High concentrations of isoflurane do not block the sympathetic nervous system activation from desflurane

Thomas J. Ebert MD PhD,
Timothy S. Trotier MD,
Shahbaz R. Arain MD,
Toni D. Uhrich MS,
Jill A. Barney MS

Purpose: The volatile anesthetic desflurane has been associated with neurocirculatory responses that have been relatively refractory to adjuvant treatment. We have employed desflurane to evaluate the integrity of the sympathetic nerve recording after establishment of the anesthetized state with another anesthetic agent. This retrospective evaluation of data from volunteers determined if higher concentrations of isoflurane that were sufficient to block the neurocirculatory response to laryngeal and tracheal stimulation would abolish the neurocirculatory response to desflurane.

Methods: Data from eight, healthy, young volunteers met our criteria for inclusion. They had been anesthetized with propofol or thiopental and intubated after neuromuscular blockade. Each subject was monitored with radial artery blood pressure (BP), heart rate (HR)(ECG), and sympathetic microneurography. Isoflurane had been administered to achieve a steady state concentration of 1.5 MAC (minimum alveolar concentration) while oxygenation and carbon dioxide were monitored with pulse oximetry and infrared spectrometry, respectively. A deep level of anesthesia was confirmed when laryngoscopy and endotracheal tube movement failed to elicit a neurocirculatory response. A brief exposure to 11% desflurane in the inspired gas was then provided.

Results: The responses to desflurane included significant increases in HR, range 32-84 b/min, and BP, range 15-72 mm Hg ($P < 0.05$). Sympathetic nerve activity increased substantially in the three volunteers with functional nerve recordings.

Conclusion: In healthy volunteers receiving 1.5 MAC isoflurane, which was sufficient to block the neurocirculatory response to laryngoscopy and tracheal stimulation, there were striking increases in sympathetic outflow, HR and BP when 11% desflurane was substituted for isoflurane.

Objectif : L'anesthésique volatil desflurane a été associé à des réponses neurocirculatoires relativement réfractaires à un traitement adjuvant. Nous avons utilisé le desflurane pour évaluer l'intégrité du nerf sympathique après l'installation de l'anesthésie avec un autre anesthésique. La présente évaluation rétrospective de participants volontaires a cherché à déterminer si une concentration élevée d'isoflurane, suffisante pour bloquer la réponse neurocirculatoire à la stimulation laryngée et trachéale, pouvait abolir la réponse neurocirculatoire au desflurane.

Méthode : Huit jeunes volontaires en santé ont participé à l'étude. Ils ont été anesthésiés avec du propofol ou du thiopental et intubés après blocage neuromusculaire. Chaque patient a été surveillé par le monitoring de la tension de l'artère radiale (TA) et de la fréquence cardiaque (FC) (ECG) et par la microneurographie sympathique. L'isoflurane a été administré jusqu'à une concentration stationnaire de 1,5 CAM (concentration alvéolaire minimale) et l'oxygénation et le gaz carbonique ont été vérifiés par l'oxymétrie pulsée et la spectrométrie à infrarouge, respectivement. Un niveau profond d'anesthésie a été confirmé lorsque la laryngoscopie et le mouvement du tube endotrachéal n'ont pu provoquer de réponse neurocirculatoire. Les sujets ont été soumis ensuite à une brève exposition au desflurane à 11 % dans le gaz inspiré.

Résultats : Les réactions au desflurane comprennent des augmentations significatives de la FC, 32-84 b/min, et de la TA, 15-72 mmHg ($P < 0,05$). L'activité du nerf sympathique a beaucoup augmenté chez les trois participants qui présentaient des enregistrements fonctionnels du nerf.

Conclusion : Chez des volontaires sains qui reçoivent 1,5 CAM d'isoflurane, dose suffisante pour empêcher la réponse neurocirculatoire à la laryngoscopie et à la stimulation trachéale, on a noté des hausses importantes de la décharge sympathique, de la FC et de la TA lorsque du desflurane à 11 % a été substitué à l'isoflurane.

From the Department of Anesthesiology, Medical College of Wisconsin and VA Medical Center, Milwaukee, WI, USA.

Address correspondence to: Dr. Thomas J. Ebert, VAMC/112A, Department of Anesthesiology, 5000 W. National Avenue, Milwaukee, WI 53295, USA. Phone: 414-384-2000, ext. 42419; Fax: 414-384-2939; E-mail: tjebert@mcw.edu

Accepted for publication November 9, 2000.

