Sympathetic Hyperactivity during Desflurane Anesthesia in Healthy Volunteers

A Comparison with Isoflurane

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Background: Desflurane has been reported to produce more tachycardia and hypertension on induction than isoflurane. The present study employed microneurography to determine whether these cardiovascular effects were related to sympathetic outflow.

Methods: In 14 healthy, young (age 20–31 yr) volunteers, arterial pressure was measured from the radial artery, forearm blood flow was derived by strain gauge plethysmography, and sympathetic nerve activity (SNA) directed to skeletal muscle blood vessels was recorded from a tungsten needle placed percutaneously into the peroneal nerve. Heart rate, blood pressure, muscle SNA, respiration, tidal volume, end-tidal carbon dioxide, and desflurane or isoflurane concentrations (Infrared spectroscopy) were continuously monitored before and during anesthesia. Two minutes after administering thiopental (5 mg/kg) and vecuronium (0.2 mg/kg), desflurane (n = 7) or isoflurane (n = 7) was titrated gradually to the inspired gas over several minutes to 1.5 MAC.

Results: The initiation of desflurane anesthesia resulted in significant changes that included a 2.5-fold increase in SNA, hypertension (peak mean arterial pressure 114 ± 3 mmHg), tachycardia (peak heart rate 102 ± 6 beats/min), facial flushing, and tearing. Moderate upper airway obstruction developed in three subjects approximately 4 min after initiating desflurane, despite neuromuscular blockade. These responses were not observed in subjects receiving isoflurane. After tracheal intubation, the anesthetic concentration was maintained at 0.5 MAC for 30 min. Steady-state measurements of hemodynamics and SNA were obtained. Similar steady-state measurements were obtained 15 min after establishing 1.0 and 1.5 MAC. Both anesthetics produced a progressive reduction in blood pressure and forearm vascular resistance, and muscle SNA gradually increased. In subjects receiving desflurane, heart rate remained unchanged until the 1.5-MAC level was reached, at which time tachycardia (a 10-beat/min increase) was noted. The transition from 1.0 to 1.5 MAC desflurane resulted in significant heart rate increases (>30 beats/min), hypertension (>30 mmHg), and a doubling of SNA that persisted for several minutes. These responses did not occur in the isoflurane group.

Conclusions: Titration of desflurane following thiopental induction and increasing the concentration of desflurane from 1.0 to 1.5 MAC resulted in sympatho-excitation, hypertension and tachycardia in healthy, young volunteers. Until methods are determined to attenuate these responses, desflurane should be administered with great caution to patients who may be placed at risk by these responses. (Key words: Anesthetic techniques: inhalational. Anesthetics, volatile: desflurane, isoflurane. Blood pressure. Laryngospasm. Sympatho-excitation. Techniques: sympathetic microneurography.)

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ade of the sympathetic nervous system. Moreover, in humans, anesthetic induction with thiopental and subsequent ventilation via mask with desflurane has been associated with higher heart rates and blood pressures than a similar group receiving isoflurane. In addition, when the inspired concentration of desflurane is increased rapidly from 1 to 1.5 MAC, significant tachycardia and hypertension have been observed. Finally, induction of anesthesia with thiopental and desflurane in patients with coronary artery disease has been associated with an incidence of myocardial ischemia greater than that in a similar group anesthetized primarily with opioids. The majority of these unexplained observations could be attributed to unusual effects of desflurane on sympathetic neural outflow.

For these reasons, the present study design employed sympathetic microneurography to record sympathetic vasconstrictor activity during induction and maintenance of anesthesia with either desflurane or isoflurane. In addition, the hemodynamic and neural responses that occurred during the transition period caused by acutely increasing the inspired anesthetic concentration from 1.0 to 1.5 MAC were evaluated. The data reveal that desflurane is associated with profound sympathetic activation during induction and transition periods that merit caution if this anesthetic is employed in a population placed at increased risk by hypertension and tachycardia.

