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Effects of Halothane and Isoflurane on Ventilation and Occlusion Pressure

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Background: **Isoflurane has been said to be more ventilatory depressant than halothane. However, data for comparing the respiratory effects of halothane and isoflurane in humans are insufficient at this time. The aim of this study was to extend our understanding of the nature of the central, as opposed to peripheral, ventilatory effect of halothane and isoflurane by comparing them at two concentrations.**

Methods: **Twenty patients were randomly assigned to receive halothane (n = 10) or isoflurane (n = 10). The patients were studied the day before surgery and during anesthesia immediately before surgery. Ventilatory effects were analyzed in terms of breathing pattern, end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$) and inspiratory occlusion pressure. After anesthetic induction and orotracheal intubation with thiopental and succinylcholine patients were allowed to breathe halothane or isoflurane in oxygen spontaneously at 1.2 (low) and 2.0 (high) minimum alveolar concentration (MAC) applied in random order. Inspiratory active impedance during anesthesia was also measured.**

Results: **Significant reduction of minute ventilation between awake and low MAC states was observed for isoflurane (−34.4%; $P < 0.001$) but not for halothane. Inspiratory occlusion pressure at 100 ms increased significantly between awake and low MAC states, from 1.43 ± 0.89 to 2.67 ± 1.05 cmH_2O ($P < 0.05$) for halothane, representing an 87% increase, whereas a nonsignificant increase (16%) was observed for isoflurane. Both anesthetics showed a dose-related ventilatory depressant effect, not attributable to changes in mechanical properties, reflected by significant reductions in minute ventilation ($P < 0.001$), tidal volume ($P < 0.001$), and inspiratory occlusion pressure at 100 ms ($P < 0.05$) and increases in respiratory rate ($P < 0.001$) and end-tidal carbon dioxide pressure ($P < 0.01$) when concentration was increased. However, at the higher concentration a significantly greater reduction of minute ventilation ($P < 0.01$) was observed for isoflurane (−25.6%) than for halothane (−9.4%). We did not observe differences in respiratory rate between the two anesthetics. Significant differences in inspiratory occlusion pressure wave were observed, characterized by a concave-upward tendency for isoflurane and for high concentration.**

Conclusions: **Our study confirms the stronger ventilatory depression induced by isoflurane compared with that induced by halothane and indicates that halothane at 1.2 MAC induces significantly less ventilatory depression than expected. (Key words: Anesthetics, volatile: halothane; isoflurane. Lungs: respiratory impedance. Ventilation: breathing pattern; inspiratory occlusion pressure.)**

HALOGENATED anesthetics induce ventilatory depression usually attributed to a central respiratory depressant effect. Ventilatory depression, however, is not necessarily equivalent to a depression of ventilatory drive when drive is defined as the rate of respiratory motoneuron output during inspiration.[1] Tusiewicz *et al.*[2] suggested that the peripheral component of the ventilatory depression induced by halogenated anesthetics may be more important than usually thought. Moreover, different halogenated agents, such as halothane and isoflurane, may show different central and peripheral behavior patterns.

Although halogenated anesthetics are often administered to patients in whom ventilation is controlled knowledge of their effects on ventilation in humans is of special physiologic and pharmacologic interest. Information about the effects of these agents on ventilatory control available in the literature at this time, however, has been obtained for the most part from animal experiments. Although a few studies in humans have also been published,[3,4] comparison of their results is difficult because of differences in anesthetic protocols, concomitantly administered drugs, and surgical influences.

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Assessment of central respiratory output has been attempted in humans by measurement of inspiratory occlusion pressure.[5] For occlusion pressure to be a true representation of central neural output, the central nervous system must operate normally and the spinal cord, peripheral nerves and muscle fibers must be normal. Muscles must also operate with normal length, attachments, contours and strength. Abnormal functioning of any of these components may modify the relation between the respiratory controller activity and the resulting occlusion pressure, either by over- or underestimating it. The rationale, caveats and practical considerations of occlusion pressure measurement have been recently reviewed in detail.[6] Altogether, measurement of occlusion pressure remains the most convenient non invasive measure of inspiratory motor activity.

Along the same lines followed by Tusiewicz *et al.*,[2] the current study was an attempt to better characterize the central component of ventilatory depression induced by halogenated anesthetics. To this end, we analyzed ventilatory pattern, end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$), and inspiratory occlusion pressure in two groups of patients during spontaneous ventilation before and during anesthesia with halothane or isoflurane at two concentrations administered in random order. Our anesthetic protocol allowed us to attribute the effects mainly to the anesthetic agent. Measurements of active mechanical properties during anesthesia were also recorded to ascertain whether respiratory mechanics might contribute to the possible differences.

Materials and Methods

Twenty patients undergoing general anesthesia for elective surgery participated in the study. Patients were free of cardiopulmonary diseases and their spirometric values were within the normal range. Institutional approval and written consent from all patients were obtained. The patients were randomly allocated to receive halothane (n = 10) or isoflurane (n = 10).

