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Desflurane-mediated Neurocirculatory Activation in Humans

Effects of Concentration and Rate of Change on Responses

Michael Muzi, M.D., Craig W. Lopatka, D.D.S., M.D.,† Thomas J. Ebert, M.D., Ph.D.‡*

Background: **Rapid increases in the inspired concentration of desflurane have been associated with sympathetic activation, tachycardia, hypertension, and in select cases, myocardial ischemia. The current study examined the effects of the rate of change of the desflurane concentration on the sympathetic and hemodynamic responses to desflurane and sought to determine whether a finite concentration (end-tidal) of desflurane consistently initiated these responses.**

Methods: **After Institutional Review Board approval, 23 healthy male volunteers were instrumented for electrocardiogram (heart rate (HR)), intraarterial blood pressure, and peroneal nerve microneurography (sympathetic nerve activity (SNA)). Subjects were given propofol (2.5 mg/kg) and vecuronium (0.15 mg/kg), and their lungs were mechanically ventilated for 30 min at a minimum alveolar concentration of 0.5 MAC with either desflurane or isoflurane (random assignment). The end-tidal concentration was increased at either 1% per min (n = 7) or 0.5% per min (n = 7) for desflurane or 0.16% per min (n = 9) for isoflurane (MAC-multiple comparable to 1% per min desflurane group) until 1.5 MAC was reached. HR, blood pressure, and SNA were averaged over 1-min segments from 0.5 to 1.5 MAC levels.**

Results: **Awake neurocirculatory variables did not differ among the three groups. At 0.5 MAC, blood pressure had decreased (12–15%) and HR increased (12–20%) similarly in both groups. SNA decreased 77% in the isoflurane group but was not significantly changed in the desflurane groups. In the desflurane groups, the threshold (end-tidal concentration associated with a 10% increase in the measured variable) ranged between 4% and 10% for HR and between 4% and 7.7% for SNA. In the isoflurane group, the threshold occurred between 1.0% and 1.6% for HR and between 0.7% and 1.3% for SNA. The rate of change did not affect the threshold concentration or the peak HR increase in the desflurane groups. In contrast, SNA responses to desflurane were directly proportional to the rate of change.**

Conclusions: **There was no consistent threshold for the neurocirculatory activation associated with desflurane, and the HR and SNA thresholds generally were less than 1 MAC. The HR increase associated with desflurane was not rate- or concentration-dependent. In contrast, SNA responses were proportional to the rate of change and the concentration of desflurane. (Key words: Anesthetics, volatile: desflurane; isoflurane. Measurement techniques: microneurography. Sympathetic nervous system: blood pressure; heart rate.)**

DESFLURANE has been associated with sympathetic activation,[1,2] tachycardia, hypertension,[1–3] and myocardial ischemia[4] when inspired concentrations are rapidly increased in steps ranging from 3% to 7%. The possibility that smaller increases in the concentration of desflurane might avoid these cardiovascular perturbations was examined by Moore *et al.*[5] In their study, an anesthetized baseline was established with 4% desflurane in healthy human volunteers. Then 1% step increases in the end-tidal desflurane concentration were established within the first 30 s of sequential 5-min periods. They found that step increases in desflurane to a concentration greater than 5% were most frequently associated with catecholamine and hemodynamic responses. Several aspects of the study design limited the characterization of the stimulus/response to desflurane, *e.g.*, the choice of only one rate of change of the end-tidal concentration of desflurane and the necessity to increase the inspired desflurane by 4% to achieve a rapid 1% end-tidal increase in desflurane. The neurocirculatory activation could have been due to high inspired concentrations, affecting airway receptors, or due to an end-tidal (systemic) effect.

* Assistant Professor of Anesthesiology, Department of Anesthesiology, The Medical College of Wisconsin and VA Medical Center, Milwaukee, Wisconsin.

† Staff Physician, McCray Memorial Hospital, Kendallville, Indiana.

‡ Professor of Anesthesiology and Physiology, Department of Anesthesiology, The Medical College of Wisconsin and VA Medical Center, Milwaukee, Wisconsin.

