The Hering-Breuer reflex in anesthetized infants: end-inspiratory vs. end-expiratory occlusion technique

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1Department of Anaesthesia, Montreal Children's Hospital, Montreal, Quebec, Canada H3H 1P3; 2Portex Anaesthesia, Intensive Therapy and Respiratory Medicine Unit, Institute of Child Health, London, WC1N 1EH, United Kingdom; and 3Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, People's Republic of China

Brown, K., J. Stocks, C. Aun, and P. S. Rabbette. The Hering-Breuer reflex in anesthetized infants: end-inspiratory vs. end-expiratory occlusion technique. J. Appl. Physiol. 84(4): 1437–1446, 1998.—Both end-inspiratory (EIO) and end-expiratory (EEO) occlusions have been used to measure the strength of the Hering-Breuer inflation reflex (HBIR) in infants. The purpose of this study was to compare both techniques in anesthetized infants. In each infant, HBIR activity was calculated as the relative prolongation of expiratory time (Tl(oc)) relative to the unoccluded expiratory time (Tl). Alternatively, functional blockade of stretch receptor activity, by EEO to prevent lung inflation, causes prolongation of inspiratory time during occlusion (Tl(oc)) proportional to the strength of the HBIR (32). The EEO is the conventional method used to measure respiratory drive at functional residual capacity (FRC) (49). The EIO and inflation techniques have the advantage of less laryngeal glottic closure, less arousal, and less chest wall afferent stimulation (36) compared with the EEO technique and form the basis of measurements of passive respiratory mechanics in infants and young children (11).

Thus the choice between EIO and EEO seems to be based largely on convention and the focus of the investigation, i.e., whether respiratory mechanics or control is being investigated. The choice of which technique to use is complicated by the use of different methods of collecting, analyzing, and reporting the data, together with the high intrinsic variability of HBIR activity and the small sample size in many of the previously published reports.

The level of HBIR activity could contribute to an infant's predisposition to respiratory depression during anesthesia. Both the occlusion and inflation techniques are noninvasive, bedside techniques that are applicable in the operating room. However, because the choice of technique may impact on both the duration of the study protocol and the interpretation of the results, a direct within-subject comparison of techniques is required.

The null hypothesis tested in this study was that there was no difference in HBIR activity when the EIO or EEO technique is used in anesthetized infants. The purpose of the study was to investigate both the respiratory timing and drive components of the HBIR at the two levels of occlusion. A secondary purpose was to examine the strength of HBIR activity after lung inflations.

RESPIRATORY PROBLEMS remain a significant cause of perioperative morbidity and mortality during infancy (33). Developmental aspects of both respiratory mechanics and control have been implicated in infants' predisposition to respiratory depression during anesthesia (4, 17).

The Hering-Breuer inflation reflex (HBIR) assesses the influence of vagal input from the pulmonary stretch receptors on both ventilatory timing and drive (47). Although the HBIR does not appear to have any physiological role in the control of tidal breathing in adults, an active HBIR may facilitate the rapid respiratory rate important for the maintenance of an adequate resting lung volume in infants (6, 24, 43). The HBIR persists beyond the newborn period (36, 44) and remains active even at 1 yr of age (37), although longitudinal measurements show a reduction in activity from 90% in early infancy (36, 44) to 50% at 1 yr of age (37). Unlike in anesthetized adults, in whom there is no response (21), end-expiratory airway occlusion (EEO) during tidal breathing, a maneuver that removes the inspiratory-inhibitory effect of lung inflation, results in a prolongation of inspiration by ~20% in anesthetized infants (3).

