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Neurocirculatory Responses to Sevoflurane in Humans

A Comparison to Desflurane

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Background: Sevoflurane and desflurane are new volatile anesthetics with low blood solubilities that confer properties of rapid anesthetic induction and emergence. Desflurane has been associated with neurocirculatory excitation after the rapid increase in inspired concentrations. The current study evaluated and compared the sympathetic and hemodynamic responses associated with the administration of sevoflurane to those associated with administration of desflurane in humans.

Methods: After Institutional Review Board approval, 21 healthy, young (19–32 yr) volunteers were randomly selected for participation. Arterial and central venous pressures were measured directly, and heart rate, forearm blood flow, and plasma norepinephrine concentrations were determined indirectly. Efferent muscle sympathetic nerve activity was recorded by microneurography. After neurocirculatory recordings at conscious baseline, measurements were repeated beginning 2 min after 2 mg/kg propofol while the anesthetic was increased incrementally by mask over a 10-min period at 1%, 2%, and 3% sevoflurane (n = 12) or 3%, 6%, and 9% desflurane (n = 9). Responses to intubation were recorded and, 20 min later, recordings were evaluated during steady-state periods of 0.41, 0.83, and 1.24 MAC. Data also were obtained after steady-state 0.83 MAC measurements when the inspired gas concentration was rapidly increased to either 3% sevoflurane or 9% desflurane ("transition" to 1.24 MAC).

Results: Neurocirculatory variables did not differ between the two groups at conscious baseline. During the period of administration *via* mask and during the "transition" period, the significant increases in sympathetic nerve activity, heart rate, mean arterial pressure, and central venous pressure associated with desflurane were not observed with sevoflurane. Ten minutes after induction, mean arterial pressure and heart rate responses to intubation did not differ between groups. With increasing anesthetic concentration, there were progressive and similar decreases in mean arterial pressure in both groups and no changes in heart rate. Central venous pressure, sympathetic nerve activity, and plasma norepinephrine increased with the greater minimum alveolar concentration multiple of desflurane but not with that of sevoflurane.

Conclusions: The neurocirculatory excitation seen with rapid increases in desflurane did not occur with sevoflurane. At steady-state, increasing the concentration of sevoflurane was associated with lower sympathetic nerve activity and central venous pressure and similar mean arterial pressure and heart rate with that of desflurane. (Key words: Anesthetics, volatile: desflurane; sevoflurane. Blood pressure. Heart rate. Measurement techniques: microneurography. Sympathetic nervous system.)

SEVOFLURANE is a new potent volatile anesthetic agent with a low blood-gas solubility (0.6) that confers desirable properties of rapid induction and emergence and quick control of anesthetic depth. Sevoflurane is not pungent, and administration of sevoflurane by mask is well tolerated.[1,2] In contrast, desflurane is extremely pungent.[3,4] The airway irritation associated with desflurane in humans may be involved in the marked activation of the neuroendocrine axis.[5-7]

Although sevoflurane is nonirritating when given *via* mask, several studies in humans[8,9] and in chronically instrumented dogs[10,11] suggest that sevoflurane also may be associated with increased heart rate (HR). In addition, sevoflurane has been associated with a smaller decrease in vascular resistance than an equipotent concentration of isoflurane.[12,13] These observations raise the possibility that sevoflurane might maintain or augment sympathetic outflow. The purpose of this study was to directly record efferent sympathetic neural activity and routine hemodynamic variables during the administration of sevoflurane to healthy volunteers. For

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desflurane.

Materials and Methods

With approval from the Institu
and after informed consent, 22 h
male volunteers, aged 19–32 yr,
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the electrocardiogram. A 20-G
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sure (BP). An 18-G catheter was i
vein and 5 ml/kg of 0.9% saline
10 min and maintained at 1 ml ·
Forearm blood flow was meas
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while the venous outflow from th
Forearm vascular resistance was
of mean arterial pressure (MAP) t
Plasma norepinephrine (Nepi)
determined in duplicate from a
pressure liquid chromatography
detection. The minimal detecta
Nepi was 35 pg/ml, and the mini
of Nepi was 15 pg/ml, based on
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and immediately spun at 4°C an
min. The plasma was pipetted int
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Sympathetic Microneurograp
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comparative purposes, the neurocirculatory responses were compared to those from a group of randomly selected subjects receiving equipotent concentrations of desflurane.

Materials and Methods

With approval from the Institutional Review Board and after informed consent, 22 healthy, normotensive, male volunteers, aged 19–32 yr, were studied. The administration of sevoflurane was part of an Abbott Laboratories (Abbott Park, IL)-sponsored study carried out with an investigational new drug exemption issued from the Food and Drug Administration. Volunteers were nonsmokers, free of systemic illness, and not taking medications or illicit drugs and had fasted for at least 12 h before testing. Volunteers were studied while supine after ingesting 30 ml of nonparticulate antacid (Bicitra). HR was monitored from leads II and V5 on the electrocardiogram. A 20-G catheter was inserted into the radial artery for determination of blood pressure (BP). An 18-G catheter was inserted into a forearm vein and 5 ml/kg of 0.9% saline was administered over 10 min and maintained at $1 \ ml \cdot kg^{-1} \cdot h^{-1}$.

