Anesthesiology
1996; 85:737-47

Site(s) Mediating Sympathetic Activation with Desflurane

Michael Muzi, M.D., Thomas J. Ebert, M.D., Ph.D.,† William G. Hope, M.D., Ph.D.,‡ Brian J. Robinson, Ph.D.,§ Leonard B. Bell, Ph.D.‖*

Background: **Three strategies were employed to better define the afferent site(s) at which desflurane initiates its neurocirculatory activation.**

Methods: **Young (aged 19–28 yr) healthy volunteers were employed in three separate studies. Monitoring included electrocardiography, radial artery blood pressure, and direct recordings of sympathetic outflow to skeletal muscle blood vessels by microneurography. In each study, anesthesia was established with 2.5 mg/kg propofol, and in studies 1 and 2 was maintained with 5.4% desflurane *via* a double-lumen tube. In study 1 (n = 7) a double-lumen tube was placed with the bronchial cuff just below the vocal cords to selectively give 14.5% desflurane or 2.4% isoflurane to the upper airway (*via* the tracheal lumen) or lower airway (*via* the bronchial lumen). Study 2 (n = 14) consisted of standard placement of a left side double-lumen tube to selectively increase the inspired desflurane concentration of either right or left lung to 11% while decreasing the inspired concentration in the opposite lung to 0%, thereby maintaining constant systemic concentrations of desflurane (gas chromatography). Study 3 consisted of lidocaine or placebo airway treatment before anesthetic induction and administration of 11% inspired desflurane by mask: group A—n = 9, topical and nebulized lidocaine, glossopharyngeal and superior laryngeal nerve blocks, and transtracheal administration of lidocaine; group B—n = 7, similar treatment as group A with placebo (saline); and group C—n = 8, systemic infusions of 2% lidocaine to match plasma concentrations of lidocaine in group A.**

Results: **In study 1, significant increases in heart rate, mean arterial pressure, and sympathetic neural activity (26%, 23%, and 62%, respectively) occurred when desflurane was directed to the upper airway. These responses were approximately twofold to sixfold larger when desflurane was given to the lower airway (lungs). There were no significant increases in these variables when isoflurane was administered to the upper airways, and a significant increase in heart rate occurred only when isoflurane was delivered to the lower airways. In study 2, separate right or left lung increases in desflurane did not change the blood concentration of desflurane or sympathetic neural activity but led to significant increases in heart rate (44%) and mean arterial pressure (32%). The simultaneous administration of desflurane to both lungs increased the millimolar (mM) concentration of desflurane in the blood from 1.17 to 2.39 mM and led to increases in sympathetic neural activity (750%), heart rate (90%), and mean arterial pressure (63%). In study 3, neither regional nor systemic administration of lidocaine reduced the significant neurocirculatory activation caused by the rapid increase in the inspired concentration of desflurane by mask.**

Conclusions: **There are sites in the upper airway (larynx and above) that respond with sympathetic activation during rapid increases in desflurane concentration independent of systemic anesthetic changes. These responses, while lesser than those seen with rapid increases to the lung, may represent direct irritation of airway mucosa. Heart rate and mean arterial pressure responses to desflurane can be initiated by selectively increasing concentrations to either right or left lung without altering systemic levels of desflurane. From this it is inferred that there are sites within the lungs, separate from systemic sites, that mediate this response. Neither systemic lidocaine nor attempted blockade of upper airway sites with cranial nerve blocks combined with topical lidocaine was effective in attenuating the neurocirculatory activation associated with desflurane. (Key words: Airways: bronchus; larynx; trachea. Anesthesia, general. Anesthetics, local: lidocaine. Anesthetics, volatile: desflurane; isoflurane. Blood pressure, measurement techniques: arterial pressure. Heart: heart rate. Monitoring: sympathetic microneurography. Sympathetic nervous system: autonomic nervous system.)**

THE common volatile anesthetics in use during the last several decades are generally thought to reduce both synaptic and neural transmission throughout the human body and to have inhibitory effects on central

*Assistant Professor of Anesthesiology.

†Professor of Anesthesiology and Physiology and recipient of research support from Abbott Laboratories and Ohmeda.

‡Research Fellow, Department of Anesthesiology.

§Postdoctoral Fellow in Anesthesiology.

‖Research Associate Professor of Anesthesiology and Physiology

Received from the Department of Anesthesiology, The Medical College of Wisconsin, and VA Medical Center, Milwaukee, Wisconsin. Submitted for publication August 17, 1995. Accepted for publication May 21, 1996. Supported in part by a VA Merit award and an RO1 National Institutes of Health Grant to Dr. Ebert and a Foundation for Anesthesia Education and Research grant and National Institutes of Health Training Grant #GM-08377 to Dr. Muzi.

Address reprint requests to Dr. Muzi: Department of Anesthesiology, VA Medical Center, 112A, 5000 West National Avenue, Milwaukee, Wisconsin 53295.

sympathetic outflow when employed in clinically relevant concentrations.[1,2]# Desflurane and, to a lesser extent, isoflurane challenge this concept. We have previously documented that progressively larger concentrations of desflurane are associated with increasing sympathetic neural outflow and plasma concentrations of norepinephrine,[3-6] and that this effect is amplified during rapid increases in the inspired desflurane concentration.[3,5] Sympathetic activation associated with desflurane has been associated with substantial increases in heart rate (HR) and blood pressure (BP),[3,5] and these responses may pose a clinical risk of myocardial ischemia to patients with ischemic heart disease.[7]

The site(s) responsible for initiating the sympathetic activation associated with desflurane is not known and has been difficult to identify because of the absence of an animal model that demonstrates similar sympathetic responses to desflurane. Desflurane may initiate these responses by actions within the central nervous system (CNS) or at peripheral sites. Because desflurane is extremely pungent and has been associated with signs of airway irritation,[8,9] we have speculated that an airway site might be responsible for initiating the sympathetic responses to desflurane. To explore this possibility, the current research used electrocardiography and direct measures of BP and sympathetic neural activity (SNA) in a series of studies to better define the site of action of desflurane-induced neurocirculatory activation in humans.

