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Effects of sevoflurane and enflurane on lower esophageal sphincter pressure and gastroesophageal pressure gradient in children

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Abstract
Purpose. The effects of sevoflurane and enflurane on the intraluminal pressure of the lower esophagus (LE), lower esophageal sphincter (LES), and stomach were investigated in paralyzed and mechanically ventilated children under general anesthesia.
Methods. A total of 14 children, ASA physical status class I without risk factors for regurgitation, scheduled for orthopedic surgery were studied. After induction of anesthesia, we inserted a gastrointestinal pressure sensor nasally and monitored the intraluminal pressure of the LE, LES, and stomach under various concentrations of sevoflurane or enflurane with 66% nitrous oxide in oxygen prior to surgical incision. The barrier pressure (BrP), which is the difference between LES pressure and intragastric pressure, was calculated.
Results. Sevoflurane at 2.0 and 2.5 minimum alveolar concentration (MAC) decreased LES pressure, and enflurane at 2.0 and 2.5 MAC decreased both LES pressure and BrP in anesthetized children. The intraluminal pressure of the LE and stomach were not altered in either group.
Conclusion. Sevoflurane and enflurane have an inhibitory effect on LES smooth muscle in anesthetized children. However, since the reduction was relatively low, even at high concentrations, these inhalation anesthetics are unlikely to influence gastroesophageal reflux during anesthesia.

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Introduction

The lower esophageal sphincter (LES), which separates the gastric and esophageal lumens, is a specialized circular smooth muscle that relaxes with swallowing to allow passage of food from the esophagus to the stomach, thus preventing reflux of acidic gastric contents into the esophagus against an abdominal-thoracic pressure gradient [1]. Furthermore, the LES is of special interest to clinicians concerned with the etiology of gastroesophageal reflux (GER) [2–4] and, in particular to anesthesiologists [5] who are concerned with preventing aspiration during anesthesia. LES tone and barrier pressure (BrP), which is the difference between LES pressure and intragastric pressure, are factors that affect the physiological barrier preventing reflux. Reduction in BrP may be associated with reflux [5]. Besides, the concept of regurgitation, including silent regurgitation, has been accepted by anesthesiologists [6]. Although the etiology of regurgitation is still not clear, LES incompetence, intragastric pressure increase due to the body position of the patient, duration of surgical procedures, and some anesthetic drugs and techniques may be involved [6]. Therefore, examining the effects on LES pressure and BrP of drugs used during the perioperative period is very important for understanding the etiology of regurgitation.

Although volatile anesthetics are widely used in pediatric anesthesia, their effects on upper gastrointestinal pressure have not been elucidated. The present study was designed to test the hypothesis that sevoflurane and enflurane affect the intraluminal pressure of the upper gastrointestinal tract in children anesthetized with nitrous oxide in oxygen, by measuring the pressure in

the lower esophagus (LE), LES, and stomach, using gastrointestinal pressure sensors that continuously monitor these pressures simultaneously.

Materials and methods

Study population

The experimental protocol was approved by the clinical investigation review board of the Nojigiku Medical Center for Disabled Children, and all patients' parents gave informed consent before participation in the study.

A total of 14 children 3 to 16 years old (10.0 ± 4.0, mean ± SD), 4 boys and 10 girls, weighing between 15.0 and 56.0 kg (31.2 ± 12.6), who were scheduled for orthopedic surgery were studied. All patients were of ASA physical status class I. Obese patients >20% heavier than their ideal body weight, those taking drugs affecting LES pressure, such as calcium antagonists or antacids, and those with a history of hiatus hernia, esophageal reflux, or peptic ulceration were excluded.

Upper gastrointestinal manometry

Because the contractility of the esophageal smooth musculature is unaffected by neuromuscular blocking agents, lower esophageal contractility is present and easily measurable during anesthesia. A gastrointestinal pressure sensor (Synectic Medical, Stockholm, Sweden) was used to detect the effects of volatile anesthetics on upper gastrointestinal pressure in vivo. The sensor includes a silicon-polyvinyl catheter with three pressure sensors at its apex. These pressure sensors are situated in the proximal, middle, and distal areas, 5 cm from each other, and enable continuous pressure monitoring of the LE, LES, and stomach. At the beginning of each study, calibration was achieved under atmospheric pressure and 50 cmH_2O, by placing the sensor in air and water. The data obtained were recorded as millimeters of mercury and analyzed by a Synectics Medical Liberty system and software, Gastrosoft Polygram upper GI edition Version 5.06C2.