Forearm blood flow was measured with a Hg-in-Silastic, temperature-compensated, strain-gauge plethysmograph system in which an upper arm cuff intermittently inflated to 60 mmHg (10 s on and 10 s off) while the venous outflow from the hand was arrested.[14] Forearm vascular resistance was calculated as the ratio of mean arterial pressure (MAP) to forearm blood flow.

Plasma norepinephrine (Nepi) concentrations were determined in duplicate from arterial blood by high-pressure liquid chromatography with electrochemical detection. The minimal detectable concentration of Nepi was 35 pg/ml, and the minimal detectable change of Nepi was 15 pg/ml, based on the variability of repeated measurements from pooled plasma. Blood samples were collected in chilled syringes, transferred to glass tubes containing EDTA and reduced glutathione, and immediately spun at 4°C and 20,000 rpm for 10 min. The plasma was pipetted into polypropylene containers and stored at −70°C until analysis.

Sympathetic Microneurography

As described previously,[15] the common peroneal nerve of the right leg, just distal to the knee, was located *via* external stimulation, and a needle was positioned within the peroneal nerve, guided by the response to small electrical impulses applied to the needle (1 Hz, 0.02 mA). When the needle impaled a nerve fascicle supplying muscle, a distinct muscular contraction occurred. For the purpose of this study, skin nerves were excluded because they influence only about 4% of the cardiac output, are not under baroreceptor control, and have mixed effector sites (skin blood vessels, sweat glands, and piloerector muscles). Characteristic spontaneous bursts of muscle sympathetic neural activity (SNA) were sought by subtle advancement or withdrawal of the needle within the muscle nerve fascicle. Once an acceptable recording was obtained, the subjects remained relaxed and quiet with an immobile leg so as not to alter the location of the needle within the nerve.

Procedures

Baseline and Induction

Once an acceptable sympathetic nerve 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. Arterial blood was obtained for blood gas and Nepi analysis. The face mask was gently placed, a priming dose of vecuronium (0.01 mg/kg) was given, and 100% O_2 was administered for a period of 5 min. End-tidal carbon dioxide and anesthetic concentrations after induction were monitored by an Ohmeda 5250 Infra-red Respiratory Gas Monitor (Madison, WI). Twelve subjects were randomized to receive sevoflurane, and nine received equipotent concentrations of desflurane. Anesthesia was established with propofol (2 mg/kg) and neuromuscular blockade accomplished with vecuronium bromide (0.15 mg/kg). Ventilation was controlled *via* the mask and without an oral airway for 12 min at a fresh gas flow rate of 6 l/min in a partial rebreathing system. Precisely 2 min after injection of propofol, the sevoflurane vaporizer was activated at a setting of 1%. In the two subsequent 1-min periods, the vaporizer was increased to 2% and 3% and maintained at 3% while end-tidal carbon dioxide concentrations were kept at awake values. In subjects receiving desflurane, a similar sequence of anesthetic administration was employed by delivering 3%, 6%, and 9% inspired concentrations (1.0 MAC for sevoflurane and desflurane in this age group is 2.4 and 7.2%, respectively). On completion of the 12-min period after anesthetic induction, the trachea was intubated by a skilled anesthesiologist

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(C.W.L.) while data were continuously collected. Ventilation was mechanically controlled to maintain end-tidal carbon dioxide at awake levels. To reduce the end-tidal concentration to 0.41 MAC, the vaporizer setting was reduced to 1% sevoflurane or 3% desflurane for an additional 20-min period of anesthesia, providing an interval of 32 min postinduction before steady-state hemodynamic and neural data were collected. This reduced the likelihood that the initial administration of propofol and the neuroendocrine responses during the induction period influenced steady-state measurements.

Steady-state/Transition Anesthesia

Hemodynamic and neural measurements and blood sampling were carried out 10 min after end-tidal sevoflurane or desflurane had reached the desired concentration. The order of anesthetic administration for determination of steady-state responses was 1%, 2%, and 3% sevoflurane and 3%, 6%, and 9% desflurane. In addition, continuous data were recorded during the first 5 min (transition) after rapidly increasing the delivered anesthetic concentration. The transition was carried out simply by advancing the sevoflurane vaporizer setting from 2% to 3% or the desflurane vaporizer from 6 to 9%. An over-pressure paradigm, *i.e.,* advancing the vaporizer beyond the desired concentration to achieve a more rapid steady-state, 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. Blood sampling for Nepi determination was carried out at conscious baseline and at steady-state periods of 0.41, 0.83, and 1.24 MAC.

Analyses

To determine the peak change in HR and MAP during intubation, the 20 s immediately before intubation was averaged, and the maximum HR and MAP that occurred in the 60 s after intubation were determined individually. The SNA occurring from baseline (preintubation) up until the time of peak MAP was averaged to determine the maximal SNA response. Consecutive hemodynamic and neural measurements were compared with analysis of variance for repeated measures, and *post hoc* analyses were performed with Dunnett's *t* tests. Peak changes in variables during induction and intubation were analyzed with unpaired Student's *t* tests. Probability values that were less than 0.05 were considered sufficient to reject the null hypothesis.

