

# The Effect of Sevoflurane and Desflurane on Upper Airway Reactivity

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**Background:** Although bronchial reactivity can be assessed by changes in airway resistance, there is no well-accepted measure of upper airway reactivity during anesthesia. The authors used the stimulus of endotracheal tube cuff inflation and deflation to assess changes in airway reactivity in patients anesthetized with sevoflurane and desflurane.

**Methods:** Sixty-four patients classified as American Society of Anesthesiologists physical status I or II participated in this randomized, double-blind study. Patients were anesthetized with either sevoflurane or desflurane at 1.0 and 1.8 minimum alveolar concentration (MAC). The trachea was stimulated by inflating the endotracheal tube cuff. A blinded observer assessed the severity of patient response to the stimulus and changes in hemodynamic variables. The process was repeated at the second MAC treatment condition.

**Results:** At 1.0 MAC, patients anesthetized with desflurane had a more intense response and a greater likelihood of significant coughing and associated hemodynamic changes (both at  $P < 0.05$ ). At 1.8 MAC, sevoflurane and desflurane both suppressed clinically significant responses to tracheal stimulation. Interrater reliability was excellent for this measure of upper airway reactivity ( $P < 0.001$ ).

**Conclusions:** The assessment of the cough response to tracheal stimulation by endotracheal tube cuff inflation is a reliable and clinically meaningful measure of upper airway reactivity. At 1.0 MAC, sevoflurane is superior to desflurane for suppressing moderate and severe responses to this stimulus.

MOST anesthesiologists recognize the concept of increased upper airway reactivity. In anesthetized patients, increased upper airway reactivity manifests in two ways: a greater likelihood that a patient will cough (or "buck") during anesthesia or an increased intensity of coughing when the cough reflex is initiated. Unlike bronchoconstriction, which manifests as increased airway resistance, there is no well-defined method to quantify this upper airway reactivity that results in coughing.

We used a simple clinical maneuver to assess upper airway reactivity after administration of two inhaled anesthetics: sevoflurane and desflurane. We investigated the effect of anesthetic agent and depth on the incidence and severity of the cough response after tracheal stimulation.

We performed a double-blind, randomized study with 64 patients to whom either sevoflurane or desflurane anesthesia was administered at 1.0 and 1.8 minimum alveolar concentration (MAC). We tested the hypothesis that responses to the maneuvers of cuff inflation and deflation would depend on anesthetic depth and agent.

## Materials and Methods

### Subjects

After approval from the Institutional Review Board (Division of Biological Sciences, University of Chicago, Pritzker School of Medicine, Chicago, IL) and written informed consent from subjects, 64 patients (American Society of Anesthesiologists physical status I or II), aged 18-65 yr, who were scheduled to undergo elective surgical procedures during general anesthesia were enrolled in the study. Exclusion criteria included history of asthma, renal insufficiency, hiatal hernia, gastroesophageal reflux disease, diabetes mellitus, morbid obesity, and requirement for rapid-sequence induction of general anesthesia. Initially, smokers were included in the study. After an interim analysis, we decided to remove smokers from the study and exclude smokers from further recruitment.

Patients were assigned to one of four experimental groups (described in table 1) by means of sequentially numbered, sealed envelopes. Midazolam, 0-2 mg, was administered to patients before induction of the anesthetic. To minimize confounding by antitussive agents, lidocaine, fentanyl, or any other opioid was not administered to patients until the experimental portion of the anesthetic was completed.

In the operating room, standard monitoring devices and a nerve stimulator were applied, and baseline vital signs were recorded. Oxygen was administered *via* face mask, and general anesthesia was induced with an initial dose of 3-5 mg/kg thiopental. The attending anesthesiologist was allowed to administer up to an additional 1 mg/kg thiopental before intubation if the patient seemed to be lightly anesthetized. To facilitate intubation of the trachea, 1-1.5 mg/kg succinylcholine was administered. To minimize gas leaking around the endotracheal tube before the cuff was inflated, an 8.0-mm ID tube was used for women, and a 9.0-mm ID tube was used for men. After intubation, the cuff was not inflated, and the patient underwent ventilation with oxygen and either sevoflurane or desflurane.

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**Table 1. Assignment of Anesthetic Agent and Sequence of Anesthetic Dose**

Group No.	Anesthetic Agent	Condition 1 [MAC (%)]	Condition 2 [MAC (%)]
1	Sevoflurane	1.0 (2.05)	1.8 (3.7)
2	Sevoflurane	1.8 (3.7)	1.0 (2.05)
3	Desflurane	1.0 (6.0)	1.8 (10.8)
4	Desflurane	1.8 (10.8)	1.0 (6.0)

Increasing doses of anesthetic were administered to half of the subjects; decreasing doses were administered to the other half.