Clinical studies investigating the activity of the HBIR have utilized three major approaches: airway occlusion at end inspiration (EIO) (36), EEO (32), and the inflation technique (7). EIO and lung inflations both use the stimulus of lung expansion to maintain vagally mediated, slowly adapting pulmonary stretch receptor input and inhibit subsequent inspiratory effort via negative feedback (20). Under these conditions, the strength of the HBIR can be assessed from the prolongation of the occluded expiration (TEocc) relative to the unoccluded expiratory time (TE). Alternatively, functional blockade of stretch receptor activity, by EEO to prevent lung inflation, causes prolongation of inspiratory time during occlusion (TI(oc)) proportional to the strength of the HBIR (32). The EEO is the conventional method used to measure respiratory drive at functional residual capacity (FRC) (49). The EIO and inflation techniques have the advantage of less laryngeal glottic closure, less arousal, and less chest wall afferent stimulation (36) compared with the EEO technique and form the basis of measurements of passive respiratory mechanics in infants and young children (11).
METHODS

Study Population

All infants were participating in a randomized controlled trial of the ventilatory effects of sevoflurane vs. halothane, the results of which are described elsewhere (2). The study population comprised infants aged 6–24 mo who were healthy, had fasted, had no history of cardiovascular disease or chest wall deformity, and were undergoing elective peripheral limb surgery or hypospadias repair. The study received institutional ethics committee approval and written informed parental consent.

Anesthetic Management

Patients were premedicated orally with atropine (20 µg/kg) and randomized to receive either halothane or sevoflurane in 33% oxygen in nitrous oxide (6 l/min) for induction and maintenance of anesthesia. All infants were monitored with pulse oximetry, which was maintained above 95% saturation. After induction of anesthesia, an appropriately sized laryngeal mask was inserted and the anesthetic vapor concentration was adjusted to 1 MAC [where 1 MAC, a measure of anesthetic depth, is the minimum alveolar concentration (MAC) of anesthetic required to prevent movement in 50% of the population]. The age-adjusted MAC of halothane and sevoflurane were assumed to be 0.9 (14) and 2.5% (26), respectively. Airflow was measured with a heated Hans Rudolph pneumotachograph (no. 3500, linear range 0–35 l/min, Kansas City, KS) attached to a piezoresistive pressure transducer (±0.2 kPa, 431 SCXLO040N, Sensym, Milpitas, CA). Volume (V) was integrated digitally from the flow signal. The pressure at the airway opening (Pao) was measured with another pressure transducer (±5.0 kPa, 511 SCXO10N, Sensym) via a side port attached to the laryngeal mask.

A pneumatically activated, hand-operated balloon-type shutter (series 9300, Hans Rudolph) was used to produce EIO. To perform EEO, it was necessary to interpose an appropriately sized, nonbreathing valve (Hans Rudolph 2200) between the pneumotachograph and the shutter to separate the inspiratory and expiratory airflow. Airway occlusions were timed from the real-time display of flow.

Flow was calibrated with rotameters, and the volume was validated with a volumetric 100-ml syringe (Hans Rudolph) containing the 66% nitrous oxide-in-oxygen mixture used for anesthesia. Pressure was calibrated against a water manometer. Pressure transducers were checked at the start and end of each study. At a flow of 100 ml/s, the resistance of the apparatus was 0.31 kPa·l⁻¹·s during EIO and 0.88 kPa·l⁻¹·s during EEO. The dead space of the measuring apparatus, estimated by water displacement, was ~9 ml. The analog outputs of flow and Pao were sampled at 100 Hz, digitized (Data Translation DT2801, Mississauga, Canada), interpolated, and recorded on a personal computer (ANADAT RHT InfoDat, Montreal, Quebec).

Protocol

After steady-state equilibration of the inspired anesthetic, a time period between 15 and 20 min, measurements of flow and Pao were recorded during spontaneous ventilation.

Data were collected during 1) baseline spontaneous ventilation, 2) respiratory efforts against an occluded airway after EIO, 3) respiratory efforts against an occluded airway after EEO, and 4) respiratory efforts against an occluded airway after a passive lung inflation. The EIO was performed at an occluded volume (Vocc) within 15% of end-tidal inspiration and held for the duration of a complete respiratory effort (Fig. 1A). The EEO was achieved by inflating the balloon shutter during expiration such that the subsequent inspiratory effort was occluded, thereby ensuring occlusion exactly at end expiration. The EEO was held for the duration of two consecutive inspiratory efforts (Fig. 1B). A minimum of eight breaths was allowed between consecutive EIO and EEO. In addition, a single, passive lung inflation, coordinated with the onset of a spontaneous inspiratory effort, was performed whenever possible. The airway was occluded at a Vocc two to three times that of the spontaneous tidal volume (VT) (Fig. 1C).