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

Accordingly, we conducted a study to clarify and answer the following questions: First, does the rate of change in the end-tidal concentration of desflurane influence the subsequent hemodynamic and sympathetic response? Second, is there a finite threshold concentration for the neurocirculatory responses associated with desflurane? Finally, does an increase in the alveolar concentration of isoflurane that is comparable to that of desflurane (as a MAC-multiple) lead to similar neurocirculatory effects? To effectively answer these questions, we employed electrocardiography, sympathetic microneurography, and direct measures of arterial pressure to record moment-to-moment responses to either 0.5% or 1% per minute increases in end-tidal concentrations of desflurane or 0.16% per minute increases in end-tidal isoflurane concentrations (MAC-multiple comparable to 1% per minute desflurane increases).

Methods and Materials

After Institutional Review Board approval, 23 healthy male volunteers were studied. The 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 of 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 after local anesthesia for direct determination of blood pressure. An 18-G catheter was inserted into a forearm vein, and 7 ml/kg of saline was administered before initiation of the study. Sympathetic nerve activity (SNA) was recorded *via* percutaneous impalement of the peroneal nerve, as described previously.[6] Characteristic bursts of efferent SNA were sought by fine manipulations of the needle within a fascicle of nerves supplying skeletal muscle. When spontaneous bursts of neural activity were evident on the amplified signal, their behavior in pulse-synchronous groupings and their more frequent occurrence in late expiratory and early inspiratory periods were noted. Neural activity could be increased by prolonged breath-holding and during the hypotension associated with phases II and III of the Valsalva maneuver but was unaffected by startle maneuvers.

Once an acceptable sympathetic recording was obtained, a 10-min quiet rest period was observed followed by a 5-min sampling of hemodynamic (HR, blood pressure) and neural (SNA) data at conscious baseline. A blood sample was obtained from the arterial catheter for blood gas analysis. A face mask was placed and 100% O_2 administered for 5 min. A priming dose of vecuronium (0.01 mg/kg) was given followed 3 min later by anesthetic induction with propofol (2.5 mg/kg) and vecuronium (0.15 mg/kg). Ventilation was controlled *via* the mask until full neuromuscular blockade was established and the trachea was intubated. Subjects were randomized to receive either isoflurane or one of the increments of desflurane. Anesthesia was maintained at 0.5 MAC (end-tidal) of either desflurane (3.6%) or isoflurane (0.6%) for 20 min after intubation (~25 min after propofol), and neurocirculatory data were obtained. The end-tidal concentration was increased at either 1% per minute (n = 7) or 0.5% per minute (n = 7) for desflurane or 0.16% per minute (n = 9) for isoflurane (comparable to a 1% per minute desflurane increase) until 1.5 MAC (11% desflurane or 1.8% isoflurane) was achieved. To achieve target end-tidal concentrations 60 s after the vaporizer increase, the inspired concentration of anesthetic was set 1% above the desired desflurane concentration each min or 0.4% above the desired isoflurane concentration and fresh gas flows ($F_{I_{O_2}}$ = 50%) were adjusted to between 6 and 10 l/min. HR, blood pressure, and SNA were averaged from the initial and final 30 s of each 1-min interval after a vaporizer increase until 1.5 MAC was achieved. End-tidal carbon dioxide and inspiratory and expiratory desflurane or isoflurane concentrations after induction were measured with a calibrated Ohmeda 5250 infrared respiratory gas monitor (Madison, WI).

Statistical analyses included analysis of variance to determine differences within groups and differences between treatment groups at rest and during 0.5 MAC anesthesia. For each variable and in each treatment group, the threshold for "activation" was defined as a 10% increase from the value determined at steady-state 0.5 MAC. Linear regression analyses were performed on SNA and HR data taken from threshold to the peak values for each variable if more than three points were available for regression. To define the frequency of linear responses, the number of individual correlation coefficients exceeding 0.7 were determined for the two rates of change of the end-tidal desflurane concentration. Maximum slopes of individuals with correlation coefficients exceeding 0.7 were averaged for each group and compared with Student's *t* tests. Mean threshold values were compared with unpaired Student's *t* tests and analysis of variance. Significance was achieved if $P < 0.05$.