MAC = minimum alveolar concentration.

The responses to cuff inflation and deflation were assessed at 1.0 and 1.8 MAC of sevoflurane or desflurane. These values correspond to the ED<sub>50</sub> concentrations of sevoflurane required to prevent movement in patients to whom 4 µg/kg fentanyl has been administered and in patients to whom no opioids have been administered, respectively.<sup>1</sup> To avoid a hysteresis artifact from slight differences in the pharmacokinetic characteristics of blood-brain equilibration, four treatment groups were used. Increasing doses of the anesthetic were administered to one half of the patients, and decreasing doses were administered to the other half (table 1).

Mechanical ventilation was performed with a target exhaled tidal volume of 7–10 ml/kg and a target end-tidal carbon dioxide value of 32–38 mmHg. The first target end-tidal anesthetic concentration (condition 1) was achieved within 1 or 2 min, after which it was maintained continuously within 10% of the target concentration for 6 min. After recovery from the succinylcholine was confirmed with a nerve stimulator applied to the ulnar nerve, the endotracheal tube cuff was inflated with 10 ml air.

The response to tracheal stimulation was assessed by an observer who was blind to the anesthetic agent and treatment condition of the patient. Coughing was graded as none, mild (fewer than four coughs), moderate (four to seven coughs), or severe (more than seven coughs), based on classifications described previously.<sup>2,3</sup> For the purposes of this study, moderate and severe responses were considered significant. When the patient had received at least three respiratory cycles after the coughing had stopped, the cuff was deflated, and the response to deflation was assessed similarly. Thereafter, the new target end-tidal concentration (condition 2) was attained and maintained for another 6 min. The blinded observer then assessed the response to inflation and deflation at this condition. We recorded the unsolicited comments of other operating room personnel regarding patient movement at the time of tracheal stimulation. After data collection was completed, the endotracheal tube cuff was inflated for a final time, and the patient received standard clinical care for the surgical procedure. The observer then asked the anesthesiologist for an assessment of the patient's response to tracheal stimulation.

Physiologic data (heart rate, blood pressure, end-tidal concentrations) were measured every minute and printed from the anesthesia monitor (Datex AS/3; Datex-Ohmeda, Tewksbury, MA). Heart rate increases of more than 10 beats/min and mean arterial pressure increases greater than 20 mmHg were considered significant.

#### Statistical Analysis

Data from subjects to whom sevoflurane or desflurane were administered were pooled to allow the statistical analysis to have sufficient power. SPSS for Macintosh, version 6.1 (SPSS, Chicago, IL), was used for analysis. Analysis of variance and the chi-square test were used to evaluate demographic differences between the treatment groups. Interrater reliability was assessed using the  $\kappa$  statistic. Values of  $\kappa$  greater than 0.85 indicate excellent reliability.<sup>4</sup> The chi-square test and the Mann-Whitney U test were used to evaluate differences in response rates and severity of response between groups. The Student *t* test (for unequal variances) was used to compare slopes of correlation coefficients. The McNemar test of difference in proportions for paired samples was used to determine whether responses to cuff deflation were more frequent than responses to cuff inflation.

#### Results

Patient demographics are given in table 2. No significant differences were observed between groups with respect to patient age, weight, height, gender, American Society of Anesthesiologists physical status, or thiopental dose.

The response to cuff inflation tended to be more severe in those patients anesthetized with 1.0 MAC of desflurane than with 1.0 MAC of sevoflurane ( $P = 0.05$ , fig. 1). When we assessed the ability of 1.0 MAC of the drugs to prevent a moderate or severe response to cuff inflation, we found that sevoflurane prevented such responses in 30 of 32 patients (94%), whereas desflurane suppressed these responses in 24 of 32 patients (75%;  $P < 0.05$ , fig. 1). The operating room staff commented on patient movement in only two of seven mild responses to tracheal stimulation. When mild responses were considered additionally at 1.0 MAC, 5 of 32 patients anesthetized with sevoflurane and 11 of 32 patients anesthetized with desflurane responded to cuff inflation (chi-square test,  $P = 0.08$ ). The difference in overall response rate did not reach statistical significance because three patients anesthetized with each drug had a mild response to cuff inflation, which diluted the difference between the drugs observed for moderate and severe responses.

One subject had a mild coughing response to cuff inflation and deflation while anesthetized with 1.8 MAC of sevoflurane. No subjects anesthetized with 1.8 MAC of desflurane had a response (not significant).