Data Analysis

Acceptance criteria for the occlusion data were a stable end-expiratory level, no evidence of a volume leak (11), and a Vocc of zero during EEO and of at least 85% of the VT during EIO. Data within five breaths of a spontaneous sigh were excluded. An additional acceptance criterion during the inflation technique was evidence of a passive lung inflation coordinated with the spontaneous inspiratory effort.

Analysis of flow and volume VT and various parameters of ventilatory timing [the total cycle time (TT), inspiratory time (TI), TE, and the inspiratory duty cycle (TI/TT)] were calculated. Reported values for the baseline spontaneous ventilation data were the mean of eight consecutive breaths. The Vocc was measured as the volume excursion between the prior end-expiratory level and the volume plateau during airway occlusion (Fig. 1, A and C).

Analysis of airway pressure. During the EIO, TEocc was measured from the expiratory zero flow crossing and rise in Pao to the onset of negative deflection on the Pao trace (Fig. 1A). TIocc was measured from the initial negative deflection to the upswing of the Pao trace. The effect of EIO on the duration of expiration (HBIRE) was assessed by the prolongation of Teocc relative to Te such that

\[ \text{HBIRE}\% = \left( \frac{T_{\text{Eocc}} - T_{\text{E}}} {T_{\text{E}}} \right) \times 100 \]  

During the EEO, both occluded inspiratory efforts obtained during EEO were analyzed. During airway occlusion, TIocc was measured from the initial negative deflection to the upswing of the Pao trace (Fig. 1B). The effect of EEO on the duration of inspiration (HBIRE) was assessed from the prolongation of Tocc relative to Ti during EEO such that

\[ \text{HBIRE}\% = \left( \frac{T_{\text{occ}} - T_{\text{i}}} {T_{\text{i}}} \right) \times 100 \]  

A physiologically significant reflex was defined as an HBIR exceeding 25%, that is, when Te or Ti increased by at least 25% relative to baseline values during EIO and EEO, respectively. This value was chosen to represent the upper 95% confidence limits for within-subject variability of Ti or Te in infants (i.e., mean plus 2 SD) (35, 36).

Lung inflation. Inflation was analyzed in a similar fashion to that for EIO data (Fig. 1C). The effect of inflation on the duration of expiration (HBIRE) was assessed by the prolonga-
Fig. 1. End-inspiratory occlusion (EIO; A), end-expiratory occlusion (EEO; B), and inflation technique (C) in an anesthetized infant. TEocc, occluded expiration; Vocc, occluded volume; Pmax, maximal excursion of airway opening pressure (Pao) during occluded inspiratory effort; TE, unoccluded expiratory time; TEOcc, occluded inspiration; TI, unoccluded inspiratory time. Derivation of various indexes of respiratory timing and drive are also indicated. Note change in scale to accommodate larger lung inflation (C).
tion of $T_{Eocc}$ relative to $T_E$ such that

$$\text{HBIR}_{\text{inf} \%} = \left(\frac{\text{TE}_{occ} - \text{TE}}{\text{TE}}\right) \times 100$$

(3)

HBIR drive. The maximal excursion of the Pao during the occluded inspiratory effort ($P_{\text{max}}$) was measured for the EIO, for both occluded inspiratory efforts during the EEO and, when obtained, for the occlusion after lung inflation. The slope of the first 100 ms of the occluded inspiration ($dP/dt_{0.1}$) was derived by linear regression of this portion of the inspiratory effort (Fig. 1). Data were only accepted if the $r^2$ value for the linear fit exceeded 0.97. The drive index $P_{0.1}$ (49), i.e., the Pao at a fixed interval of 100 ms $T_{Iocc}$, was derived as

$$P_{0.1} = 0.1 \times dP/dt_{0.1}$$

(4)