Results

The age, height, weight, and body mass index of the subjects did not differ between groups. There were no differences in hemodynamic measurements and SNA between groups at conscious baseline (fig. 1). Responses to anesthetic induction with propofol and the subsequent 10-min administration *via* mask of sevoflurane or desflurane are depicted in figures 1 and 2. Propofol administration resulted in significant reductions in SNA and MAP and a significant increase in HR, and these responses did not differ between groups. The inhalation *via* mask of sevoflurane in incremental steps from 1% to 2% and 2% to 3% (inspired) did not lead to significant changes in SNA or HR. There was a gradual and significant reduction in MAP during the 10-min administration period (figs. 1 and 2). In contrast, the step increase in the inspired concentration of desflurane from 3% to 6% and 6% to 9% led to significant increases in SNA and HR and a biphasic response in MAP. The peak absolute increases in these variables from the propofol baseline are depicted in figure 2.

Laryngoscopy and subsequent tracheal intubation began 10 min after beginning the administration of the volatile anesthetic *via* mask. At this time, the end-tidal desflurane concentration had achieved 7.9% (approximately 1.1 MAC; fig. 1), whereas the end-tidal concentration of sevoflurane was 2.1% (approximately 0.88 MAC). The subsequent hemodynamic responses to laryngoscopy and tracheal intubation are depicted in figure 3. The HR and MAP responses did not differ between groups, whereas the SNA response was less in the desflurane group.

The steady-state responses to sevoflurane and desflurane are depicted in figure 4. There were similar and progressive decreases in MAP and forearm vascular resistance with increasing MAC multiple of each anesthetic. There were no changes in HR with increasing concentration of sevoflurane or at 3% and 6% desflurane, whereas 9% desflurane resulted in a significant increase in HR compared to 6% desflurane. Sevoflurane did not alter central venous pressure (CVP), SNA, or plasma Nepi concentrations at any end-tidal concentration level; however, desflurane resulted in significant and progressive increases in CVP, SNA, and Nepi with increasing MAC multiples ($P < 0.05$; fig. 4).

The minute-by-minute responses to the rapid increase in the inspired concentration of desflurane and sevoflurane ("transition") are depicted in figure 5. The increase was initiated from either 2% or 3% sevoflurane.
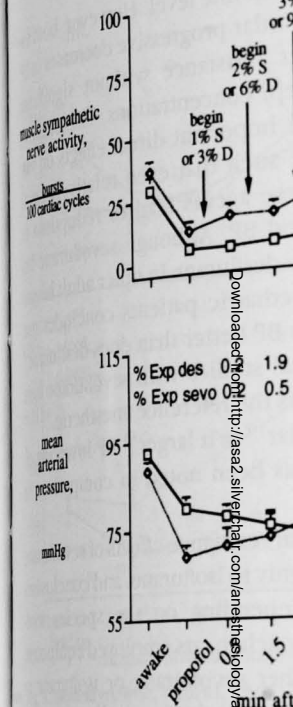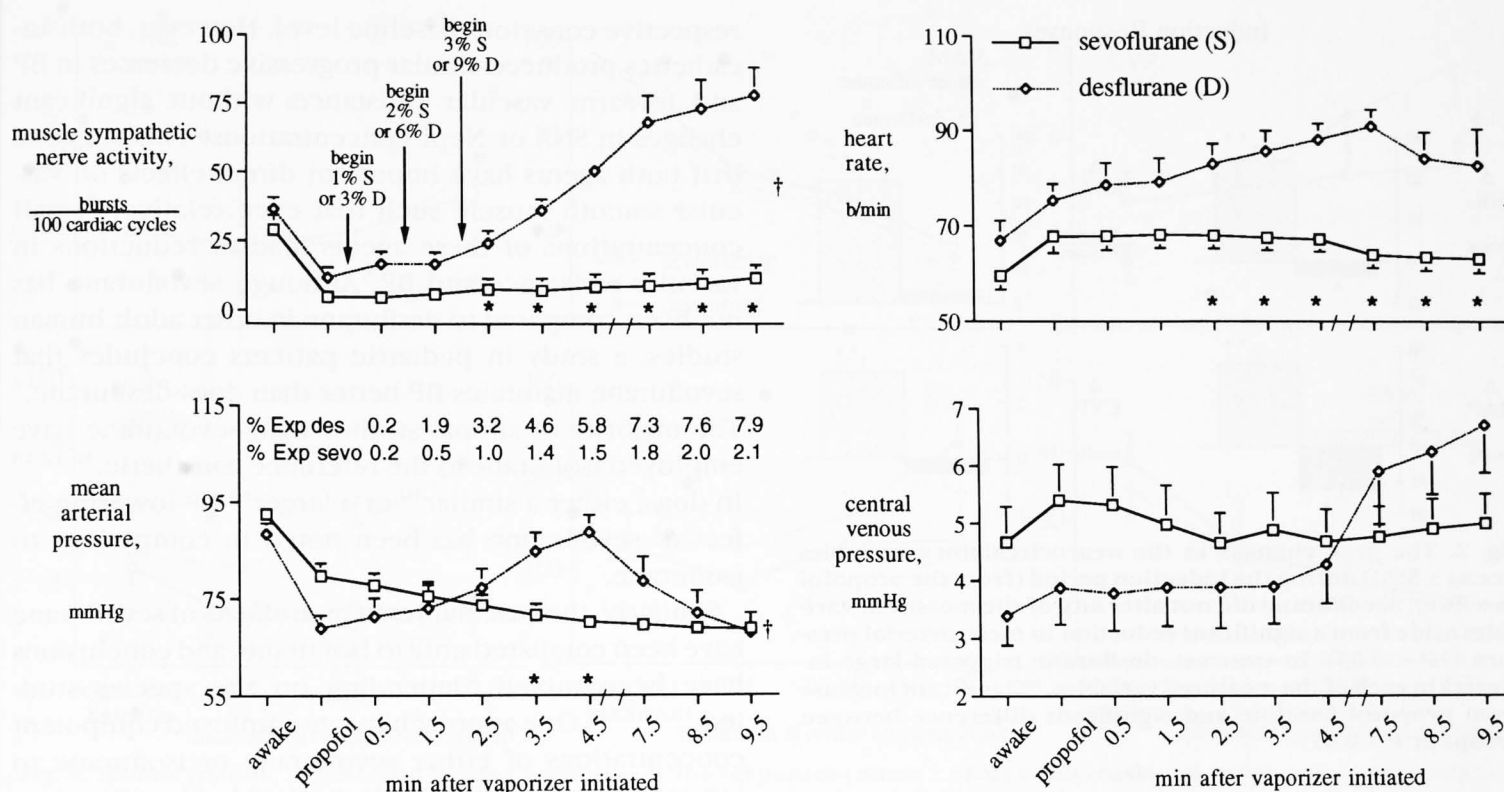
Fig. 1. Consecutive measurements of neurocirculatory variables (mean ± SEM) during induction of anesthesia with propofol and the subsequent mask administration of sevoflurane or desflurane for a 10-min period. The inspired concentration of these anesthetics was increased at 1-min intervals beginning precisely 2 min after propofol administration (0.41 MAC of sevoflurane 1% and of desflurane 3.65%). The average end-tidal concentrations (Exp) recorded and averaged over each minute of anesthetic administration are depicted above the mean arterial pressure (MAP) tracing. In both groups, propofol reduced sympathetic nerve activity (SNA) and MAP and increased heart rate (HR). The subsequent administration of sevoflurane did not alter HR or SNA but led to a progressive decline in MAP. In contrast, desflurane resulted in significant increases in neurocirculatory variables that persisted throughout the 10-min mask administration period. The end-tidal anesthetic concentrations during the 10th minute of mask administration revealed that desflurane had achieved a higher relative minimum alveolar concentration than had sevoflurane. *Significant difference between groups at specific times; $P < 0.05$. †Significant interaction between groups over time (analysis of variance); $P < 0.05$.