Table 1. Steady-state Neurocirculatory Parameters

	Desflurane, 0.5% per min	Desflurane, 1% per min	Isoflurane, 0.16% per min
Heart rate (beats/min)			
Conscious baseline	60 ± 4	66 ± 5	61 ± 3
0.5 MAC	71 ± 5*	74 ± 5*	75 ± 4*
Mean arterial pressure (mmHg)			
Conscious baseline	94 ± 3	93 ± 3	92 ± 3
0.5 MAC	83 ± 4*	80 ± 3*	78 ± 4*
Sympathetic nerve activity, (units)			
Conscious baseline	119 ± 34	140 ± 47	105 ± 29
0.5 MAC	65 ± 19	123 ± 63	17 ± 7*†

Data are mean ± SEM.

Units = burst frequency × mean burst amplitude per 100 cardiac cycles.

* Significant change from conscious baseline, $P < 0.05$.

† Isoflurane change from conscious baseline different from desflurane change, $P < 0.05$.

Results

Study participants were healthy men aged 19–24 yr. Resting neurocirculatory parameters did not differ in the three study groups (table 1). Mean arterial pressure (MAP) significantly decreased and HR significantly increased in all groups at the steady-state 0.5 MAC measurement period (table 1), whereas SNA was only significantly changed (decreased) in the isoflurane group.

Figure 1 displays regression analyses relating the average target end-tidal anesthetic concentration to the average achieved concentration in each of the three anesthetic groups. There were linear increases in the end-tidal concentrations, and the target concentrations were successfully achieved in the desflurane groups. Despite the use of high fresh gas flows, the target isoflurane concentration was underachieved by a small

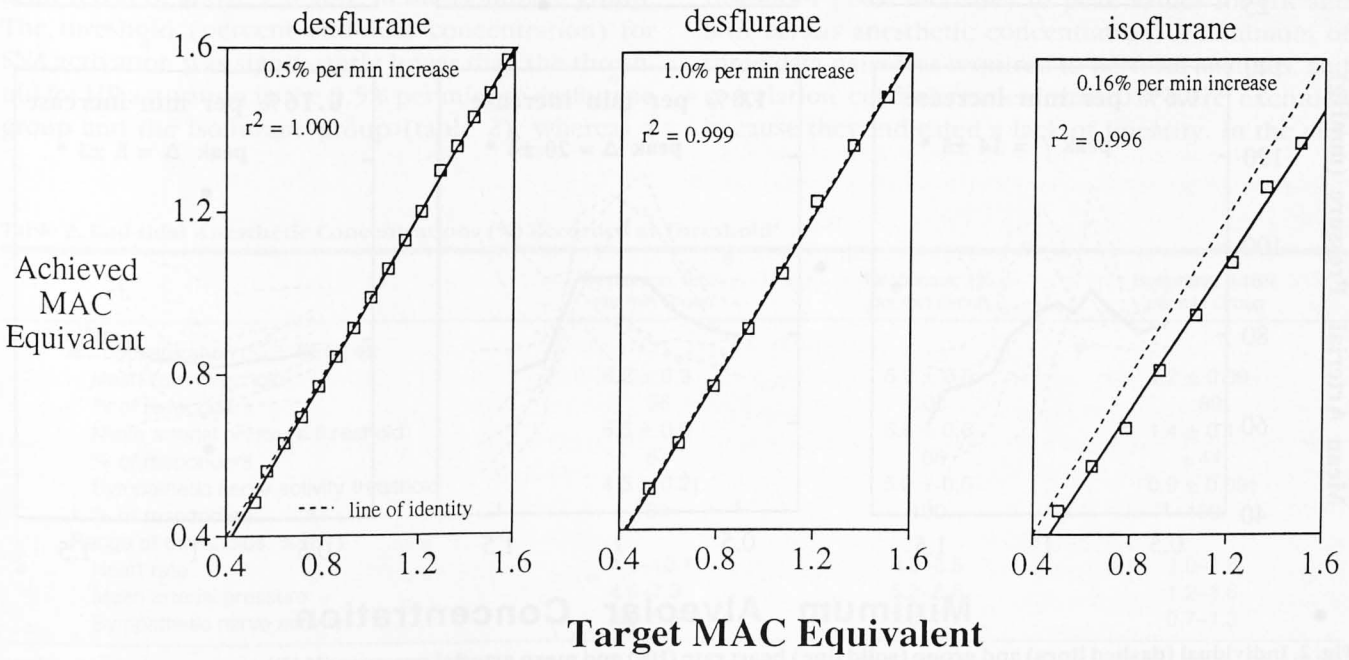

Fig. 1. Linear regression analysis of target *versus* actual end-tidal anesthetic concentrations in each study group. Correlation coefficients and the line of identity (dashed line) are displayed. Isoflurane target concentrations were underachieved consistently, but the slope of the relationship did not differ from the line of identity.