Materials and Methods

After approval from the Human Research Review Committee and informed consent were obtained, 14 healthy, normotensive male volunteers aged 20–31 yr were studied. These volunteers were free of systemic illness, were not receiving medications, did not take any drugs, and fasted for at least 12 h before testing. Each ingested 30 ml nonparticulate antacid. Volunteers were studied while supine. Heart rate (HR) was monitored from leads II and V5 on the electrocardiogram. A 20-G catheter was inserted into the radial artery for direct determination of blood pressure (BP). An 18-G catheter was inserted into a forearm vein and 5–7 ml/kg of saline was administered before initiation of the study. Forearm blood flow was measured with a mercury-in-Silastic, temperature-compensated, strain gauge plethysmograph system in which an upper arm cuff intermittently (8 s on and 8 s off) inflated to 60 mmHg while the venous outflow from the hand was arrested. Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow.

Peroneal Nerve Recordings

The right leg was supported and cushioned. The bony prominence at the proximal head of the fibula on the lateral aspect of the leg was identified and marked. Brief electrical impulses (1 Hz, 3–7 mA) were delivered below this mark to identify the location of the peroneal nerve. The skin was cleansed, and two 5-μm-tipped, epoxy-coated tungsten needles (TMI, Iowa City, IA) were inserted. One needle was advanced to an area just outside the peroneal nerve; the second was advanced into the peroneal nerve. The location of the nerve was identified by applying brief impulses (1 Hz, 0.02–0.03 mA) to the needle. When a muscle nerve fascicle within the peroneal nerve was entered, a distinct muscle contraction in the distribution of the deep or superficial peroneal nerve was noted. The stimulation was halted and neural activity was amplified (100,000×), rectified, and integrated. Signals common to both needles (e.g. background noise) were canceled in a custom-made preamplifier by common-mode rejection. Characteristic bursts of efferent sympathetic nerve activity (SNA) were sought by fine manipulations of the needle within the motor nerve fascicle. The identification of these bursts and their distinction from activity occurring in skin sympathetic efferent nerve fibers have been described in detail elsewhere. Briefly, spontaneous bursts of neural activity were evident on the amplified signal, occurred in pulse-synchronous groupings, and often were phase-locked to late expiratory and early inspiratory periods. Neural activity could be increased by prolonged breath-holding, during phases II and III of the Valsalva maneuver and in response to nitroprusside, but was unaffected by startle maneuvers.

Procedures

Baseline and Induction. Once an acceptable sympathetic recording was obtained, a 10-min quiet rest period was observed followed by 5 min of hemodynamic (HR, BP, forearm blood flow) and neural (SNA) measurements. A blood sample was obtained from the arterial catheter for blood gas analysis. The face mask was placed, and 100% O2 was administered for 5 min. End-tidal carbon dioxide and inspiratory and expiratory desflurane or isoflurane concentrations after induction were monitored by an Ohmeda 5250 infrared respiratory gas monitor (Madison, WI). A priming dose of vecuronium (0.01 mg/kg) was given, followed by an-
esthetic induction with thiopental (5 mg/kg) and vecuronium (0.2 mg/kg). Ventilation was controlled through the mask and without an oral airway for 12 min. Neuromuscular function was evaluated by train-of-four responses from the ulnar nerve. In seven subjects, exactly 2 min after injection of thiopental, the desflurane vaporizer was activated at a setting of 3.6% (0.5 MAC). In the two subsequent 1-min periods, the desflurane vaporizer setting was increased to 7.25% (1.0 MAC) followed by 10.9% (1.5 MAC) while manual ventilation continued and end-tidal carbon dioxide concentrations were maintained at awake values. In seven additional subjects, isoflurane was administered at time intervals and MAC equivalents identical to those employed in the subjects receiving desflurane. Upon completion of the 12-min period following anesthetic induction, the volunteer’s trachea was intubated and ventilation was controlled to maintain end-tidal carbon dioxide at awake levels. The vaporizer setting was reduced to 0.5 MAC for an additional 20 min of anesthesia, providing a 32-min postinduction interval before hemodynamic and neural data were collected, to reduce the likelihood that the initial administration of thiopental influenced the subsequent measurement of steady-state responses.