In three separate studies, we selectively stimulated or blocked various portions of the airway to better discern the location and degree of contribution of afferent sites responsible for the desflurane-induced stimulation of the cardiovascular system. In study 1, we determined the contribution of direct stimulation of the upper airway with desflurane to the full neurocirculatory response seen when both lungs are stimulated by desflurane. We selectively stimulated the upper airway with high concentrations of either desflurane or isoflurane and compared the neurocirculatory response to that elicited by systemic delivery of these anesthetics to the lungs in the same subjects. In the second study, systemic concentrations of desflurane were maintained constant and desflurane concentrations to one lung were rapidly increased while the opposite lung received decreased desflurane concentrations. Because there are anatomic differences in blood flow, surface area, and neural innervation between the left and right lungs, we randomly tested stimulation to either the right or left lung and compared the responses. Each subject was then stimulated with increases in desflurane to both lungs, to compare the relative contributions of stimulation of one lung *versus* both lungs (with concomitant systemic increases in desflurane). In the third study, a local anesthetic was employed (topically, nebulized, and with nerve blocks) in an attempt to block potential airway sites that may be responsible for the desflurane-mediated sympathoexcitation. A second group was given the same local anesthetic systemically, in doses designed to match the systemic concentrations resulting from local application, to discern if the effect of the blockade itself could be isolated from the effect of the drug action systemically. All three studies were designed to isolate portions of the airways and evaluate the relative contribution of these sites in mediating the neurocirculatory activation resulting from desflurane delivered rapidly in high concentrations.

Materials and Methods

After institutional review board approval of the study protocols, written informed consent was obtained from healthy, male volunteers (aged 18–27 yr), who had no history of asthma, chronic obstructive pulmonary disease, smoking, coughing with exercise, or past pneumonia. Subjects were asked to refrain from coffee, alcohol, and oral intake for at least 12 h before the study. In each study, catheters were inserted into a peripheral vein and radial artery and monitoring included electrocardiogram, arterial BP, and direct recordings of sympathetic nerve activity to skeletal muscle blood vessels (muscle SNA) *via* percutaneous needle placement in the peroneal nerve (microneurography) as described elsewhere[10] (see also Sympathetic Microneurography and Limitations sections). Calibrated infrared spectroscopy was employed to maintain normocarbia throughout each study and to measure inspired and end-tidal concentrations of desflurane and isoflurane.

Study 1: Upper and Lower Airway Responses to Desflurane or Isoflurane

Lines and monitors were placed in seven volunteers, after which a 20-min rest period was observed. Baseline

#Ebert TJ: Autonomic balance and cardiac function. Current Opinion in Anaesthesiology 1992; 5:3–10

measurements of HR, BP, and SNA were then recorded and averaged over 5 min. Mean arterial pressure (MAP) was calculated as diastolic pressure plus 1/3 pulse pressure (systolic minus diastolic pressures) for each beat, averaged over each measurement interval. Anesthesia was then induced with 2.5 mg/kg propofol and 0.15 mg/kg vecuronium and the lungs were manually ventilated with oxygen and desflurane at 5.4% (inspired) *via* a face mask until neuromuscular blockade was established.

A 39-French right-sided, double-lumen, endobronchial tube was positioned with the bronchial cuff just distal to the vocal cords to permit selective administration of desflurane or isoflurane to: (1) the mucosa at and above the vocal cords, including the larynx, pharynx, and nasal and oral mucosa (*via* the tracheal lumen); and (2) to both lungs, *via* the bronchial lumen. The position of the double-lumen tube was confirmed by direct visualization. The bronchial cuff was inflated with air to seal the trachea during continued positive airway pressure at 20 cm H_2O pressure (confirmed by listening for a leak and by looking for air bubbles arising above the bronchial cuff), while the tracheal cuff was left deflated. Bilateral lung, mechanical ventilation was maintained during control, upper airway stimulation, and recovery periods with 0.75 minimum alveolar concentration (5.4%) desflurane/oxygen (6 l/min) at 10 breaths/min with tidal volumes adjusted to maintain normocarbia. The tracheal lumen of the endobronchial tube was attached to a second anesthesia machine and continuous flow of 6 l/min oxygen was delivered through this port. A scavenging system was established over the subject's nose and mouth using a standard oxygen mask sealed with tape and attached to wall suction.

After a 20-min accommodation period, 5 min of steady state neurocirculatory measurements were collected and averaged. Desflurane (14.5%) or isoflurane (2.4%) (order of first anesthetic randomly assigned by a coin toss: desflurane = 4; isoflurane = 3) was added to the oxygen flowing to the upper airway *via* the tracheal lumen. Data were recorded during 5 min of administration. End-tidal anesthetic concentrations were continuously monitored from the bronchial lumen to rule out any systemic absorption from the upper airway exposure. After 5 min, the anesthetic to the upper airway was discontinued and 100% oxygen was resumed. After a 20-min recovery, the second anesthetic gas (isoflurane or desflurane) was delivered to the upper airway.

After another 20-min recovery and repeat baseline recordings, desflurane (14.5%) or isoflurane (2.4%; ordered as earlier) was abruptly administered through the bronchial lumen to both lungs while oxygen was continued in the upper airway. Five minutes of data were recorded, followed, in order, by a 20-min recovery at 5.4% desflurane, repeat baseline recordings and rapid administration of the second anesthetic gas to the lungs. The peak changes in HR, BP, and SNA from the prestimulus, anesthetized baseline were determined and Student's *t* tests were employed for comparisons between treatments.

