

Fentanyl Does Not Reduce the Incidence of Laryngospasm in Children Anesthetized with Sevoflurane

Thomas O. Erb, M.D., M.H.S.,* Britta S. von Ungern-Sternberg, M.D.,† Kathrin Keller, C.R.N.A.,‡ Gary L. Rosner, Sc.D.,§ Damian Craig, M.S., M.H.S.,|| Franz J. Frei, M.D.*

ABSTRACT

Background: The modifying effects of fentanyl on protective airway reflexes have not been characterized in children. The aim of this study was to assess the impact of increasing doses of fentanyl on laryngeal reflex responses in children anesthetized with sevoflurane. The authors hypothesized that the incidence of laryngospasm evoked by laryngeal stimulation is reduced with increasing doses of fentanyl.

Methods: Sixty-three children, aged 2–6 yr, scheduled for elective surgery, were anesthetized with sevoflurane (1 minimum alveolar concentration). By using an established technique, laryngeal and respiratory responses were elicited by spraying distilled water on the laryngeal mucosa: (1) before the administration of fentanyl, (2) after the administration of 1.5 $\mu\text{g}/\text{kg}$ fentanyl, and (3) after the administration of a second dose of 1.5 $\mu\text{g}/\text{kg}$ fentanyl. In 10 children, serving as a time control, three successive laryngeal stimulations were performed without the administration of fentanyl. The responses were assessed by a blinded reviewer.

Results: The study was completed in 60 patients. The incidence of laryngospasm was not reduced when up to two successive doses of 1.5 $\mu\text{g}/\text{kg}$ fentanyl were administered. The incidence of laryngospasm lasting for more than 10 s was 26% before receiving fentanyl, 31% after receiving 1.5 $\mu\text{g}/\text{kg}$ fentanyl, and 18% after receiving a second dose of 1.5 $\mu\text{g}/\text{kg}$ fentanyl ($P = 0.36$ and 0.78 , respectively). This response was similar to that observed in the time control group ($P = 0.21$).

Conclusion: Two successive doses of 1.5 $\mu\text{g}/\text{kg}$ fentanyl did not effectively prevent laryngospasm in children, aged 2–6 yr, anesthetized with sevoflurane.

What We Already Know about This Topic

- ❖ Laryngospasm is more common in children than adults
- ❖ Whether opioids reduce laryngospasm in children has not been studied

What This Article Tells Us That Is New

- ❖ In 63 children anesthetized with sevoflurane, two successive doses of 1.5 $\mu\text{g}/\text{kg}$ fentanyl did not reduce the incidence of laryngospasm from spray of water onto the laryngeal mucosa

* Associate Professor, ‡ Certified Registered Nurse Anesthetist, Department of Anesthesia, University Children's Hospital, Basel, Switzerland. † Clinical Associate Professor, School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia, and Consultant, Department of Anesthesia, Princess Margaret Hospital for Children, Perth, Western Australia, Australia. § Professor, Division of Oncology Biostatistics/Bioinformatics, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University, Baltimore, Maryland. || Statistician, Department of Medicine, Center for Human Genetics, Duke University, Durham, North Carolina.

Received from the Department of Anesthesia, University Children's Hospital, Basel, Switzerland. Submitted for publication February 20, 2009. Accepted for publication February 16, 2010. Supported by the Swiss National Science Foundation (SNSF 3200BO-109322), Bern, Switzerland, and the Department of Anesthesia, University Hospital Basel, Basel, Switzerland. Presented in part at the American Society of Anesthesiologists Annual Meeting, San Francisco, California, October 14, 2007.

Address correspondence to Dr. Erb: Department of Anesthesia, University Children's Hospital, 8 Roemergasse, CH-4058 Basel, Switzerland. thomas.erb@ukbb.ch. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

LARYNGEAL reflexes such as coughing, laryngospasm, expiration reflex, and apnea are important to protect the lower airway from aspiration. However, exaggerated upper airway reflexes, such as prolonged laryngospasm, also have the potential to cause harm due to hypoxemia.¹ Apnea and laryngospasm are both more common and more severe in young children in comparison with other populations^{2,3} and, therefore, have a greater potential to result in hypoxemia.⁴

Overall, little quantitative and qualitative information is available on these reflexes.⁵ A previous study described the laryngeal reflex responses in children anesthetized with sevoflurane.⁶ However, the interaction of opioids on laryngeal and respiratory reflex responses in children anesthetized with sevoflurane has not been explored.⁷ Because fentanyl is a centrally acting agent and because the central respiratory network may be involved in reflex responses,^{8–10} this may potentially result in a dose-related depression of airway reflexes, including laryngospasm.