Rapid increases in the inspired concentration of sevoflurane did not alter HR or SNA but reduced MAP, whereas rapid increases in the inspired concentration of desflurane were associated with large and significant increases in SNA, HR, and MAP.

Discussion

The major findings of this study were as follows: (1) sevoflurane anesthesia was not associated with significant increases in HR or sympathetic nerve activity (SNA) at any steady-state period of anesthesia, whereas higher concentration of the inspired desflurane was associated with increases in these variables; (2) in contrast to desflurane, a rapid increase in the inspired concentration of sevoflurane was not associated with increases in SNA, HR, or BP.

Conscious Baseline and Anesthetic Induction

Neurocirculatory variables at rest did not differ between groups (figs. 1 and 4). Propofol was used to induce anesthesia and resulted in a significant reduction in SNA and MAP and an increase in HR consistent with our previous observations with propofol.[16] Moreover, we have shown that the sympathoinhibitory effects of propofol reduce the neurocirculatory activation associated with the administration of desflurane.[17]

The 10-min administration of sevoflurane by mask after propofol administration did not alter SNA, HR, or CVP, but there was a gradual decrease in MAP that probably represents a direct effect of sevoflurane on vascular smooth muscle. In contrast, the administration of desflurane *via* mask after propofol resulted in substantial increases in HR, CVP, and sympathetic outflow and a biphasic MAP response. Although the stimulus
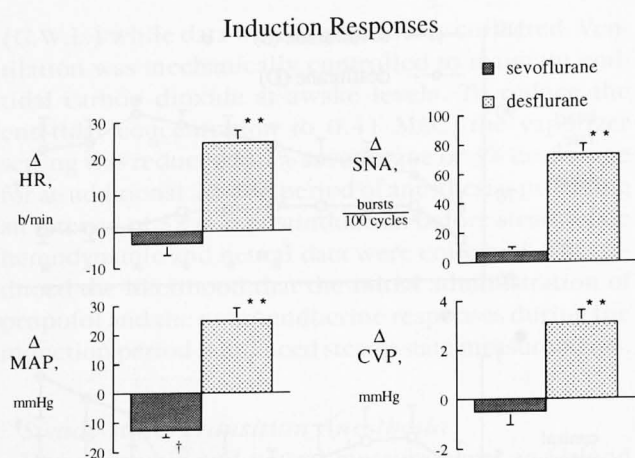
Induction Responses

Fig. 2. The peak changes in the neurocirculatory variables (mean ± SEM) during the induction period (from the propofol baseline). Sevoflurane did not alter any of the measured variables aside from a significant reduction in mean arterial pressure (†$P < 0.05$). In contrast, desflurane triggered large increases in each of the measured variables. **Significant increase from propofol baseline and significant difference between groups at $P < 0.01$.

for this neurocirculatory activation is unknown, we speculate that the response to the markedly different pungencies of these anesthetics might explain the difference.