**Steady-state/Transition Anesthesia.** The order of anesthetic administration was 0.5, 1.0, and 1.5 MAC for all subjects. Steady-state hemodynamic and neural measurements as well as blood sampling were carried out 15 min after each change in the vaporizer setting; this was several minutes after end-tidal concentrations had reached a plateau. In addition, continuous data were recorded during the first 12 min (transition) after rapidly changing the inspired concentration of desflurane or isoflurane from 0.5 to 1.0 MAC and 1.0 to 1.5 MAC. These transitions were carried out by advancing the vaporizer setting from either 3.6–7.25% or 7.25–10.9% for desflurane and from either 0.7–1.4% or 1.4–2.1% for isoflurane. An over-pressure paradigm, *i.e.*, advancing the vaporizer beyond the desired concentration to achieve a more rapid steady-state at 1.0 or 1.5 MAC, was not employed. End-tidal carbon dioxide was maintained constant throughout the experimental protocol and confirmed by arterial blood gas analysis at each steady-state measurement period.

**Analyses**

Consecutive hemodynamic and neural measurements were compared with analysis of variance for repeated measures, and post hoc analyses were performed with Bonferroni correction. Probability values less than 0.05 were considered sufficient to reject the null hypothesis.

**Results**

**Baseline and Induction**

All participants were in good health, exhibiting low resting heart rates (58 ± 4 beats/min) and normal blood pressures (mean arterial pressure 90 ± 4 mmHg). The initiation of anesthesia with thiopental was associated with a small tachycardia (70 ± 4 beats/min) and no significant changes in mean arterial pressure (90 ± 5 mmHg) and SNA (25 ± 3 to 22 ± 7 bursts). However,
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![Graph showing sympathetic nervous activity, heart rate, and mean arterial pressure over time during induction of anesthesia.]

Fig. 2. Average group responses (mean ± SEM) to induction of anesthesia. Desflurane or isoflurane administration began 2 min after sodium thiopental (STP) administration. Sympathoexcitiation (total activity = burst amplitude × burst frequency = mV × bursts/100 cardiac cycles), tachycardia, and hypertension were noted in subjects receiving desflurane. These responses persisted 4–5 min after initiating desflurane anesthesia and gradually abated with time. *Different group response. †Desflurane response different from STP value. ‡Isoflurane response different from STP value.

Adding desflurane to the inspired gas in progressively higher concentrations resulted in marked sympathetic activation (peak increase to 59 ± 12 burst units), hypertension (peak mean arterial pressure 114 ± 3 mmHg), and tachycardia (peak HR 102 ± 6 beats/min; fig. 1). This differed remarkably from data in subjects receiving isoflurane (fig. 2). All subjects receiving desflurane displayed facial flushing and tearing, and oral secretions developed. In addition, three subjects developed moderate upper airway obstruction about 3–4 min after initiating desflurane that required aggressive ventilation to maintain tidal volume and end-tidal carbon dioxide. There was no evidence of bronchospasm (by auscultation) and no further difficulty after tracheal intubation. However, the upper airway obstruction did not subside during the 12-min induction period despite loss of train-of-four responses 5 min after induction.

Steady-state/Transition Anesthesia

Steady-state measurements of hemodynamic and neural parameters during increasing concentrations of desflurane and isoflurane are displayed in figure 3. Both anesthetics produced a significant and progressive reduction in blood pressure and, in general, progressive reductions in forearm vascular resistance. Small increases in HR were observed early with isoflurane and persisted at all MAC levels. In contrast, tachycardia did not occur in desflurane-treated subjects until 1.5 MAC was reached. There was a significant progressive increase in sympathetic nerve activity at 1.0 and 1.5 MAC compared to the 0.5 MAC measurement. However, muscle SNA was not significantly changed from awake values during any steady-state anesthetic concentration.