Flow was recorded with a wire-mesh screen pneumotachograph (Fleisch n° 2, Sibel, Spain) coupled to a differential pressure transducer (±2 cmH_2O; MP-45, Validyne, Northridge, CA). Airway opening pressure was measured by connecting an analog pressure transducer (±50 cmH_2O; MP-45 Validyne) through a sideport of the connector between the equipment and the tracheal tube or through the mouthpiece in the awake period. Flow and pressure were digitized at 100 Hz by an analog-to-digital converter (2801-A, Data Translation, Marlboro, MA) and stored in a microcomputer (Vectra QS/16S, Hewlett-Packard, Palo Alto, CA) for later analysis. These signals were visualized in real time on the monitor of the microcomputer. $P_{ET_{CO_2}}$ and end-tidal anesthetic agent concentration were continuously monitored at the distal end by a gas analyzer (5250 RGM, Ohmeda, Louisville, CO). A two-way nonrebreathing valve (2600, Hans Rudolph, Kansas City, MO) separated the inspiratory and expiratory lines. An occlusion pressure valve (9326, Hans Rudolph), remotely controlled by an electromagnetic valve (M311, Bürkert Steuer, Germany) set into the inspiratory line, was used to occlude the airway opening. The dead space of the two-way circuit was 110 ml. The inspiratory tubing was connected to the gas outlet of the ventilator through a reservoir bag. The expiratory tubing was open to atmospheric air.

Protocol

Patients were studied the day before surgery to obtain baseline measurements in awake state. The patients lay supine for 10 min and then breathed oxygen through a mouthpiece connected to the equipment while wearing a nose clip and noise-reduction earphones. After a 3-min period of adaptation, the flow signal was recorded for an additional 3 min. During this time $P_{ET_{CO_2}}$ was recorded at approximately 30-s intervals. After a brief disconnection and a new period of adaptation, short occlusions of the inspiratory tubing at end-expiration were made to measure mouth occlusion pressure at the onset of inspiration. A minimum of five inspiratory occlusions with intervals of at least five nonoccluded breaths were made.

The patients received 5 mg oral diazepam the night before and the morning of surgery. Anesthetic induction was accomplished with thiopental (6 $mg \cdot kg^{-1}$) and succinylcholine (1.5 $mg \cdot kg^{-1}$) to facilitate intubation. All tracheas were intubated with cuffed tracheal tubes of 8.0 mm inner diameter. The tubes were connected to the ventilator for controlled ventilation. In random order the patients received two end-tidal concentrations of the same halogenated anesthetic in oxygen according to the anesthetic group assigned. Assignment was done by block randomization to ensure the same number of patients in each situation.[7] The low concentration was adjusted to 1.2 minimum alveolar concentration (MAC) and the high concentration to 2.0 MAC. Assumed MAC values were 0.75% for halothane[8]

and 1.15% for isoflurane.[9] Initially, a high concentration was used to speed equilibration. After this, a slow reduction of the concentration was done until the target concentration was attained. When the effects of muscle paralysis had worn off, patients were allowed to breathe spontaneously through the tracheal tube connected to the distal end of the measuring equipment. When $P_{ET_{CO_2}}$ was stable for 1 min at each end-tidal anesthetic concentration, data collection was begun. All data were collected before surgery. Measurements consisted of 3 min of continuous recording of the flow signal and simultaneous recording of $P_{ET_{CO_2}}$ approximately every 30 s. A minimum of five technically satisfactory inspiratory occlusion maneuvers, whose duration was at least that of one nonoccluded cycle, were recorded. Between occlusion maneuvers, five nonoccluded breaths were allowed. Airway opening pressure returned to zero before and after each occlusion. At the end of this first set of measurements, end-tidal anesthetic concentration was changed according to the random order assigned. After a period of stabilization an analogous set of measurements was performed. The time elapsed between anesthetic induction and the reassuming of spontaneous ventilation was 15 ± 5 min; 7 ± 3 min more passed, for a total of 22 ± 4 min, before the beginning of the first set of measurements after stabilization. The period of stabilization before the beginning of the second set of measurements was 6 ± 2 min, and the mean time for performing each set of measurements was 8 ± 2 min. On the average, full data collection lasted 42 ± 5 min. The electrocardiogram and arterial hemoglobin oxygen saturation by pulse oximetry were monitored continuously during the experiments; in all patients, 100% arterial hemoglobin oxygen saturation was maintained.

Respiratory Measurements

From the set of measurements in the awake state and during anesthesia, ventilatory parameters and inspiratory occlusion pressure at 100 ms ($P_{0.1}$) were measured. From every set of measurements during anesthesia, a complete inspiratory occlusion curve was recorded and active inspiratory mechanics calculated. The following ventilatory pattern parameters were obtained breath-by-breath during continuous flow: tidal volume (V_T); respiratory rate (RR); and minute ventilation ($\dot{V}E$). We also obtained the ratio of inspiratory to total time (the effective timing ratio) and mean inspiratory flow rate (V_T/T_i, where T_i = inspiratory time), a mechanical transformation of the rate of increase in central inspiratory activity.[10] The value of $P_{0.1}$ was obtained from the mean of five measured inspiratory occlusion maneuvers for each subject in every condition. The beginning of inspiration was defined as the intersection of the zero pressure line with the regression line for the first 200 ms of the occluded inspiratory pressure curve. To adjust the complete tracheal occlusion inspiratory pressure curve, a third-order polynomic regression, with zero as the independent term ($y = ax^3 + bx^2 + cx$), was fitted from every inspiratory occluded maneuver of each patient at both MAC.

