intravenous lidocaine group did not differ from that in the control group except at 13 min. The increase of nasal lidocaine group HR was significantly less than that of the intravenous lidocaine group at 13 and 15 min ($P < 0.05$).

SBP also significantly increased during 3% isoflurane administration in the control and intravenous lidocaine groups. Maximum increases in SBP were comparable in both groups during 3% isoflurane (16 ± 5 and 15 ± 6 mmHg, respectively). In contrast, maximum increases in SBP in the clonidine and nasal lidocaine group were 4 ± 4 and 2 ± 1 mmHg, respectively, during 3% isoflurane. The increase in SBP in the nasal lidocaine group was significantly less than that in the control (P

Table 4. Effect of Increasing Isoflurane Concentration on Systolic Blood Pressure (mmHg)

Time (min)	0	5	10	15	20
Isoflurane concentration (%)	0	1	2	3	4
Control	112 ± 3	104 ± 2*	105 ± 2	111 ± 5	108 ± 4
Clonidine	111 ± 3	95 ± 2*†‡§	93 ± 4*†§	94 ± 5*†§	87 ± 5*†§
Nasal lidocaine	115 ± 3	104 ± 2*	98 ± 3*§	98 ± 3*§	97 ± 3*†
IV lidocaine	120 ± 3	110 ± 3*	111 ± 3*	114 ± 6	106 ± 3*

Values are as mean ± SEM.

* $P \leq 0.05$ versus time 0 (awake) in the group.

† $P \leq 0.05$ versus the control group.

‡ $P \leq 0.05$ versus the nasal lidocaine group.

§ $P \leq 0.05$ versus the intravenous (IV) lidocaine group.

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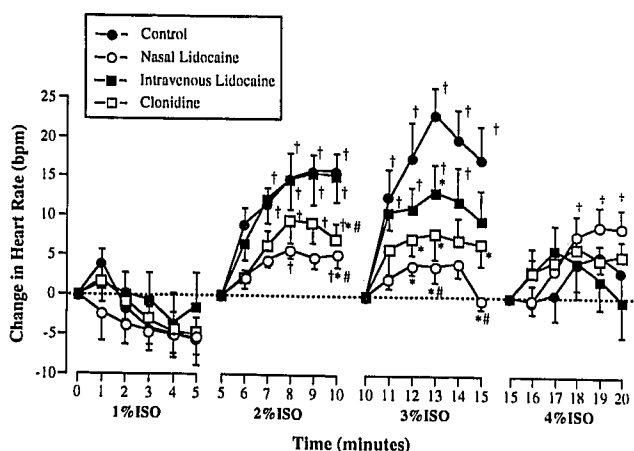


Fig. 1. Changes in heart rate from the respective baseline (the time the inspired isoflurane concentration was increased) in the four groups. Data are expressed as means \pm standard error of the mean. $\dagger P \leq 0.05$ compared with baseline within the group; $* P \leq 0.05$ compared with the control group; $\# P \leq 0.05$ compared with the intravenous lidocaine group.

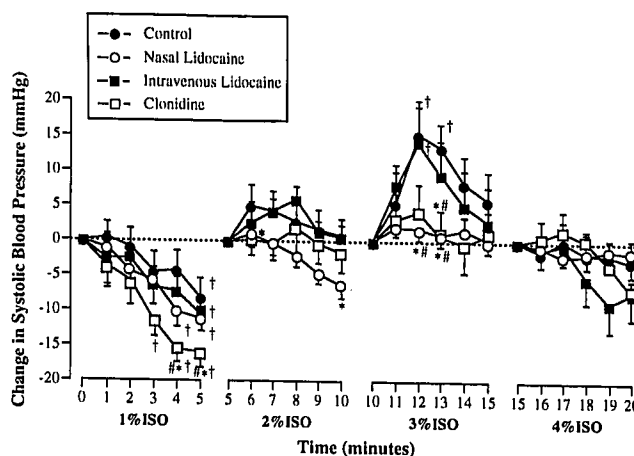


Fig. 2. Changes in systolic blood pressure from the respective baseline (the time the inspired isoflurane concentration was increased) in the four groups. Data are expressed as means \pm standard error of the mean. $\dagger P \leq 0.05$ compared with baseline within the group; $* P \leq 0.05$ compared with the control group; $\# P \leq 0.05$ compared with the intravenous lidocaine group.

