Active inspiratory impedance and neuromuscular respiratory output during halothane anaesthesia in humans


Abstract: The aim of this study was to measure, in 11 patients with healthy lungs, active inspiratory impedance during anaesthesia. In addition, we recorded changes in inspiratory occlusion pressure at 100 ms ($P_{oa}$) and ventilatory pattern while awake and during anaesthesia with a mean inspiratory fraction ($F_i$) of 0.017 halothane in $O_2$. The total active inspiratory resistance and elastance values were $5.4\pm3.3$ hPa·s·l$^{-1}$ and $29.9\pm6.2$ hPa·l$^{-1}$, respectively. $P_{oa}$ and the ratio between $P_{oa}$ and mean inspiratory flow ($P_{oa}/(VT/Ti)$) increased 124% ($p<0.001$) and 68% ($p<0.001$), respectively, during anaesthesia. Respiratory frequency rose significantly from $12.2\pm1.5$ (mean±sd) to $24.6\pm4.6$ cycles·min$^{-1}$, while tidal volume and inspiratory duty cycle lowered significantly from $0.599\pm0.195$ to $0.404\pm0.04$ to $0.372\pm0.08$ and $0.40\pm0.04$ ($p<0.05$), respectively. Minute ventilation ($V_{E}$) and $V_{E}/T_{i}$ did not change significantly. During halothane anaesthesia with an $F_i$ of $0.017$, the increase in neuromuscular respiratory output appears to compensate for the increased mechanical load, thus resulting in maintenance of $V_{E}$ at levels similar to those of an awake state.

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General anaesthesia with halogenated gases induces deep mechanical and regulatory changes in the respiratory system. These changes may include an increase in respiratory system elastance and resistance on the one hand [1], and respiratory depression and alteration of the ventilatory pattern [2], on the other. While there exists a wealth of information concerning these effects, studies analysing and comparing the respiratory mechanics and ventilatory pattern of breathing in humans before and after anaesthetic induction are relatively few. One reason for this might be the difficulty of applying precisely the same measurement procedures in both awake and anaesthetized states. Even less information is available on changes in neuromuscular respiratory output, as represented by the measurement of pressure generated during the first 100 ms of an occluded inspiration ($P_{oa}$) [3]. Available data on respiratory system mechanics and central regulation during anaesthesia are contradictory as to the effects of the anaesthetic agents studied. In part, conflicting results are due to the fact that the anaesthetic pharmacological protocols followed may be interfering with results, masking the actual effects of the anaesthetic agent being studied. Interference comes most commonly from the use of atropine [4] or narcotics [5] during anaesthesia, performance of measurements while surgery is being done, and modification of the measuring procedure between the awake and anaesthetized states.

The aim of this study was to examine the changes in respiratory system mechanics and central neuromuscular output due to anaesthesia with halothane. To this end, an anaesthetic protocol solely based on halothane administration was followed so that any possible changes could be attributed to the anaesthetic drug and the orotracheal intubation. We set out to determine: firstly, total active inspiratory resistance and elastance during halothane anaesthesia; secondly, $P_{oa}$ and breathing pattern before and after anaesthetic induction; and thirdly, any possible correlation between these indices of mechanics and respiratory control that would suggest an adaptive breathing response.
Patients and methods

Patients

Eleven patients (two female) undergoing general anaesthesia for elective orthopaedic limb surgery participated. The patients had a mean age of 28±7 yrs, height of 1.68±0.05 m and weight of 69±10 kg; they were free of cardiopulmonary disease and their spirometry was within the normal range. Institutional approval and written consent from all patients were obtained.

Measurements

Airflow and pressures. Flow (V) was recorded with a wire-mesh screen pneumotachograph (0.34 hPa·l·s⁻¹; Jaeger, Würzburg G) coupled to a differential pressure transducer (±2 hPa; MP-45 Validyne). Volume (V) was calculated by digital integration of the flow signal. Tracheal pressure (Ptr) was measured by connecting an analogue pressure transducer (±15 hPa; MP-45 Validyne) through a side-port mounted at the distal end of the endotracheal tube (fig. 1). Flow and pressure were digitized at 32 Hz, and stored in a microcomputer (PC-AT, IBM) for later analysis. These signals were visualized in real time on the monitor of the microcomputer. A unidirectional valve (Hans-Rudolph #1400, Kansas City, USA) separated the inspiratory and expiratory lines. A hand-controlled silent valve included within the inspiratory line was used to occlude the airway opening. The dead space of the two-way circuit was 70 ml. The gas ventilator outlet was connected to the inspiratory line of the circuit (fig. 1). While awake the patients breathed through a mouthpiece with a noseclip in place. During anaesthesia the endotracheal tube was connected to the distal end of the circuit. Flow pattern was registered twice at intervals of 32 s each. A minimum of five satisfactory inspiratory occlusion manoeuvres, whose duration was at least that of an unoccluded cycle, were performed. Between occlusion manoeuvres, 10 unoccluded breaths were allowed. Ptr returned to zero before and after each occlusion. P de was measured from all occlusion manoeuvres, in which active resistance (R'rs) and active elastance (E'rs) were measured, whether in the awake or anaesthetized state. For the measurement of the so-called “inspiratory impedance” (P de/V r/T i), the mean inspiratory flow (V r/T i) was obtained from the preceding unoccluded cycle.

