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Depression of Ventilation by Desflurane in Humans

Stephen H. Lockhart, Ph.D., M.D., Ira J. Rampil, M.D.,† Nobuhiko Yasuda, M.D.,‡*
Edmond I. Eger II, M.D.,§ Richard B. Weiskopf, M.D.¶

We studied the ventilatory effects of desflurane (formerly I-653) with and without N_2O in healthy male volunteers. After insertion of venous and arterial (radial and pulmonary) catheters, baseline measurements of tidal volume (V_T), respiratory rate (RR), ventilatory response to CO_2, and arterial and mixed venous blood gases were made. Subjects were randomly assigned to receive either desflurane with O_2 (n = 6) or with O_2 and 60% N_2O (n = 6). Anesthesia was induced by inhalation of desflurane followed by tracheal intubation without muscle relaxants. In each volunteer, at end-tidal concentrations totaling 0.83, 1.24, and 1.66 MAC, we repeated measurements of V_T, RR, response to CO_2, and arterial and mixed venous blood gases. As depth of anesthesia increased, V_T significantly ($P < 0.05$) decreased from 363 ± 22 ml awake to 76 ± 22 ml at 1.66 MAC without N_2O and from 473 ± 70 ml awake to 128 ± 6 ml at 1.66 MAC with N_2O (mean ± SE). Similarly, RR increased from 15 ± 0.5 breaths per min awake to 32 ± 2 breaths per min at 1.66 MAC without N_2O and from 14 ± 0.5 breaths per min awake to 40 ± 3 breaths per min at 1.66 MAC with N_2O. Desflurane without N_2O depressed the ventilatory response to CO_2 to 45 ± 9, 31 ± 5, and 11 ± 4% of the awake values at 0.83, 1.24, and 1.66 MAC, respectively. With N_2O, values were 52 ± 14, 23 ± 5, and 26 ± 9% of the awake value at 0.83, 1.24, and 1.66 MAC, respectively. With or without N_2O, arterial CO_2 tension ($PaCO_2$) increased, not always significantly, with depth of anesthesia. At 1.24 and 1.66 MAC, Pa_{CO_2} was significantly higher in the group that received desflurane in O_2 (58 ± 2 and 84 ± 5 mm, respectively) than in the group that received desflurane with N_2O (50 ± 2 and 59 ± 2 mm, respectively). We conclude that desflurane is a ventilatory depressant in humans. At anesthetic concentrations up to 1.24 MAC, with or without N_2O, the depression observed is comparable to that found in previous studies with isoflurane. At deeper levels (up to 1.66 MAC), depression of ventilation with desflurane is comparable to that previously reported with enflurane. (Key words: Anesthesia, complications: ventilatory depression. Anesthetics, gases: nitrous oxide. Anesthetics, volatile: desflurane. Carbon dioxide. Ventilation.)

DESFLURANE (CF_3-CHF-O-CHF_2), formerly I-653, is a new volatile agent being investigated for use as a general anesthetic. Although it is structurally similar to isoflurane (CF_3-CHCl-O-CHF_2), it is less soluble in blood and tissues.[1,2] As a consequence, anesthetic uptake and elimination are more rapid with desflurane than isoflurane.[3] These properties suggest that desflurane may be a useful addition to currently available volatile agents, particularly for surgical procedures of short duration. Although the potency of desflurane has been determined (MAC is 7.25% for patients 18–30 yr and 6% for patients 31–65 yr of age),[4] the physiologic effects of this agent in humans have not been described previously.

The purpose of this study was to determine the effects of desflurane (with and without N_2O) on ventilation in humans.

Materials and Methods

With approval from the University of California, San Francisco, Committee on Human Research, and informed consent, we studied 12 healthy male volunteers 20–26 yr of age. Each subject was studied in the morning after at least 8 h of fasting. No medications were given prior to inducing anesthesia. Using local anesthesia, we inserted catheters into the radial and pulmonary arteries to monitor these pressures and to obtain blood for sampling. Subjects then rested quietly in a darkened room for at least 40 min, after which we obtained baseline measurements of tidal volume (V_T), respiratory rate (RR), end-tidal CO_2 tension ($PETCO_2$), ventilatory response to CO_2, and arterial and mixed venous blood gases. During the acquisition of baseline measurements, each subject, with a nose clip in place, breathed O_2 through a mouthpiece connected to the anesthetic circle system. Volunteers then were randomly assigned to receive three concentrations of either desflurane alone (n = 6) or desflurane with 60% N_2O (n = 6).