Study 2: Desflurane Increases to the Lower Airways with or without Changing the Systemic Concentration of Desflurane

Fourteen volunteers were monitored as described earlier and awake baseline data were obtained after a 20-min accommodation period. Induction of anesthesia and intubation were identical to those in study 1 with one exception: a left-sided double-lumen tube was placed in the usual position with the bronchial portion in the proximal left mainstem bronchus and the bronchial cuff placed just past the level of the carina. The double-lumen tube was pressure tested to 20 cm H_2O (again checking for bubbles above the bronchial cuff), and the position was confirmed by fiberoptic visualization. Both lungs were mechanically ventilated (fresh gas flow = 6 l/min) at a rate of 10 breaths/min with tidal volume regulated to maintain normocarbia. After 20 min and achievement of stable, end-tidal desflurane concentrations at 5.4%, HR, BP, and SNA were recorded for 5 min and averaged.

The breathing system of a second anesthesia machine was purged with oxygen. The ventilator of this machine was synchronized to the same respiratory cycle as the first anesthesia machine. The second anesthesia machine was then attached to either the tracheal or bronchial lumen (randomly assigned as left or right by coin toss in each subject) while the original anesthesia machine was attached to the other lumen. Extreme care was taken to avoid tube movement, which might have stimulated a hemodynamic response. Tidal volumes for both machines were set at one half the original value. The inspired desflurane concentration of the first anesthesia machine was doubled from 5.4% to 11% desflurane while the second anesthesia machine venti-

lated the opposite lung with 0% desflurane in 100% oxygen. In this way, tidal volume, respiratory rate, and systemic concentrations of desflurane were held constant while the inspired concentration of desflurane delivered to one lung was doubled. Continuous neurocirculatory measurements were made over the next 5 min and averaged in consecutive 1-min epochs for further analysis.

The breathing system of the original anesthesia machine was then reconnected to both lumens of the double-lumen tube, the tidal volume was reset and the inspired desflurane was set to 5.4%. After a 20-min recovery period and repeat baseline measurements at 5.4% desflurane, a rapid increase in the inspired desflurane concentration to 11% was directed simultaneously to both lungs. A subset of four volunteers were studied on days separate from their study days to confirm the stability of systemic desflurane levels during one-lung stimulations. In these four subjects, arterial blood samples were drawn during the 5.4% baseline period, and at each minute for 10 min after desflurane increases to one lung.

Blood desflurane concentration was measured by analyzing the gas phase above the blood sample that is in equilibrium with it. The gas was analyzed in duplicate by head space analysis *via* gas chromatography. The assay is sensitive to 0.01 mM. The variance of known standards of the same order of magnitude as typical levels in this study is 1%.

Heart rate, MAP, and SNA responses to right *versus* left lung stimuli were compared using analysis of variance. There were no statistical differences between right and left lung responses and the data were combined for comparison to the two-lung condition using repeated-measures analysis of variance. Fisher's least significant difference test was used to make comparisons at equivalent time points when analysis of variance had shown significance between paired means. Significance was achieved if P was less than 0.05.

Study 3: Airway and Systemic Administration of Lidocaine

Twenty-four subjects were randomly assigned to one of three groups. Nine subjects received lidocaine anesthesia of the upper airway (airway lidocaine) consisting of pledgets soaked with 4% lidocaine and applied to the glossopharyngeal region along the glossopalatine arch and nebulized 4% lidocaine mist given while subjects breathed deeply through their mouth and nose. A 25-G needle was used to administer 1% lidocaine bilaterally to the glossopharyngeal (1 ml/side) and superior laryngeal nerves (2 ml/side). In addition, 4 ml 4% lidocaine were administered transtracheally through the cricothyroid membrane. The total dose of lidocaine administered by these combined routes was 520 mg given over approximately 15 min. A test of airway anesthesia by gentle direct laryngoscopy to view the epiglottis produced a negative gag reflex in all subjects. Eight other subjects received intravenous lidocaine followed by a continuous lidocaine infusion designed to give similar systemic lidocaine concentrations to those measured in the first phase of this study. (One subject in this group did not complete the study protocol because of bronchospasm shortly after increasing the inspired desflurane concentration. This subject experienced inspiratory and expiratory wheezing that required multiple doses of albuterol by metered dose inhaler, and terbutaline, 0.25 mg subcutaneously; the SpO_2 remained in the low 80's for several minutes until the bronchoconstriction was relieved. This subject's data were excluded from the group analysis.) A third group comprised seven subjects who served as time controls and received similar administration of saline to the airways.

After instrumentation and before lidocaine or saline pretreatment, a 20-min rest period was allowed. Baseline measurements of HR, BP, and SNA were then recorded and averaged over 5 min. Recordings were repeated 5 min after lidocaine/saline administration and an arterial blood sample was obtained to determine the plasma concentration of lidocaine. Anesthesia was induced as in study 1 except that ventilation was maintained *via* a face mask with 100% O_2 (6 l/min) for 2 min. The desflurane anesthetic vaporizer was then activated at 11% and ventilation was continued for the next 10 min. Neurocirculatory parameters were recorded and averaged for each minute after the increase in desflurane concentration with the exception of minutes 5–7 (to permit computer buffer downloading).

Serum lidocaine levels were measured using a homogeneous enzyme immunoassay technique. The assay is accurate to 0.1 μg/ml with a coefficient of variance of 0.08 μg/ml. Changes in HR, BP, and SNA were plotted over time after advancement of the desflurane vaporizer. Significance was assessed by analysis of variance. Fisher's least significant difference was employed to compare measurements at equivalent time points, when significant differences of the means were found

with analysis of variance. Significance was set at the 0.05 level.

Sympathetic Microneurography

Sympathetic neural recordings are made from peripheral, multifiber nerves using percutaneously positioned microelectrodes. Neural recordings do not contain efferent motor or afferent stretch receptor input when the leg is relaxed in awake subjects, or after neuromuscular blockade. Skin afferents also may be recorded with this technique, however, the electrodes are meticulously adjusted to omit skin afferent signals as tested by the absence of activity in response to lightly stroking the skin and the observation of purely motor responses during electrical stimulation. Sympathetic recordings from skin sites demonstrate responses to emotion and temperature changes and the absence of pulse synchrony.