Resistance and elastance. The pressure-flow characteristics of the endotracheal tube plus pneumotachograph, valve, and connectors (henceforth referred to as equipment) were curvilinear, defined by Rohrer's equation (P=K 1 V+K 2 V 2 ). The flow-resistance constants K 1 (laminar) and K 2 (turbulent) were obtained as described by Behrakis et al. [4]. The measurements were performed in the laboratory with an 8 mm endotracheal tube of the same kind and a 15 cm tube connected to the endotracheal tube to simulate an artificial trachea. O 2 100% was used for calibration as in our study. Values obtained for K 1 and K 2 were 1.04 hPa·l·s⁻¹ and 6.23 hPa·l·s⁻², respectively (fig. 2).

R'rs and E'rs were computed according to Behrakis et al. [4]. Resistive pressure due to equipment was subtracted from driving pressure, -Ptr. R'rs and E'rs were calculated according to the equation

\[ (-\text{Ptr} - K_1 \dot{V} - K_2 \dot{V}^2)/\dot{V} = R'rs + E'rs \frac{\dot{V}}{\dot{V}} \]
where \((K, \dot{V} + K_a \dot{V}^2)\) represents the pressure drop due to equipment. This equation is a linear function, where \(E'rs\) is the slope and \(R'rs\) is the intercept on the ordinate axis. \(P_{tr}\) values were obtained during the occluded inspiratory effort, and \(V\) and \(V\) from the breath previous to an occlusion manoeuvre (fig. 3) at 100 ms intervals after the onset of inspiration during the first 800 ms. The beginning of inspiration was defined as the first 200 ms after a deflection, by mathematical back extrapolation from the flow ramp or the pressure curve, depending on whether the cycle was unoccluded or occluded. For each patient, \(R'rs\) and \(E'rs\) were calculated from the mean of 3–5 satisfactory occlusion manoeuvres and their preceding unoccluded cycles. The time constant \(\tau'rs\) was expressed as the ratio \(R'rs/ E'rs\).

**Ventilatory pattern.** The following ventilatory pattern variables were taken breath-by-breath during continuous flow, whether in the awake or anaesthetized state: total time \((Tror)\); inspiratory time \((Ti)\); expiratory time \((Te)\); respiratory duty cycle \((Ti/Tror)\); tidal volume \((Vt)\); respiratory frequency \((f)\); minute ventilation \((Ve)\); and \(Vt/ Ti\).
Procedure

The patients were medicated the night before and two hours prior to the study with diazepam 10 mg by mouth. The study was performed before surgery within the surgical area in a room contiguous to the operating room. Monitoring was done with continuous ECG recording, blood pressure was measured by sphygmomanometry and arterial haemoglobin saturation by pulse oximeter.

The patients lay in supine position throughout the study. Awake measurements were carried out just before anaesthetic induction. Patients breathed 100% O₂ spontaneously through the circuit for 5 min to assure adaptation. The flow signal was then recorded for three additional minutes. With the patients connected to the circuit and the mouthpiece still in place, short occlusions of the inspiratory line at end-expiration were made in order to register the mouth occlusion pressure at the start of inspiration [3]. Five to ten occlusions with intervals of ten unoccluded breaths were made for all patients.