Active inspiratory elastance (E'_{rs}) and resistance (R'_{rs}) were computed by the method reported by Behrakis *et al.*,[11] which is based on the following equation of motion:

$$(-P_{otr} - K_1 \cdot \dot{V} - K_2 \cdot \dot{V}^2)/V = R'_{rs} + E'_{rs} \cdot \Delta V/\dot{V}$$

where P_{otr} = the tracheal pressure during an inspiratory effort with the airways occluded at functional residual capacity (FRC), representing the inspiratory driving pressure; K_1 and K_2 = laminar and turbulent (respectively) flow-resistance constants representing the pressure–flow ratio of the tracheal tube plus equipment; and $\dot{V}$ and ΔV = the instantaneous flow and volume (respectively) changes during a control breath immediately preceding the occluded cycle. This equation is a linear function, where E'_{rs} is the slope and R'_{rs} is the intercept on the ordinate axis. The beginning of inspiration was defined, as was $P_{0.1}$, from the pressure curve or the flow ramp, depending on whether the cycle was occluded or nonoccluded. For every patient at each anesthetic concentration, E'_{rs} and R'_{rs} were calculated from the mean of five occlusion maneuvers and their preceding nonoccluded cycles.

Measurements of K_1 and K_2 were performed in the laboratory with an 8-mm-diameter tracheal tube of the same kind used in the study and a 15-cm-long, 2-cm-ID tube connected to the tracheal tube to simulate an artificial trachea. Oxygen was used for calibration as in the clinical part of our study. Values obtained for K_1 and K_2 were 3.42 $cmH_2O \cdot l^{-1} \cdot s$ and 7.71 $cmH_2O \cdot l^{-2} \cdot s^2$, respectively.

Statistical Analysis

Data were expressed as means ± SD. General patient characteristics and variables measured in the awake state for the two anesthetic groups were compared with a nonpaired *t* test. Comparisons, within each anesthetic group, between awake measurements and those obtained during the low MAC state were made with a

Table 1. Anthropometric and Pulmonary Function Data of Patients

Group	HAL	ISO
N	10	10
Sex M:F	4:6	3:7
Age (yr)	26.0 ± 67.3	24.9 ± 6.2
Weight (kg)	63 ± 10	67 ± 12
Height (cm)	164 ± 10	167 ± 12
FVC (L)	4.06 ± 1.05	4.20 ± 1.01
FEV_1 (L)	3.50 ± 0.98	3.57 ± 0.76
FEF_{25-75} ($L \cdot s^{-1}$)	4.19 ± 1.66	4.10 ± 1.04

HAL = halothane; ISO = isoflurane; FVC = forced vital capacity; FEV_1 = forced expired volume in one second; FEF_{25-75} = forced expiratory flow between 25 and 75% of the vital capacity.

paired *t* test. A two-way analysis of variance for repeated measures was used to analyze differences between anesthetics and between concentrations for variables measured during anesthesia, including coefficients of the third-order polynomic equation of the fitted inspiratory occluded pressure curves. Anesthetic was treated as a between-group factor and concentration as a within-group factor. Correlation coefficients were calculated between $P_{0.1}$ values and the coefficients of the third-order polynomic equation. Also, correlation coefficients were calculated between $P_{0.1}$ and $\dot{V}E$ with actual values of alveolar concentration and MAC for all subjects irrespective of anesthetic agent received. A value of $P < 0.05$ was considered significant.

Results

The two patient groups were similar with respect to anthropometric characteristics and preoperative lung function tests (table 1). Apnea appeared in three out of ten patients given isoflurane at high MAC. For this reason, new adjustments of the end-tidal concentration were made in them to prevent apnea. Thus, the actual mean alveolar concentration for this group was 2.03 ± 0.17%, representing a MAC multiple of 1.77 ± 0.13. The actual inspired and end-tidal concentrations and MAC multiple for each anesthetic agent are presented in table 2.

The values of ventilatory pattern parameters, $P_{ET_{CO_2}}$ and $P_{0.1}$ during awake and anesthetized states at low and high MAC for the two groups of patients are shown in table 3. Preanesthetic values for all parameters were similar for the two groups. When parameters for preanesthetic and low MAC states were compared, significant decreases in $\dot{V}E$ ($P < 0.001$) and V_T/T_i ($P < 0.05$) were observed only for the isoflurane group; a significant decrease in V_T ($P < 0.001$) and increases in both $P_{ET_{CO_2}}$ ($P < 0.01$) and RR ($P < 0.01$) were observed for both anesthetics. $P_{0.1}$ increased significantly between awake and low MAC states from 1.43 ± 0.89 to 2.67 ± 1.05 cmH_2O ($P < 0.05$) for halothane, whereas the $P_{0.1}$ increase for isoflurane was not significant. The percent increase of $P_{0.1}$ between awake and low MAC states was 86.7 and 15.8% for halothane and isoflurane, respectively.