< 0.03) and intravenous lidocaine group ($P < 0.05$) at 12 and 13 min. The increase in SBP in the clonidine group was also less than those in the control and intravenous lidocaine groups at 13 min ($P = 0.011$ and $P = 0.040$, respectively).

As figure 3 illustrates, plasma epinephrine concentrations decreased significantly from awake values to the lowest concentrations at 2% isoflurane administration in all groups. After 2% isoflurane administration, epinephrine concentrations increased as the concentration of isoflurane increased, although significant differences were observed only between 3% and 4% isoflurane administration. The control and intravenous lidocaine groups did not differ significantly. Plasma epinephrine concentrations in the nasal lidocaine and clonidine groups were significantly less than those in the control group at 4% isoflurane administration ($P = 0.014$ and $P = 0.019$, respectively).

As shown in figure 4, the awake plasma norepinephrine concentration in the clonidine group was significantly less than in the other three groups ($P < 0.003$ vs. the control and intravenous lidocaine groups, $P = 0.043$ vs. the nasal lidocaine group). The plasma norepinephrine concentration in the clonidine group was also significantly less than in the other three groups at 2% isoflurane ($P = 0.002$ vs. the control and intravenous groups, $P = 0.049$ vs. the nasal lidocaine group).

Discussion

Our findings show that (1) even a stepwise increase in isoflurane concentration altered not only circulatory variables but also plasma catecholamine concentra-

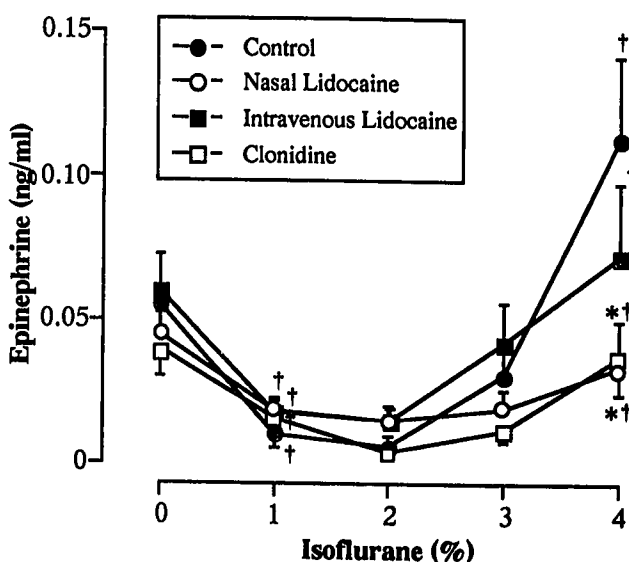


Fig. 3. Plasma epinephrine concentrations in the four groups. Data are expressed as means \pm standard error of the mean. $\dagger P \leq 0.05$ compared with the value at the next lowest concentration of isoflurane within the group; $* P \leq 0.05$ compared with the control group.