We used a conventional anesthetic circle system but replaced the reservoir bag with a 6-l bag enclosed in a rigid container (bag-in-box) that was airtight except for an opening leading either to a Fleisch pneumotachometer or to an Ohmeda® volume monitor. Both devices were calibrated with a bell-type water-seal spirometer. The pneumotachometer was used to transduce airway gas flow, from which V_T and RR were calculated online with Labview® software on a Macintosh® IIx computer. PET_{CO_2}, inspired N_2O, and inspired and end-tidal desflurane concentrations were measured continuously by a Datex® 254 infrared gas analyzer modified to reflect linearly concentrations of up to 18% desflurane. The Datex® was cali-

* Assistant Professor, Department of Anesthesia, University of California President's Fellow.

† Assistant Professor, Department of Anesthesia, University of California, San Francisco.

‡ Fellow, Department of Anesthesia, University of California, San Francisco; Assistant Professor, Jikei University, Tokyo Japan.

§ Professor of Anesthesia, University of California, San Francisco.

¶ Professor of Anesthesia and Physiology; Staff, Cardiovascular Research Institute, University of California, San Francisco.

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Address reprint requests to Dr. Lockhart: Department of Anesthesia, Room S-455, Box 0464, University of California, San Francisco, California 94143-0464.

TABLE 1. The Effects of Desflurane Anesthesia with and without N_2O on Resting Ventilation

Desflurane End-tidal Concentration (%)	MAC Multiple	Pa_{CO_2} (mmHg)	$\dot{V}_E$ (l/min)	V_T (ml)	RR (breaths per min)	O_2 Consumption (ml/min)	Estimated Values* $\dot{V}_A$ (l/min)	V_D/V_T (%)	Q_S/Q_T (%)
Desflurane with O_2									
Awake		40 ± 1	5.30 ± 0.80	363 ± 22	15 ± 0.5	207 ± 15	3.1 ± 0.3	40 ± 5	3.4 ± 1.7
6.0	0.83	49 ± 1†	5.53 ± 0.52	235 ± 21†	24 ± 1.5†	237 ± 15	3.2 ± 0.2	42 ± 4	18.8 ± 2.3
9.0	1.24	58 ± 2‡	4.32 ± 0.74	148 ± 22‡	26 ± 0.2†	227 ± 16	2.6 ± 0.2	47 ± 5	19.2 ± 2.7
12.0§	1.66	84 ± 5‡	2.41 ± 0.72	76 ± 22¶	32 ± 2.0‡	228 ± 15	1.7 ± 0.2	55 ± 4	21.9 ± 1.7
Desflurane with 60% N_2O									
Awake		43 ± 1	6.52 ± 1.27	473 ± 70	14 ± 0.5	204 ± 19	2.9 ± 0.3	42 ± 9	3.5 ± 1.8
3.0	0.83	48 ± 1†	5.69 ± 0.67	216 ± 13†	26 ± 2.0†	227 ± 20	2.9 ± 0.3	47 ± 5	14.0 ± 2.3
6.0	1.24	50 ± 2†**	5.01 ± 0.64	153 ± 8‡	32 ± 2.0‡**	216 ± 15	2.7 ± 0.2	48 ± 5	18.4 ± 2.8
9.0	1.66	59 ± 2**††	5.19 ± 0.63**	128 ± 6‡	40 ± 3.0‡**	204 ± 20	2.1 ± 0.2	58 ± 4	22.3 ± 6.2

All values are reported as mean ± SE. Differences are considered significant when $P < 0.05$. Except where noted, $n = 6$.

* Only descriptive statistics are provided for estimated values.

† Differs from awake value.

‡ Differs from value at 6% desflurane in O_2 and awake value.