Significant increases in the ratio of inspiratory to total time ($P < 0.01$), RR ($P < 0.001$) and $P_{ET_{CO_2}}$ ($P < 0.01$) and decreases in V_T ($P < 0.001$), $\dot{V}E$ ($P < 0.001$), V_T/T_i ($P < 0.001$) and $P_{0.1}$ ($P < 0.05$) between the low and high MAC were observed for both anesthetics. Significant interaction between the main factors—anesthetic agent and concentration—was found for $\dot{V}E$ ($P < 0.01$) and V_T/T_i ($P < 0.01$). The interaction between anesthetic agent and MAC for $\dot{V}E$ is shown in figure 1, in which the lines for each anesthetic diverge as MAC increases, indicating a more marked reduction in $\dot{V}E$ for isoflurane at high MAC. In fact, a mean reduction in $\dot{V}E$ of 9.4 and 25.6% for the halothane and isoflurane groups, respectively, was observed at increasing concentration. Figure 1 also depicts the values of $P_{ET_{CO_2}}$ for each anesthetic agent and MAC, showing a parallel increase for both groups. Significantly lower

Table 2. Mean Values of Anesthetic Concentration in the Two Groups of Patients

	HAL		ISO	
Group	LOWMAC	HIGHMAC	LOWMAC	HIGHMAC
% end tidal agent	0.93 ± 0.05	1.51 ± 0.02	1.38 ± 0.06	2.03 ± 0.17
% inspired agent	1.73 ± 0.39	2.80 ± 0.31	2.30 ± 0.37	3.85 ± 0.37
% end tidal/% insp	0.54	0.54	0.60	0.53
MAC multiple	1.24 ± 0.05	2.01 ± 0.03	1.20 ± 0.05	1.77 ± 0.13

HAL = halothane; ISO = isoflurane.

Table 3. Mean Values of Ventilatory Parameters and Inspiratory Occlusion Pressure for the Two Groups of Patients, Awake and Anesthetized

	Awake		Anesthetized			
			HAL		ISO	
Group	HAL	ISO	LOWMAC	HIGHMAC	LOWMAC	HIGHMAC
Ti/Ttot	0.46 ± 0.03	0.46 ± 0.04	0.45 ± 0.04	0.46 ± 0.04†	0.41 ± 0.05*	0.43 ± 0.04†
RR ($c \cdot min^{-1}$)	12.5 ± 3.6	15.3 ± 4.9	28.2 ± 5.4*	32.0 ± 6.3†	24.8 ± 7.7*	26.8 ± 5.9†
V_T (L)	0.76 ± 0.31	0.60 ± 0.11	0.25 ± 0.03*	0.20 ± 0.02†	0.24 ± 0.04*‡	0.16 ± 0.02†‡
V'E ($L \cdot min^{-1}$)	8.68 ± 2.04	8.92 ± 2.54	7.12 ± 1.63	6.45 ± 1.74†	5.85 ± 1.49*	4.35 ± 1.42†‡
V_T/Ti ($L \cdot s^{-1}$)	0.32 ± 0.06	0.33 ± 0.09	0.27 ± 0.04	0.24 ± 0.05†	0.25 ± 0.04*	0.18 ± 0.04†‡
$P_{ET}CO_2$ (mmHg)	39.2 ± 3.2	38.8 ± 2.8	47.6 ± 5.3*	51.1 ± 6.4†	53.5 ± 6.8*‡	57.4 ± 3.4†‡
$P_{0.1}$ (cmH_2O)	1.43 ± 0.89	1.52 ± 0.83	2.67 ± 1.05*	2.31 ± 0.62†	1.76 ± 0.82‡	1.43 ± 0.72†‡

HAL = halothane; ISO = isoflurane; Ti/Ttot = inspiratory duty cycle; RR = breathing frequency; V_T = tidal volume; V'E = minute ventilation; V_T/Ti = mean inspiratory flow; $P_{ET}CO_2$ = end tidal CO_2 concentration; $P_{0.1}$ = pressure recorded during the first 100 ms of an occluded inspiration.

* Significantly ($P < .05$) different from awake.

† Significantly ($P < .05$) different form low MAC.

‡ Significantly ($P < .05$) different from halothane.

values of V_T ($P < 0.05$) and $P_{0.1}$ ($P < 0.05$) and significantly higher values of $P_{ET}CO_2$ ($P < 0.05$) were evident for the isoflurane group at both low and high MAC, and decreased $\dot{V}E$ ($P < 0.01$) and V_T/T_i ($P < 0.01$) were observed at high MAC compared with the values observed in the halothane group.

When pooled data for $\dot{V}E$ and $P_{0.1}$ from all subjects—irrespective of anesthetic agent given at either MAC—were correlated with the actual alveolar concentrations or MAC values for each patient, significant correlations were found only with alveolar concentration ($\dot{V}E$ $r = 0.47$, $P < 0.01$, $P_{0.1}$ $r = 0.43$, $P < 0.01$). Correlations between $\dot{V}E$ and $P_{0.1}$ with actual MAC values were lower and not significant.

Values of E'_{rs} and R'_{rs} for each anesthetic and concentration are shown in table 4. A small but significant increase in E'_{rs} ($P < 0.05$) was observed at the higher concentration for both anesthetics, indicating that there were no differences in mechanical respiratory properties between anesthetic agents.