The hemodynamic and neural data obtained during the transition periods between 0.5 and 1.0 MAC and between 1.0 and 1.5 MAC are displayed in figures 4, 5, and 6. Acutely increasing the inspired concentration of desflurane from 3.6% to 7.25% led to a gradual reduction in blood pressure that was not associated with an increase in heart rate but caused a subtle but significant increase in sympathetic nerve activity. In contrast, 30–45 s after increasing the inspired concentration of desflurane from 7.25% to 10.9%, massive sympathetic activation, hypertension, and tachycardia consistently were observed. Facial flushing and tearing were noted in all subjects, and atrial premature contractions developed in one subject. Heart rate increased from a baseline of 55 ± 5 beats/min to a peak of 101 ± 6 beats/min. Mean arterial pressure increased from a baseline of 62 ± 2 mmHg to a peak of 83 ± 7 mmHg, and sympathetic nerve activity more than doubled (figs. 5 and 6). The hypertension and tachycardia persisted for 3–5 min following the vaporizer change and was followed by a gradual and significant reduction in blood pressure and heart rate. Interestingly, as blood pressure decreased, sympathetic nerve activity showed a gradual
(and perhaps reflex) increase. In contrast, increasing the inspired concentration of isoflurane from 1.4% to 2.1% led to a gradual decline in BP with no initial hypertensive response. Moreover, only minimal and insignificant changes in HR and SNA were noted.

Discussion

The present study demonstrates consistent and remarkable sympatho-excitation during the administration of desflurane to healthy, unpremedicated volunteers. This sympathetic activation leads to transient but pronounced tachycardia and hypertension. The observations of profound hemodynamic changes during desflurane anesthesia are not unique to this study.7,10-12 A number of comments pertaining to hypertension and tachycardia in patients enrolled in early clinical trials with desflurane have been published.7 These observations and the present data suggest extreme caution be taken when administering desflurane to patients who may be placed at risk by increases in HR, BP, and catecholamines.

Induction Responses

We were unable to study sympathetic responses during a pure inhalational induction technique because any movement of the leg would have dislodged the sympathetic recording needle from its location in the peroneal nerve. Therefore, large bolus doses of thiopental and vecuronium were given simultaneously. We previously demonstrated that thiopental is sympatho-inhibitory; when a similar group of subjects was anesthetized with 4–5 mg/kg thiopental, SNA decreased, HR increased, and mean arterial pressure remained unchanged during a 4-min sampling period after anesthetic induction.15 In contrast, in the present study, the administration of desflurane in increasing concentrations beginning 2 min after thiopental administration resulted in a marked increase in SNA (200%) and substantial increases in HR and BP. Though these responses began to abate 9–10 min after induction (7–8 min after initiating desflurane), intubating conditions were not ideal until 13–15 min after induction. Intubation may have been mandated earlier if the airway obstruction, noted in three subjects, had worsened. The presence of airway obstruc-
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Fig. 4. Average response (mean ± SEM) initiated by advancing the vaporizer from 0.5 to 1.0 MAC desflurane or isoflurane. The y-axis scale is identical to that used in figure 6, where the transition from 1.0 to 1.5 MAC desflurane or isoflurane is plotted, for comparison. There was a gradual decrease in BP associated with a progressive increase in sympathetic nerve traffic. Desflurane response different from 0.5 MAC desflurane steady-state value. Isoflurane response different from 0.5 MAC isoflurane steady-state value.