The muscle SNA recording is further qualified by determining that the nerve activity is pulse synchronous, occurring approximately 1.0–1.5 s after the arterial pressure pulse, and that the bursts are symmetrical, and are stimulated by spontaneous decreases in diastolic pressure, painful stimulation, and brief elevations in arterial carbon dioxide levels during voluntary, prolonged apnea. Further adjustments in the microelectrode position are made before initiating the experimental protocol, until burst amplitudes of muscle SNA are at least three times the background noise. A custom-written, semiautomated, computerized analysis system identifies single sympathetic bursts and quantifies their amplitude, frequency, and duration. Each computer-derived measurement is visually confirmed using a list of objective criteria developed to distinguish bursts from background noise.

Results

In study 1, neurocirculatory variables did not differ during consecutive baseline recording periods at 5.4% desflurane before desflurane or isoflurane administration to upper or lower airways (fig. 1). Administration of 14.5% desflurane to the upper airway *via* a continuous fresh gas flow system led to significant increases above baseline in HR, MAP, and SNA that averaged 26 ± 13, 23 ± 9, and 92 ± 36%, respectively. The administration of desflurane to the lower airway (lungs) resulted in significantly larger increases in HR, MAP,

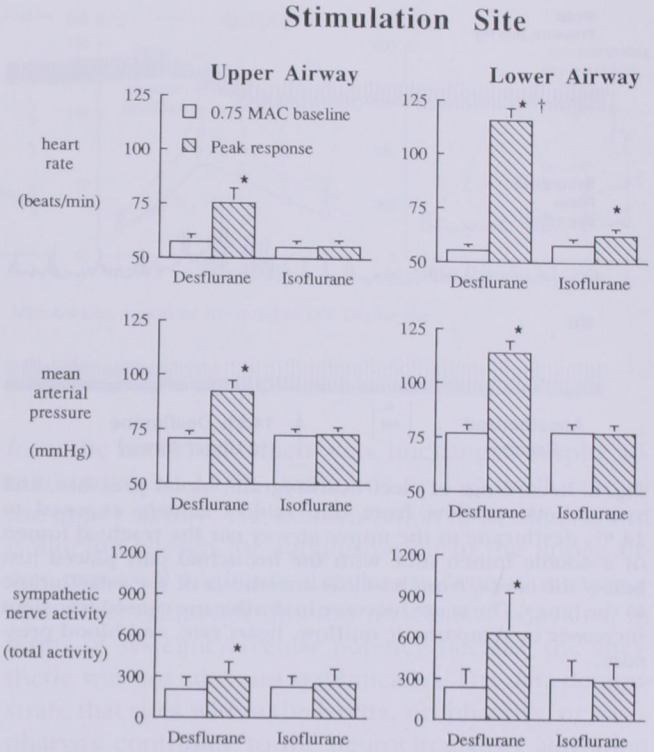

Fig. 1. Neurocirculatory responses to administration of increased concentrations of desflurane (14.5%) or isoflurane (2.4%) to the upper or lower airways (lungs). The peak response represents a 1-min average (± standard error of the mean) of the largest response during the 5-min exposure period. Total activity = (burst frequency × mean burst amplitude) per 100 heart beats. *$P < 0.05$ compared to corresponding baseline at 0.75 minimum alveolar concentration. †$P <$ 0..05 *versus* upper airway response.

and SNA ,which averaged 112 ± 15, 48 ± 5, and 266 ± 92%, respectively (fig. 1). The administration of isoflurane to upper or lower airways did not lead to significant increases in any measured variable except HR, which increased 4.5 ± 1.1 beats/min when isoflurane was administered to the lungs. A recording from one volunteer receiving desflurane to the upper airway is displayed in figure 2.

In study 2, the selective increase in desflurane to either lung without altering systemic concentrations of desflurane was successfully achieved. Serial measurement of the blood concentrations of desflurane in four volunteers are shown in figure 3 and reveal no significant changes over time for either right or left lung stimulation. At 5.4% desflurane baseline, average HR, MAP, and SNA were 65 ± 3 beats/min, 69 ± 2 mmHg, and 147 ± 36 units ([burst frequency × mean burst

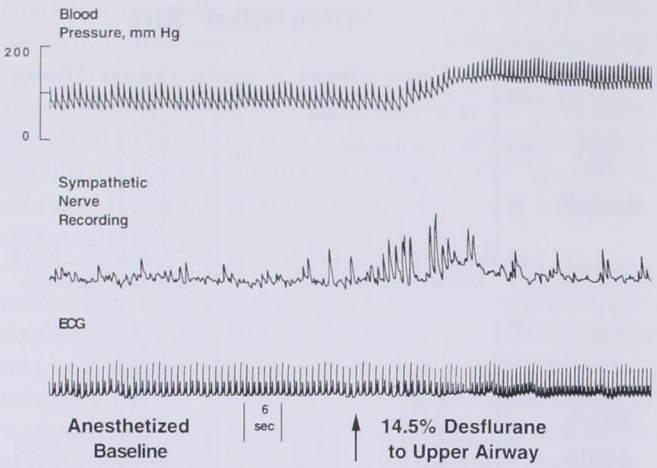

Fig. 2. Recordings of electrocardiogram, blood pressure, and sympathetic outflow from one subject acutely exposed to 14.5% desflurane to the upper airway *via* the tracheal lumen of a double lumen tube with the bronchial cuff placed just below the cords, from baseline anesthesia of 5.4% desflurane to the lungs. The acute increase in desflurane caused transient increases in sympathetic outflow, heart rate, and blood pressure.

amplitude] per 100 heart beats), respectively (fig. 4). Increases in the desflurane concentration to either the right or left lung led to significant increases in HR and MAP but did not alter SNA (fig. 4). These changes did not differ between right and left lung desflurane stimulation periods. Heart rate increased an average of 44 ± 8% when desflurane was increased in one lung and this increase was significantly increased to 90 ± 6% when the desflurane concentration was simultaneously increased in both lungs. Similarly, MAP increased an average of 32 ± 4% when desflurane was increased in either lung but this was nearly twofold larger (63 ± 6%) when desflurane was simultaneously increased in both lungs (fig. 4). Although SNA was not significantly increased when desflurane was directed to a single lung, SNA was significantly increased 777 ± 320% within 2 min after desflurane increases were directed to both lungs.