The purpose of this study was to characterize the fentanyl-induced modification of laryngeal and respiratory reflex responses to laryngeal stimulation in children anesthetized with sevoflurane anesthesia and to determine the existence of a dose-related depression of these airway reflexes. We tested the hypothesis that the incidence of laryngospasm evoked by a laryngeal stimulation is diminished by fentanyl in a dose-related fashion in children during sevoflurane anesthesia.

Materials and Methods

Subjects

This study was approved by the local Ethics Committee (Ethik Kommission beider Basel, Basel, Switzerland). In total, 136 children, aged 2–6 yr and scheduled for elective surgery, were invited to participate. Of these, the parents of 73 children declined their child's participation. However, 63 children were approved for participation by written informed consent supplied by their parent or guardian. Exclusion criteria included clinical evidence of cardiopulmonary disease, cerebral dysfunction, and neuromuscular disease. In addition, children with a history of a respiratory infection in the two preceding weeks, or under medial treatment for bronchial hyperreactivity, or having a positive family history of neuromuscular diseases or malignant hyperthermia were excluded from participation in the study.

Anesthesia and Preparation of the Patients

Preanesthetic medication consisted of 0.3 mg/kg midazolam (maximum 10 mg) given either rectally or orally 10 and 20 min before the induction of anesthesia, respectively. Routine monitoring included electrocardiography, noninvasive blood pressure measurements, capnography, and pulse oximetry. Real-time bispectral index (BIS) data were obtained *via* electroencephalogram electrodes applied in a frontotemporal montage (BIS[®] sensor, Aspect Medical Systems, Natick, MA). The electroencephalogram was recorded using a BISx Power Link[™] (Philips, Böblingen, Germany), and the averaged values were stored using a computerized data recording system.

In all patients, anesthesia was induced with inhalation of 8% sevoflurane in a mixture of 50% nitrous oxide and 50% oxygen *via* face mask. As soon as a peripheral venous access was established, nitrous oxide was discontinued, and the fresh gas flow was set to 6 l/min oxygen applied through a semiclosed anesthetic circuit for the remainder of the study. On achieving a sufficient level of anesthesia (no reaction to the jaw thrust maneuver), a Laryngeal Mask Airway Classic[™] (The Laryngeal Mask Company, Mahe, Seychelles) was inserted. Thereafter, anesthesia was adjusted to achieve an end-tidal fraction of sevoflurane of 2.5%.

The experimental setup has been described previously in detail.⁶ *Via* an elbow connector attached to the Laryngeal Mask Airway Classic[™], end-tidal sevoflurane concentration was continuously measured using a calibrated sidestream gas

monitor (Avance S/5, Datex Ohmeda, Helsinki, Finland). A mainstream capnography adapter (Philips) and a dual-hotwire anemometer (Florian, Acutronic Medical Systems AG, Hirzel, Switzerland) were placed alongside the elbow connector to measure ventilatory airflow and airway pressure next to the anemometer. A fiberoptic endoscope connected to a video camera was passed through the diaphragm of the elbow connector, and the tip of the bronchoscope was positioned to allow for visualization of the laryngeal aperture. All data including video images were stored simultaneously in digital format using Labview (version 7.1, National Instruments, Austin, TX), customized in our laboratory.

Laryngeal Stimulation

An epidural catheter (G20) was advanced through the suction channel of the endoscope, and the tip of the catheter was placed above the glottic level. Airway reflexes were elicited by spraying 0.2 ml distilled water through the catheter onto the laryngeal mucosa surrounding the vocal cords. The respiratory responses and the endoscopic images were continuously registered before, during, and after the stimulation for a total of 4 min.

Experimental Procedures

An experienced pediatric anesthesiologist (T.O.E.) performed all studies in collaboration with research staff before the start of surgical intervention. In addition, a pediatric anesthesiologist independent of the study team was responsible for the monitoring of the patient.