but consistent amount. This underachievement was due to the greater blood:gas solubility of isoflurane and the decision not to use higher inspired concentrations of isoflurane. Figures 2 and 3 display the individual and group responses to increasing concentrations of desflurane or isoflurane. The average peak increase in HR and MAP did not differ between the two desflurane groups. In the isoflurane group, peak increases in HR were not different from the desflurane groups, but peak MAP increases were two- to threefold less than the desflurane responses (fig. 2), and peak SNA increases in response to isoflurane were six- to ninefold less than the peak desflurane effects ($P < 0.01$; fig. 3). In the two desflurane groups, there were equivalent maximal HR and MAP responses; however, peak increases in SNA (from the anesthetized 0.5 MAC baseline) were nearly twofold greater in the 1.0% per minute compared to the 0.5% per minute desflurane group ($P < 0.05$).

The end-tidal anesthetic concentrations associated with a 10% increase (threshold) in HR, MAP, or SNA from the steady-state value at the 3.5% desflurane baseline or 0.6% isoflurane baseline are shown in table 2.

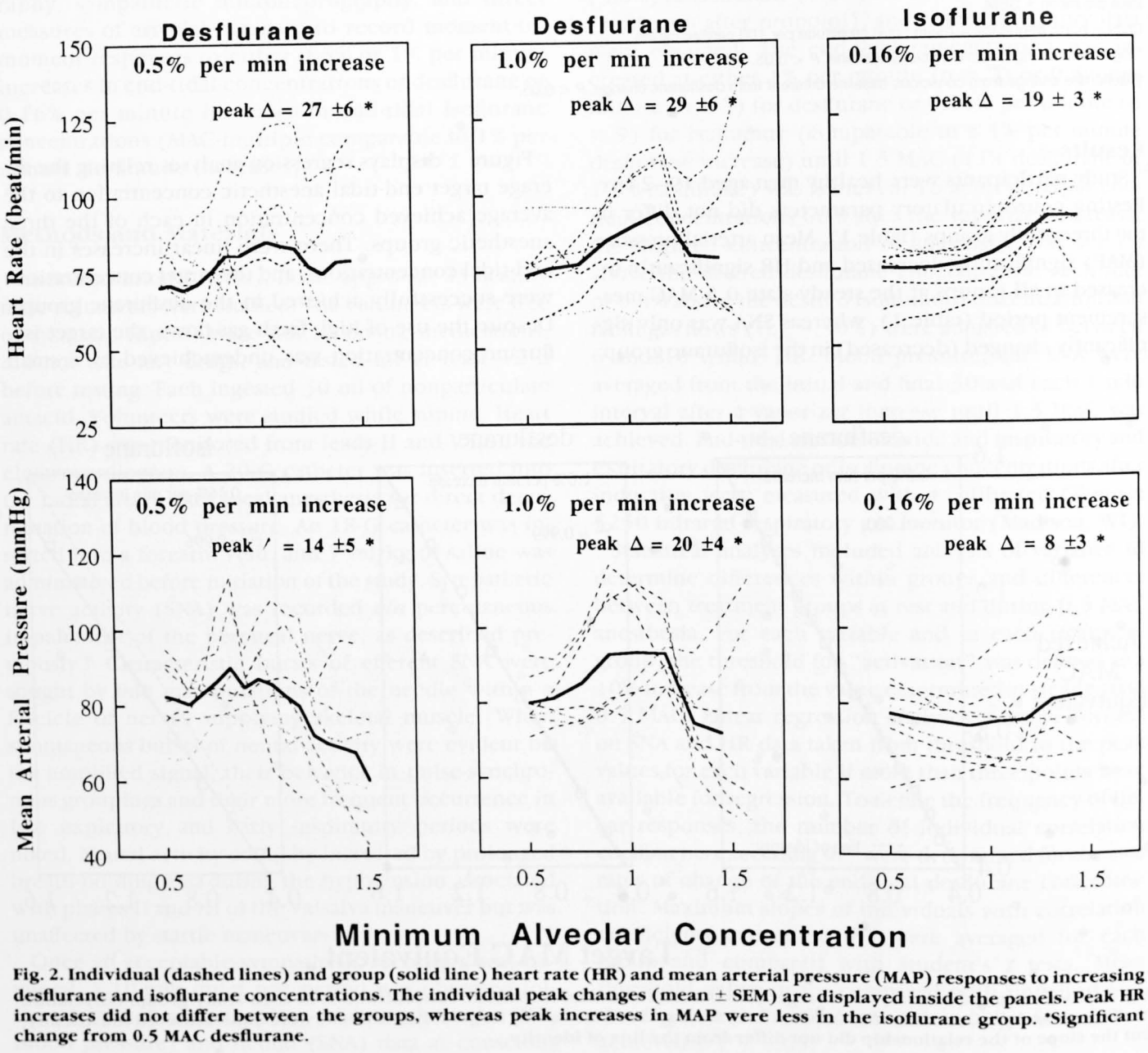

Fig. 2. Individual (dashed lines) and group (solid line) heart rate (HR) and mean arterial pressure (MAP) responses to increasing desflurane and isoflurane concentrations. The individual peak changes (mean ± SEM) are displayed inside the panels. Peak HR increases did not differ between the groups, whereas peak increases in MAP were less in the isoflurane group. *Significant change from 0.5 MAC desflurane.