In study 3 there were no differences in baseline variables between the treatment groups (fig. 5). Saline administration (placebo) did not significantly alter neurocirculatory variables whereas the topical (airway) and systemic administration of lidocaine led to significant increases in HR and MAP without changes in SNA. The change in MAP was greater with systemic than with topical lidocaine administration (15 ± 4 *vs.* 4 ± 2%). The majority of subjects receiving lidocaine by either route reported feeling anxious and appeared restless. Anesthetic induction with propofol resulted in significant decreases in MAP and SNA and increases in HR in topical lidocaine and placebo groups but did not change HR or SNA in the systemic lidocaine group (fig. 5). Maximal neurocirculatory activation triggered by rapidly increasing the inspired concentration of desflurane anesthesia to 11% in the placebo pretreatment (control) group averaged 53 ± 7%, 29 ± 11%, and 1,584 ± 702%, for HR, MAP, and SNA, respectively. There were no significant differences between treatment groups or placebo in the measured end-tidal desflurane concentrations or in the neurocirculatory activation over the course of the desflurane administration. Plasma concentrations of lidocaine measured immediately after the fifth minute of desflurane exposure averaged 3.6 ± 0.5 μg/ml in the topical lidocaine group and 3.7 ± 0.2 μg/ml in the systemic lidocaine group.

Discussion

It is now clear that rapid increases in the concentration of desflurane are associated with sympathetic activation, tachycardia, and hypertension in humans,[3,5,11] and in patients with coronary artery disease these responses have been associated with myocardial ischemia.[7] A potential relationship between the pungency of desflurane, the incidence of untoward airway complications associated with administration of desflurane *via* mask and the neurocirculatory activation has been

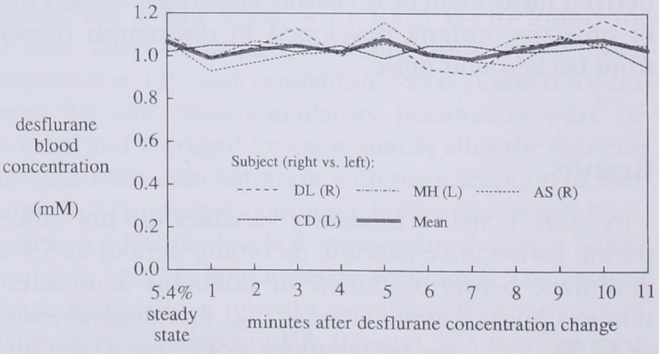

Fig. 3. Desflurane blood concentrations as measured by gas chromatography in four subjects undergoing the study 2 protocol. Arterial samples were drawn at 5.4% (end tidal) steady state and at each minute after initiating 11% desflurane to either the right or left lung. Systemic desflurane concentrations remained relatively constant throughout in all four subjects.

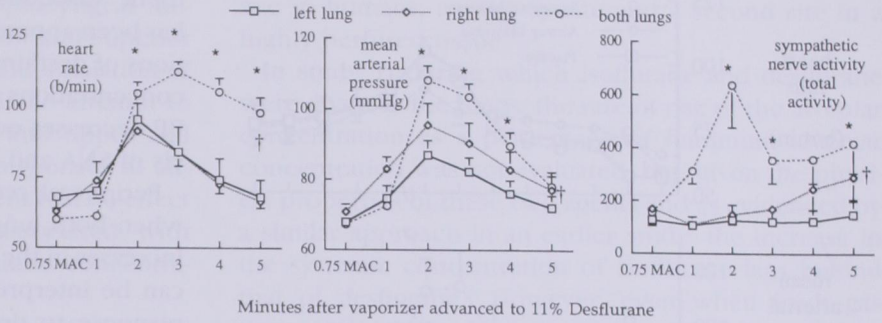

Fig. 4. Neurocirculatory responses initiated by increasing the delivered concentration of desflurane to right, left, or both lungs. Time 0 represents the anesthetized baseline at 5.4% desflurane (0.75 minimum alveolar concentration) before unilaterally increasing the desflurane to 11%. Total activity = (burst frequency × mean burst amplitude) per 100 heart beats. *Significantly different response of both lungs compared to the response of either lung alone at a specific time point, $P < 0.05$, † = significantly different response over time between both lungs compared to either lung alone, $P < 0.05$.

suggested but never explored.[3,5] The current research provides new information on the location of the sites involved in transduction of the desflurane stimulus. Study 1 employed selective stimulation of the upper and lower airway to demonstrate that both locations have sites that are activated by desflurane. The upper airway sites seem to contribute less to the total response. Study 2 indicates that pulmonary airway afferents are involved in the HR and MAP increases but suggests that a systemic site might be more importantly involved in the peripheral sympathetic response to desflurane. Study 3 indicates that when airway reflexes are presumably attenuated with lidocaine, neurocirculatory activation *via* desflurane is not inhibited.