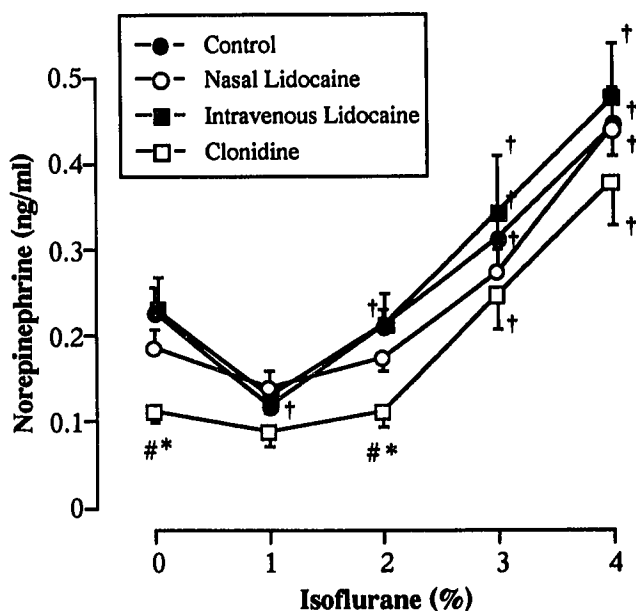


Fig. 4. Plasma norepinephrine concentrations in the four groups. Data are expressed as means \pm standard error of the mean. $\dagger P \leq 0.05$ compared with the value at the next lowest concentration of isoflurane within the group; $* P \leq 0.05$ compared with the control group; $\# P \leq 0.05$ compared with the intravenous lidocaine group.

tions, and (2) lidocaine applied to the nasal mucosa and oral clonidine premedication significantly blunted the isoflurane-evoked circulatory responses.

Effects of Isoflurane in the Control Group

Changes in circulatory variables and plasma catecholamine concentrations indicated that increases in the inspired concentration of isoflurane activated adrenergic function in the control group. However, the adrenergic activation we observed is not consistent with our previous understanding of isoflurane-induced tachycardia. An increase in HR accompanied an increase in SBP on most occasions, indicating that the tachycardia was not caused by baroreflex-induced sympathetic activity or reduced systemic vascular resistance. The HR and SBP did not change significantly during 4% isoflurane administration. An increase in anesthetic depth is probably responsible for this lack of change because isoflurane by itself diminishes sympathetic activation.¹³

Recently, sympathetic nervous system activation and hyperdynamic circulatory responses associated with desflurane and isoflurane anesthesia have been described.¹⁴⁻¹⁶ Ebert and Muzi¹⁴ reported that an abrupt

increase in the inspired concentration of isoflurane or desflurane enhanced sympathetic nerve activity in the peroneal nerve as well as hypertension and tachycardia. Several questions, however, remain including (1) what the mechanism(s) are that lead to the changes, and (2) whether the changes can be predictably avoided.¹⁷

Buffington² investigated airway reflexes such as coughing and breath-holding during anesthesia induction, maintenance, and recovery in 6,798 isoflurane anesthesia cases. He found that an inspired isoflurane concentration greater than 2.5% was associated with an increased risk of airway reflex activity during induction. In the current study, circulatory changes were greatest when the inspired concentration of isoflurane increased from 2% to 3%; an increase in plasma norepinephrine accompanied the circulatory changes. The results indicate that circulatory changes are related to airway reflex activity during isoflurane anesthesia, although no direct evidence connecting the two issues has been reported previously.

Although some methodological differences exist, our findings are quite similar to those reported by Yli-Hankala *et al.*⁵ They increased the inspired concentration of isoflurane to 5% to rapidly increase the end-tidal concentration of isoflurane from 1.3% to 2.6%, and their patients' tracheas were intubated. We increased the inspired concentration of isoflurane stepwise as in a clinical situation, but our patients' tracheas were not intubated. However, in both studies isoflurane increased blood pressure and HR shortly after each increase in inspired concentration. This finding is consistent with previous reports that the epipharynx and nose are more sensitive to mucosal irritation that can induce cardiovascular responses than the trachea-bronchi.⁸ Allen also reported that the nasal mucosa was particularly sensitive to chemical and mechanical irritation.¹⁸

Effect of Oral Clonidine Premedication

Clonidine reduces sympathetic activity and decreases circulating plasma norepinephrine concentrations not only in surgical patients¹⁹ but also in normotensive individuals.^{10,20} It decreases both blood pressure and HR in surgical patients.^{19,21} In the current study, baseline HR in the clonidine group was significantly less than in the other three groups. Oral clonidine premedication, however, did not influence baseline SBP in our patients. The difference is probably a result of the patient population, dose, and choice of the premedication because our patients were young and normotensive,

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received a smaller dose of clonidine only, and the other three groups received intramuscular midazolam instead of clonidine.