After induction of anesthesia and intubation, a gastrointestinal pressure sensor was inserted into the stomach and pulled through slowly, leaving the middle sensor at the LES. The exact position of the catheter was confirmed by the characteristic waves of the LE, LES, and stomach. When there was intrinsic activity of the LE or LES, which is related to consciousness or awareness [7], such as primary or secondary peristaltic waves, we added volatile anesthetics and repositioned the catheter.

The pressures of the LE, LES, and stomach were recorded as mean resting pressures within the last 1 min at each concentration of the anesthetics, and for the percentage of relaxation. Furthermore, BrP was calculated as (BrP) = (LES pressure) − (intragastric pressure).

General study design

Milk or solids were administered orally until 9:00 P.M. on the day before surgery, and patients were instructed to ingest clear fluids until 6 h before surgery. No preanesthetic medication was given.

The 14 children were allocated randomly into two groups by opening a sealed envelope before induction of anesthesia. Anesthesia was induced by inhalation of sevoflurane and 66% nitrous oxide in oxygen in the sevoflurane group (S group), or by inhalation of enflurane and 66% nitrous oxide in oxygen in the enflurane group (E group). Ventilation by face mask was performed gently so as not to distend the stomach. Tracheal intubation was facilitated by intravenous vecuronium (0.2 $mg \cdot kg^{-1}$). In both groups, administration of volatile anesthetics was discontinued after the trachea was intubated by a cuffed endotracheal tube, and anesthesia was maintained with 66% nitrous oxide in oxygen without volatile anesthetics for about 15 min by mechanical ventilation, adjusting the end-tidal concentration of carbon dioxide by 35 to 40 mmHg. The airway pressure during mechanical ventilation was not particularly adjusted; however, the peak inspiratory pressure did not exceed 20 cmH_2O in all cases. A gastrointestinal pressure sensor was then inserted nasally and its exact position was determined by the methods described above. Additional muscle relaxants were applied (0.04 $mg \cdot kg^{-1}$) every 1 h and were confirmed by percutaneous stimulation of the ulnar nerve (train-of-four method) every 30 min. Routine patient monitoring included noninvasive arterial pressure, electrocardiogram, and oxygen saturation. The concentrations of inspired and expired volatile anesthetics and carbon dioxide were monitored by an anesthetic gas monitor (Colin BP-508 type S, Nippon Colin, Tokyo, Japan).

The patients were studied in the supine position, and aspiration of gastric fluids was not performed. After the exact position of the catheter had been confirmed and the end-tidal concentration of sevoflurane or enflurane had reached less than 0.1%, sevoflurane or enflurane was administered at 0.5, 1.0, 1.5, 2.0, and 2.5 minimum alveolar concentrations (MAC) for 5 min at each concentration without surgical stimulation. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) at each MAC were recorded. In a preliminary study, we observed that the pressure of these sites in children reached a constant level within 1 min when inspired anesthetic gas was cumulatively added. Therefore, 5 min for each concentration of anesthetic

gas would be enough to evaluate the treated values. After inhalation of 2.5 MAC of the volatile anesthetic, administration was discontinued again, and we examined whether the values at the LE, LES, and stomach returned to their pretreatment levels, in order to evaluate the effect of time on gastroesophageal smooth muscle. The end-tidal concentration of volatile anesthetics for each MAC in children was determined by previously reported investigations: the concentration of sevoflurane for 1 MAC has been reported by Lerman et al. [8] and that of enflurane by Imamura et al. [9]. The reduction of the MAC of the anesthetic gas by nitrous oxide was reported to be 24% for sevoflurane [8] and 66% for enflurane [10].