One objective of this research was to localize the site at which desflurane initiates its response. The first approach was to identify whether upper airway receptors might be involved. Several studies have reported substantial airway irritability including coughing, breath holding, and laryngospasm during the administration of desflurane *via* mask.[9,**] By sealing the bronchial lumen of a double lumen tube at a level just distal to the vocal cords, high concentrations of desflurane (or isoflurane) were selectively delivered to the region from the cords to the oropharynx and nasopharynx and exhausted *via* a face mask sealed around the nose and mouth. This approach revealed a small but significant neural and hemodynamic response to desflurane in the upper airways and no response to isoflurane (figs. 1 and 2). Systemic absorption or leakage of the anesthetic around the cuff to the lung was not involved because end-tidal anesthetic concentrations sampled from the bronchial lumen were unchanged despite administration of 14.5% desflurane or 2.4% isoflurane to the upper airway. The concentration of desflurane and isoflurane chosen for administration to the upper airway was a ~2 minimum alveolar concentration-equivalent dose, (although this has no clinical relevance in terms of systemic/alveolar potency because the anesthetic was not taken up systemically). The data demonstrate that sites within the larynx, oropharynx, or nasopharynx contribute to the neurocirculatory activation observed with desflurane but that the relative contribution to the net neurocirculatory activation from upper airway sites is substantially less than the contribution from lower airway regions. We had presumed that, because of the noxious nature of desflurane, the contributions from upper airway irritation would play a more significant role.

In study 2, desflurane was selectively given to the right or left lung without altering systemic desflurane concentrations. Several interesting results were obtained. First, an increase in desflurane to either lung led to increases in HR and MAP, but did not increase SNA to skeletal muscle blood vessels in the lower extremity. Second, although the surface area of the right lung is greater than that of the left lung, there was only a suggestion that right lung responses might exceed those initiated from the left lung. Third, the sum of the hemodynamic responses to right and left lungs was nearly equivalent to the HR and MAP response when both lungs and systemic sites were exposed to desflurane. This suggests that a simple summation of responses from the right and left lung occurs and this makes it difficult to propose any unusual interaction, potentiation, or inhibition when both lungs and systemic sites are simultaneously exposed to desflurane.

**Lerman J: Sevoflurane and desflurane in paediatric patients. Current Opinion in Anesthesiology 1993; 6:527–531

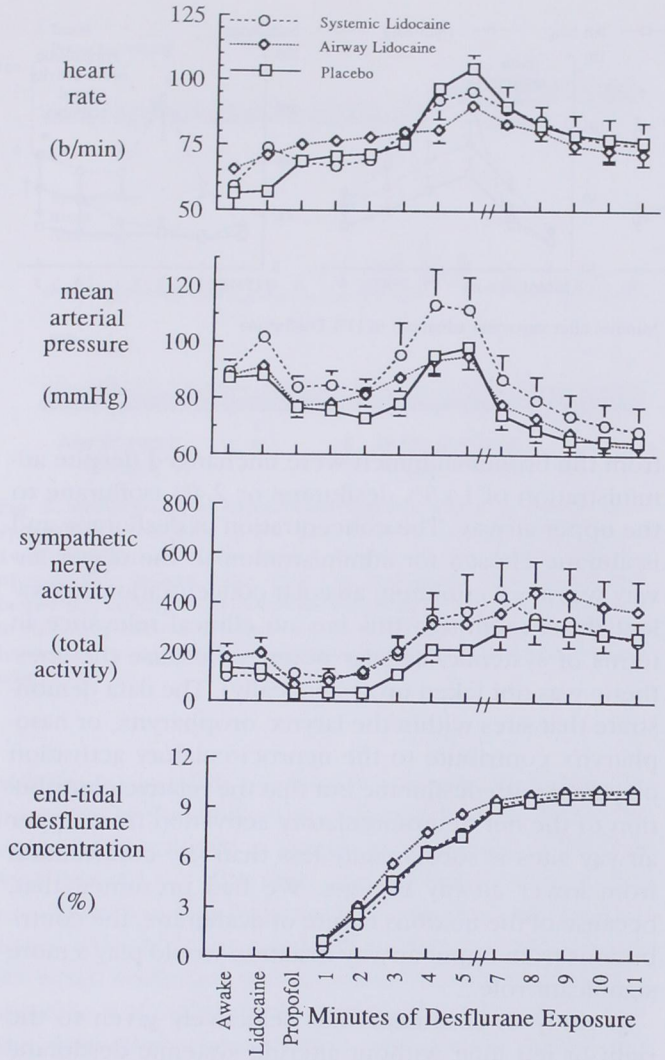

Fig. 5. Average (± SEM) neurocirculatory responses and end-tidal anesthetic concentrations during the administration of 11% desflurane *via* face mask after anesthetic induction with propofol. Lidocaine (or placebo) was used to pretreat subjects before the induction of anesthesia and this was given either directly to the airways or systematically (see text for details). There were no differences in the responses between treatment groups. Total activity = (burst frequency × mean burst amplitude) per 100 heart beats.

The data also suggest that increases in SNA to the peripheral vasculature in response to desflurane contribute only minimally to the increase in the hemodynamic response. This might be caused by a powerful influence of the volatile anesthetics to relax vascular smooth muscle, thereby opposing neural vasoconstrictor influences and inducing reflex increases in sympathetic vasoconstrictor activity in the periphery. This has been apparent when higher steady-state concentrations of desflurane have been compared to equipotent concentrations of isoflurane and sevoflurane; similar BP decreases occurred despite significantly higher levels of SNA and norepinephrine.[5,6]

Peripheral recordings of SNA were only increased when both lungs and systemic sites were exposed to increases in the desflurane anesthetic. This observation can be interpreted several ways: (1) HR increases in response to desflurane might be mediated solely by withdrawal of vagal nerve activity to the sinoatrial node. Therefore, HR increases would account for the majority of the MAP increases with little or no need for sympathetically induced MAP increases; or (2) SNA activation to the heart (and perhaps other regional circulations) might differ from muscle SNA responses. The possibility of selective sympathetic responses to desflurane is consistent with our understanding of the highly differentiated sympathetic control mechanisms in humans.[12,13] The selectivity of SNA (and HR) control mechanisms in response to desflurane has been demonstrated in several studies that employed opioids or clonidine in an attempt to reduce neurocirculatory responses to desflurane.[14-16] These pretreatment strategies led to partial attenuation of the HR component but preserved or augmented SNA and norepinephrine responses to desflurane.

