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\textsubscript{ET\textsubscript{CO}}\textsubscript{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\textsubscript{2}O (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.

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.
Assessment of central respiratory output has been attempted in humans by measurement of inspiratory occlusion pressure. 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. 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., 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 (PetCO$_2$), 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 assigned 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$_2$O; MP-45, Validyne, Northridge, CA). Airway opening pressure was measured by connecting an analog pressure transducer (±50 cmH$_2$O; 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 Q5/16S, Hewlett-Packard, Palo Alto, CA) for later analysis. These signals were visualized in real time on the monitor of the microcomputer. PetCO$_2$ 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 nonbreathing 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 PetCO$_2$ was recorded at approximately 30-s intervals. After a brief disconnection and a new period of adaptation, short occlusions of the inspiratory tubing at endexpiration 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·kg$^{-1}$) and succinylcholine (1.5 mg·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. 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.
and 1.15% for isoflurane. 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 PetCO$_2$ 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 PetCO$_2$ approximately every 30 s. A minimum of five technically satisfactory inspiratory occlusion maneuvers, whose duration was at least 2 min 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 (VT); respiratory rate (RR); and minute ventilation (VE). We also obtained the ratio of inspiratory to total time (the effective timing ratio) and mean inspiratory flow rate (V$_{i}$/T$_{i}$, where T$_{i}$ = inspiratory time), a mechanical transformation of the rate of increase in central inspiratory activity. 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 polynomial 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$^{s}_{a}$) and resistance (R$^{s}_{a}$) were computed by the method reported by Behrakis et al., which is based on the following equation of motion:

\[-P_{or} - K_1 \cdot \dot{V} - K_2 \cdot \dot{V}^2 \] \[\div V = R_{or} + E_{or} \cdot \Delta V/\dot{V}\]

where P$_{or}$ = 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 \(\Delta V\) = the instantaneous flow and volume (respectively) changes during a control breath immediately preceding the occluded cycle. This equation is a linear function, where E$_{or}$ is the slope and R$_{or}$ 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$_{or}$ and R$_{or}$ 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$_2$O·L$^{-1}$·s and 7.71 cmH$_2$O·L$^{-2}$·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

<table>
<thead>
<tr>
<th>Group</th>
<th>HAL</th>
<th>ISO</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sex M:F</td>
<td>4:6</td>
<td>3:7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>26.0 ± 67.3</td>
<td>24.9 ± 6.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 ± 10</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 ± 10</td>
<td>167 ± 12</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.06 ± 1.05</td>
<td>4.20 ± 1.01</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.50 ± 0.98</td>
<td>3.57 ± 0.76</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L·s⁻¹)</td>
<td>4.19 ± 1.68</td>
<td>4.10 ± 1.04</td>
</tr>
</tbody>
</table>

HAL = halothane; ISO = isoflurane; FVC = forced vital capacity; FEV₁ = forced expired volume in one second; FEF₂₅₋₇₅ = forced expiratory flow between 25 and 75% of the vital capacity.

A 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 polynomial 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 P₀,₁ values and the coefficients of the third-order polynomial equation. Also, correlation coefficients were calculated between P₀,₁ and VE 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, PETCO₂ and P₀,₁ 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 VE (P < 0.001) and V₁/T₁ (P < 0.05) were observed only for the isoflurane group; a significant decrease in V₁ (P < 0.001) and increases in both PETCO₂ (P < 0.01) and RR (P < 0.01) were observed for both anesthetics. P₀,₁ increased significantly between awake and low MAC states from 1.43 ± 0.89 to 2.67 ± 1.05 cmH₂O (P < 0.05) for halothane, whereas the P₀,₁ increase for isoflurane was not significant. The percent increase of P₀,₁ 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 tidal time (P < 0.01), RR (P < 0.001) and PETCO₂ (P < 0.01) and decreases in V₁ (P < 0.001), VE (P < 0.001), V₁/T₁ (P < 0.001) and P₀,₁ (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 VE (P < 0.01) and V₁/T₁ (P < 0.01). The interaction between anesthetic agent and MAC for VE is shown in figure 1, in which the lines for each anesthetic diverge as MAC increases, indicating a more marked reduction in VE for isoflurane at high MAC. In fact, a mean reduction in VE 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 PETCO₂ 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

<table>
<thead>
<tr>
<th>Group</th>
<th>HAL LOWMAC</th>
<th>HAL HIGHMAC</th>
<th>ISO LOWMAC</th>
<th>ISO HIGHMAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>% end tidal agent</td>
<td>0.93 ± 0.05</td>
<td>1.51 ± 0.02</td>
<td>1.38 ± 0.06</td>
<td>2.03 ± 0.17</td>
</tr>
<tr>
<td>% inspired agent</td>
<td>1.73 ± 0.39</td>
<td>2.80 ± 0.31</td>
<td>2.30 ± 0.37</td>
<td>3.05 ± 0.37</td>
</tr>
<tr>
<td>% end tidal/% insp</td>
<td>0.54</td>
<td>0.54</td>
<td>0.60</td>
<td>0.53</td>
</tr>
<tr>
<td>MAC multiple</td>
<td>1.24 ± 0.05</td>
<td>2.01 ± 0.03</td>
<td>1.20 ± 0.05</td>
<td>1.77 ± 0.13</td>
</tr>
</tbody>
</table>

HAL = halothane; ISO = isoflurane.
### Table 3. Mean Values of Ventilatory Parameters and Inspiratory Occlusion Pressure for the Two Groups of Patients, Awake and Anesthetized