The following drugs were used: enflurane (Ethrane, Dainabot, Osaka, Japan) and sevoflurane (Sevofrane, Maruishi Pharmaceutical, Osaka, Japan).

Statistical analysis

One-way repeated-measures analysis of variance was used to test the significance of the difference between each concentration of anesthetic gas for numerical gastrointestinal and blood pressure data and for HR. The Mann-Whitney U test was used to test the significance of the difference between the groups. When anesthetic gas concentration was determined to be a significant factor, Dunnett's post hoc procedure was used to test the significance over each concentration versus control values. A P value <0.05 was considered significant.

Results

The patient characteristics were similar for the two groups (Table 1).

Typical pressure recordings for the LE, LES, and stomach are shown in Fig. 1. The waveform of the LES consists mainly of heartbeat and respiration and shows a wide wavelength, whereas that of the LE is smaller than that of the LES. The waveform of the stomach shows little spontaneous activity and is nearly a straight line because it is not influenced by intrathoracic pressure. In this study intrinsic activity of the LE and LES was observed in two patients during positioning of the catheter. The application of additional muscle relaxant did not affect any of the pressures. In all cases, the pressures returned to their pretreatment values within 10 min when administration of volatile anesthetics was discontinued from 2.5 MAC.

Table 1. Patient characteristics

Characteristic	Sevoflurane group ($N = 7$)	Enflurane group ($N = 7$)
Sex	2 males, 5 females	2 males, 5 females
Age (yr)	9.0 ± 4.0	11.0 ± 3.0
Height (cm)	124.4 ± 17.0	134.3 ± 18.8
Weight (kg)	27.6 ± 12.1	34.9 ± 12.9

Values are expressed as means ± SD.
There were no significant differences between the two groups.

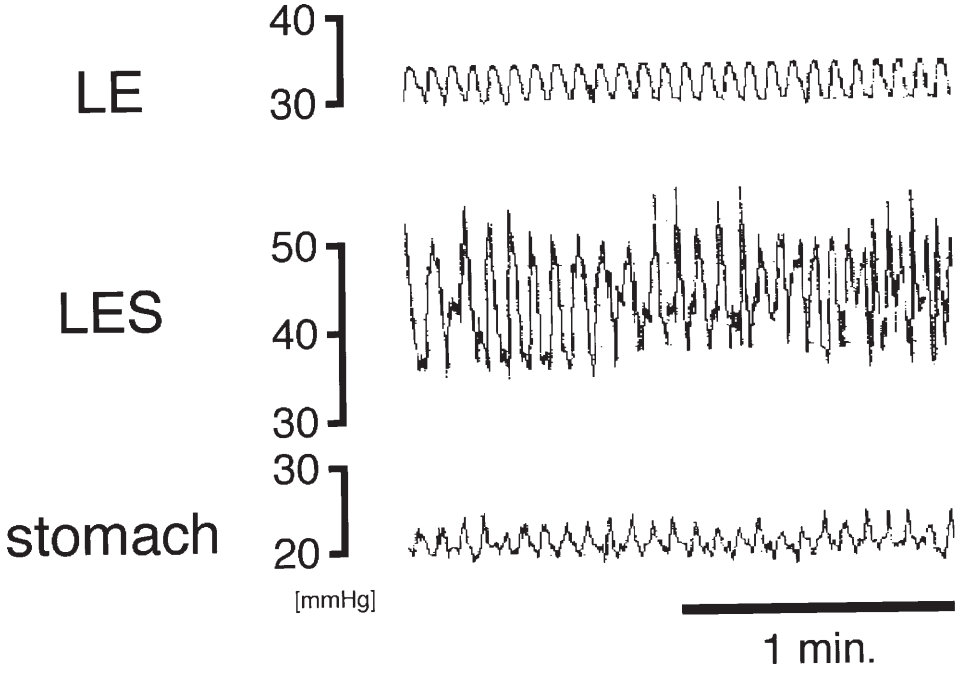

Fig. 1. Typical recordings of the waveform of the lower esophagus (*LE*), lower esophageal sphincter (*LES*), and stomach in a paralyzed and mechanically ventilated child under general anesthesia, confirming the position of the pressure sensors. Because the LE and LES are located in the thorax, they are influenced by mechanical ventilation. *Horizontal bar* indicates 1 min