The SNA responses in this study suggest that there may be sites outside the airways that respond to increasing blood concentrations of desflurane or that peripheral SNA is only activated when both lungs are exposed to desflurane, leading to a large afferent neural input into the CNS. Because the solubility of desflurane permits rapid uptake into the CNS, we have speculated that there might be a transient disinhibition of centers modulating sympathetic efferent outflow.[3] In support of this, a recent study also has suggested that, in addition to airway sites, a second site mediating desflurane responses might exist in a highly perfused tissue.[17]

If airway sites are pivotal in initiating a response to desflurane then airway or systemic lidocaine might prove effective in attenuating the response. Lidocaine has been reported to lessen the hemodynamic response to laryngoscopy and tracheal intubation when applied topically or given systemically to patients.[18,19] It also reduces the bronchospasm associated with histamine.[20] Study 3 involved the selective administration of lidocaine to block neural pathways from the cranial

nerves supplying the tongue and oropharyngeal mucosa. In addition, transtracheal injection and superior laryngeal nerve block with lidocaine and inhalation of aerosolized lidocaine were employed in an attempt to attenuate/block vagal afferent nerves and upper and lower airway receptors that mediate responses to airway nociceptive input. This pretreatment had no effect on the neurocirculatory activation associated with rapid increases in the inspired desflurane concentration.

To evaluate the potential effectiveness of systemic lidocaine without topical application and nerve blocks, we employed systemic infusions of lidocaine chosen to replicate the concentrations recorded during selective nerve blocks and topical lidocaine. This approach also failed to attenuate the neurocirculatory activation associated with desflurane. Large systemic concentrations of lidocaine can produce CNS excitation and seizures. The relatively high lidocaine concentrations achieved in this study probably account for the small increases in HR and BP noted before anesthetic induction and the excitation/agitation of pretreated subjects before induction of anesthesia. The lack of effectiveness of local or systemic lidocaine can be interpreted in several ways: (1) lidocaine did not block all of the afferent stimulation sites and pathways in the airways or CNS that are associated with desflurane's response. This could occur if there was insufficient distribution of the local anesthetic or insufficient density of the blockade; (2) afferent sites that are associated with the response to desflurane are present in regions outside the site of action of lidocaine; or (3) lidocaine was effective at desflurane stimulation sites, but the CNS excitatory properties of lidocaine (or desflurane) opposed or superseded the effector response.

Limitations

These studies have improved our understanding of sites involved in transducing the responses to desflurane. However, one interpretation of our data is that there are multiple locations, for example, there may be systemic, and upper and lower airway locations. The efferent response profile might be altered substantially by central integration of the entire afferent profile. Selective stimulation of a single site might not give a true indication of the importance of that site in the overall response. Consistent with the speculation of multiple sites, a recently published study suggests that there may be two sites mediating responses to desflurane in humans; an airway site and a second site in a highly perfused tissue.[17]

In study 1, during which isoflurane and desflurane were given to the lungs, the rate of rise of the alveolar concentration as a percentage of minimum alveolar concentration was not evaluated, but, given the physical properties of these two agents and as evidenced by a similar approach in an earlier study, the increase in the systemic concentration of isoflurane lags behind that of desflurane.[3] However, even when fresh gas flows and delivered concentrations of isoflurane have been increased in an attempt to approach the speed of uptake of desflurane, the rate of rise of isoflurane concentration still lags behind that of desflurane.[11] Thus, we cannot rule out the possibility that a greater rate of rise of the alveolar concentration of isoflurane might have initiated some degree of neurocirculatory response.

In study 3, we attempted to anesthetize the afferent pathways innervating the airways so as to block a potential site of stimulation by desflurane. Through a series of nerve blocks, topicalization, and nebulized inhalation of local anesthetic, we aggressively exposed as much of the airway to lidocaine as we deemed possible in an awake human subject. Without a positive control we cannot be certain as to the adequacy of airway anesthesia, and this limits the interpretation of our negative results. The smaller bronchioles and alveoli were the most likely sites to have been missed with the nebulized lidocaine. We theorized that any substance such as a saline spray down the trachea as a positive control would not be reasonable in awake subjects before lidocaine treatment. We worried that an injected substance might not reach the distal airways as would a gaseous agent and that the strength of the stimulus to the airway with a positive control substance might not match the strength of the desflurane stimulus thereby misleading the interpretation of such a response. In addition, we know that the response to desflurane accommodates with repeated exposures. Stimulation with a positive control may have likewise altered the subsequent response to stimulation by a volatile anesthetic.

We erroneously assumed that lidocaine would be at least partially effective in attenuating the response to desflurane thereby simplifying our interpretation. There were virtually no differences between the responses of the blocked group and those of the placebo group, leading us to one (of three) interpretations, *i.e.*,

that airway afferents, at least from the upper segments of the lung and oropharyngeal regions, may not play a significant role in the neurocirculatory response to desflurane. This is supported by the results of study 1, which demonstrated a lesser maximal response from the upper airway. Two other recent studies lend support to our data suggesting that both nebulized and intravenous lidocaine are ineffective at attenuating the sympathetic responses to increasing concentrations of desflurane in humans.[21,22]

Neural recordings reflect sympathetic activity that regulates the tone of blood vessels within skeletal muscle of the lower leg. Because skeletal muscle blood volume accounts for 30–40% of the recruitable blood volume, the activity of these nerves has significant effects on BP. These nerves are under baroreceptor control such that even changes in BP of 1 or 2 mmHg can substantially alter their activity. While we have employed these recordings to gain access to sympathetic nerves with important physiological roles, we recognize that a single recording site may not correspond to sympathetic activity in other beds such as the splanchnic or cardiac systems. Thus, we have avoided drawing generalizations about the entire sympathetic nervous system from this single measurement technique.