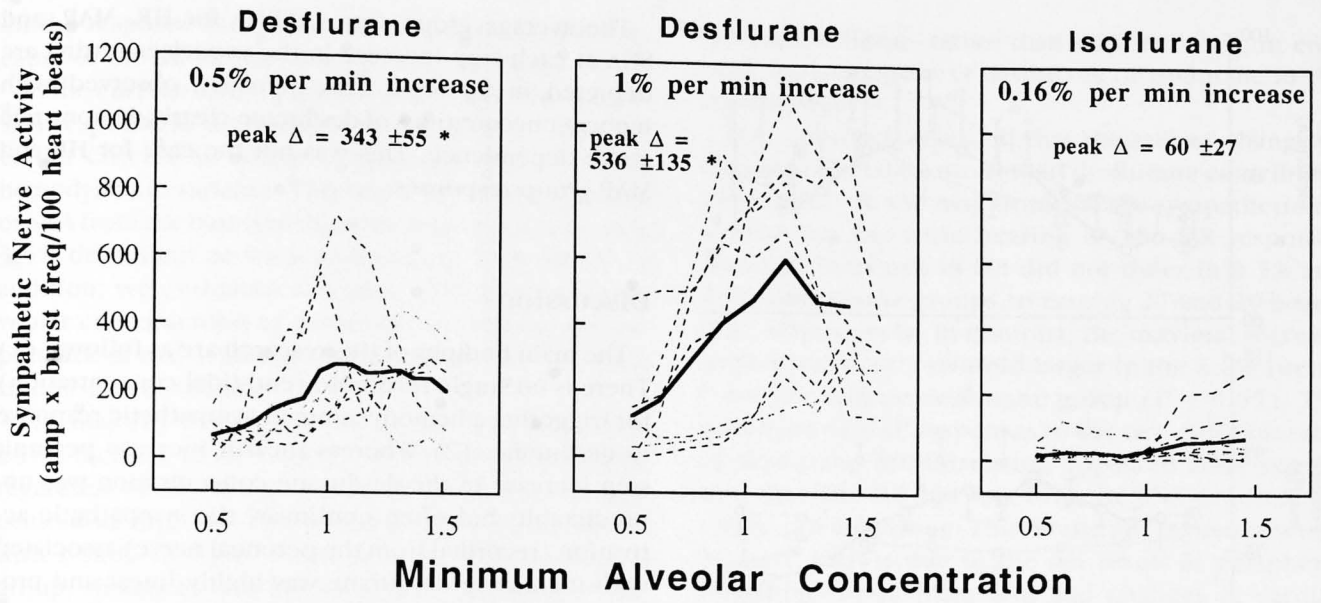

Fig. 3. Individual (dashed lines) and group (solid line) sympathetic nerve activity (SNA) responses to increasing desflurane and isoflurane concentrations. The individual peak changes (mean ± SEM) are displayed inside the panels. Isoflurane did not cause significant increases in SNA, whereas desflurane was associated with significant increases in SNA that were augmented in the 1% per minute desflurane group. *Significant change from 0.5 MAC desflurane.

Whereas the activation thresholds for HR generally were achieved at end-tidal concentrations of less than 1.0 MAC in the desflurane groups, these were primarily achieved at or above 1.0 MAC in the isoflurane group. The threshold (percent end-tidal concentration) for SNA activation was significantly lower than the threshold for HR activation in the 0.5% per minute desflurane group and the isoflurane group (table 2), whereas a similar but nonsignificant trend was observed in the 1% per minute desflurane group.

Linear regression analyses were performed from threshold (10% increase) to peak values for HR and SNA *versus* anesthetic concentration. A minimum of three data pairs was required to perform analyses, and correlation coefficients less than 0.7 were excluded because they indicated a lack of linearity. In the des-

Table 2. End-tidal Anesthetic Concentrations (%) Recorded at Threshold*

	Desflurane, 0.5% per min Group	Desflurane, 1% per min Group	Isoflurane, 0.16% per min Group
ET concentration (% ± SEM) at:			
Heart rate threshold	6.2 ± 0.9	6.2 ± 0.5	1.2 ± 0.09
% of responders	86	100	89
Mean arterial pressure threshold	5.5 ± 0.6	6.6 ± 0.6	1.4 ± 0.1
% of responders	57	86	44
Sympathetic nerve activity threshold	4.5 ± 0.2†	5.0 ± 0.5	0.9 ± 0.09†
% of responders	100	100	100
Range of thresholds, % (ET)			
Heart rate	4.1–10.1	4.5–8.5	1.0–1.6
Mean arterial pressure	4.6–7.3	5.3–8.8	1.2–1.6
Sympathetic nerve activity	3.9–5.6	3.5–7.7	0.7–1.3

% of responders = % of individuals in each group that achieved threshold.

* Threshold is defined as a 10% increase in the measured parameter from the 0.5 MAC steady-state measurement.

† Significantly lower than the heart rate threshold, $P < 0.05$.