During the administration of these anesthetics *via* mask, the alveolar (end-tidal) rate of rise of sevoflurane was slower than that of desflurane despite identical fresh gas flows and identical (with respect to MAC-equivalent) increases in the delivered concentrations of these two gases. The slightly slower increase in the end-tidal concentration of sevoflurane might be due in part to the slightly greater blood-gas partition coefficient of sevoflurane compared to desflurane (0.60 *vs.* 0.42) and perhaps due, to a small extent, to the greater degree of metabolism of sevoflurane (3% *vs.* 0.02%). The more gradual increase in the alveolar concentration of sevoflurane resulted in achievement of a lower MAC-equivalent of sevoflurane at the time of tracheal intubation. This is a likely explanation for the larger sympathetic consequences of laryngoscopy and tracheal intubation in the sevoflurane group. Despite this difference, the peak MAP response to intubation in the sevoflurane group was not significantly different from the desflurane group.

Steady-state Responses

At 0.41 and 0.83 MAC, neither sevoflurane nor desflurane was associated with changes in HR from the

respective conscious baseline level. However, both anesthetics produced similar progressive decreases in BP and forearm vascular resistance without significant changes in SNA or Nepi concentrations. This suggests that both agents have important direct effects on vascular smooth muscle such that even relatively small concentrations of these agents lead to reductions in vascular resistance and BP. Although sevoflurane has not been compared to desflurane in other adult human studies, a study in pediatric patients concludes that sevoflurane maintains BP better than does desflurane.[9] The majority of animal studies with sevoflurane have employed isoflurane as the reference anesthetic.[10,12,18] In dogs, either a similar[10] or a larger[18] BP-lowering effect of sevoflurane has been noted in comparison to isoflurane.

Similarly, the vascular resistance effects of sevoflurane have been compared only to isoflurane, and conclusions have been mixed, depending on the species studied.[10,12,13,19] One approach in rats employed equipotent concentrations of either sevoflurane or isoflurane to lower MAP to 50 mmHg.[12] At this level of hypotension, systemic vascular resistance was maintained better in the rats receiving sevoflurane than in those receiving isoflurane.

There was a progressive and significant increase in CVP with increasing concentrations of desflurane but no change in CVP in subjects receiving sevoflurane. The increase in CVP could be due to several effects of
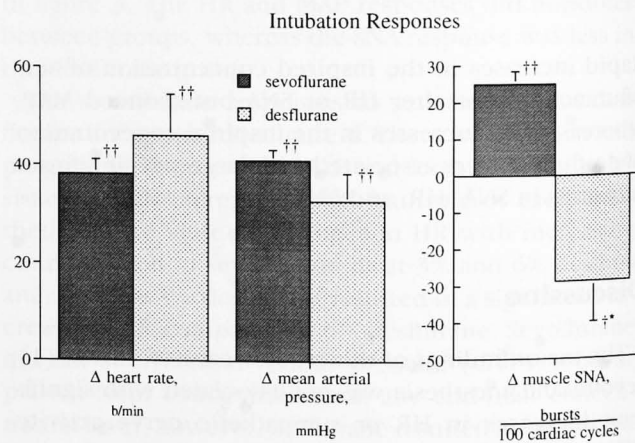
Intubation Responses