DESFLURANE is one of the new potent volatile anesthetics with a low blood:gas solubility (1:0.42). This property allows the clinician to make rapid changes in anesthetic depth. Because of its insolubility, desflurane has proven to be advantageous when attempting to quickly eliminate the anesthetic at the end of surgical procedures. However, the use of desflurane to deepen anesthesia rapidly during anesthetic induction and during periods of increasing surgical stimulus has been problematic.¹⁻⁴ This is because desflurane has the ability to activate the sympathetic nervous system when inspired concentrations are increased either gradually⁴ or rapidly.¹ Sympathetic stimulation leads to hypertension, tachycardia and, in select cases, myocardial ischemia.⁵ Several of our previous studies have focused on determining methods to attenuate this potentially harmful response. For example, one study indicated that pretreatment with $2.5 \mu\text{g}\cdot\text{kg}^{-1}$ fentanyl was insufficient, but pretreatment with $5.0 \mu\text{g}\cdot\text{kg}^{-1}$ fentanyl was adequate to minimize the sympathetic activation and subsequent hemodynamic response to the administration of desflurane.⁶ Several other studies have indicated that pretreatment with oral clonidine only partially inhibited the response to desflurane,^{7,8} and, in separate studies, topical or systemic lidocaine failed to attenuate the hemodynamic response to inhaled desflurane.⁹⁻¹¹

Based upon the inability of most adjuvants to abolish the neurohumoral response to desflurane, it appears to be quite a potent stimulus. We have used this to our advantage in several of our previous research protocols to test the integrity of an experimental preparation employing sympathetic microneurography during general anesthesia in healthy volunteers. In some individuals, 1.5 MAC (minimum alveolar concentration) isoflurane reduces or abolishes sympathetic nerve activity (SNA). It then is essential to determine if the modified SNA recording is the result of a disturbance of the recording needle or an effect of the anesthetic. To test the integrity of the peroneal nerve preparation, laryngoscopy and endotracheal tube movement are performed. If hemodynamic and sympathetic responses are not observed following this stimulus, 11% desflurane is briefly administered into the inspired gas mixture. A profound neurocirculatory response is initiated by this exposure. We have retrospectively analyzed data from these tests and this report summarizes these data and serves to emphasize the potency of desflurane as a stimulus to the sympathetic nervous system.

Materials and methods

Volunteers were enrolled in an Institutional Review Board-approved protocol, and informed consent was

obtained from all subjects. All volunteers were free of systemic illness and were not taking any medications. Subjects fasted for at least 12 hr prior to the study. An 18-gauge intravenous catheter was inserted into the forearm for drug and fluid administration. Monitoring consisted of heart rate (HR) via surface electrocardiogram, blood pressure (BP) via cannulation of the radial artery, and muscle sympathetic nerve activity (SNA) via percutaneous impalement of the peroneal nerve. This technique, which has been described previously,¹ involves locating the nerve with an external probe that delivers brief electrical pulses (1 Hz, 3-7mA) to the region just distal to the fibular head. Two 5- μ -tipped, epoxy-coated tungsten needles (TMI, Iowa City, IA) were inserted into the leg; one needle was placed just outside the nerve fascicle (reference electrode) and one was advanced into the peroneal nerve (recording electrode). Characteristic bursts of efferent neural activity were obtained by fine manipulations of the recording electrode. After filtration and amplification of the signal, muscle SNA was observed and quantified.

Following five minutes of preoxygenation, anesthetic induction was performed with $2.5 \text{ mg}\cdot\text{kg}^{-1}$ propofol or $5 \text{ mg}\cdot\text{kg}^{-1}$ thiopental. The trachea was intubated after neuromuscular blockade had been achieved with $0.10 \text{ mg}\cdot\text{kg}^{-1}$ vecuronium. Isoflurane was initiated and maintained at various concentrations based upon the protocol directives. In a number of subjects, questionable SNA recordings were observed during steady-state observation periods at 1.5 MAC isoflurane. Isoflurane was at a steady-state level of 1.5 MAC for at least 20 min and was only evaluated after at least an hour of lower MAC concentrations. We then attempted to establish the integrity of the SNA recording, since signal degradation can occur as a result of movement of the leg or needle. The lack of SNA responsiveness to laryngoscopy and endotracheal tube movement was established. In some individuals (who were not included in this report) HR and BP responses could be observed without a SNA response. In these individuals, the SNA recording was scored as compromised, i.e., a hemodynamic response must be accompanied by a change in sympathetic nerve activity. In eight subjects (six male and two female), neither a hemodynamic nor SNA response was observed. We presumed we had achieved "MAC-intubation" (MAC_{EI} = the minimum alveolar concentration that blocks adrenergic responses to laryngeal and tracheal stimulation in 50% of patients), and a decision about the integrity of the SNA recording could not be made. In these eight individuals, a final test was applied by administering 11% desflurane. The transition from isoflurane to desflurane was accomplished by turning

off the isoflurane vaporizer and immediately initiating desflurane at 11% inspired concentration at a fresh gas flow of 6 L·min⁻¹. Hemodynamic and SNA data were collected and averaged in 30-sec increments for five minutes beginning immediately prior to the initiation of desflurane.