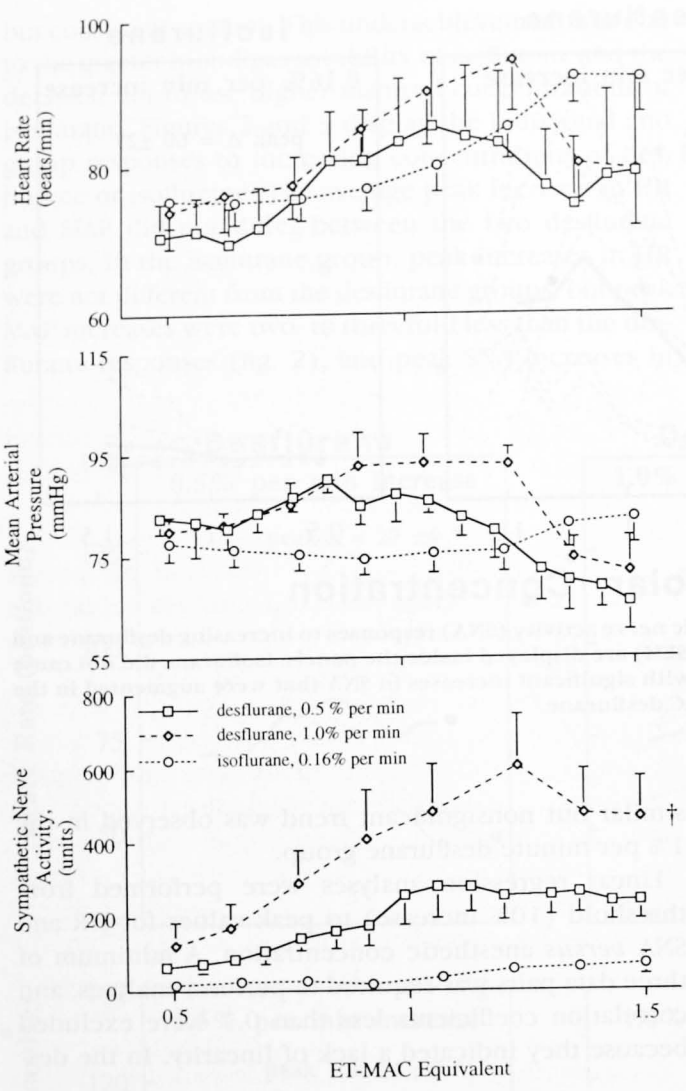

Fig. 4. Group response (mean ± SEM) to linear increases in the end-tidal concentrations of either isoflurane or desflurane. The SNA responses to desflurane were rate-dependent, and the slope of the response to 1% per minute increases in the desflurane concentration was steeper than the slope of the slower rate of desflurane increase and isoflurane (†, $P < 0.05$).

flurane groups, 12 of 14 subjects had acceptable SNA data for linear regression analyses, whereas only 6 of 14 subjects had acceptable HR data for regression analyses (chi-square, $P < 0.05$). For SNA *versus* anesthetic concentration, the average slope of the regression analysis was 22% greater in the 1% per minute desflurane group compared to the 0.5% per minute group ($P < 0.05$), whereas the limited number of slopes in the HR analyses precluded further statistical analysis and presumably indicated a lack of or an inconsistent linear effect of anesthetic concentration on HR increases.

The average group data (±SEM) for HR, MAP, and SNA at each step increase in the vaporizer setting are depicted in figure 4. SNA increases observed with higher concentrations of desflurane clearly demonstrate a rate dependence. This was not the case for HR and MAP group responses.

Discussion

The main findings of this research are as follows: (1) There is no single threshold (end-tidal concentration) for triggering a hemodynamic or sympathetic response to desflurane. (2) Whereas the HR increase per unit step increase in the desflurane concentration was unpredictable and often nonlinear, the sympathetic activation (recorded from the peroneal nerve) associated with increasing desflurane was highly linear and proportional to the rate of change of the expired concentration of desflurane. (3) Step increases in the end-tidal concentration of isoflurane that were comparable (on a MAC-equivalent basis) to slightly less than 1% per minute desflurane increases resulted in substantially less sympathetic activation (five- to ninefold less) than noted with desflurane. (4) HR increases associated with increasing concentrations of desflurane occurred primarily at or below 1 MAC, whereas HR increases associated with isoflurane were primarily at or above 1 MAC.