A continuous infusion of 5% dextrose was started and 5 mg of diazepam was administered i.v.. Anaesthetic induction was accomplished with thiopental (5–6 mg·kg⁻¹) and succinylcholine (1.5 mg·kg⁻¹) to facilitate intubation. All patients' tracheas were intubated with cuffed endotracheal tubes of 8.0 mm inner diameter. The tubes were connected to the ventilator for controlled ventilation. Anaesthesia was maintained at a mean inspired concentration of 1.68±0.39% halothane in O₂, so that patients were haemodynamically stable and did not reject the endotracheal tube. Throughout the study mean heart rate and systolic blood pressure were 80±13 bpm and 100±14 mmHg, respectively. When the effects of muscle paralysis had worn off, approximately 20 min after intubation, the patients were allowed to breathe the same mixture of anaesthetic gas spontaneously through an open circuit. The flow signal was checked to verify ventilatory stability; in fact, the coefficient of variation of tidal volume lowered from a mean value of 17.2% to 2.6% between awake and anaesthetized states.

Statistical analysis

The distribution of data was analysed for Gaussianity by the Kolmogorov-Smirnov test. The results demonstrated normality of distribution in all instances. Therefore, paired t-tests were done for the analysis of differences of all variables measured in awake and anaesthetized states. A linear correlation analysis was done for the parameters of occlusion pressure, ventilatory pattern and active inspiratory impedance. A value of p<0.05 was considered significant.

Results

Data obtained for the 11 patients are reported as their mean and sd values. Figure 4 shows a plot of (P₀tr−Peq)/V vs V/V obtained in a subject during an inspiration. Linear relationships steadily maintained a correlation coefficient greater than 0.99. Mean R'rs, E'rs and τ'rs during anaesthesia were 5.4±3.3 hPa·l⁻¹·s, 29.9±6.2 hPa·l⁻¹ and 0.19±0.10 s, respectively. Table 1 includes the individual results of P₀, and P₀(V/Ti) in the two states. The increase of P₀ during anaesthesia was significant and on the average amounted to 124% of the awake value. The ratio P₀(V/Ti) significantly increased 68% during anaesthesia. Table 2 shows the mean values for the breathing pattern variables before
Table 1. - Airway occlusion pressure and effective impedance during awake and anaesthetized states

<table>
<thead>
<tr>
<th>Patient</th>
<th>Awake</th>
<th>Anaesthesia</th>
<th>Δ%</th>
<th>Awake</th>
<th>Anaesthesia</th>
<th>Δ%</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1.36</td>
<td>2.28</td>
<td>68</td>
<td>3.16</td>
<td>6.70</td>
<td>112</td>
</tr>
<tr>
<td>2</td>
<td>0.81</td>
<td>2.58</td>
<td>219</td>
<td>4.01</td>
<td>7.69</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>0.68</td>
<td>2.37</td>
<td>249</td>
<td>1.41</td>
<td>5.65</td>
<td>301</td>
</tr>
<tr>
<td>4</td>
<td>0.98</td>
<td>2.09</td>
<td>113</td>
<td>3.74</td>
<td>6.17</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1.33</td>
<td>1.81</td>
<td>36</td>
<td>4.49</td>
<td>6.11</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>0.90</td>
<td>2.34</td>
<td>160</td>
<td>3.27</td>
<td>8.17</td>
<td>150</td>
</tr>
<tr>
<td>7</td>
<td>1.52</td>
<td>2.63</td>
<td>73</td>
<td>5.51</td>
<td>8.59</td>
<td>56</td>
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<tr>
<td>8</td>
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<td>21</td>
<td>3.62</td>
<td>4.67</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>0.81</td>
<td>3.69</td>
<td>356</td>
<td>6.69</td>
<td>8.51</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>1.21</td>
<td>3.70</td>
<td>206</td>
<td>5.65</td>
<td>8.74</td>
<td>55</td>
</tr>
</tbody>
</table>

Mean: 1.14 * 2.55 124 4.20 * 7.07 68
SD: 0.31 0.66 1.44 1.36

Δ%: represents the percentage increase between awake and anaesthetized states. \( P_{oa} \): airway occlusion pressure; \( \frac{P_{oa}}{(VT/Tt)} \): effective impedance. *: \( p<0.001 \).