§ Apnea occurred in two subjects at this depth of anesthesia. Values for V_T, $\dot{V}_E$, and $\dot{V}_A$ include values of zero for each of these subjects. For the remaining parameters, values for these subjects were considered missing and $n = 4$.

¶ Differs from values at 6 and 12% desflurane in O_2 and awake value.

** Differs from corresponding MAC equivalent in O_2.

†† Differs from values at 6 and 3% desflurane/N_2O and awake values.

brated with secondary (tank) standards of desflurane and CO_2. The ventilatory response to CO_2 was measured by the Read rebreathing technique.** Arterial and mixed venous blood gases were measured with a Corning 178® blood-gas analyzer calibrated before each use. Hemoglobin O_2 saturation Sp_{O_2} in arterial blood was monitored continuously by pulse oximetry (Nellcor® model N-200).

Because of its high vapor pressure, desflurane was administered from a modified (pressurized) vaporizer in a Ohmeda DSM-5000® anesthesia machine. Anesthesia was induced by administering desflurane by mask, and the trachea then was intubated without the use of muscle relaxants. After at least 15 min of stable end-tidal desflurane concentrations of 0.83, 1.24, and 1.66 MAC,[4] we measured V_T, RR, PET_{CO_2}, arterial and mixed venous blood gases, and ventilatory response to CO_2. Because we expected cardiovascular depression to be dose-dependent—the greatest degree occurring at the deepest levels of anesthesia[5]—we administered the two lowest concentrations in random order and the highest concentration last. This allowed us to evaluate the degree of cardiovascular depression observed at lighter planes of anesthesia (0.83 and 1.24 MAC) first. End-tidal desflurane concentrations in subjects anesthetized with N_2O were 3, 6, and 9%, compared with 6, 9, and 12%, respectively, in those without N_2O.

Arterial and mixed venous O_2 saturations (Sa_{O_2} and Sv_{O_2} respectively) were calculated from the partial pressure data by the Severinghaus slide rule[6] and then converted to O_2 content as follows:

$$Ca_{O_2} = 1.34\ ml/g \cdot Hb \cdot Sa_{O_2} + 0.0031 \cdot Pa_{O_2} \quad (1)$$

$$Cv_{O_2} = 1.34\ ml/g \cdot Hb \cdot Sv_{O_2} + 0.0031 \cdot Pv_{O_2} \quad (2)$$

where Ca_{O_2} and Cv_{O_2} are arterial and mixed venous O_2 contents and Hb is the hemoglobin concentration (in grams per deciliter) measured at the beginning and end of each study. Cardiac output was determined by a thermodilution technique. O_2 consumption ($\dot{V}_{O_2}$) was calculated by multiplying arteriovenous O_2 content difference by cardiac output. Alveolar ventilation ($\dot{V}_A$) was estimated from the relationship:

$$\dot{V}_A = (\dot{V}_{O_2} \cdot R \cdot P_B)/PA_{CO_2} \quad (3)$$

where R, the respiratory quotient, was assumed to be 0.8; P_B represents barometric pressure; and alveolar CO_2 tension (PA_{CO_2}) and Pa_{CO_2} were assumed to be equal. (We did not determine whether subjects achieved steady-state gas exchange, but a steady state has been shown to reestablish typically within 10 min of perturbations in CO_2).[7] Dead space ventilation (V_D) was calculated from the estimates of $\dot{V}_A$ and expressed as a proportion of tidal ventilation. Intrapulmonary shunt fraction (Q_S/Q_T) was computed as follows:

$$Q_S/Q_T = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - Cv_{O_2}) \quad (4)$$

where Cc_{O_2} is the pulmonary capillary O_2 content, which was computed in the same manner as Ca_{O_2} and Cv_{O_2} (equations 1 and 2) but with the assumption that pulmonary capillary O_2 tension equals alveolar O_2 tension PA_{O_2}. The values $\dot{V}_A$, V_D/V_T, and Q_S/Q_T are estimations calculated from arterial and mixed venous blood gas data and are not directly measured values.

** Read DJC: A clinical method for assessing the ventilatory response to carbon dioxide. Australas Ann Med 16:20–32, 1967.