In 53 patients, the larynx of each patient was stimulated on three consecutive occasions: (1) under baseline conditions during sevoflurane anesthesia, (2) after the intravenous administration of a 1.5 $\mu\text{g}/\text{kg}$ bolus of fentanyl, and (3) after the administration of a second dose of 1.5 $\mu\text{g}/\text{kg}$ bolus of fentanyl. The fentanyl was diluted with 0.9% NaCl, such that a bolus of 5 ml contained 1.5 $\mu\text{g}/\text{kg}$ fentanyl. A prefilled infusion pump (Asena[®]PK, Alaris Medical Systems, Basingstoke, United Kingdom) was programmed to administer the bolus over 60 s. The bolus administration was started after completion of the data registration (lasting 240 s) of the previous stimulation. Laryngeal stimulations were always performed exactly 5 min after completion of the bolus administration. Thus, this course separated each of the laryngeal stimulations by 10 min and resulted in a gap of 10 min between the two fentanyl administrations.

In 10 children, three successive laryngeal stimulations were completed during sevoflurane anesthesia without the administration of fentanyl and followed the same time course as the children receiving fentanyl boluses. This group of children (the saline group) served as a time control and was examined after the completion of the fentanyl group.

All patients were breathing spontaneously during the entire study. However, if fentanyl induced excessive respiratory depression (respiratory rate <6 breaths/min or

end-tidal $\text{PCO}_2 > 60$ mmHg), the patient's ventilation was assisted manually. To ensure similar stimulation conditions, assisted ventilation was always stopped at least 10 s before the stimulation was performed under zero end-expiratory pressure.

Safety measures included a laryngospasm rescue protocol. In the case of a complete closure of the glottis (as assessed from online video images) that exceeded 10 s, jaw thrust and continuous positive airway pressure 10 cm H_2O were applied.^{11,12} If this measure did not relieve laryngospasm and saturation according to the pulse oximetry dropped to less than or equal to 90%, 1 mg/kg succinylcholine and 0.01 mg/kg atropine were administered intravenously.

Respiratory Parameter Analyses

Respiratory responses elicited by the laryngeal stimulation were classified into the following categories that were adapted from previous descriptions^{6,7}: (1) laryngospasm, defined as a complete closure of the glottis on the video images and cessation of airflow lasting more than 10 s; (2) central apnea, defined as a apnea without complete closure of the glottis lasting more than 10 s; (3) cough reflex, defined as a forceful expiration with previous inspiration; (4) expiration reflex, defined as a forceful expiration without a preceding inspiration; and (5) spasmodic panting, defined as a rapid, shallow breathing (respiratory frequency > 60 breaths/min) lasting more than 10 s. Furthermore, the time interval between the stimulation of the laryngeal mucosa and reestablishment of a stable breathing pattern was measured to evaluate the duration of respiratory reflex responses.¹³ All events that occurred within 3 min after laryngeal stimulation were evaluated. All analyses were performed offline, and all data containing video sequences were clipped and presented in random order to a blinded reviewer.

Statistical Analysis

This study was designed to detect the advantages of additional administration of fentanyl compared with pure sevoflurane anesthesia. The primary analyses compared the risk of laryngospasm with fentanyl to the baseline risk (before the administration of fentanyl) for each of the two fentanyl administrations. Because these data were paired within each child, the method of analysis was a McNemar test. Assuming a power of 80%, paired data from 50 patients were required to detect a difference in proportions of 0.2 when the proportion of discordant pairs was expected to be 0.23 and the level of significance was 0.025 (0.05 divided by 2 to adjust for two dose-specific analyses). Computation was performed using nQuery Advisor 4.0 (Statistical Solutions Ltd., Cork, Ireland). Because of nonadherence to the protocol (*e.g.*, Laryngeal Mask Airway ClassicTM could not be placed to provide full view of the glottic opening, or failure of data registration or storage), expected in 6% of the subjects, three additional patients were included.

Dichotomous parameters were compared between the fentanyl and the saline group using Fisher exact test. For

Table 1. Demographic Data (n = 63)

Age, mo	50 (37, 68)
Sex	
Male	43
Female	20
Height, cm	104 (95, 114)
Weight, kg	17 (14.5, 21)
ASA status, n	
I	57
II	6
Presence of household smokers, n	13

Data are presented as medians (25th, 75th percentile).