Figure 2 represents the mean inspiratory occlusion wave curves for the first 700 ms for the two groups of anesthetic and MAC. Every curve was calculated from the mean polynomic coefficients obtained from all subjects, computed as the mean coefficients of the set of occluded inspiratory curves of every subject at each MAC and fitted to a third-order polynomic equation.

Table 4 also shows the mean third-order polynomic regression coefficients of the occluded inspiratory pressure curve for every anesthetic group at each concentration. An excellent fit was obtained in all cases ($r > 0.995$). The first-degree coefficient (c) was significantly lower for the isoflurane group ($P < 0.05$) and at the high concentration ($P < 0.01$) for both groups. Correlation coefficients between $P_{0.1}$ and the first-degree coefficients were higher than 0.98 at both MAC. Significantly higher values (*i.e.*, less negative) of the second-degree coefficient (b) ($P < 0.05$) were obtained for the isoflurane group at the two concentrations, as shown by a concave-upward tendency. Significant correlation was also observed between $P_{0.1}$ and the second-degree coefficients at low ($r = 0.91$) and high ($r = 0.86$) MAC. Again, lower but significant correlation ($r = 0.85$ and 0.67 at low and high MAC, respectively) was observed for the third-degree coefficients (a).

Discussion

The anesthetic protocol in this experimental study allowed us to exclude surgical and hypoxic stimulation and, as far as possible, the effects of other medications. The doses of oral diazepam given for premedication and the time elapsed from administration made it very unlikely that they had a significant impact on the results. Likewise, the time elapsed after administration of thiopental and succinylcholine ruled out any significant effect of these drugs. In any event, these pharmacologic effects were the same for both anesthetic groups and, overall would have contributed to increase any central ventilatory depressant effect. The time elapsed between anesthetic induction and the beginning of measurements assured us that the equilibration

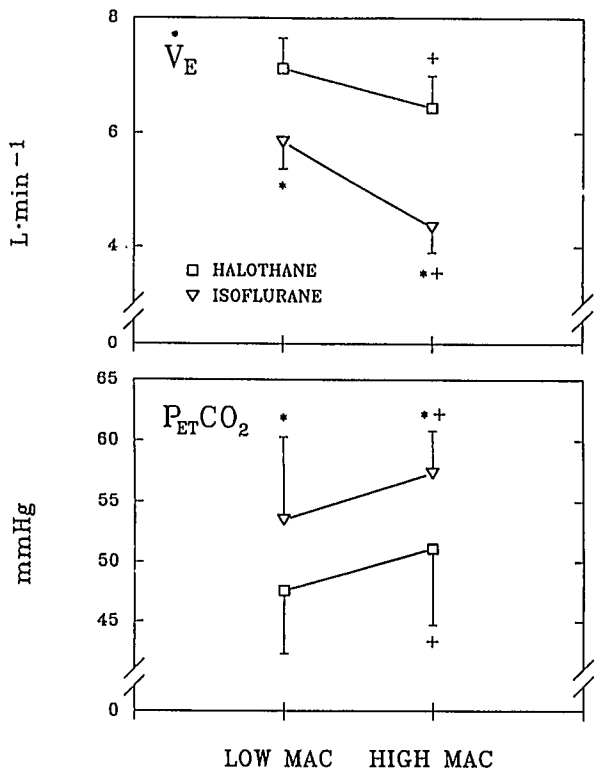

Fig. 1. Minute ventilation and end-tidal carbon dioxide concentration (mean values) during halothane and isoflurane anesthesia. Bars = SE. *$P < 0.05$ compared with halothane. †$P < 0.05$ compared with low MAC.

of anesthetic concentrations at each end-tidal concentrations for both anesthetics had been attained.

Ventilation

The only study comparing the ventilatory effects of halothane and isoflurane in pure conditions at different concentrations was carried out by Fourcade *et al.*[4] However, these authors compared two groups of subjects studied under different experimental conditions and the anesthetic concentrations were not applied in random order. Nevertheless, our results confirm their main finding that isoflurane is a stronger ventilatory depressant than halothane. At low MAC for both anesthetics, the $P_{ET_{CO_2}}$ values indicated some degree of hypoventilation in comparison with the awake state. Accordingly, the values of $\dot{V}E$ in our patients were similar for halothane and lower for isoflurane. During anesthesia, halothane and isoflurane showed dose-dependent effects characterized by a decrease in $\dot{V}E$, V_T, and V_T/T_i. Our results also showed a steeper slope of $\dot{V}E$ at increasing concentration with isoflurane (fig. 1). Additionally, we observed an increase of $P_{ET_{CO_2}}$ at increasing concentration for both anesthetics, but with significantly higher values for isoflurane (fig. 1). The difference in the ventilatory depressant effects of halothane and isoflurane is even more evident when we consider that in our study three patients given isoflurane at high MAC developed apnea, and the resulting adjustment meant that the actual mean MAC multiple in the isoflurane (1.8) group was lower than that for halothane (2.0) (table 2). Our results showed a dose-dependent increase in RR mainly at the expense of a greater reduction of expiratory time, as reflected by a significant increase in the ratio of inspiratory to total time for both anesthetics. We did not find differences in RR between patients given halothane and isoflurane at any concentration, unlike Fourcade *et al.*,[4] who found a higher RR in patients given halothane.