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tion on induction with desflurane has been reported and discussed.\textsuperscript{5,16} In children induced with desflurane by mask, a very high incidence of laryngospasm has been noted and described as a “near death” experience because of its severity, intractable nature, and association with marked hypoxemia.\textsuperscript{5,16}

Though our direct documentation of profound sympatho-excitation on induction with thiopental and desflurane is unique and unchallenged, the observation of tachycardia and hypertension has other experimental support. In a preliminary report, investigators at Columbia University, New York, retrospectively analyzed data from 2 groups of surgical patients given midazolam for sedation (0.03 mg/kg intravenously) and thiopental (4–7.5 mg/kg) for induction of anesthesia. The lungs were ventilated via mask while either isoflurane or desflurane was administered gradually.\textsuperscript{16} At 5–6 min after induction, HR had increased 30–40 beats/min and BP had increased 20–26 mmHg in the desflurane group, and these changes were significantly larger than those noted in the isoflurane group. Substantial tachycardia and hypertension also have been noted in a population with coronary artery disease undergoing desflurane anesthesia for coronary artery revascularization.\textsuperscript{12} Patients received morphine and midazolam intramuscularly 60–90 min before surgery and, after preoxygenation, anesthesia was induced with up to 0.1 mg/kg midazolam and up to 7 mg/kg thiopental. One hundred patients were given 1.0–2.0 MAC desflurane by mask for 15 min before intubation. After tracheal intubation, anesthesia was maintained with desflurane at 1.0 MAC. Hemodynamics were tightly controlled within 20% of baseline with adjustments in the inspired desflurane concentration and, failing an adequate response, appropriate vasoactive drugs or esmolol were given. A control group of 100 coronary artery disease patients in whom anesthesia was induced with midazolam and thiopental and who received sufentanil instead of desflurane was used for comparison. The authors noted significantly greater use of esmolol in the desflurane group, which persisted up to cardiopulmonary bypass. Despite esmolol therapy, the desflurane group had nearly a doubling of pulmonary artery pressures, significant increases in HR, BP, systemic vascular resistance, and pulmonary wedge pressure, and decreases in stroke volume. On Holter and transesophageal echocardiography analyses, 9% and 13%, respectively, of patients who received desflurane developed electrocardiographic changes suggestive of ischemia, compared with 0% who received sufentanil.\textsuperscript{12} Prelim-
inary data further suggest that chronic therapy with β-adrenergic blocking medications in patients with ischemic heart disease does not confer protection from ischemia during desflurane administration.17

The majority of the early work describing the cardiovascular effects of desflurane was carried out with healthy volunteers in whom anesthesia was induced with desflurane by mask.6,8,18 Increases in HR and BP were noted on induction but were attributed to stage II excitation. However, the present research and supporting data suggest that other mechanisms are involved.

Steady-state Responses

Consistent with previous reports, we observed a progressive decrease in BP with increasing concentrations of desflurane and a relatively unchanged HR until 1.5 MAC desflurane was reached.6 The mechanism of the mild tachycardia at 1.5 MAC desflurane is not known but may be related to increased sympathetic drive, because we observed significant increases in SNA at this anesthetic depth. We also observed decreases in forearm vascular resistance during desflurane, which is inconsistent with the data published by Weiskopf et al.5 but similar to what has been noted previously with isoflurane.19 The reduction in blood pressure and forearm vascular resistance at 1.5 MAC desflurane despite sympathetic activation and tachycardia indicates that desflurane has potent direct effects on vascular smooth muscle.

Sympathetic activation during steady-state desflurane anesthesia has been apparent in chronically instrumented dogs.5 For example, desflurane-anesthetized dogs had smaller decreases in BP, systemic vascular resistance, and myocardial contractility than did dogs receiving equipotent concentrations of isoflurane.9 These differences could be abolished by blockade of the autonomic nervous system. Our data in healthy volunteers receiving isoflurane indicate that sympathetic activation noted with desflurane is somewhat larger than that produced with equipotent concentrations of isoflurane. The presence of tachycardia and sympathetic activation at higher concentrations of desflurane could be due to functional baroreceptor reflex mechanisms responding to the systemic hypotension. Though the baroreceptor reflex has not been evaluated in any animal or human model during desflurane anesthesia, we have shown that isoflurane maintains reflex control of heart rate better than does halothane or enflurane.20 Perhaps the structural similarity between these two ether compounds confers equal maintenance of reflex function.