ASA = American Society of Anesthesiologists.

these comparisons, we categorized each child according to the occurrence of the response to the stimulus at each of the three occasions. These response pattern categories correspond to the eight possibilities, ranging from no occurrence on any occasion to the occurrence on each of the three occasions. The demographic and procedural data were analyzed for normal distribution by the Shapiro–Wilk test. Data are reported as mean \pm SD or median (interquartile range). Repeated measurements of continuous variables were analyzed with a two-factor ANOVA using PROC MIXED procedures in SAS software version 9.1 (SAS Institute, Cary, NC). We also fit a logistic regression model to characterize the risk of laryngospasm as a function of the fentanyl doses. The model accounted for the multiple measurements per patient by including patient-specific random effects, allowing each patient to have his or her own underlying risks.¹⁴ Furthermore, the statistical model considered the random patient-specific model parameters to follow a normal distribution *via* a hierarchical Bayesian model and included imputation to account for any missing values. The model also adjusted for the effect of covariates, such as BIS, carbon dioxide, and requirement of assisted manual ventilation after the administration of fentanyl. The model was fit with the program WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge and Imperial School of Medicine, London, United Kingdom). *P* values less than 0.05 were considered statistically significant except for the analyses with McNemar's test, as stated previously.

Results

Sixty-three healthy children, aged 2–6 yr, scheduled to undergo elective surgery or dental procedures during general anesthesia, were included in the study. Participants were predominantly male, and their demographic data are shown in table 1.

In two children, laryngeal stimulations were not performed. In one of them, the laryngeal aperture was not adequately visible despite repeated placements of the Laryngeal Mask Airway ClassicTM. In the second patient, laryngospasm occurred during the induction of anesthesia. In one additional patient, analysis could not be performed because of the failures of the data storage system.

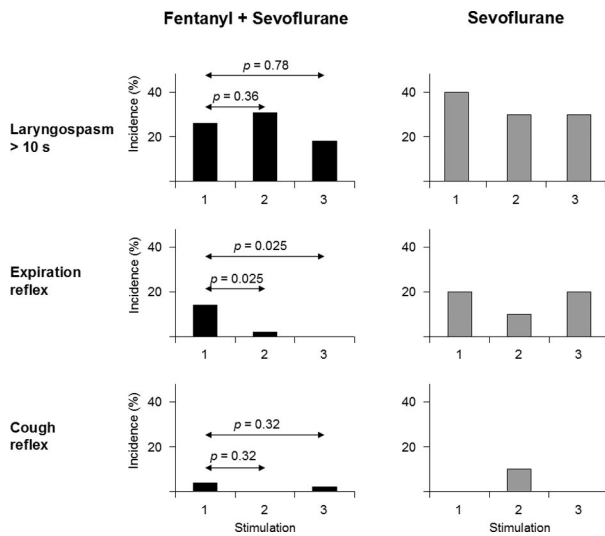


Fig. 1. Laryngeal and respiratory responses to laryngeal stimulation in children anesthetized with sevoflurane (1 minimum alveolar concentration). Stimulation 1: baseline (fentanyl group, $n = 50$; saline group, $n = 10$). Stimulation 2: after application of one dose of $1.5 \mu\text{g}/\text{kg}$ fentanyl ($n = 49$) or saline ($n = 10$). Stimulation 3: after application of two doses of $1.5 \mu\text{g}/\text{kg}$ fentanyl ($n = 45$) or saline ($n = 10$).

This resulted in a total of 60 patients. Laryngeal stimulations could be performed according to the protocol in all 10 patients of the saline group and in 45 of 50 patients receiving fentanyl. In one patient, the study had to be stopped after the baseline stimulation, and in four patients, the study had to be stopped after the stimulation of one dose of fentanyl. Prolonged laryngospasms, which were all resolved immediately after administration of succinylcholine, were observed in each of these five patients. Succinylcholine did not have to be administered on any occasion after the second dose of fentanyl and in none of the children undergoing repeated stimulation without fentanyl.

Figure 1 summarizes the incidences of laryngospasm, expiration reflex, and cough reflex observed during baseline sevoflurane anesthesia and after the application of the first and second $1.5 \mu\text{g}/\text{kg}$ dose of fentanyl and after repeated stimulation during sevoflurane anesthesia.