Table 2. - Breathing pattern during awake and anaesthetized states

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>Anaesthesia</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{E} ) l min(^{-1} )</td>
<td>7.31±2.39</td>
<td>8.94±1.75</td>
<td>0.218</td>
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<tr>
<td>( V_{T} ) l</td>
<td>0.599±0.193</td>
<td>0.372±0.088</td>
<td>&lt;0.05</td>
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<tr>
<td>( f ) breaths min(^{-1} )</td>
<td>12.2±1.5</td>
<td>24.6±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( T_{TOT} ) s</td>
<td>4.95±0.50</td>
<td>2.51±0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( T_{I} ) s</td>
<td>1.42±0.29</td>
<td>1.00±0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( T_{E} ) s</td>
<td>2.67±0.35</td>
<td>1.46±0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( T_{I}/T_{TOT} )</td>
<td>0.44±0.04</td>
<td>0.40±0.04</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>( V_{T}/T_{I} ) l s(^{-1} )</td>
<td>0.279±0.090</td>
<td>0.349±0.049</td>
<td>0.095</td>
</tr>
</tbody>
</table>

\( V_{E} \): minute ventilation; \( V_{T} \): tidal volume; \( f \): breathing frequency; \( T_{TOT} \): total time of breathing cycle; \( T_{I} \): inspiratory time; \( T_{E} \): expiratory time; \( T_{I}/T_{TOT} \): respiratory duty cycle; \( V_{T}/T_{I} \): mean inspiratory flow.

anaesthetic induction and during halothane anaesthesia, with the patients breathing spontaneously. The increase in \( V_{E} \) reached 22% of the awake value but the change was not statistically significant. The increase was solely due to a 102% increase in breathing frequency since the value of \( V_{T} \) was reduced by almost 38% during anaesthesia. In keeping with the increase of \( f \), inspiratory and expiratory times, particularly \( T_{I} \), were significantly reduced. \( V_{T}/T_{I} \) increased by 25% under anaesthesia but the change was not found to be significant (\( p=0.09 \)). Figure 5 illustrates these ventilatory pattern changes in a volume-time diagram.

The analysis of correlation between inspiratory impedance and ventilatory pattern variables was carried out with and without the resistive pressure drop attributed to the endotracheal tube. The results showed no
anaesthetic induction. The Jack of studies may measured variables, we failed to find a systematic comparison of whatever relationships may actually be operating. There was a significant correlation between R'rs and the ratio P01/(VT/Ti) (r=0.77; p<0.01) as well between R'rs and Ti (r=0.72; p<0.05). R'rs showed a somewhat higher correlation with P01/(VT/Ti) (r=0.81; p<0.01) and Ti (r=0.75; p<0.01). E'rs on the other hand, showed no significant correlation with any of the measured variables. During anaesthesia P01 showed a significant correlation with VT/Ti (r=0.65; p<0.05).

Discussion

Active inspiratory impedance

Under active conditions, i.e. when muscles contract, the muscle properties of force-length and force-velocity are added to the volume-elastic and flow-resistive impedances, respectively [6]. Thus, impedance of the respiratory system increases during active breathing [4]. Few studies measure active inspiratory impedance in anaesthetized humans [4, 5]. Our mean result for E'rs (29.9±6.2 hPa·l·s) was very similar to that of BEHRAKIS et al. [4] (31.2±5.2 hPa·l·s) and BAYDUR et al. [5] (28.3±3.3 hPa·l·s). However, our mean value for R'rs (5.4±3.3 hPa·l·s) was higher than those reported in these studies (2.1±0.7 and 3.3±1.9 hPa·l·s, respectively). Since in all of these studies the resistance due to equipment was subtracted from the calculations, other factors must be called upon to account for the differences observed. Atropine has been demonstrated to reduce flow resistance by 33% [7]. This drug was not used in the present study and in fact our results for resistance are similar to those of researchers using comparable measurement techniques and not including atropine in the anaesthetic protocol [8]. Another factor that might help to explain our patients' relatively high R'rs value is the physical characteristics of the anaesthetic mixture used [1]. Notwithstanding the possible effect these factors may have had on measurements, the present study shows that during halothane anaesthesia the respiratory system undergoes important changes in resistance and elastance resulting in an increased respiratory system time constant.

Central respiratory output

Our results show that P01 increases significantly during halothane anaesthesia as compared to the immediately preceding awake state (table 1). P01 is used as an index of neuromuscular output to the respiratory pump in humans [3]. Despite the great number of studies of anaesthetized patients in whom P01 was one of the measured variables, we failed to find a systematic comparison of P01 measurements before and after anaesthetic induction. The lack of studies may be due to the difficulty of interpreting such measurements.