Clonidine can reduce reflex sympathetic activation in both awake humans¹⁰ and anesthetized animals.⁹ In the current investigation, clonidine not only decreased HR and SBP during isoflurane administration, but also inhibited isoflurane-induced transient increases in HR and SBP. These results suggest that reflex activation of the sympathetic nervous system may be involved in isoflurane-induced tachycardia. In other words, reflex activation of the sympathetic nervous system is necessary to maintain SBP at the preanesthetic levels even during isoflurane anesthesia. However, clonidine can decrease anesthetic requirements^{19,22} and may change the depth of anesthesia, which may account in part for the smaller variation in hemodynamics observed when the isoflurane concentration was increased.

Effects of Nasal and Intravenous Lidocaine

We applied 80 mg of lidocaine to the nasal mucosa in the nasal lidocaine group patients, which produced mean plasma lidocaine concentrations of less than $1.0 \mu\text{g} \cdot \text{ml}^{-1}$ throughout the study period. This concentration was too low to influence hemodynamic changes in awake subjects.²³ However, this concentration of lidocaine can decrease the anesthetic requirement of nitrous oxide, halothane, and enflurane slightly (less than 15%).^{24,25} We do not know how lidocaine and isoflurane interact in humans or in experimental animals. In the current study, mean plasma lidocaine concentrations of approximately $1.0 \mu\text{g} \cdot \text{ml}^{-1}$ did not influence isoflurane-induced changes in hemodynamic variables and plasma catecholamine concentrations compared with the control group, except for blunting the HR response during 3% isoflurane administration. It is, therefore, very unlikely that the low concentration of plasma lidocaine can exclusively explain the circulatory changes observed in the nasal lidocaine group.

In the current study, nasal lidocaine considerably weakened the circulatory responses as isoflurane concentration increased when compared with the control and intravenous lidocaine groups. Nishino *et al.*⁷ reported that nasal insufflation of 5% isoflurane was associated with airway reflex activity, but this activity was abolished when topical lidocaine was applied to the nasal mucosa. In light of our results and those of the Nishino group, it is most likely that isoflurane stimulated the airway receptors in the nose during mask ventilation, which evoked adrenergic activity,

including tachycardia and hypertension. As expected, the nasal mucosa is not the only area at which an airway reflex can be induced. This explains why topical lidocaine could not completely abolish the HR responses especially during 4% isoflurane administration.

Plasma Catecholamine Concentrations

The results obtained for plasma catecholamine concentrations are somewhat perplexing. We observed significant trends in plasma catecholamine concentrations within the groups. However, we failed to show significant differences in plasma catecholamine concentrations between the groups as had been observed for the circulatory changes at 3% isoflurane. This problem may be partly explained by baroreflex-mediated activation of the sympathetic nervous system²⁶ because SBP decreased significantly in the lidocaine and clonidine groups after the isoflurane administration.

Mixed venous blood sampled from the pulmonary artery is the best choice to measure whole body catecholamines because the lungs selectively take up catecholamines, especially norepinephrine, to a considerable extent.^{27,28} Because we sought to keep our investigation as noninvasive as possible, we did not insert a central venous catheter or a pulmonary arterial catheter. Instead we took blood samples from the forearm vein. This decision might have resulted in the lack of significant difference between the groups. Randell *et al.* administered $6.0 \pm 0.9 \text{ mg} \cdot \text{kg}^{-1}$ thiopentone, followed by 3% isoflurane with nitrous oxide by mask ventilation.²⁹ They showed that isoflurane significantly increased HR compared with their control group. However, no difference was found in the plasma norepinephrine concentration (blood samples were taken *via* central venous catheter) between the groups. This report, as well as ours, may be consistent with previous reports that plasma catecholamine concentrations do not necessarily reflect adrenergic function during anesthesia administration.^{30,31}

Limitations of Our Study

We recognize several limitations to our study. The group receiving intravenous lidocaine was not randomized, unlike the other groups. Although this somewhat weakens the study design, we do not believe that it is a serious limitation.