After stimulation, the incidence of laryngospasm lasting for more than 10 s was similar before and after the administration of fentanyl (26% [no fentanyl] *vs.* 31% [$1.5 \mu\text{g}/\text{kg}$ fentanyl] *vs.* 18% [2 times $1.5 \mu\text{g}/\text{kg}$ fentanyl] $P = 0.36$ and $P = 0.78$ *vs.* no fentanyl). The response pattern proved to be similar to that observed in the saline group ($P = 0.21$). The logistic regression model including the effect of covariates revealed that the relative risk of laryngospasm after two successive doses of $1.5 \mu\text{g}/\text{kg}$ fentanyl relative to no fentanyl in patients without ventilation was 0.4 (95% prediction interval 0.06–1.38) and in patients with ventilation 0.87 (95% prediction interval 0.21–2.26). Furthermore, in case laryngospasm was induced by laryngeal stimulation, the duration was also similar before (48 ± 34 s) and after the first ($42 \pm$

32 s, not significant) and second (40 ± 26 s, not significant) fentanyl dose. Episodes of laryngospasm lasting less than 10 s were observed very rarely under all study conditions. In addition, video analysis revealed that the closure of the glottic aperture was more often visible at the level of the vocal cords rather than at the level of the false cords after the administration of fentanyl, especially after increasing doses.

Expiration reflex, cough reflex, and spasmodic panting were progressively depressed by repeated doses of fentanyl. However, apart from expiration reflex, the incidence of these responses was very low under the conditions of this study (sevoflurane at 2.5%), and only expiration reflex was significantly depressed ($P = 0.04$) compared with the saline group, in contrast to cough reflex and spasmodic panting ($P = 0.33$ and $P = 0.38$, respectively). The incidence of irrigation-induced central apnea was similar in spontaneously breathing patients in both groups ($P = 0.64$).

In the patients breathing spontaneously, the period until the reestablishment of normal breathing after laryngeal stimulation was similar before (40 ± 61 s) and after the first (51 ± 63 s, not significant) and second (51 ± 73 s, not significant) administration of fentanyl.

Repeated stimulation during sevoflurane anesthesia resulted in a stable incidence of the various laryngeal and respiratory reflex responses (fig. 1). The concordance of the reflex response laryngospasm was 70% between stimulation 1 and 2 and 100% between stimulation 2 and 3 check.

The characteristics of the respiratory and hemodynamic status and level of hypnosis immediately before stimulation are shown in table 2. The increasing doses of fentanyl resulted in a progressive depression of respiration. In accordance with the protocol, ventilation was assisted in 10 and 34 patients after the first and second $1.5 \mu\text{g}/\text{kg}$ bolus of fentanyl, respectively.

Desaturation (pulse oximetry $\leq 90\%$) after stimulation occurred in one patient before and in four patients after the first administration of $1.5 \mu\text{g}/\text{kg}$ fentanyl. The lowest value registered on pulse oximetry was 75%. On all occasions, the desaturations were short-lasting and were not accompanied by bradycardia.

Discussion

This study showed that the stimulation of the larynx in children, aged 2–6 yr, undergoing sevoflurane anesthesia caused various types of respiratory and laryngeal reflex responses before and after the intravenous administration of fentanyl. In contrast to our hypothesis, the incidence of laryngospasm was not diminished even after the administration of two successive $1.5 \mu\text{g}/\text{kg}$ doses of fentanyl 10 min apart. Nevertheless, spasmodic panting and expiration reflexes were depressed.

The current findings were similar to those obtained by Oberer *et al.*⁶ in a previous study, which revealed laryngospasm and central apnea as the most frequently occurring responses to laryngeal stimulation in children anesthetized with sevoflurane. The major findings of this current study,

Table 2. Conditions Immediately before Laryngeal Stimulation in Patients Anesthetized with Sevoflurane and Receiving Fentanyl or Saline