The two most important factors affecting the transfer of neural discharge to pressure are the length-tension relationship of the muscles and their mechanical advantage. Thus, in addition to the motor output of the respiratory centres, mouth occlusion pressure may be affected by changes in the functional residual capacity (FRC) of the lung. A decrease in FRC could result in an increase in precontraction length for the inspiratory muscles. This would increase the P01 obtained with the same neural output. However, MATTHEWS and HOWELL [9] found no significant changes in mouth occlusion pressure after induced increases in FRC of up to 3 l in awake sitting subjects. Burki [10] also found that P01 was not affected by changes in FRC of up to 1.4 l induced by shifting the patient from sitting to supine position. Our subjects did not change position throughout the measurement period and FRC was not measured. Anaesthetic induction has been reported to reduce FRC in supine subjects [11], however, and according to the equation proposed by REHDER and MARSH [1], the reduction of FRC in our patients could be estimated to have a mean value of 15%, i.e. slightly above 400 ml. This estimate is well below the figures for changes in FRC from the studies mentioned above [9, 10]. Therefore, it seems unlikely that the small reduction of FRC anticipated from the anaesthetic induction would account for the increase of P01 observed in our patients. TUSIŃWICZ et al. [12] posed a word of caution on the interpretation of P01 measurement as an index of neuromuscular output during anaesthesia because of the depression of intercostal muscle function due to halothane. Mouth occlusion pressure may then be generated in part by the relaxation of expiratory muscles allowing chest wall elastic recoil to be felt in the mouth, although this mechanism seems unlikely in the anaesthetized supine subjects [13].

Ventilation and breathing pattern

One of the most striking findings of our study is the absence of significant changes in Vc. Most previous reports associated halothane anaesthesia with a reduction of Vc [2, 12, 14, 15]. The comparison of our ventilation data with those in the literature is hampered by difference in the anaesthetic protocols used. In some studies, for example, basal and intraoperative data were obtained on separate days [14]; in others, measurements in anaesthetized patients were obtained during surgery [15]. Moreover, nitrous oxide was part of the anaesthetic gas mixture in some studies and this gas has been shown to reduce Vc [16]. Finally, other investigators included drugs known to modify the central respiratory response [17]. Our measuring circuit (fig. 1) had a dead space which would explain the slightly elevated Vc during the awake state. Vc further increased during anaesthesia, although not significantly. This, together with the reduction of anatomical and instrumental dead space due to placement of the endotracheal tube [18], may have offset the reduction of Vc as far as alveolar
ventilation is concerned. Since carbon dioxide tension (Pco₂) was not measured in the present study we can only speculate that alveolar ventilation was probably not depressed.

Our patients were breathing 100% O₂ in both states and were not subjected to any additional mechanical load during anaesthesia, with the exception of the endotracheal tube. The increase of f and reduction of VT have been found by some investigators to be more marked for halothane than for other halogenated gases [19], and this has been attributed to a central effect not vagally mediated [20]. An alternative explanation considers the increase in f to be an adaptive response to increased mechanical load, a response similar to that observed in patients with chronic obstructive lung disease [21, 22]. Such patients tend to maintain Vₘ and Vₘ/Ti, while increasing f, and decreasing Vₗ and Ti/TTror. The reduction of Ti and Te of our subjects was not proportional since Ti/TTror changed from 0.44 to 0.40; this seems to be the case for all halogenated gases [19].

Nevertheless, our results are consistent with a qualitative increase in respiratory neuromuscular output during halothane anaesthesia. The increased neuromuscular drive would also be reflected by the increase of Vₗ/Ti, which correlated with the increase in Pₐ, (r=0.65; p<0.05). The absence of respiratory depression suggested by these findings might be related to the low concentration of halothane we used, estimated to be about 1.5 MAC. Progressive increments of halothane concentration have been associated with reduction of Vₗ and increases of Pco₂ [14].

As pointed out by some investigators [23, 24], the greater part of ventilatory depression related to halogenated anesthetic gases is not due to decrease in inspiratory drive but rather to increase in respiratory system impedance. This observation is at variance with that of Derenne et al. [25] who studied patients under methoxyflurane anaesthesia and reported a relatively unaltered mouth occlusion pressure. However, recent studies indicate that in humans the respiratory centres are capable of adapting respiration during halothane anaesthesia to the changing extrinsic [26-28] and intrinsic mechanical loads [29].

This study was aimed at examining changes in respiratory mechanics and their relation to central neural output and ventilation during anaesthesia without the interference of surgical stimuli, postural changes or additional pharmacological effects. The results lead to the conclusion that halothane at the usual anaesthetic dosage does not depress ventilation. Despite the increase in mechanical load during anaesthesia, the concomitant increase in Pₐ, succeeds in maintaining Vₗ and Vₗ/Ti at least at the level of the awake state.

References

18. Nunn JF, Hill DW. - Respiratory dead space and arterial