**Table 2. Patient Demographics**

	M, F	Age (yr)	Weight (kg)	Thiopental (mg/kg)	ASA I (n)	Esmolol (n)	Ephedrine (n)
Group 1	6, 10	44 ± 11	79 ± 15	5.1 ± 0.72	6		1
Group 2	6, 10	39 ± 13	75 ± 18	5.3 ± 0.89	7	1	
Group 3	6, 10	47 ± 14	75 ± 12	5.1 ± 0.64	9	2	
Group 4	4, 12	39 ± 13	75 ± 15	5.2 ± 0.72	5	1	

Age, weight, and thiopental dose are reported as mean ± SD. There were no significant differences between groups with respect to age, weight, American Society of Anesthesiologists (ASA) physical status, thiopental dose, or proportion to whom esmolol or ephedrine was administered.

### Hemodynamics

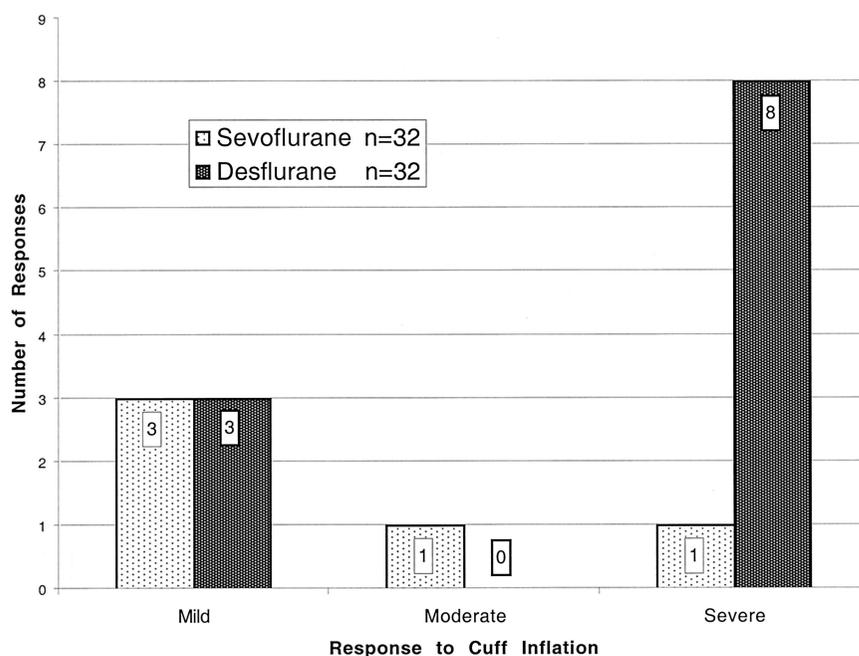
Ephedrine was administered to one patient for hypotension while the patient was anesthetized with 1.8 MAC of sevoflurane. In three patients in the desflurane groups and in one patient in sevoflurane group 2, esmolol was administered (not significant) for tachycardia, which the attending anesthesiologist was compelled to treat. Patients to whom these drugs were administered before tracheal stimulation were excluded from hemodynamic analysis.

At 1.0 MAC, heart rate increased significantly after cuff inflation in 11 of 30 patients in the desflurane groups and in 1 of 31 patients in the sevoflurane groups ( $P < 0.01$ , odds ratio of significant heart rate increase with desflurane = 7.3 [95% confidence interval = 1.11–48.6], fig. 2). Mean arterial pressure increased significantly in six patients anesthetized with desflurane and one patient anesthetized with sevoflurane (Fisher exact test,  $P = 0.05$ , fig. 2). As shown in figure 3, we found that the severity of coughing correlated significantly with increases in heart rate for sevoflurane and desflurane ( $r = 0.38$  for each drug,  $P < 0.05$ ), and increases in mean arterial pressure ( $r = 0.51$  for sevoflurane,  $P < 0.01$ , and  $r = 0.35$  for desflurane,  $P < 0.05$ ). The slope of the