The resting LES pressures before sevoflurane or enflurane inhalation were 42.9 ± 12.3 mmHg in the S group and 47.6 ± 6.2 mmHg in the E group (mean ± SD), respectively. Application of sevoflurane and enflurane caused a concentration-dependent reduction in resting LES pressure (Fig. 2B), which was significant at 2.0 and 2.5 MAC of sevoflurane and at 2.0 and 2.5 MAC of enflurane. Maximal responses were observed at 2.5 MAC (40.2 ± 12.7 mmHg, 6.4% decrease) for the S group and 2.5 MAC (45.1 ± 7.7 mmHg, 5.3% decrease) for the E group. There were no significant differences in LES pressure between the two groups for each concentration.

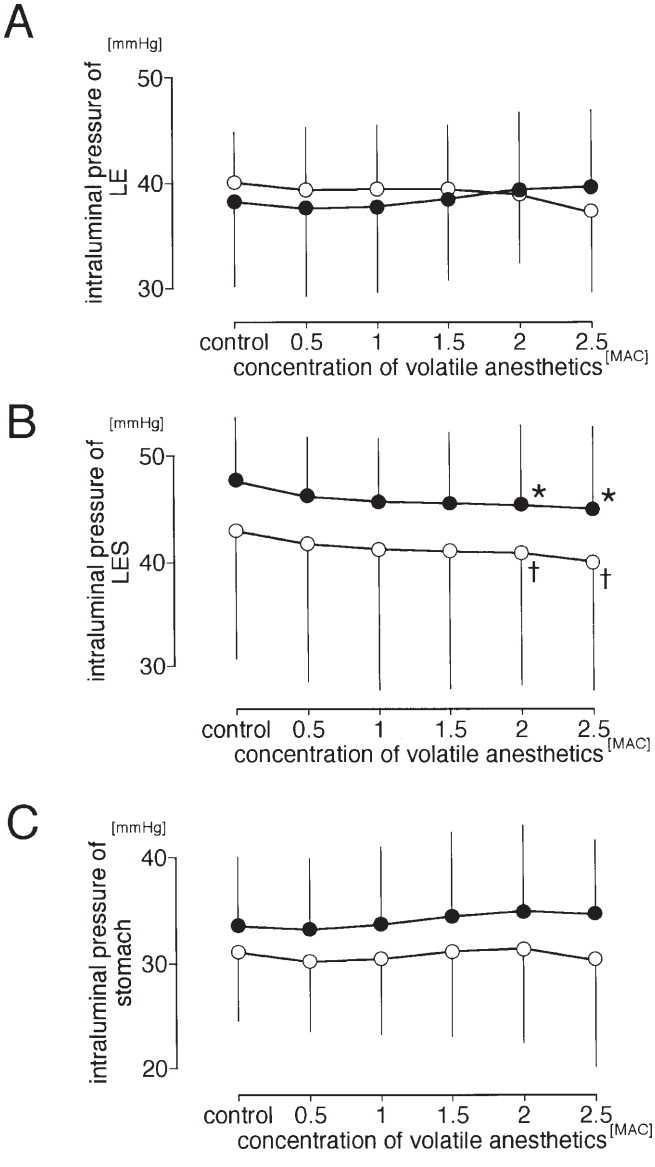

Fig. 2. Concentration–response curves for sevoflurane (*open circles*)- and enflurane (*closed circles*)-induced intraluminal pressure changes in the lower esophagus (*LE*) (**A**), lower esophageal sphincter (*LES*) (**B**), and stomach (**C**) in anesthetized children. Each point represents the mean value from seven patients for each group; *vertical lines* show standard deviations. *Significantly different from the control value of the enflurane group. †Significantly different from the control value of the sevoflurane group

No significant pressure changes were observed in LE pressure and intragastric pressure for either group (Fig. 2A and C).