	Group	Stimulation 1	Stimulation 2	Stimulation 3	P Value	P Value	P Value
					Group (Fentanyl vs. Saline)	Stimulations	Interaction (Group× Stimulation)
RR, breaths/min	Fentanyl	31.6 ± 6.5	16.1 ± 10.8	12.9 ± 9.2	<0.0001	<0.0001	<0.0001
	Saline	32.9 ± 7.3	32.7 ± 7.1	32.7 ± 7.1			
V _E , ml · kg ⁻¹ · min ⁻¹	Fentanyl	151 ± 32	67 ± 32	69 ± 26	<0.0001	<0.0001	<0.0001
	Saline	160 ± 31	156 ± 30	156 ± 29			
ETCO ₂ , mmHg	Fentanyl	43.1 ± 4.8	50.0 ± 5.9	57.0 ± 9.5	0.0021	<0.0001	<0.0001
	Saline	42.0 ± 5.6	44.0 ± 4.8	44.7 ± 5.3			
SpO ₂ , %	Fentanyl	99.9 ± 0.5	99.9 ± 0.4	99.9 ± 0.2	0.64	0.22	0.45
	Saline	99.8 ± 0.6	100	100			
HR, beats/min	Fentanyl	111 ± 13	104 ± 16	98 ± 14	0.58	<0.0001	0.0008
	Saline	108 ± 11	107 ± 11	107 ± 11			
MAP, mmHg	Fentanyl	51.8 ± 6.6	47.2 ± 5.8	46.7 ± 6.2	0.054	<0.0001	0.58
	Saline	55.2 ± 4.3	51.7 ± 4.4	49.8 ± 4.1			
BIS	Fentanyl	43.1 ± 9.7	49.5 ± 10.8	48.9 ± 10.3	0.026	0.39	<0.0001
	Saline	43.5 ± 6.2	39.4 ± 5.8	36.8 ± 5.7			
ET _{Sevo} , vol%	Fentanyl	2.5 ± 0.1	2.43 ± 0.1	2.43 ± 0.1	0.07	0.20	0.0027
	Saline	2.48 ± 0.1	2.5 ± 0.1	2.51 ± 0.1			

BIS = bispectral index score; ETCO₂ = end-tidal carbon dioxide; ET_{Sevo} = end-tidal sevoflurane; HR = heart rate; MAP = mean arterial pressure; RR = respiratory rate; SpO₂ = pulse oximeter peripheral oxygen saturation; V_E = minute ventilation.

that the administration of fentanyl depressed expiration reflexes and spasmodic panting in a dose-dependent fashion while laryngospasm with apnea appeared much less susceptible, are in line with the results reported by Tagaito *et al.*,⁷ who examined the effect of increasing doses of fentanyl in women anesthetized with propofol. Nonetheless, this does not exclude that the combination of fentanyl with other anesthetic agents, the combination of sevoflurane with other opioids, or the administration of higher doses of fentanyl may not result in different outcomes. Furthermore, the effects might be different if the total dose of 3 µg/kg fentanyl administered in the current study had been given in a single bolus rather than two separated doses of 1.5 µg/kg.

The central mechanisms responsible for respiratory and laryngeal reflex responses are unclear.^{9,10} Nonetheless, it is generally accepted that opioids, such as fentanyl, act *via* functional components of the central respiratory network.¹⁵ Furthermore, differences in the pathways of laryngeal and tracheobronchial induced coughing have been suggested.⁸ This is based on the observation that opioids were less depressant when coughing was induced by a laryngeal or upper airway disorder compared with coughing originating from the lower airways.¹⁵ Thus, our finding that reflexes originating from the larynx are difficult to modify with opioids is consistent with observations obtained in nonanesthetized patients.¹⁵ In contrast, several studies and reports document the effects of opioids on laryngeal function in both adults and children. Interestingly, the administration of various opioids such as fentanyl,¹⁶ sufentanil,¹⁷ and remifentanil¹⁸ induced laryngospasm or closure of the vocal cords. This resulted in difficulties in maintaining adequate oxygenation and in document-

ing that opioid administration might have detrimental effects on laryngeal patency.

Alteration of reflex responses might also be induced by secondary effects of opioids such as a decrease in ventilatory drive resulting in an increase of carbon dioxide. Interestingly, an increase in end-tidal carbon dioxide diminished respiratory reflexes in patients anesthetized with enflurane¹⁹ in response to tracheal stimulation. In addition, experimental work in animals showed that laryngeal responsiveness also diminishes with an increase in carbon dioxide.²⁰ Overall, this suggests that the observed lack of effect on laryngospasm observed in our study, in the presence of increased end-tidal CO₂, might be attributed to a direct counteracting effect of the drug on reflex regulation.

Interestingly, at the time of laryngeal stimulation, the recorded BIS values were higher (5 min after the administration of bolus(es) of fentanyl). This remains unexplained because alterations of the concentration of carbon dioxide²¹ and administration of opioids²² were shown to have no systematic effect on BIS recordings.