Neuromuscular Output

Measurement of occlusion pressure in anesthetized humans was done first by Derenne *et al.*[12] in patients during methoxyflurane anesthesia. Since then, only one study has analyzed occlusion pressure changes at increasing concentrations of halogenated anesthetic agent,[13] showing a reduction of occlusion pressure with increasing anesthetic concentration. An interpretation of changes of inspiratory occlusion pressure during anesthesia should be made cautiously, however. Selective effects of anesthetics on medullary center neurons and contraction processes of the respiratory muscles and their configuration would all underestimate the actual value of occlusion pressure.[2] On the other hand, a decrease in FRC during anesthesia would result in an increase in precontraction length for the inspiratory muscles. This would overestimate central activity increasing the $P_{0.1}$ obtained with the same neural output.

In this study, we observed an increase of 15.8% in $P_{0.1}$ with respect to supine preanesthetic values in isoflurane-anesthetized patients and an increase of 86.7% in halothane-anesthetized patients. Using the equation proposed by Rehder and Marsh,[14] we estimated the reduction of FRC related to anesthetic induction in our subjects to be 14% (*i.e.*, 400 ml). According to Eldridge and Vaughn,[15] such a decrease in FRC would explain an increase of about 12% in mouth occlusion pressure. These figures are consistent with the possibility that the increase of $P_{0.1}$ observed in the isoflurane group between awake and anesthetized states are entirely attributable to the change of diaphragm position, whereas

Table 4. Mean Values of Respiratory System Mechanics and Occluded Inspiratory Pressure Curve Coefficients for the Two Groups of Patients

	HAL		ISO	
Group	LOWMAC	HIGHMAC	LOWMAC	HIGHMAC
E'rs ($cmH_2O \cdot L^{-1}$)	33.0 ± 4.8	34.8 ± 4.8*	34.3 ± 0.8	36.4 ± 11.2*
R'rs ($cmH_2O \cdot L \cdot s^{-2}$)	2.7 ± 1.5	2.4 ± 2.1	3.7 ± 1.8	3.9 ± 1.9
Occlusion pressure curve coefficients				
a	8.6 ± 19.2	2.3 ± 15.8	−5.4 ± 14.2	−9.4 ± 8.0
b	−26.8 ± 28.9	−19.6 ± 19.5	−3.0 ± 22.6†	2.2 ± 14.4†
c	29.8 ± 12.5	25.0 ± 7.2*	18.7 ± 10.1†	13.3 ± 7.9*†

HAL = halothane; ISO = Isoflurane; E'rs = active inspiratory elastance; R'rs = active inspiratory resistance; a, b, and c represent the third, second, and first degree coefficients, respectively, of the third order polynomic regression equation ($y = ax^3 + bx^2 + cx$) used to compute and handle the occluded inspiratory pressure curves.

* Significantly ($P < .05$) different from low MAC.

† Significantly ($P < .05$) different from halothane.

in the halothane group the $P_{0.1}$ increase is not solely explained by a greater mechanical advantage of the diaphragm. Rather, an increased central respiratory drive in patients given halothane is likely to be responsible. In addition, if we consider the depressant effects of halothane on diaphragm[16] and intercostal[2] muscle function, the measured $P_{0.1}$ probably underestimates the actual increase of central respiratory activity.

In the current study, we observed a significant reduction of $P_{0.1}$ with high MAC for both anesthetics in comparison with values recorded during low MAC anesthesia, but with significantly higher values—compared with the awake state—for halothane than for isoflurane at both MAC (table 3). In all probability, this reduction of $P_{0.1}$ was not related to changes either in respiratory mechanical properties or in FRC, because changes in FRC with anesthetic agents take place immediately after anesthetic induction and are not related to the concentration of anesthetic agent.[14] Similarly, our patients did not show relevant changes in their inspiratory active impedance related to anesthetic or concentration (table 4). Halothane at both concentrations allowed an increase in central respiratory output as a response to the increase in respiratory impedance and $P_{ET_{CO_2}}$ induced by anesthesia. Such increase in $P_{0.1}$ was not observed in the case of isoflurane, thus suggesting a more accentuated central ventilatory depression by the latter. In anesthetized animals, occlusion pressure responses to intrinsic[17] or extrinsic[18] resistive loading have been observed. In halothane-anesthetized humans ventilatory compensation for extrinsic[19,20] or intrinsic[21,22] loading has also been demonstrated. In the clinical setting, patients with chronic obstructive disease in acute respiratory failure show high values of $P_{0.1}$ as a way to compensate for poor mechanical respiratory conditions.[23] Although inhalation anesthetics may depress chemical drive, we think that a good part of the ventilatory depression observed during anesthesia is effective peripherally and could be attributed to a combination of changes in dead space[24] and