The changes in BrP at various MAC values of volatile anesthetics are shown in Fig. 3. Concentration-dependent decreases in BrP were observed. The decrease was significant at 2.0 and 2.5 MAC for the E group, but not for the S group. The maximal pressure reductions were observed at 2.0 MAC for the S group (9.5 ± 11.3 mmHg, 19.5% decrease) and 2.5 MAC for the E group (10.4 ± 10.0 mmHg, 26.7% decrease). No significant differences in BrP were found between the two groups.

The changes in LES pressure and BrP for each of the patients in both groups are indicated in Fig. 4A and B. The LES pressure value before application of volatile anesthetics was in the range from 35 to 55 mmHg in most cases, and the value was either decreased or not changed in both groups. The BrP value was in the range from 0 to 30 mmHg before the application of volatile anesthetics, and the value showed either some decrease or no remarkable change in most of the cases for both groups, except for some increase in the S group. In one case, BrP decreased below 0 mmHg after inhalation of 2.5 MAC of enflurane.

The changes in mean SBP, DBP, and HR during examination are indicated in Table 2. There were no significant differences between the two groups for any variable. Mean SBP significantly decreased over 2.0 MAC for both groups. A decrease in mean DBP was observed over 2.5 MAC for the S group and 2.0 MAC for the E group, and an increase in mean HR over 2.0 MAC for the E group. In the S group, a significant increase in mean HR was not observed.

Discussion

The resting LES pressure, which constitutes an important antireflux mechanism, has been reported to be affected by some gastrointestinal disorders, intraabdominal pressure, and exogenous drugs [11], which have been considered possible factors that induce GER [2]. Especially in anesthetic practice, LES malfunction, low LES pressure, unusual body position, and increases in abdominal pressure or gastric contraction resulting from some anesthetics and/or surgical procedures would lead to GER and subsequent events. Among the perioperative drugs, the effects of atropine upon LES pressure in humans [12] and of ketamine upon isolated LES smooth muscle in rabbits [13] have been examined.

However, the effects of volatile anesthetics upon LES pressure or BrP have not been elucidated in animals or humans. In the present study, high concentrations of sevoflurane and enflurane with 66% nitrous oxide in oxygen had an inhibitory effect on the LES, and in addition, those of enflurane decreased BrP. However, even at 2.5 MAC, the decrease in LES pressure was only 2.8 ± 3.2 mmHg in the S group and 2.5 ± 3.1 mmHg in the E group (mean ± SD). In addition, low concentrations of these volatile anesthetics did not induce significant changes in LES pressure and BrP. Therefore, the effects of these anesthetics on gastrointestinal smooth muscle would be unlikely to be the influencing factor on GER during anesthesia.

In a case in this study, BrP decreased below 0 mmHg after inhalation of 2.5 MAC of enflurane. No clinical symptoms of regurgitation were observed in this case. However, the possibility of local GER cannot be excluded, since the pH of the lower esophagus was not measured in this study.

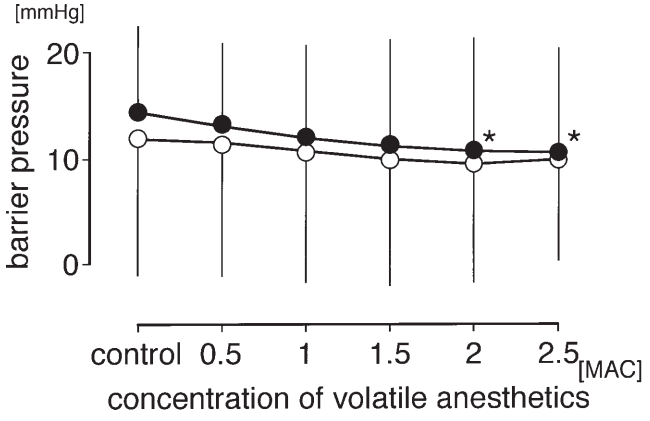

Fig. 3. Concentration-response curves for sevoflurane (*open circles*)- and enflurane (*closed circles*)-induced changes in barrier pressure in anesthetized children. Each point represents the mean value from seven patients for each group; *vertical lines* show standard deviations. *Significantly different from the control value of the enflurane group

We measured upper gastrointestinal pressure under various concentrations of volatile anesthetics, along with 66% nitrous oxide in oxygen. Nitrous oxide would have no effect on upper gastrointestinal pressure, since 50% nitrous oxide has been reported not to influence LES pressure and BrP in healthy adult volunteers [14]. However, the possibility that nitrous oxide may affect upper gastrointestinal pressure in children, or that nitrous oxide may affect it by some interaction of volatile anesthetics, cannot be excluded. If we could place the catheter in awake children who then inhaled volatile anesthetics, the effect of nitrous oxide would be excluded.