Statistical analysis employed Student's *t* tests to determine significant changes from baseline (during 1.5 MAC isoflurane) in HR and BP. Significance was achieved if *P* < 0.05. Statistical analysis was not performed on the nerve data because of the small number of individuals with an intact nerve recording at the initiation of desflurane (*n*=3).

Results

At 1.5 MAC isoflurane, eight subjects had no neuro-circulatory response to laryngeal and endotracheal stimulation, but had both HR and BP increases in response to desflurane. In three of these eight subjects a SNA response also was observed. This meant that five subjects had compromised SNA recordings because a hemodynamic event occurred without a preceding change in SNA. The data from all eight subjects demonstrated increases in HR and BP in response to desflurane compared with baseline (isoflurane) values (Figure 1). The increase in HR ranged from 32 to 84 b·min⁻¹ and peaked at approximately 2.5 min after initiating desflurane. The mean arterial BP increase also peaked at approximately 2.5 min after initiating desflurane and ranged from 15 to 72 mmHg. SNA increased in the three individuals with functional nerve recordings (Figure 2). A representative tracing of this response is shown in Figure 3.

Discussion

Stressful periods during the perioperative period include laryngoscopy, tracheal intubation, and surgical stimulation. These periods have been associated with profound hemodynamic perturbations if adequate pretreatment is not employed. The concept of blocking the adrenergic response to such manoeuvres led to the description of MAC-BAR.¹² The MAC-BAR concentration of volatile anesthetics is about 1.3 times MAC.¹³ The MAC to block hemodynamic responses to tracheal intubation (MAC_{ET}) is even greater.¹⁴

The technique of sympathetic microneurography requires percutaneous placement of a small needle electrode into the peroneal nerve and positioning the exposed tip of the epoxy-coated electrode into or next to a fascicle of sympathetic c-fibres within the peroneal nerve.^{1,15} This is done while volunteers are conscious. To study the effects of the volatile anesthetics, volunteers must be anesthetized without movement, must

FIGURE 1 The heart rate and blood pressure response to desflurane. Isoflurane 1.5 MAC was discontinued and desflurane 11% initiated at a FGF of 6 L·min⁻¹. The increases in both variables peaked at around 2 to 2.5 min after desflurane. * *P* < 0.05 = significantly different from baseline (isoflurane anesthesia); b·min⁻¹ = beats per minute, B = baseline isoflurane measurement.

remain immobile throughout all periods of anesthetic administration, and external disturbance of the patient or the bed must be avoided to assure the electrode position is maintained. This report summarizes our experiences while attempting to establish the integrity of the SNA recordings during a period of time when SNA can be reduced or abolished by the study drug (i.e., 1.5 MAC isoflurane) or by unwanted movement of the leg or needle.

FIGURE 2 The sympathetic nerve activity response to desflurane in the three individuals with intact nerve recordings. Isoflurane was discontinued and desflurane initiated immediately. The increases in nerve activity peaked about 1.5 min after desflurane was initiated. Statistics were not performed on these data because of the small sample size ($n=3$). B = baseline isoflurane measurement.

This study found that in some individuals, 1.5 MAC of isoflurane was sufficient to block sympathetic and hemodynamic responses to noxious upper airway stimuli, but was ineffective in preventing the hemodynamic response to a rapid increase in the inspired concentration of desflurane. This demonstrates the potency of the desflurane stimulus on the sympathetic nervous system. This finding is consistent with an earlier study that indicated that $2.5 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl failed to abolish the response to desflurane.⁶ Moreover, the sympatho-inhibitory drug clonidine or topical and/or intravenous applications of lidocaine to anesthetize the airway have proven to be ineffective in attenuating the response to desflurane.^{8-11,16}

We implicate the sympathetic nervous system in the subsequent hemodynamic response, despite the fact that SNA responses were observed in only three of eight subjects. This is based upon the consistent observation of an SNA response that preceded the hemodynamic response in previous studies where the integrity of the SNA recording was not in question.^{1,2,4,11} In these studies, the initiation of desflurane into the inspired gas shortly after anesthetic induction, or the sudden increase in the inspired concentration of desflurane above 0.75 or 1.0 MAC, resulted in a substantial increase in SNA in 100% of subjects in whom leg movement was not observed. The site of action for the desflurane-initiated increase in sympathetic activity is currently unknown. Our earlier work suggested that

FIGURE 3 This is a tracing from one of the three subjects with an intact nerve recording during the transition from isoflurane to desflurane anesthesia. Note the lack of nerve activity during isoflurane and then the dramatic increase in nerve activity beginning about one minute after initiation of desflurane anesthesia. Also evident is the tachycardia and hypertension that resulted from the increase in sympathetic nerve activity. ETiso = end-tidal isoflurane; MSNA = muscle sympathetic nerve activity.