Fig. 3. The peak responses to laryngoscopy and intubation (mean ± SEM) after 10 min of mask administration of desflurane or sevoflurane. Heart rate and mean arterial pressure increased similarly and significantly in both groups: †$P < 0.05$; ††$P < 0.01$). Sympathetic nerve activity increased in the sevoflurane group and decreased in the desflurane group. *Significant difference between groups at $P < 0.05$.
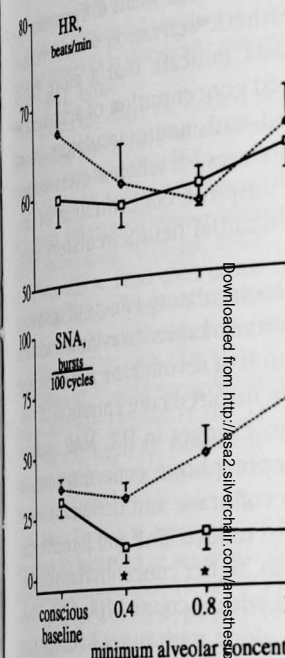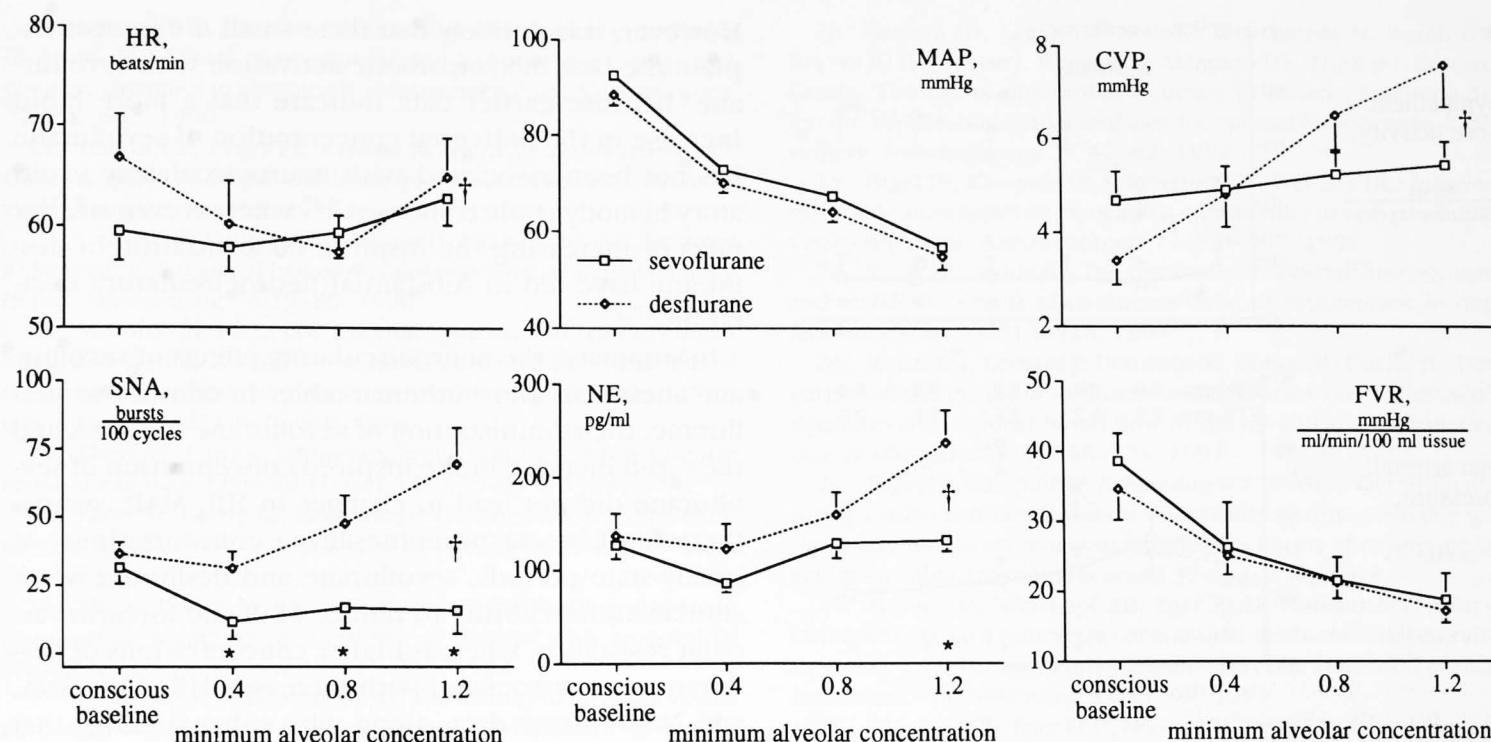
Fig. 4. Hemodynamic, neural, and plasma norepinephrine responses (mean ± SEM) to increasing mean alveolar concentrations of sevoflurane and desflurane. The measured responses represent those obtained during steady-state periods of observation. *Significant difference between groups at specific times; $P < 0.05$. †Significant interaction between groups over time (analysis of variance); $P < 0.05$.

desflurane that include pulmonary hypertension,[20] myocardial depression,[21] or venoconstriction. In chronically instrumented dogs, the myocardial depressant effects of sevoflurane and desflurane were indistinguishable.[11]

At the 1.24 MAC steady-state measurement period, there was a significant increase in basal HR, CVP, SNA, and Nepi in subjects receiving desflurane but no change in these variables in subjects receiving sevoflurane. Moreover, the rapid increase in the inspired concentration of desflurane from 6% to 9% resulted in large increases in SNA, HR, and MAP, whereas a similar rapid increase in the inspired concentration of sevoflurane was uneventful. Previous work also has indicated that the rapid increase in the inspired concentration of desflurane results in 10- to 15-fold increases in plasma epinephrine and vasopressin.[7] These data reveal a substantial effect of desflurane that initiates a significant neurocirculatory response. The initial concern that sevoflurane also might produce tachycardia and increase sympathetic outflow was not substantiated in the current study. Prior data from pediatric patients aged 3–12 yr[9] and adult patients, ASA physical status 1 and 2, undergoing elective surgery and receiving