LES pressure can be measured by the open-tip method, the slow pull-through method, or the rapid pull-through method [15], which requires continuous saline perfusion. However, these methods require identification of the LES by rapid or slow withdrawal of the catheter and many repetitions of the pull-through movement [5]. Our system can measure the pressure at the LE, LES, and stomach simultaneously, continuously, and directly, without catheter movement. Other investigators have shown that the resting LES pressure was 21.3 ± 9.5 mmHg [12], which is less than our post-treatment values. The LE pressure also appears to be relatively high in our study. The reason for this discrepancy may be partly due to the difference in measuring apparatus and methods, and partly due to positive-pressure ventilation.

When the middle sensor was situated at the LES, the distal sensor had to be in the stomach. However, the position of the proximal sensor might be varied in some cases. The esophageal length, from incisor to LES, has

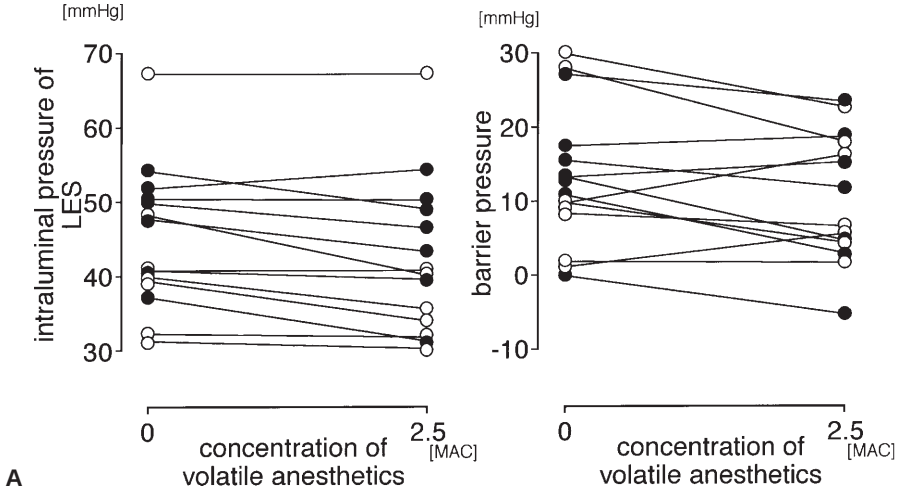

Fig. 4. Schematic representation of the changes in lower esophageal sphincter (*LES*) pressure (**A**) and barrier pressure (**B**) for all patients in the sevoflurane group (*open circles*) and the enflurane group (*closed circles*) before and after the application of 2.5 MAC of each volatile anesthetic

Table 2. Hemodynamic variables during examination

Variable	Group	Control	Minimum alveolar concentration				
			0.5	1.0	1.5	2.0	2.5
Mean SBP	S	111 ± 7	112 ± 9	109 ± 11	102 ± 10	95 ± 5*	92 ± 5*
	E	117 ± 12	114 ± 10	111 ± 9	106 ± 9	98 ± 12*	92 ± 8*
Mean DBP	S	61 ± 9	66 ± 12	58 ± 11	55 ± 12	49 ± 6	46 ± 5*
	E	62 ± 5	59 ± 6	58 ± 8	55 ± 9	53 ± 8*	48 ± 6*
Mean HR	S	88 ± 13	81 ± 12	86 ± 15	87 ± 18	92 ± 17	99 ± 19
	E	72 ± 15	77 ± 17	78 ± 15	82 ± 16	94 ± 23*	106 ± 19*

Values are expressed as means ± SD.
SBP, Systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; S, sevoflurane; E, enflurane.
*Significantly different from control values of each group for each variable.
There were no significant differences between the two groups for any variable.

been shown to have a good correlation with height in children [16]. If we convert height into esophageal length according to this literature, esophageal length distributes from about 28 cm to 44 cm in our study. Therefore, in children whose heights are low, the relative position of the proximal sensor would be nearer to the mid-esophagus. However, as the manometric findings of the esophageal body did not show pressure gradients except the upper esophageal sphincter (UES) and LES, our experimental data from the LE would be reasonably assessed.