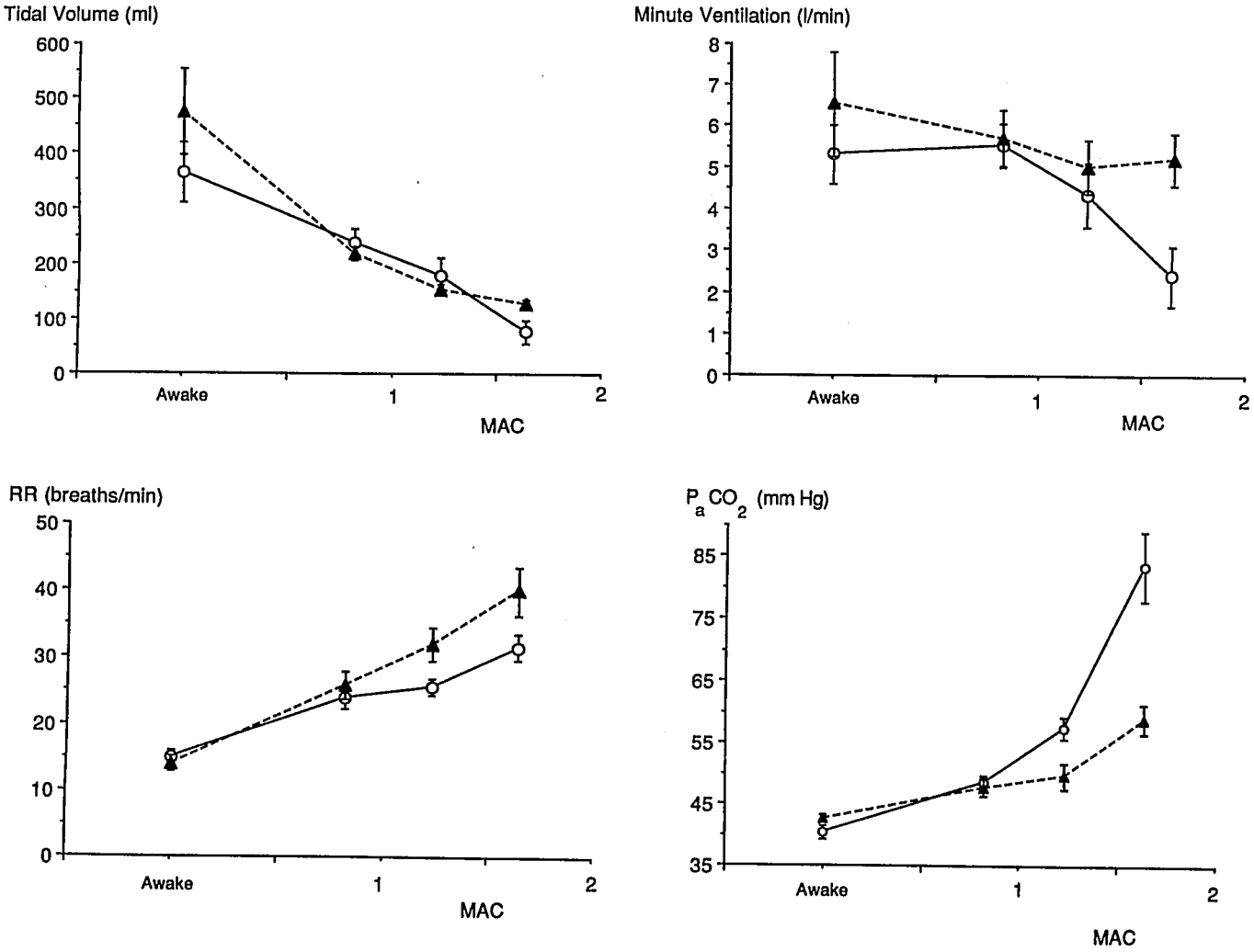

FIG. 1. Desflurane produces dose-related decreases in V_T and increases RR, and resting Pa_{CO_2}. $\dot{V}_E$ is decreased only at the highest level of anesthesia with desflurane in O_2, a level that produced apnea in two patients. Measurements were made awake and at 0.83, 1.24, and 1.66 MAC desflurane anesthesia with (triangles, n = 6) and without (circles, n = 6) 60% N_2O. All values are expressed as mean ± SE.