Individual subjects vary quite strikingly with regard to their basal SNA. Resting SNA of young healthy persons participating in this study vary by as much as one order of magnitude from person to person. However, measurements of SNA in the same person on different days tends to be quite reproducible. Therefore, interindividual variability of SNA is much greater than intraindividual variability. This leads us to believe that some persons regulate blood pressure and systemic vascular resistance predominantly *via* SNA alterations, while others employ different regulatory mechanisms (*e.g.*, changes in HR or contractility). Because of this interindividual variability, we express responses of SNA as changes rather than in absolute terms whenever possible. In addition, we attempt to have the same subject participate in all phases of the study, to control for these differences in basal SNA between subjects.

In summary, there appear to be sites in both the upper and lower airways that respond to increasing concentrations of desflurane. Lower airway stimulation initiates a large hemodynamic (HR, MAP, and SNA) response, whereas upper airway stimulation initiates an increase of lesser magnitude in these same variables. Heart rate and MAP responses to desflurane can be initiated by selectively increasing concentrations to either right or left lung without altering systemic levels of desflurane. The application of rapid increases in inspired desflurane concentration to both lungs as seen clinically, supersedes the responses from either of these localized stimulation sites. Finally, neither blockade of cranial nerves IX and X combined with topical lidocaine nor systemic lidocaine were effective in attenuating the neurocirculatory activation associated with desflurane. The possibility of stimulatory sites outside the airway (but in near proximity to the airways) and not influenced by systemic lidocaine must be considered.

The authors thank Linda D. Messana, B.S., and Toni D. Uhrich, M.S., for their careful evaluation of the data, Jill Barney, M.S., for her careful critique and editing of this work, and William T. Schmeling, M.D., Ph.D. for creative thoughts on methodological approaches to study the site of action of desflurane.

References

1. Seagard JL, Hopp FA, Bosnjak ZJ, Osborn JL, Kampine JP: Sympathetic efferent nerve activity in conscious and isoflurane-anesthetized dogs. ANESTHESIOLOGY 1984; 61:266–70

2. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP: Halothane and the carotid sinus reflex: Evidence for multiple sites of action. ANESTHESIOLOGY 1982; 57:191–202

3. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. A comparison with isoflurane. ANESTHESIOLOGY 1993; 79:444–53

4. Ebert TJ, Muzi M: Sympathetic activation with desflurane in humans, Advances in Pharmacology, Vol. 31: Anesthesia and Cardiovascular Disease. Edited by Bosnjak Z, Kampine JP. San Diego, Academic, 1994, pp 369–78

5. Ebert TJ, Muzi M, Lopatka CW: Neurocirculatory responses to sevoflurane in humans. A comparison to desflurane. ANESTHESIOLOGY 1995; 83:88–95

6. Ebert TJ, Harkin CP, Muzi M: Cardiovascular responses to sevoflurane: A review. Anesth Analg 1995; 81:S11–22

7. Helman JD, Leung JM, Bellows WH, Pineda N, Roach GW, Reeves JD, III, Howse J, McEnany MT, Mangano DT, The S.P.I. Research Group: The risk of myocardial ischemia in patients receiving desflurane versus sufentanil anesthesia for coronary artery bypass graft surgery. ANESTHESIOLOGY 1992; 77:47–62

8. Eger EI,II: New inhaled anesthetics. ANESTHESIOLOGY 1994; 80:906–22

9. Smiley RM: An overview of induction and emergence characteristics of desflurane in pediatric, adult, and geriatric patients. Anesth Analg 1992; 75:S38–46

10. Ebert TJ, Kampine JP: Nitrous oxide augments sympathetic outflow: Direct evidence from human peroneal nerve recordings. Anesth Analg 1989; 69:444–9

11. Weiskopf RB, Moore MA, Eger EI,II, Noorani M, McKay L, Chortkoff B, Hart PS, Damask M: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. ANESTHESIOLOGY 1994; 80:1035-45

12. Abboud FM, Heistad DD, Mark AL, Schmid PG: Reflex control of the peripheral circulation. Prog Cardiovasc Dis 1976; 18:371-403

13. Wallin BG, Fagius J: Peripheral sympathetic neural activity in conscious humans. Ann Rev Physiol 1988; 50:565-76

14. Pacentine GG, Muzi M, Ebert TJ: Effects of fentanyl on sympathetic activation associated with the administration of desflurane. ANESTHESIOLOGY 1995; 82:823-31

15. Devcic A, Muzi M, Ebert TJ: The effects of clonidine on desflurane-mediated sympathoexcitation in humans. Anesth Analg 1995; 80:773-9

16. Weiskopf RB, Eger EI,II, Noorani M, Daniel M: Fentanyl, esmolol, and clonidine blunt the transient cardiovascular stimulation induced by desflurane in humans. ANESTHESIOLOGY 1994; 81:1350-5

17. Weiskopf RB, Eger EI,II, Daniel M, Noorani M: Cardiovascular stimulation induced by rapid increases in desflurane concentration in humans results from activation of tracheopulmonary and systemic receptors. ANESTHESIOLOGY 1995; 83:1173-8

18. Helfman SM, Gold MI, DeLisser EA, Herrington CA: Which drug prevents tachycardia and hypertension associated with tracheal intubation: Lidocaine, fentanyl, or esmolol? Anesth Analg 1991; 72:482-6

19. Hamill JF, Bedford RF, Weaver DC, Colohan AR: Lidocaine before endotracheal intubation: Intravenous or laryngotracheal? ANESTHESIOLOGY 1981; 55:578-81

20. Brown RH, Robbins W, Staats P, Hirshman C: Prevention of bronchoconstriction by an orally active local anesthetic. Am J Respir Crit Care Med 1995; 151:1239-43

21. Bunting HE, Kelly MC, Milligan KR: Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. Br J Anaesth 1995; 75:631-3

22. Gormley WP, Murray JM, Trinick TR: Intravenous lidocaine does not attenuate the cardiovascular and catecholamine response to a rapid increase in desflurane concentration. Anesth Analg 1996; 82:358-61