sevoflurane[8] indicated that HR was increased 5–10 bpm in tracheally intubated patients before surgical stimulation. The only clear evidence for sevoflurane-mediated tachycardia during steady-state periods of anesthesia has been in chronically instrumented dogs.[10,11] However, these data must be interpreted cautiously because of species differences in the effects of volatile anesthetics on the autonomic nervous system. For example, numerous studies in dogs have failed to demonstrate an effect of desflurane on the autonomic nervous system,[22-24] whereas in humans, the administration of desflurane has been associated consistently with large increases in sympathetic outflow, catecholamines, vasopressin, HR, and BP.[5-7,25] Other work has indicated that the neurocirculatory excitation associated with rapid increases in the inspired concentration of desflurane lessens with repeated exposures.[26] Because of the initial large increase in the desflurane concentration on induction, it is conceivable that the neurocirculatory response recorded during the transition period might have been less than maximal because it was the second application of a large increase in the inspired concentration to the desflurane-treated subjects.
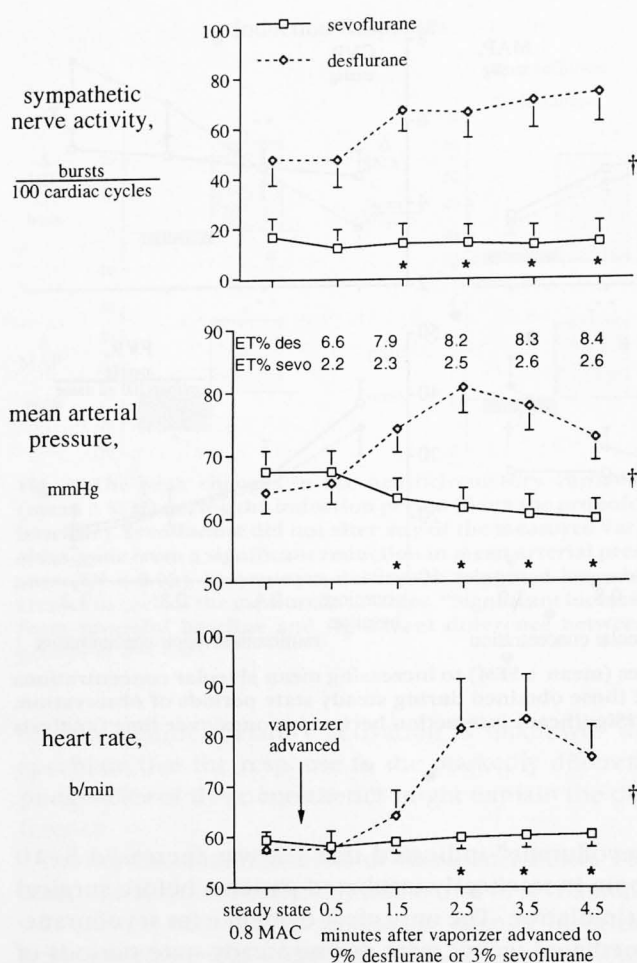
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Fig. 5. Transition responses (mean ± SEM) recorded when rapidly increasing the inspired concentration of either sevoflurane or desflurane from steady-state at 0.83 MAC to either 3% sevoflurane or 9% desflurane. This rapid change in the inspired concentration of sevoflurane triggered no untoward hemodynamic responses, whereas a similar rapid change in the inspired concentration of desflurane resulted in a doubling of sympathetic nerve activity and a significant increase in heart rate and mean arterial pressure. *Significant difference between groups at specific times; $P < 0.05$. †Significant interaction between groups over time (analysis of variance); $P < 0.05$.

Limitations

At steady-state measurement periods, the comparisons of the neurocirculatory responses to the anesthetics were unquestionably valid. However, comparisons are limited partially during periods of rapid changes in the inspired concentration. This limitation is due to the fact that the alveolar concentration (as a percent of minimum alveolar concentration) at intubation and the rate of rise of the alveolar concentration during induction and transition periods were greater with desflurane.

However, it is unlikely that these small differences explain the lack of sympathetic activation with sevoflurane, because earlier data indicate that a more rapid increase in the delivered concentration of sevoflurane has not been associated with neurocirculatory excitatory hemodynamic responses,[9,27] whereas even smaller rates of increasing the inspired concentration of desflurane have led to substantial neurocirculatory excitation.[17,25]

In summary, the neurocirculatory effects of sevoflurane anesthesia were unremarkable. In contrast to desflurane, the administration of sevoflurane *via* mask and the rapid increase in the inspired concentration of sevoflurane did not lead to changes in HR, MAP, sympathetic outflow, or norepinephrine concentrations. At steady-state periods, sevoflurane and desflurane were similar in their ability to reduce MAP and forearm vascular resistance, whereas higher concentrations of desflurane were associated with increased HR, CVP, SNA, and Nepi. These data, along with other findings that sevoflurane does not produce coronary steal,[28] suggest that the likelihood of untoward cardiovascular events with sevoflurane anesthesia might be negligible.