Midazolam was given to the control and lidocaine groups but not to the clonidine group. This additional variable adds to complexity and limits analysis. However, the control, nasal, and intravenous lidocaine

group patients did all receive midazolam for premedication, validating nasal lidocaine's ability to suppress the cardiovascular changes during isoflurane anesthesia. We intended all our patients to be sedated equally, although we do not know of any comparative study showing the relative potencies of midazolam and clonidine for premedication. Intramuscular midazolam has potent amnesic and anxiolytic properties with minimal cardiovascular depression.³² Clonidine, in a dose of 0.2–0.3 mg, can also produce marked sedation and anxiolysis.^{33,34} Therefore, we considered that 3–4 $\mu\text{g} \cdot \text{kg}^{-1}$ of oral clonidine could replace 2.5 mg of intramuscular midazolam in our study. Both drugs have sedative and hypotensive effects that possibly occur through a central reduction in sympathetic tone.^{11,32} Consequently, we felt that an alternative, that of administering a combination of clonidine and midazolam, was impossible because of the chance that oversedation and hypotension might occur during anesthesia.

Our use of thiamylal for induction may have influenced the hemodynamic changes induced by isoflurane. In a preliminary study, we administered 3 $\text{mg} \cdot \text{kg}^{-1}$ thiamylal for induction, which was followed by 1% isoflurane with mask ventilation for 20 min. In those patients, HR transiently increased after thiamylal injection and returned to baseline in 5 min. SBP decreased by 10–15 mmHg 3 min after thiamylal injection but did not change significantly afterward. Therefore, we believe that 3 $\text{mg} \cdot \text{kg}^{-1}$ thiamylal might have influenced the hemodynamics in the first 5 min but had minimum effect on the circulatory changes during the remainder of the current study.

We did not conduct dose–response studies of nasal lidocaine and clonidine. Larger doses of lidocaine applied to the airways might have abolished the isoflurane-induced hemodynamic responses completely, but this is difficult to accomplish in a clinical situation. We rather considered it more applicable to clinical anesthesia if 2 ml of lidocaine applied to the nose could blunt the circulatory response. In our preliminary study, a group of patients received 5 $\mu\text{g} \cdot \text{kg}^{-1}$ of clonidine for premedication. However, SBP decreased below 80 mmHg in these patients during 3% isoflurane administration. Therefore we could not include such a group in the study.

Our investigation showed that clonidine premedication as well as nasal application of 4% lidocaine effectively prevents isoflurane-induced tachycardia. Such prevention might be valuable in those patients with cardiovascular disease for whom tachycardia is dele-

terious. However, 40 young ASA 1 patients participated in this study—elderly patients with cardiovascular disease may not show the same cardiac responses.¹ Opioids are an alternative to avoid isoflurane-induced tachycardia.^{1,35} Moreover, our investigation did not show that these interventions prevent respiratory complications, such as breath-holding, cough, or laryngospasm, during isoflurane anesthesia.² Further study is necessary to discover whether such intervention can prevent respiratory complications.

In conclusion, even a stepwise increase of the isoflurane concentration administered *via* mask activates adrenergic function. Nasally applied lidocaine as well as oral clonidine premedication partially but significantly inhibit this activation. Our results strongly suggest that isoflurane has an irritating effect on the airways that elicits hypertension and tachycardia.

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