The effect of the duration of $T_{Iocc}$ on $P_{0.1}$ was assessed by calculating the occluded Pao at a fixed proportion of $T_{Iocc}$ arbitrarily set at 10% ($P_{10\%}$)

$$P_{10\%} = dP/dt_{0.1} \times (T_{Iocc} \times 0.1)$$

(5)

Reported values of $V_{occ}$, $T_{Eocc}$, $T_{Iocc}$, HBIR, $P_{0.1}$, $P_{10\%}$ and $P_{\text{max}}$ during the airway occlusions were the mean of a minimum of four technically acceptable occluded efforts in each infant. Data reported for the inflation were derived from a single occlusion.

Statistical Analysis

The power to detect a difference between the EIO and EEO techniques equivalent to 1 SD of the main outcome variables (i.e., ∼15% for HBIR and 0.12 kPa for $P_{10\%}$) at the 5% level of significance was in excess of 95% for paired comparisons in a sample size of 20. Potential effects of the anesthetic agent and technique of regional blockade were assessed with a one-way ANOVA. Differences between EIO and EEO values for HBIR and $P_{10\%}$ were assessed with paired t-tests and the calculation of 95% confidence intervals (CI) for the group mean difference (EIO – EEO). A P value < 0.05, together with 95% CI that did not encompass zero, was considered statistically significant (8).

RESULTS

Recruitment

Of the 30 infants recruited for this study, technically satisfactory, paired measurements of EIO and EEO data were completed in 22 [age: 14.3 ± 6.4 (SD) mo; weight: 10.5 ± 2.4 kg]. Twelve of the infants were anesthetized with halothane and the remainder with sevoflurane. One-way ANOVA showed a potential effect of the anesthetic agent on the HBIR, with significantly less activity being observed during EIO in those who had received halothane ($P < 0.05$). Consequently, all scatterplots indicate the type of anesthetic agent administered.

Insertion of the occlusion valves altered the pattern of spontaneous breathing, causing an increase in $V_T$ and a decrease in $T_I$ and $T_I/T_T$ (Fig. 2) compared with unloaded breathing. However, the baseline respiratory parameters before the EIO and EEO data were very similar, irrespective of the type of occlusion device used (Table 1).

Respiratory Timing

EIO. In this group of anesthetized infants, there was no significant HBIR during EIO. Indeed, $T_{Eocc}$ was shorter than $T_E$ in the majority of infants (Fig. 3A), such that measured mean HBIR$_{EI}$ was −12% (Fig. 4, Table 1). Four of the five infants with values of HBIR$_{EI}$ below −25% were <12 mo old, and all but one had been anesthetized with halothane (Fig. 5). Many of the Pao waveforms showed an upward convexity during the brief $T_{Eocc}$ suggestive of some expiratory muscle activity.

EEO. $T_{Iocc}$ was significantly longer than the baseline $T_I$ in the majority of infants (Fig. 3B) such that the mean HBIR$_{EE}$ for the pooled data was 27.2 ± 17.4% (Fig. 4, Table 2). No relationship between age and HBIR$_{EE}$ was seen (Fig. 5). The $T_{Iocc}$, and hence HBIR$_{EE}$, for the second EEO were similar to values for the first occluded effort (Table 1). The mean (95% CI) difference in HBIR (EIO – EEO) was −39%−50, −29%, $P < 0.01$.