Previous work[5] has suggested a threshold of 6% desflurane for the hemodynamic response associated with a rapid increase in the anesthetic concentration. This was established by determining the number of volunteers responding with greater than a 10% change in HR or blood pressure to sequential 1% step increases in the end-tidal concentration of desflurane. When increasing the desflurane from 4% to 5% in this earlier study, only 1 of 13 subjects responded, whereas 8 of 13 responded to an increase from 5% to 6% end-tidal desflurane. Interpretation of the data from this earlier study was limited by the protocol design. The study required the inspired concentration of desflurane to be increased by 4% to achieve a 1% end-tidal increase in less than 30 s. Inspired rather than end-tidal concentrations of desflurane may have initiated hemodynamic responses, and the resulting calculation of threshold would have been different if inspired concentrations were driving the hemodynamic responses. Moreover, the rate of change of the inspired or expired concentration of desflurane might have had a significant effect

on the response but could not be commented on because of the use of only a single rate of change.

In the current study, a finite threshold for the HR and SNA response to desflurane was not evident. We used earlier criteria[5] to define a significant increase in the hemodynamic variable. This was a 10% increase in HR or SNA from the baseline value measured at steady-state 3.5% desflurane or 0.6% isoflurane (~0.5 MAC). In addition, we evaluated two rates of change in the alveolar concentration of desflurane to evaluate the importance of rate of change on the "threshold" and peak response to desflurane.