receptors in both the upper and lower airway might react to the pungency of desflurane.^{4,11} Others have suggested that receptors may be located in a highly perfused region near the lung because of the rapidity of the response after initiating a desflurane stimulus.¹⁷

The initiation of airway reflexes after desflurane anesthesia is most likely a function of the low potency of this highly pungent agent. Compared with isoflurane, the low potency of desflurane mandates higher inspired concentrations to maintain adequate anesthesia. Isoflurane also is pungent, but is substantially more potent than desflurane, and, therefore, is used in smaller concentrations. When isoflurane is briefly administered in a high concentration (5%), it, too, causes a sympatho-excitatory response. However, the magnitude of the response is less than desflurane,^{18,19} and it has not resulted in the substantial increases in epinephrine and antidiuretic hormone noted with desflurane.¹⁹

In summary, healthy volunteers receiving 1.5 MAC of isoflurane, who did not exhibit a neurocirculatory response to laryngeal and tracheal stimulation, were subjected to desflurane in the inspired gas mixture, which resulted in striking increases in sympathetic outflow and subsequent increases in HR and BP. The clinical implications of this report concern the potency of the desflurane stimulus. We advise caution when desflurane is employed in the "at risk" patient, such as those with severe cardiovascular and/or neurological disease. An increasing proportion of patients with underlying cardiovascular disease are presenting for ambulatory procedures where minimal anesthetic adjuvants are employed. Because desflurane is well suited for these outpatient procedures, the clinician should be aware that aggressive pretreatment with opioids and the immediate availability of esmolol or other beta adrenergic antagonist drugs may be required to mitigate against the neurocirculatory activation from desflurane.

References

- 1 Ebert TJ, Muzi M. Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. A comparison with isoflurane. *Anesthesiology* 1993; 79: 444–53.
- 2 Ebert TJ, Muzi M, Lopatka CW. Neurocirculatory responses to sevoflurane in humans. A comparison to desflurane. *Anesthesiology* 1995; 83: 88–95.
- 3 Moore MA, Weiskopf RB, Eger EI II, Noorani M, McKay L, Damask M. Rapid 1% increases of end-tidal desflurane concentration to greater than 5% transiently increase heart rate and blood pressure in humans. *Anesthesiology* 1994; 81: 94–8.
- 4 Muzi M, Lopatka CW, Ebert TJ. Desflurane-mediated neurocirculatory activation in humans. Effects of concentration and rate of change on responses. *Anesthesiology* 1996; 84: 1035–42.
- 5 Helman JD, Leung JM, Bellows WH, et al. The risk of myocardial ischemia in patients receiving desflurane versus sufentanil anesthesia for coronary artery bypass graft surgery. *Anesthesiology* 1992; 77: 47–62.
- 6 Pacentine GG, Muzi M, Ebert TJ. Effects of fentanyl on sympathetic activation associated with the administration of desflurane. *Anesthesiology* 1995; 82: 823–31.
- 7 Devic A, Muzi M, Ebert TJ. The effects of clonidine on desflurane-mediated sympatho-excitation in humans. *Anesth Analg* 1995; 80: 773–9.
- 8 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.
- 9 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.
- 10 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.
- 11 Muzi M, Ebert TJ, Hope WG, Robinson BJ, Bell LB. Site(s) mediating sympathetic activation with desflurane. *Anesthesiology* 1996; 85: 737–47.
- 12 Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (Stress) and cardiovascular responses to incision—MAC BAR. *Anesthesiology* 1981; 54: 390–8.
- 13 Daniel M, Weiskopf RB, Noorani M, Eger EI II. Fentanyl augments the blockade of the sympathetic response to incision (MAC-BAR) produced by desflurane and isoflurane. *Anesthesiology* 1998; 88: 43–9.
- 14 Kimura T, Watanabe S, Asakura N, Inomata S, Okada M, Taguchi M. Determination of end-tidal sevoflurane concentration for tracheal intubation and minimum alveolar anesthetic concentration in adults. *Anesth Analg* 1994; 79: 378–81.
- 15 Wallin BG, Fagius J. Peripheral sympathetic neural activity in conscious humans. *Annu Rev Physiol* 1988; 50: 565–76.
- 16 Berntson GG, Cacioppo JT, Quigley KS. Autonomic cardiac control. I. Estimation and validation from pharmacological blockades. *Psychophysiology* 1994; 31: 572–85.
- 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 Ebert TJ, Muzi M. Sympathetic activation with desflurane in humans. *In: Advances in Pharmacology*, Vol.

- 31: Anesthesia and Cardiovascular Disease. San Diego: Academic Press, 1994: 369–78.
- 19 *Weiskopf RB, Moore MA, Eger EI II, et al.* 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.