A model using laryngeal stimulation, as developed in adults by Nishino and coworkers⁷ and adapted to the pediatric setting, was applied as in previous studies.^{6,23} This allowed for a comprehensive characterization of these clinically relevant, although seldomly examined, respiratory and laryngeal reflex responses⁵ under consistent and safe examination conditions.

For safety reasons, the ventilation of some children was assisted in accordance with the study protocol. This was progressively more necessary with increasing doses of fentanyl and potentially created a bias of unknown effect in the assessment conditions. However, laryngeal stimulations were al-

ways performed under similar conditions. The use of a Laryngeal Mask Airway Classic™ is a further limitation of this model. Previous work speculated that the insertion of a Laryngeal Mask Airway Classic™ might result in immeasurable minor injuries, including edema of the receptors at the peripheral site, thus, affecting the afferent reflex arc.¹³ In fact, defensive reflexes were depressed over time with the Laryngeal Mask Airway Classic™ *in situ*.¹³ In our model, however, measurements were performed immediately after the induction of anesthesia. Moreover, this potential time effect should have favored dampening of the laryngospasm reflex, which did not occur and, thus, did not invalidate the core finding of the current study.

Furthermore, the administration of midazolam as a pre-anesthetic medication could have modified the results of this study. Midazolam alone or through its interactions with the study drugs might modify respiratory reflex responses to an unknown extent. However, its use as a preanesthetic medication is very common and still represents the current standard of practice in many institutions.

Performance of repeated stimulations in each subject might cause a bias. The stability of the current model over time was, therefore, examined in a parallel group of children, the saline group, during constant sevoflurane anesthesia without fentanyl administration. The small number of patients recruited and the fact that these children were consecutively examined after completion of the fentanyl group limit the general validity of comparisons between the two groups. However, the observed laryngeal and respiratory reflex responses were remarkably steady in successive stimulations. Furthermore, these results are in line with the work of Tagaito *et al.*,⁷ showing no significant differences in the incidence of respiratory and laryngeal reflex responses that could be attributed to repeated stimulation procedures.

When applying models, assessments should be based on definitions that are of potential relevance for the population under investigation. In children, the normal range of respiratory rates differs from those of adults. This implies that the time of cessation of breathing might differ and that apnea of shorter duration may be relevant (*e.g.*, in children with obstructive sleep apnea, apnea >5 s are considered relevant compared with >10 s in adults²⁴). However, analyses of the data in the current study revealed that there were very few events lasting 5–10 s. Therefore, episodes lasting for more than 10 s, the definition applied in most studies, were used.

Recent data document that exaggerated laryngeal or respiratory reflexes leading to laryngospasm and breath holding still represent significant complications, which potentially lead to cardiac arrest in children undergoing anesthesia.⁴ Although sevoflurane obtunds pharyngeal and laryngeal reflexes,²⁵ an aspect that partially accounts for its widespread use for induction of anesthesia in pediatric patients, defensive laryngeal reflexes, especially laryngospasm, may occur in this situation. With the aim to further prevent

laryngeal reflexes, it is common practice to administer fentanyl before manipulating the airways.

In general, it is argued that the prevention of complications is the best treatment approach. Therefore, reducing the incidence of laryngeal reflexes will potentially enhance the safety of children undergoing anesthesia. The current study details that although fentanyl generally obtunds respiratory reflexes in a dose-related fashion, the incidence of laryngospasm remains high.

We found that laryngeal defensive reflexes occur in children anesthetized with sevoflurane before and after the intravenous administration of fentanyl. Although the administration of up to two successive doses of 1.5 µg/kg fentanyl modified airway reflexes considerably, it does not effectively suppress laryngospasm in a clinical model of laryngeal stimulation.

The authors thank all the children and their families who participated in this study, and Allison Dwileski, B.S. (Secretary, Department of Anesthesia, University Hospital Basel, Basel, Switzerland), for her expert help with manuscript preparation.