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Transition Responses

The acute response to increasing the inspired concentration of isoflurane or desflurane from 0.5 to 1.0 MAC was relatively unremarkable. A gradual decrease in BP that reached statistical significance 4.5 min after the change in the vaporizer setting was associated with small but significant increases in SNA. Again, we speculate that these effects are reflexively mediated. In contrast, the transition from 1.0 to 1.5 MAC desflurane was astonishing. This transition occurred about 2 h after thiopental induction, while subjects were at a stable surgical plane of anesthesia. All desflurane-treated subjects demonstrated facial flushing and tearing during this transition. In all cases, the sympathetic activation was of greater magnitude and longer duration than were responses noted during laryngoscopy and tracheal intubation in our previous studies.15,21 We are not the first to observe hypertension and tachycardia during the transition to a higher MAC of desflurane. In a preliminary report on ASA physical status 1 and 2 patients with intracranial mass lesions, anesthesia was induced with thiopental and, after tracheal intubation, anesthesia was maintained with 1.0 MAC isoflurane or desflurane.11 Forty minutes after induction, HR and BP were similar in both groups and the anesthetic concentrations were acutely increased to 1.5 MAC. Hemodynamic changes did not occur in the isoflurane group, but significant 15–20% increases in HR and BP were noted in the desflurane group.11 Interestingly, other investigators have carried out studies on healthy human volunteers and have noted only occasional transient HR responses to changes in anesthetic concentrations that were not considered a potential problem.5–8 Our opinion differs substantially. Because these responses were larger in magnitude and longer in duration than were hemodynamic responses previously noted after intubation and because intubation frequently is associated with myocardial ischemia, we emphasize that desflurane must be administered cautiously to patients whose cardiac (or neurologic) risk might be worsened by sympathetic activation, hypertension, and tachycardia. Such effects would augment myocardial oxygen demand substantially and could lead to new or worsening arrhythmias secondary to myocardial stress and/or an increase in catecholamines.

Isoflurane

As mentioned previously, steady-state effects of isoflurane and desflurane were generally similar, except
for the small increasing HR at lower concentrations of isoflurane. Moreover, the induction and transition responses were relatively unremarkable with isoflurane. In both situations, there were gradual reductions in BP without a preceding hypertensive response. Heart rate and SNA were altered minimally and inconsistently. These data contrast to the recently published data by Yli-Hankala et al., who demonstrated increases in HR, BP, and catecholamines in intubated subjects acutely exposed to 5% isoflurane. In the present study, isoflurane was increased to 2.1% (1.5 MAC) for the sole purpose of a direct comparison to desflurane on an equipotential basis.

Mechanisms

The stimulus that drives the augmentation in sympathetic outflow during higher inspired concentrations of desflurane (and isoflurane) is not known. One strong possibility, however, is a reflex response initiated by airway irritation. Though previous work has suggested that ventilation via a mask with low concentrations (1.8–5.4%) of desflurane in adults is well tolerated, larger concentrations appear to be extremely pungent and perhaps the most irritating of the currently marketed volatile anesthetics. On induction, the high incidence of airway irritation with desflurane is not reduced by concurrent use of nitrous oxide or fentanyl. Because the airway reflexes are able to initiate potent sympathetic and pressor responses even in the face of anesthetics that profoundly depress sympathetic outflow, we conjecture that the airway irritation seen with larger concentrations of desflurane triggers sympathetic responses.

The present research demonstrates consistent and profound sympathetic activation, hypertension, and tachycardia when desflurane is titrated into the inspired gas following anesthetic induction with thiopental. A similar response is observed when acutely increasing the anesthetic depth from 1.0 to 1.5 MAC. These responses do not occur in subjects receiving equipotent concentrations of isoflurane. Further research should be directed toward defining the mechanism(s) of the sympathetic activation and determining methods or pharmacologic agents that consistently obtund this response.

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