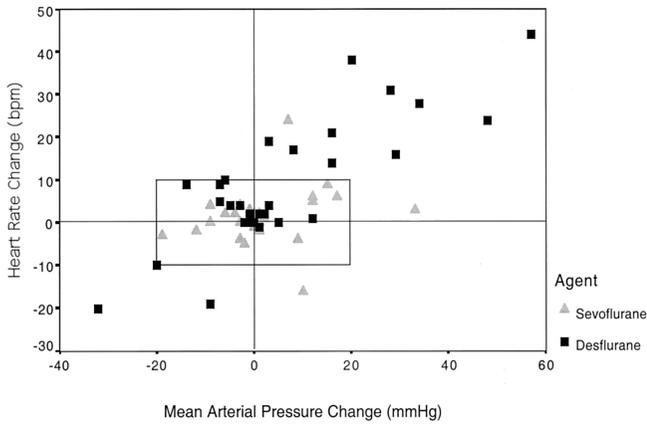
regression curve between severity of coughing and heart rate increase was significantly greater for desflurane than for sevoflurane (coefficient of correlation ± SE of the coefficient was  $4.4 \pm 2.0$  for desflurane and  $2.3 \pm 1.04$  for sevoflurane,  $P < 0.01$ ). One patient anesthetized with desflurane and one anesthetized with sevoflurane responded at 1.8 MAC to cuff inflation with a heart rate increase of more than 10 beats/min.

We were surprised to find that cuff deflation was more likely to produce a response than was cuff inflation. The coughing response to cuff deflation was more vigorous than the response to inflation in seven subjects and was less vigorous in three subjects ( $P < 0.05$ , fig. 4). Significantly more subjects responded to deflation than to inflation (21 of 64 vs. 16 of 64, respectively,  $P < 0.001$ ). When the proportion of moderate and severe responses were addressed, the effect of cuff deflation was even more pronounced; deflation produced 16 of these responses versus only 10 with inflation ( $P < 0.001$ ).

The endotracheal tube was inflated twice and deflated twice in each patient. Therefore, there were 256 inflations and deflations. The blinded observer recorded the response to inflation and deflation and then asked the unblinded anesthesiologist for an assessment. Agree-



**Fig. 1. Responses to cuff inflation during 1-MAC anesthesia with sevoflurane or desflurane. Not shown are the subjects who did not respond to cuff inflation (27 sevoflurane subjects and 21 desflurane subjects).**

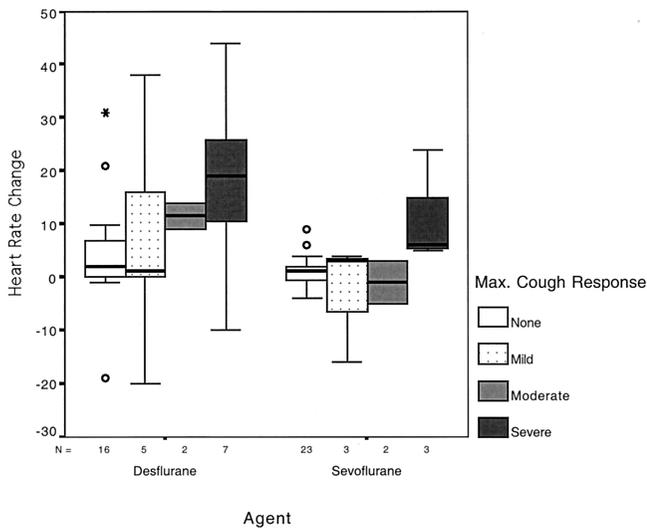


**Fig. 2.** Changes in heart rate (beats/min [bpm]) and changes in mean arterial pressure (mmHg) after tracheal stimulation of patients anesthetized with 1 MAC of sevoflurane or desflurane.

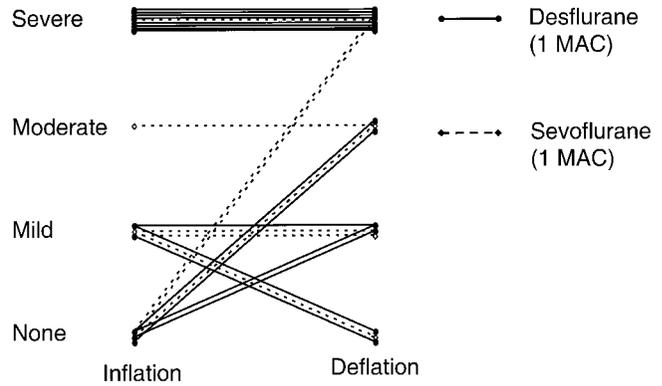
ment was perfect for 255 of 256 assessments ( $\kappa = 0.98$ ,  $P < 0.001$ ). The single discrepancy was the anesthesiologist's rating of mild and the blinded observer's rating of moderate for a response to cuff inflation.

**Discussion**

Cuff inflation and deflation during standardized conditions can be used to assess airway reactivity. We observed excellent interrater reliability for our scoring system. We were able to distinguish upper airway reactivity during anesthesia with two commonly used agents at 1.0 MAC, with sevoflurane being more effective in atten-



**Fig. 3.** Box plot of changes in heart rate (beats/min) versus severity of coughing response after tracheal stimulation at 1 MAC. The format presents the first and third quartiles as the top and bottom of the box, the median as the middle line, and the 90th percentiles as whiskers. Outliers are represented by open circles, and the extreme outlier is represented by an asterisk. A significant correlation was observed between heart rate increases and severity of coughing response.