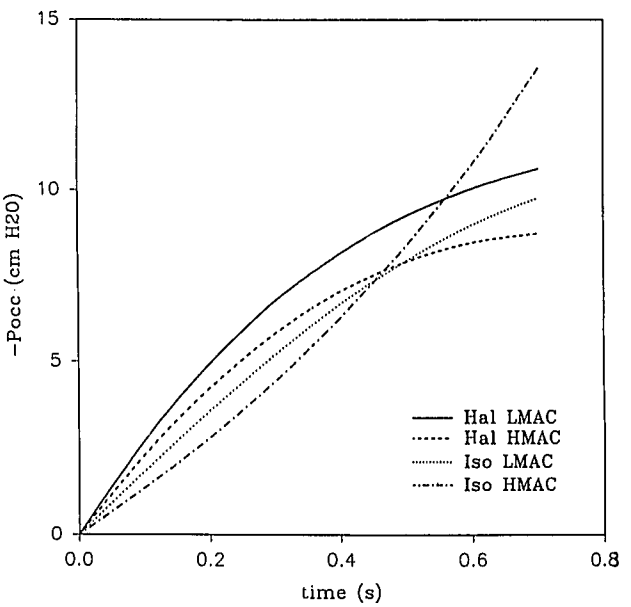

Fig. 2. Mean inspiratory occlusion pressure curves observed with halothane and isoflurane at low (L) and high (H) minimum alveolar concentrations (MAC).

neuromuscular effects of anesthetics,[2,12,13] and potentiated by adjuvant drugs.[25]

The airway occlusion pressure wave closely reflects the shape of the inspiratory neural drive in cats.[26] In previous studies, the time course of the occlusion pressure wave has been shown to exhibit an upward convexity in methoxyflurane-,[12] enflurane-,[13] and halothane- anesthetized[27] humans. However, studies of the shape of the occlusion pressure wave in humans are too scarce to allow conclusions on the effects of anesthetics on the inspiratory neural drive.[28] Studies in animals have fitted the curves to a simple power function.[26] The fitting of a polynomic equation has been suggested as a means to assess the shape of the inspiratory neural drive more accurately[28] and for this reason, in our study we took this step. We observed a strong correlation between $P_{0.1}$ and the first polynomic equation coefficient, which defines mainly the beginning of the slope of the curve. Thus, $P_{0.1}$ is a satisfactory approximate reflection, we think, of neuromuscular output, although for definition of the occlusion pressure curve as a whole a more accurate mathematical approach is necessary. We also observed differences in the shape of the curve for the two anesthetics, with a clear concave-upward tendency in the group given isoflurane, especially with high MAC (fig. 2). Kochi *et al.*[27] also observed a concave-upward shape of the occlusion pressure wave for sevoflurane-anesthetized humans in comparison with that for halothane-anesthetized humans. This different shape for both isoflurane and sevoflurane suggests a slower transformation of central respiratory drive into occlusion pressure as a result of an alteration in respiratory drive or peripheral factors. Our results may confirm a reduction of neuromuscular output with isoflurane anesthesia as compared with halothane. Furthermore, a convex upward tendency for a given stimulus implies that over the same time the V_T obtained is higher than it would be with a concave curve[29] and may represent a central compensatory mechanism. This was the case for our patients giving isoflurane who showed lower values of V_T (table 3).

An additional observation of our study was the progression of values in the ventilatory parameters between the group of patients at low MAC with halothane and the group at high MAC with isoflurane (table 3). Thus, $\dot{V}E$, V_T/T_I, and $P_{0.1}$ were lower at the low MAC of isoflurane than at the high MAC of halothane, whereas the opposite was true for $P_{ET_{CO_2}}$. This finding confirms that isoflurane, even at low concentration, is more depressant than halothane at high concentration. Because MAC is defined as a response to a nociceptive stimulus, however, our results suggest that irrespective of anesthetic, the ventilatory depressant effects of halogenated anesthetics may be related more to alveolar concentration than to MAC multiple. In support of this contention, we noted a low but significant correlation between alveolar concentration and $\dot{V}E$ and $P_{0.1}$ ($P < 0.01$), irrespective of the anesthetic agent. In fact, new halogenated anesthetics with higher MAC values seem to be even more depressant than isoflurane.[30] The progression of changes in the shape of the occlusion wave between halothane at low MAC and isoflurane at high MAC, with a change from convex to concave-upward, also supports this hypothesis, although more investigation is needed to confirm this point.

In conclusion, our study clarifies and extends previous observations regarding the stronger ventilatory depression induced by isoflurane compared with that induced by halothane. Differences in $P_{0.1}$, $P_{ET_{CO_2}}$ and $\dot{V}E$ between the two anesthetics and concentrations allow us to conclude that during halothane anesthesia at 1.2 MAC there is an increased central neural drive that allows the maintenance of $\dot{V}E$ and a slight increase in $P_{ET_{CO_2}}$. Isoflurane even at MAC 1.2, on the other hand, induces a clear ventilatory depression with lower central neural drive. Both anesthetics, however, show deeper depression of ventilation as MAC increases.