References

1. Fink BR: The etiology and treatment of laryngeal spasm. *ANESTHESIOLOGY* 1956; 17:569–77
2. Olsson GL, Hallen B: Laryngospasm during anaesthesia. A computer-aided incidence study in 136,929 patients. *Acta Anaesthesiol Scand* 1984; 28:567–75
3. Morray JP, Geiduschek JM, Caplan RA, Posner KL, Gild WM, Cheney FW: A comparison of pediatric and adult anesthesia closed malpractice claims. *ANESTHESIOLOGY* 1993; 78:461–7
4. Bhananker SM, Ramamoorthy C, Geiduschek JM, Posner KL, Domino KB, Haberkern CM, Campos JS, Morray JP: Anesthesia-related cardiac arrest in children: Update from the Pediatric Perioperative Cardiac Arrest Registry. *Anesth Analg* 2007; 105:344–50
5. Warner DO: Laryngeal reflexes. *ANESTHESIOLOGY* 1998; 88:1433–4
6. Oberer C, von Ungern-Sternberg BS, Frei FJ, Erb TO: Respiratory reflex responses of the larynx differ between sevoflurane and propofol in pediatric patients. *ANESTHESIOLOGY* 2005; 103:1142–8
7. Tagaito Y, Isono S, Nishino T: Upper airway reflexes during a combination of propofol and fentanyl anesthesia. *ANESTHESIOLOGY* 1998; 88:1459–66
8. Bolser DC, Davenport PW: Functional organization of the central cough generation mechanism. *Pulm Pharmacol Ther* 2002; 15:221–5
9. Bolser DC, Poliacek I, Jakus J, Fuller DD, Davenport PW: Neurogenesis of cough, other airway defensive behaviors and breathing: A holoarchival system? *Respir Physiol Neurobiol* 2006; 152:255–65
10. Shannon R, Baekey DM, Morris KF, Lindsey BG: Brainstem respiratory networks and cough. *Pulm Pharmacol* 1996; 9:343–7
11. Roy WL, Lerman J: Laryngospasm in paediatric anaesthesia. *Can J Anaesth* 1988; 35:93–8
12. Wheeler M, Coté CJ, Todres DI: Pediatric airway, A Practice of Anesthesia for Infants and Children, 3rd edition. Edited by Coté CJ, Todre DI, Ryan JF, Goudsouzian NG. Philadelphia, W.B. Saunders Company, 2001, pp 79–113
13. Tanaka A, Isono S, Ishikawa T, Nishino T: Laryngeal reflex before and after placement of airway interventions: Endo-

- tracheal tube and laryngeal mask airway. *ANESTHESIOLOGY* 2005; 102:20-5
14. Davidian M, Giltinan DM: *Nonlinear Models for Repeated Measurement Data*. Edited by Giltinan DM. London, Chapman and Hall, 1995, pp 97-150
 15. Bolser DC: Current and future centrally acting antitussives. *Respir Physiol Neurobiol* 2006; 152:349-55
 16. Fahnenstich H, Steffan J, Kau N, Bartmann P: Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med* 2000; 28:836-9
 17. Bennett JA, Abrams JT, Van Riper DF, Horrow JC: Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. *ANESTHESIOLOGY* 1997; 87:1070-4
 18. Kohno T, Ikoma M: [Sudden vocal cord closure during general anesthesia using remifentanil]. *Masui* 2008; 57: 1213-7
 19. Nishino T, Hiraga K, Honda Y: Inhibitory effects of CO₂ on airway defensive reflexes in enflurane-anesthetized humans. *J Appl Physiol* 1989; 66:2642-6
 20. Nishino T, Yonezawa T, Honda Y: Modification of laryngospasm in response to changes in PaCO₂ and PaO₂ in the cat. *ANESTHESIOLOGY* 1981; 55:286-91
 21. Turnbull D, Furlonger A, Andrzejowski J: The influence of changes in end-tidal carbon dioxide upon the Bispectral Index. *Anaesthesia* 2008; 63:458-62
 22. Olofsen E, Sleight JW, Dahan A: The influence of remifentanil on the dynamic relationship between sevoflurane and surrogate anesthetic effect measures derived from the EEG. *ANESTHESIOLOGY* 2002; 96:555-64
 23. Ishikawa T, Isono S, Tanaka A, Tagaito Y, Nishino T: Airway protective reflexes evoked by laryngeal instillation of distilled water under sevoflurane general anesthesia in children. *Anesth Analg* 2005; 101:1615-8
 24. Rosen CL, D'Andrea L, Haddad GG: Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. *Am Rev Respir Dis* 1992; 146:1231-4
 25. Doi M, Ikeda K: Airway irritation produced by volatile anaesthetics during brief inhalation: Comparison of halothane, enflurane, isoflurane and sevoflurane. *Can J Anesth* 1993; 40:122-6