**Fig. 4.** Responses to cuff inflation and cuff deflation. The response to cuff deflation was more intense than the response to inflation in seven patients and less intense in three patients. All subjects who had a moderate or severe response to inflation had the same response to deflation. Not shown are the 39 subjects who did not respond to inflation or deflation.

uating hemodynamic and coughing responses to tracheal stimulation. We also showed a unique dose-response relation for each drug. The higher 1.8-MAC dose of either drug prevented a significant response to tracheal stimulation.

The physicians who inflated and deflated the cuff and the blinded observer were surprised by how infrequently other staff in the operating room noticed a mild response to tracheal stimulation. Even the surgical resident or nurse preparing the patient for surgery noticed a mild response less than 30% of the time. Patients who coughed enough to have a severe rating usually moved their arms and legs, eliciting comments from the operating room staff. Thus, our grading system (none, mild, moderate, severe) extended beyond the number of coughs; the grades also represent intensity of response. This result supports the classification of moderate and severe responses as being clinically relevant.

Others have evaluated the effect of airway stimulation by sevoflurane and desflurane alone.<sup>5</sup> Desflurane has produced significant rates of coughing, laryngospasm, breath holding,<sup>6</sup> and increases in heart rate and sympathetic nerve activity<sup>7</sup> during inhalation induction. However, whether desflurane is a greater irritant of the airway epithelium or whether sevoflurane better inhibits reflex responses to airway stimulation is difficult to determine. This study differs from others because we used a uniform stimulus to compare the effect of the two agents on airway reflexes. Several studies have evaluated respiratory resistance after intubation as an effect of inhaled anesthetic agent,<sup>8</sup> induction agent,<sup>9</sup> or preanesthetic administration of bronchodilators.<sup>10</sup> Although it is vitally important to prevent bronchospasm in asthmatic patients, the commonly observed mild increase in lower airway resistance observed after intubation usually has no impact on patient treatment. However, patient coughing or "bucking" during critical parts of an anesthetic can result in significant complications. At 1.0 MAC, which is a common

concentration during induction and emergence, patient coughing can be particularly troublesome. We sought to evaluate the utility of using the easily performed intervention of cuff inflation and the easily measured outcome of coughing to measure upper airway reactivity.

The preliminary study design included smokers and nonsmokers. An interim analysis showed that only three current smokers had enrolled. Because the smokers had severe airway reactivity independent of drug or dose and they were not distributed evenly between groups, we excluded these subjects from analysis to prevent confounding and completed the study by accruing a total of 16 nonsmokers in each group. We do not know whether our results can be extrapolated to patients who smoke. The generalized increase in airway reactivity in smokers is not surprising and supports our method as a valid measure of upper airway reactivity.

Although measuring patient coughing or movement that could disrupt surgery was the primary goal, we wondered whether sevoflurane would be superior to desflurane in prevention of other reflex responses to tracheal stimulation. In particular, preventing the hemodynamic sequelae associated with tracheal stimulation might be clinically useful. According to our definition of an increase in heart rate of more than 10 beats/min, sevoflurane was better than desflurane at preventing a significant heart rate response, and a similar trend was observed for blood pressure response.

The hemodynamic effect of endotracheal tube cuff inflation in some patients was surprising. Considering that most anesthesiologists inflate the endotracheal tube cuff immediately after laryngoscopy and intubation, it is difficult to determine which part of the intubation sequence has the greatest hemodynamic effect. Leaving the cuff deflated after intubation until a patient reaches a deep level of anesthesia may be helpful if coughing, tachycardia, or increases in blood pressure are particularly undesirable in that patient. With the large propor-

tion of patients who responded to cuff deflation while anesthetized at 1 MAC, consideration should be given to removing the endotracheal tube at a depth of anesthesia greater than 1 MAC if deep extubation is planned and a cough response is to be avoided.

Our data suggest that the simple maneuver of inflating and deflating the endotracheal tube cuff is a reliable and valid means of assessing upper airway reactivity. We also showed differences in the effect of anesthetic agent and depth of anesthesia on upper airway reactivity. At deep levels of anesthesia, sevoflurane and desflurane both suppress responses to tracheal stimulation. At the lighter level of 1 MAC, sevoflurane was superior to desflurane for suppressing clinically relevant responses to this stimulus.

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