To determine the ventilatory response to CO_2, the slope of the line relating PET_{CO_2} to minute ventilation ($\dot{V}_E$) was estimated by linear least-squares regression[8] and expressed in liters per minute per millimeter Hg PACO2. Using least-squares estimation, we looked for trends in V_T, RR, and $\dot{V}_E$ with increasing depth of anesthesia by performing a test of the hypothesis that there is no correlation between each variable and anesthetic depth. Values also were analyzed for the effect of desflurane and N_2O by means of *t* tests corrected for multiple comparisons with the Bonferroni method. Differences were considered significant if $P < 0.05$. For estimated values ($\dot{V}_A$, Q_S/Q_T, and V_D/V_T), only descriptive statistics (mean ± SE) are reported. If the true value for R used in equation 3 was less than 0.8 due to the unsteady state during hypoventilation, $\dot{V}_A$ and V_D/V_T would be lower and higher, respectively.

Results

A decrease in V_T and a corresponding increase in RR were observed with increasing depth of desflurane anesthesia with or without N_2O (table 1 and fig. 1). At each level of anesthesia, tidal volumes were comparable with or without N_2O but RRs were greater in the N_2O group at 1.24 and 1.66 MAC. $\dot{V}_E$ did not decrease significantly with increasing depth of anesthesia in either the desflurane/O_2 or the desflurane/N_2O group. At 0.83 MAC and 1.24 MAC, there was no difference in $\dot{V}_E$ between the two groups. At 1.66 MAC, $\dot{V}_E$ was greater in the desflurane/N_2O group, and this concentration produced apnea in two subjects in the desflurane/O_2 group. Pa_{CO_2} increased, although not always significantly, with depth of anesthesia in both groups (table 1 and fig. 1). In the desflurane/O_2 group, Pa_{CO_2} increased significantly at each

successive level of anesthesia. In the desflurane/N_2O group, values for Pa_{CO_2} at 0.83 and 1.24 MAC were significantly greater than the awake values but not different from each other; at 1.66 MAC, Pa_{CO_2} exceeded all other values. Pa_{CO_2} differed significantly between groups only at 1.24 and 1.66 MAC. Increases in Pa_{CO_2} corresponded with increases in end-tidal desflurane concentration and were not affected by the addition of N_2O. The ventilatory response to CO_2 decreased as depth of anesthesia increased and was independent of N_2O (table 2 and fig. 2). We detected no significant changes in $\dot{V}_{O_2}$ during desflurane anesthesia in either group (table 1).

Decreases in estimates of $\dot{V}_A$ are consistent with dose-related increases in measured Pa_{CO_2}. Similarly, changes in estimated values for V_D/V_T corresponded with measured changes in V_T and RR. Estimates of Q_S/Q_T suggest that intrapulmonary shunting is increased by desflurane anesthesia but not in a dose-dependent manner.

Discussion

Our findings indicate that desflurane is a ventilatory depressant, as manifested by an increase in resting Pa_{CO_2} and depression of the ventilatory response to CO_2. Ventilatory depression caused by desflurane is dose-related. Depression of the ventilatory response to CO_2 was dose-related and comparable at each level of desflurane anesthesia both with and without N_2O. In contrast, increases in Pa_{CO_2} corresponded to end-tidal desflurane concentrations and were unaffected by the addition of N_2O. Our results suggest that desflurane's effects on ventilation are comparable to those previously reported for volatile agents currently used clinically.

TABLE 2. The Effects of Desflurane Anesthesia with and without N_2O on the Ventilatory Response to CO_2

Desflurane End-tidal Concentration (%)	Slope ($l \cdot min^{-1} \cdot mmHg\ Pa_{CO_2}^{-1}$)	CO_2 Response as Fraction of Awake Slope
Desflurane with O_2		
Awake	1.64 ± 0.27	1.0
6.0	0.65 ± 0.09	0.45 ± 0.09†
9.0	0.42 ± 0.07	0.31 ± 0.05‡
12.0	0.17 ± 0.07	0.11 ± 0.04‡
Desflurane with 60% N_2O		
Awake	2.28 ± 0.35	1.0
3.0	0.98 ± 0.16	0.52 ± 0.14†
6.0	0.50 ± 0.07	0.23 ± 0.05‡
9.0	0.47 ± 0.06	0.26 ± 0.09§

All values are reported as mean ± SE. Differences are considered significant when $P < 0.05$. Except where noted, $n = 6$.