The mean SBP and DBP decreased with more than 2.0 MAC of volatile anesthetics, and HR increased with more than 1.0 MAC in the E group. The effect of changes in these circulatory factors on upper gastrointestinal pressure have not been elucidated. Decreases in SBP and DBP were due to the direct vasodilating effect of volatile anesthetics, and increase in HR was due to the decrease in peripheral vascular resistance. The relation between circulatory change and decrease in LES pressure was not fully demonstrated in this study.

Pediatric patients are considered to be more vulnerable to regurgitation for many reasons [17], and a relatively high incidence of aspiration during general anesthesia has been reported [18]. Since incomplete LES function may be one of the reasons for this, we selected pediatric patients for our clinical investigation. Incomplete LES function is attributed to decreased muscle mass and to undeveloped function of intrinsic sphincteric mechanisms, such as reduced LES muscle responsiveness to gastrin, which has been known to contract the LES [19]. These functions and responses improve as the muscle matures [11]. It is not known whether the LES in adults has the same response to volatile anesthetics as in children.

We examined the volatile anesthetics sevoflurane and enflurane. Sevoflurane has been established as an appropriate drug for pediatric anesthesia [20], and recent studies have demonstrated the MAC of sevoflurane for pediatric patients [8,21]. Anesthetics other than sevoflurane must be chosen to compare with sevoflurane in order to determine whether the effects of sevoflurane on the upper gastrointestinal tract in children are specific or nonspecific. Halothane is the most frequently used and best established anesthetic for children and has a different chemical structure from sevoflurane. Therefore, it would be more appropriate than enflurane for our study. However, we could not help but choose enflurane in this study for our institutional reasons.

Sevoflurane and enflurane had almost similar inhibitory patterns on the LES in paralyzed children in this study, and these inhibitory effects appear to be nonspecific. The mechanism of the inhibitory effects of volatile anesthetics, especially on LES smooth muscle, is not clear. However, they would at least act on the enteric nervous system, which covers the circular LES smooth muscle all around, or on smooth muscle itself. The mechanism of action on the enteric nervous system is by decreasing the release of excitatory and inhibitory neurotransmitters, hormones, and/or peptides that are released from the enteric nervous system [19,22]. The mechanism of action on smooth muscle itself concerns intracellular actions. Although volatile anesthetics have been reported to affect the intracellular concentration of Ca^{2+} [23] in airway smooth muscle or second messengers, such as cAMP [23], the effects of volatile anesthetics on gastrointestinal smooth muscle have not been elucidated.

In recent years, a relatively high incidence of regurgitation or reflux episodes associated with the use of the laryngeal mask airway (LMA) has been reported [24], and patients without risk factors for aspiration have been reported to aspirate during anesthesia with LMA [24]. The possible etiology of reflux during anesthesia with LMA has been ascribed to low LES pressure [25] or reflux relaxation of the LES by insertion of the LMA [24]. However, the possibility of associating volatile anesthetic-induced reduction in LES pressure and BrP with the initiation of reflux would be relatively low.

In conclusion, high concentrations of sevoflurane decrease LES pressure, and high concentrations of enflurane decrease both LES pressure and the gastroesophageal pressure gradient in paralyzed and mechanically ventilated children. However, on the basis of the relatively small changes observed even at high concentrations, these inhalation anesthetics are unlikely to be the predominant cause of GER during anesthesia. The integration of the physiological control mechanisms of LES and the structures surrounding the LES, and of the appreciations regarding several clinical experiences or clinical investigations, will enhance our understanding of the nature of regurgitation during anesthesia and the regulation of LES function in humans.

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