References

1. Pavlin EG, Hornbein TF: Anesthesia and the control of ventilation, The Respiratory System, section 3. Control of Breathing, volume II. Handbook of Physiology, part 2. Edited by Cherniak NS, Widdicombe JG. Bethesda, American Physiological Society, 1986, pp 793–813

2. Tusiewicz K, Bryan AC, Froese AB: Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. ANESTHESIOLOGY 47:327–337, 1977

3. Munson ES, Larson CP, Babad AA, Regan MJ, Buechel DR, Eger EI II: The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. ANESTHESIOLOGY 27:716–728, 1966

4. Fourcade HE, Stevens WC, Larson CP, Cromwell TH, Bahlman SH, Hickey RF, Halsey MJ, Eger EI II: The ventilatory effects of Forane, a new inhaled anesthetic. ANESTHESIOLOGY 35:26–31, 1971

5. Whitelaw WA, Derenne JP, Milic-Emili J: Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 23:181–199, 1975

6. Whitelaw WA, Derenne JP: Airway occlusion pressure. J Appl Physiol 74:1475–1483, 1993

7. Altmann DG: Practical statistics for medical research. London, Chapman & Hall, 1991, pp 87–88

8. Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. ANESTHESIOLOGY 25:302–306, 1964

9. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, de Jong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 42:197–201, 1975

10. Milic-Emili J, Grunstein MM: Drive and timing components of ventilation. Chest 70(suppl):131–133, 1976

11. Behrakis PK, Higgs BD, Baydur A, Zin WA, Milic-Emili J: Active inspiratory impedance in halothane-anesthetized humans. J Appl Physiol 54:1477–1481, 1983

12. Derenne JP, Couture J, Iscoe S, Whitelaw WA, Milic-Emili J: Occlusion pressures in men rebreathing CO_2 under methoxyflurane anesthesia. J Appl Physiol 40:805–814, 1976

13. Wahba WM: Analysis of ventilatory depression by enflurane during clinical anesthesia. Anesth Analg 59:103–109, 1980

14. Rehder K, Marsh HM: Respiratory mechanics during anesthesia and mechanical ventilation, The Respiratory System, section 3. Mechanics of Breathing, volume III. Handbook of Physiology, part 2. Edited by Macklem PT, Mead J. Bethesda, American Physiological Society, 1986, pp 737–752

15. Eldridge FL, Vaughn KZ: Relationship of thoracic volume and airway occlusion pressure: Muscular effects. J Appl Physiol 43:312–321, 1977

16. Clergue F, Viires N, Lemesle P, Aubier M, Viars P, Pariente R: Effect of halothane on diaphragmatic muscle function in pentobarbital-anesthetized dogs. ANESTHESIOLOGY 64:181–187, 1986

17. Savoy J, Arnup ME, Anthonisen NR: Response to external inspiratory resistive loading and bronchospasm in anesthetized dogs. J Appl Physiol 53:355–360, 1982

18. Segal BS, Inman JG, Moss IR: Occlusion pressure response to inspiratory flow-resistive loading in anesthetized swine. J Appl Physiol 71:1774–1779, 1991

19. Moote CA, Knill RL, Clement J: Ventilatory compensation for continuous inspiratory resistive and elastic loads during halothane anesthesia in humans. ANESTHESIOLOGY 64:582–589, 1986

20. Canet J, Zegrí A, Sanchis J, Farré R, Navajas D: Ventilatory compensation for inspiratory resistive load during anesthesia with halothane or isoflurane (abstract). ANESTHESIOLOGY 79:A1219, 1993

21. Baydur A, Swank SM, Stiles CM, Sassoon CSH: Respiratory elastic load compensation in anesthetized patients with kyphoscoliosis. J Appl Physiol 67:1024–1031, 1989

22. Canet J, Sanchis J, Navajas D, Farré R, Rotger MM, Casan P: Active inspiratory impedance and neuromuscular respiratory output during halothane anaesthesia in humans. Eur Respir J 4:703–710, 1991

23. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne JP: Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 122:191–199, 1980

24. Nunn JF, Hill DW: Respiratory dead space and arterial to end-tidal CO_2 tension difference in anesthetized man. J Appl Physiol 15: 383–389, 1960

25. France CJ, Plumer MH, Eger EI II, Wahrenbrock EA: Ventilatory effects of isoflurane (Forane) or halothane when combined with morphine, nitrous oxide and surgery. Br J Anaesth 46:117–120, 1974

26. Siafakas NM, Chang HK, Bonora M, Gautier J, Milic-Emili J, Duron B: Time course of phrenic activity and respiratory pressures during airway occlusion in cats. J Appl Physiol 51:99–108, 1981

27. Kochi T, Izumi Y, Isono S, Ide T, Mizuguchi T: Breathing pattern and occlusion pressure waveform in humans anesthetized with halothane or sevoflurane. Anesth Analg 73:327–332, 1991

28. Milic-Emili J, Zin WA: Relationship between neuromuscular respiratory drive and ventilatory output, The Respiratory System, section 3. Mechanics of Breathing, volume III. Handbook of Physiology, part 2. Edited by Macklem PT, Mead J. Bethesda, American Physiological Society, 1986, pp 631–646

29. Younes M, Riddle W: Relation between respiratory neural output and tidal volume. J Appl Physiol 56:1110–1119, 1984

30. Lockhart SH, Rampil IJ, Yasuda N, Eger EI II, Weiskopf RB: Depression of ventilation by desflurane in humans. ANESTHESIOLOGY 74:484–488, 1991