* Apnea occurred in two subjects at this depth of anesthesia. In these cases, the slope of the CO_2 response curve was assumed to be zero.

† Differs from awake value.

‡ Differs from preceding value and awake value.

§ Differs from value at 3% desflurane with N_2O and awake value.

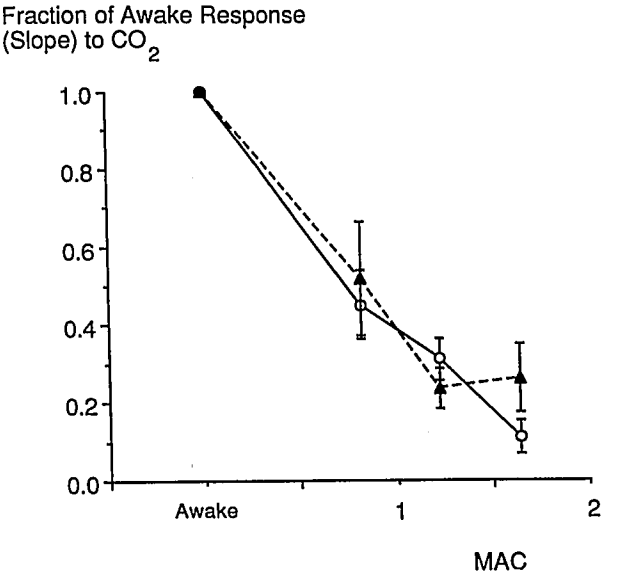

FIG. 2. Desflurane decreased the slopes of the ventilatory response to CO_2 (given here as a fraction of the awake slope) with (triangles, n = 6) and without (circles, n = 6) 60% N_2O. All values are expressed as mean ± SE.

Desflurane depresses ventilation primarily by reducing V_T. As reported with isoflurane,[9] enflurane,[10] and halothane,[9] increasing ventilatory frequency during desflurane anesthesia does not compensate for the reduction in V_T, such that Pa_{CO_2} increases. At anesthetic concentrations of less than 1.24 MAC (in unstimulated volunteers), the resultant dose-related increases in Pa_{CO_2} are greatest with enflurane,[10] followed in magnitude by the changes with desflurane, isoflurane,[9] and finally halothane.[2] At 1.66 MAC, values for desflurane and those reported for enflurane are comparable and exceed reported values for isoflurane and halothane.

The ventilatory response to imposed increases in CO_2 is blunted at concentrations of desflurane exceeding 0.82 MAC. The effects of desflurane on the response to CO_2 are comparable with effects previously described for isoflurane,[9] enflurane,[10] and halothane.[10] Estimates of the anesthetic concentration producing apnea can be obtained from the x-intercept of the regression line relating slope of response to CO_2 and MAC. On the basis of our results as well as results of prior studies, these estimates are 1.8 MAC desflurane, 1.7 MAC isoflurane,[9] 1.6 MAC enflurane,[10] and 2.3 MAC halothane.[10] Apnea occurs at higher anesthetic concentrations because the slope becomes negative (an increase in Pa_{CO_2} decreases ventilation and thereby further increases Pa_{CO_2} and decreases ventilation).[11,12] The ventilatory response for desflurane is unaffected by the substitution of N_2O for an equivalent MAC-fraction of volatile agent, a finding previously reported for enflurane.[13]

In summary, the ventilatory effects of desflurane are comparable to those of currently available agents. Desflurane anesthesia causes a decrease in V_T and an increase in RR. The effects of desflurane on Pa_{CO_2} are comparable to those reported for isoflurane at lighter levels of anesthesia (below 1.24 MAC) and comparable to those reported for enflurane at deeper levels (1.66 MAC). The depression of the ventilatory response to CO_2 observed with desflurane is indistinguishable from the depression reported for isoflurane and enflurane and only slightly greater than that reported for halothane.

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