References

1. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. ANESTHESIOLOGY 54:100–106, 1981

2. Yurino M, Kimura H: Vital capacity breath technique for rapid anaesthetic induction: Comparison of sevoflurane and isoflurane. Anaesthesia 47:946–949, 1992

3. Hemelrijck JV, Smith I, White PF: Use of desflurane for outpatient anesthesia. ANESTHESIOLOGY 75:197–203, 1991

4. Smiley RM: An overview of induction and emergence characteristics of desflurane in pediatric, adult, and geriatric patients. Anesth Analg 75:S38–S46, 1992

5. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. ANESTHESIOLOGY 79:444–453, 1993

6. Ebert TJ, Muzi M: Sympathetic activation with desflurane in humans, Advances in Pharmacology. Volume 31. Anesthesia and Cardiovascular Disease. Edited by Bosnjak Z, Kampine JP. San Diego, Academic, 1994, pp 369–378

7. 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 80:1035–1045, 1994

8. Frink EJ Jr, Malan TP, Atlas M, Dominguez LM, DiNardo JA, Brown BR Jr: Clinical comparison of sevoflurane and isoflurane in healthy patients. Anesth Analg 74:241–245, 1992

9. Lerman J, Sikich N, Kleinman S, Yentis S: The pharmacology of sevoflurane in infants and children. ANESTHESIOLOGY 80:814–824, 1994

10. Bernard J-M, Wouters PF, Dourso...
JE, Merin RG: Effects of sevoflurane and...
coronary dynamics in chronically instrum...
72:659–662, 1990

11. Harkin CP, Pagel PS, Kersten JR, ...
Direct negative inotropic and lusitropic...
THESIOLOGY 81:156–167, 1994

12. Conzen PF, Vollmar B, Habazettl H...
K: Systemic and regional hemodynamics o...
in rats. Anesth Analg 74:79–88, 1992

13. Manohar M, Parks CM: Porcine sy...
blood flow during 1.0 and 1.5 minimum...
sevoflurane anesthesia without and with...
macol Exp Ther 231:640–648, 1984

14. Ebert TJ: Carotid baroreflex regu...
resistance in man. J Physiol (Lond) 337:...

15. Ebert TJ, Kotrly KJ, Kampine JP: E...
efferent nerve activity is augmented by ...
68:S1–S321, 1989

16. Ebert TJ, Muzi M, Berens R, Goff D...
responses to induction of anesthesia in...
etomidate. ANESTHESIOLOGY 76:725–733, ...

17. Lopatka CW, Muzi M, Ebert TJ: The...
etomidate in reducing desflurane-media...
in humans (abstract). ANESTHESIOLOGY 81:...

18. Kazama T, Ikeda K: The comparat...
sevoflurane with halothane and isofluran...

19. Crawford MW, Lerman J, Saldivia...
dynamic and organ blood flow respon...
anesthesia during spontaneous ventilatio...
1006, 1992

10. Bernard J-M, Wouters PF, Doursout M-F, Florence B, Chelly JE, Merin RG: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. ANESTHESIOLOGY 72:659–662, 1990

11. Harkin CP, Pagel PS, Kersten JR, Hettrick DA, Warltier DC: Direct negative inotropic and lusitropic effects of sevoflurane. ANESTHESIOLOGY 81:156–167, 1994

12. Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messmer K: Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. Anesth Analg 74:79–88, 1992

13. Manohar M, Parks CM: Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. J Pharmacol Exp Ther 231:640–648, 1984

14. Ebert TJ: Carotid baroreflex regulation of forearm vascular resistance in man. J Physiol (Lond) 337:655–664, 1983

15. Ebert TJ, Kotrly KJ, Kampine JP: Human muscle sympathetic efferent nerve activity is augmented by nitrous oxide. Anesth Analg 68:S1–S321, 1989

16. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. ANESTHESIOLOGY 76:725–733, 1992

17. Lopatka CW, Muzi M, Ebert TJ: The efficacy of propofol versus etomidate in reducing desflurane-mediated sympathetic activation in humans (abstract). ANESTHESIOLOGY 81:A136, 1994

18. Kazama T, Ikeda K: The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. J Anesth 2:63–68, 1988

19. Crawford MW, Lerman J, Saldivia V, Carmichael FJ: Hemodynamic and organ blood flow responses to halothane and sevoflurane anesthesia during spontaneous ventilation. Anesth Analg 75:1000–1006, 1992

20. Helman JD, Leung JM, Bellows WH, Pineda N, Roach GW, Reeves JD III, Howse J, McEnany T, 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 77:47–62, 1992

21. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Influence of volatile anesthetics on myocardial contractility in vivo: Desflurane versus isoflurane. ANESTHESIOLOGY 74:900–907, 1991

22. Milde LN, Milde JH: The cerebral and systemic hemodynamic and metabolic effects of desflurane-induced hypotension in dogs. ANESTHESIOLOGY 74:513–518, 1991

23. Merin RG, Bernard J, Doursout M, Cohen M, Chelly JE: Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. ANESTHESIOLOGY 74:568–574, 1991

24. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Evaluation of myocardial contractility in the chronically instrumented dog with intact autonomic nervous system function: Effects of desflurane and isoflurane. Acta Anaesthesiol Scand 37:203–210, 1993

25. 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 81:94–98, 1994

26. Weiskopf RB, Eger EI II, Noorani M, Daniel M: Repetitive rapid increases in desflurane concentration blunt transient cardiovascular stimulation in humans. ANESTHESIOLOGY 81:843–849, 1994

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

28. Kersten JR, Brayer AP, Pagel PS, Tessmer JP, Warltier DC: Perfusion of ischemic myocardium during anesthesia with sevoflurane. ANESTHESIOLOGY 81:995–1004, 1994