The majority of subjects (10 of 13) responded with a 10% increase in HR between 4.5% and 8% desflurane regardless of the rate of change of the desflurane concentration, and 70% responded at concentrations less than 1 MAC. In eight of nine subjects in the isoflurane group, threshold was achieved with increases in the alveolar concentration, and in contrast to desflurane, HR increases with isoflurane occurred primarily with step increases above the 1 MAC level (85% of responders).

The SNA responses also did not behave as if a finite threshold for activation was present. Instead, increases in SNA were linearly related to the absolute level of desflurane, and the slope of the response was steeper (by 22%) in the desflurane group with the faster rate of change of concentration. The concentration dependence in the SNA response was noted previously by this laboratory when SNA responses and plasma norepinephrine concentrations progressively increased at 1.0 and 1.5 MAC desflurane but did not change after increases in the MAC of isoflurane.[1,2] Unlike the broad range of desflurane concentrations that triggered HR increases (4–10%), the 10% threshold for increases in SNA occurred over a smaller range (4–7.7%) in the desflurane groups (table 2). These differences suggest that HR and SNA responses to desflurane may be mediated by dissimilar mechanisms as further discussed below.

In this study, we were able to effect a linear increase in the end-tidal concentrations of desflurane and isoflurane by delivering an inspired concentration of not greater than 1% above the target desflurane concentration and not more than 0.4% above the target isoflurane concentration. This was done by adjusting the fresh gas flow of the two volatile anesthetics. The 0.5% or 1.0% per minute increases in the end-tidal concentrations were achieved in 1-min intervals in contrast to 1% steps in 5-min intervals employed in an earlier study.[5] This resulted in linear, rather than step increases, in end-tidal concentrations of desflurane or isoflurane in the current study.

This approach revealed that the rate of change in the end-tidal concentration of desflurane contributes importantly to the magnitude of the sympathetic response but has little bearing on the HR response. Maximal increases in HR did not differ in 0.5% and 1.0% per minute groups, averaging 27 and 29 beats/min, respectively. In contrast, the maximal increase in SNA was nearly twofold larger in the 1.0% *versus* 0.5% per minute desflurane group ($P < 0.05$). The gradation of MAP responses to the two different rates of desflurane administration appeared more consistent than the HR but less than the SNA dependence on the rate of change. This would not be unexpected, because MAP is due to the net result of peripheral vasoconstriction from SNA and changes in cardiac output due to HR fluctuations. In addition, there is an opposing force throughout the period of increasing desflurane and isoflurane to reduce MAP *via* their direct effects on vascular smooth muscle.

The less consistent effect of the rate of change of desflurane on HR *versus* SNA is not clearly understood but might be related to the multiple control mechanisms governing HR. Both vagal and sympathetic neural input (and several local and circulating factors) are involved. Moreover, the neural control of HR in humans is primarily *via* fluctuations in cardiac-vagal drive with minimal influence of sympathetic mechanisms.[7,8] If desflurane has an inconsistent or nonparallel influence on the control of sympathetic and vagal drive to the heart and vagal drive is the primary determinant of HR, highly variable HR responses to desflurane, in terms of absolute concentration or the rate of change of the concentration, would not be unexpected.

Limitations

We were able to effect a linear increase in the end-tidal concentrations of desflurane and isoflurane by delivering an inspired concentration of not greater than 1% above the target desflurane concentration and not more than 0.4% above the target isoflurane concentration. High fresh gas flows were employed to ensure a rapid delivery of the anesthetic to the alveoli and pulmonary blood. Because of the slightly higher inspired *versus* target end-tidal anesthetic concentration, we cannot be certain that responses to desflurane and isoflurane were not triggered by inspired rather than end-tidal concentrations. However, we separately analyzed

responses during the first and last 30 s of each 1-min file after increasing the vaporizer setting. In no case did the initial 30-s response exceed the final 30-s response, suggesting that the inspired concentration was less likely a factor.

In summary, there was no consistent threshold for the neurocirculatory activation associated with desflurane, and the HR and SNA thresholds were generally less than 1 MAC. The HR increase was not rate- or concentration-dependent. In contrast, SNA responses were proportional to the rate of change and the concentration of desflurane.

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