<table>
<thead>
<tr>
<th>Group</th>
<th>Awake</th>
<th>HAL</th>
<th>ISO</th>
<th>LOWMAC</th>
<th>HIGHMAC</th>
<th>Anesthetized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.46 ± 0.03</td>
<td>0.45 ± 0.04</td>
<td>0.46 ± 0.04</td>
<td>0.41 ± 0.05*</td>
<td>0.43 ± 0.04†</td>
<td></td>
</tr>
<tr>
<td>RR (c·min⁻¹)</td>
<td>12.5 ± 3.8</td>
<td>28.2 ± 5.4*</td>
<td>32.0 ± 6.3†</td>
<td>24.8 ± 7.7*</td>
<td>26.8 ± 5.9†</td>
<td></td>
</tr>
<tr>
<td>Vt (L)</td>
<td>0.76 ± 0.31</td>
<td>0.25 ± 0.03*</td>
<td>0.20 ± 0.02†</td>
<td>0.24 ± 0.04‡</td>
<td>0.16 ± 0.02†‡</td>
<td></td>
</tr>
<tr>
<td>VE (L·min⁻¹)</td>
<td>8.68 ± 2.04</td>
<td>7.12 ± 1.63</td>
<td>6.45 ± 1.74†</td>
<td>5.85 ± 1.49*</td>
<td>4.35 ± 1.42†‡</td>
<td></td>
</tr>
<tr>
<td>Vt/Ti (L·s⁻¹)</td>
<td>0.32 ± 0.06</td>
<td>0.27 ± 0.04</td>
<td>0.24 ± 0.05†</td>
<td>0.25 ± 0.04*</td>
<td>0.18 ± 0.04†‡</td>
<td></td>
</tr>
<tr>
<td>Pco₂ (mmHg)</td>
<td>39.2 ± 3.2</td>
<td>47.5 ± 5.3*</td>
<td>51.1 ± 6.4†</td>
<td>53.5 ± 6.8†‡</td>
<td>57.4 ± 3.4‡‡</td>
<td></td>
</tr>
<tr>
<td>Pao₂ (cmH₂O)</td>
<td>1.43 ± 0.89</td>
<td>2.67 ± 1.05*</td>
<td>2.31 ± 0.82†</td>
<td>1.76 ± 0.82‡</td>
<td>1.43 ± 0.72‡‡</td>
<td></td>
</tr>
</tbody>
</table>

HAL = halothane; ISO = isoflurane; Ti/Tot = inspiratory duty cycle; RR = breathing frequency; Vt = tidal volume; VE = minute ventilation; Vt/Ti = mean inspiratory flow; Pco₂ = end tidal CO₂ concentration; Pao₂ = pressure recorded during the first 100 ms of an occluded inspiration.

* Significantly (P < 0.05) different from awake.
† Significantly (P < 0.05) different form low MAC.
‡ Significantly (P < 0.05) different from halothane.

Values of Vt (P < 0.05) and P0.1 (P < 0.05) and significantly higher values of Pco₂ (P < 0.05) were evident for the isoflurane group at both low and high MAC, and decreased VE (P < 0.01) and Vt/Ti (P < 0.01) were observed at high MAC compared with the values observed in the halothane group.

When pooled data for VE and P0.1 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 (VE r = 0.47, P < 0.01, P0.1 r = 0.43, P < 0.01). Correlations between VE and P0.1 with actual MAC values were lower and not significant.

Values of E0 and Rn for each anesthetic and concentration are shown in table 4. A small but significant increase in E0 (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 polynomial coefficients obtained from all subjects, computed as the mean coefficients of the set of occluded inspiratory curves for each subject at each MAC and fitted to a third-order polynomial equation.

Table 4 also shows the mean third-order polynomial 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 P0.1 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 P0.1 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
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. 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 PetCO2 values indicated some degree of hypventilation in comparison with the awake state. Accordingly, the values of VE 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 VE, Vr, and Vr/Ti. Our results also showed a steeper slope of VE at increasing concentration with isoflurane (fig. 1). Additionally, we observed an increase of PetCO2 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., 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. in patients during methoxyflurane anesthesia. Since then, only one study has analyzed occlusion pressure changes at increasing concentrations of halogenated anesthetic agent, 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. 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 P0.1 obtained with the same neural output.

In this study, we observed an increase of 15.8% in P0.1 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, we estimated the reduction of FRC related to anesthetic induction in our subjects to be 14% (i.e., 400 ml). According to Eldridge and Vaughan, 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 P0.1 observed in the isoflurane group between awake and anesthetized states are entirely attributable to the change of diaphragm position, whereas
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 and intercostal 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. 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 $P_{tCO_2}$ 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 or extrinsic resistive loading have been observed. In halothane-anesthetized humans ventilatory compensation for extrinsic or intrinsic resistive 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. 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 and

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neuromuscular effects of anesthetics, and potentiated by adjuvant drugs.

The airway occlusion pressure wave closely reflects the shape of the inspiratory neural drive in cats. In previous studies, the time course of the occlusion pressure wave has been shown to exhibit an upward convexity in methoxyflurane, enflurane, and halothane-anesthetized 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. Studies in animals have fitted the curves to a simple power function. The fitting of a polynomial equation has been suggested as a means to assess the shape of the inspiratory neural drive more accurately and for this reason, in our study we took this step. We observed a strong correlation between $P_{0.1}$ and the first polynomial 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. 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 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, VE, $V_t/T_i$, 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 $P_{ETCO2}$. 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 VE 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. The progression of changes in the shape of the occlusion curve 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 $P_{0.1}$, $P_{ETCO2}$, and VE 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 VE and a slight increase in $P_{ETCO2}$. Isoflurane even at MAC 1.2, on the other hand, induces a clearer ventilatory depression with lower central neural drive. Both anesthetics, however, show deeper depression of ventilation as MAC increases.

References


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