Respiratory Drive

Although the second inspiratory effort during EEO was recorded in all 22 infants, data from one infant had to be excluded because of an $r^2 < 0.97$ (see METHODS). Values of $P_{0.1}$, $P_{10\%}$ and $P_{\text{max}}$ for the second EEO were similar to those derived from the first EEO (Table 1). Similar values for $P_{0.1}$ were also obtained during EIO and EEO. However, the mean $T_{Iocc}$ (0.4 s) during the EIO was lower than that during EEO (0.7 s, $P < 0.01$). When corrected for this shorter $T_{Iocc}$, the respiratory drive index, $P_{10\%}$ was lower during the EIO [mean (95%...
Table 1. Comparison of ventilatory parameters before and during end-inspiratory and end-expiratory occlusions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EIO</th>
<th>EEO</th>
<th>2nd EEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT, ml/kg</td>
<td>6.2 ± 0.8</td>
<td>6.2 ± 0.9</td>
<td>As for EEO</td>
</tr>
<tr>
<td>Vocc, ml/kg</td>
<td>5.8 ± 0.8</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Tt, s</td>
<td>1.50 ± 0.3</td>
<td>1.53 ± 0.4</td>
<td>-</td>
</tr>
<tr>
<td>Ti, s</td>
<td>0.52 ± 0.1</td>
<td>0.54 ± 0.1</td>
<td>-</td>
</tr>
<tr>
<td>Te, s</td>
<td>0.98 ± 0.3</td>
<td>0.99 ± 0.3</td>
<td>-</td>
</tr>
<tr>
<td>Ti/Tt</td>
<td>0.35 ± 0.04</td>
<td>0.35 ± 0.04</td>
<td>-</td>
</tr>
<tr>
<td>During occlusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teocc, s</td>
<td>0.87 ± 0.3</td>
<td>0.69 ± 0.2</td>
<td>0.67 ± 0.13</td>
</tr>
<tr>
<td>Tiocc, s</td>
<td>0.42 ± 0.1*</td>
<td>0.27 ± 0.1</td>
<td>0.37 ± 0.1†</td>
</tr>
<tr>
<td>HBIR, %</td>
<td>-11.8 ± 15.9*</td>
<td>27.2 ± 10.4</td>
<td>24.5 ± 13.7</td>
</tr>
<tr>
<td>P0.1, kPa</td>
<td>0.54 ± 0.37</td>
<td>0.58 ± 0.33</td>
<td>0.57 ± 0.27†</td>
</tr>
<tr>
<td>P10%, kPa</td>
<td>0.20 ± 0.09*</td>
<td>0.37 ± 0.15</td>
<td>0.37 ± 0.15†</td>
</tr>
<tr>
<td>Pmax, kPa</td>
<td>1.34 ± 0.50*</td>
<td>1.94 ± 0.81</td>
<td>2.12 ± 0.79</td>
</tr>
</tbody>
</table>

Values are means ± SD. EIO, end-inspiratory occlusion; EEO, end-expiratory occlusion; VT, tidal volume; Vocc, volume above functional residual capacity during occlusion; Tt, total cycle time; Ti, inspiratory time; Te, expiratory time; Teocc, occluded expiratory time; Tiocc, occluded inspiratory time; HBIR, Hering-Breuer inflation reflex; P0.1, and P10%, change in airway pressure during 100-ms interval and 10% of Teocc, respectively; Pmax, maximal excursion of airway opening pressure during occluded inspiratory effort. 2nd EEO refers to analysis of 2nd inspiratory effort during EEO. Significant differences between EIO and EEO, *P < 0.01. †P0.1 and P10% for 2nd EEO data calculated for 21 patients.

CI) difference in P10% (EIO - EEO): -0.17 kPa (-0.25, -0.09 kPa, P < 0.01) (Fig. 6). Pmax was also smaller (P < 0.01) during the EIO than during the EEO (Table 1).

Inflation Technique

Technically acceptable passive inflations of the lung, which were coordinated with the spontaneous inspiratory effort, were only achieved in seven patients. The Vocc during inflation ranged from 10 to 23 ml/kg. Inflation resulted in a prolongation of Teocc in all but one of the infants (Fig. 1C, Table 2). The infant in whom no response could be elicited was the youngest at time of study (subject 1 = aged 6.8 mo) and also the one with the lowest inflation volume. The average HBIRref was 137% (range = 3 to 310%), considerably greater than that observed for EIO during tidal breathing in either this subgroup of seven infants [-6 ± 8 (SD) %] or the entire group [HBIRref = -12 ± 16 (SD) %].

Although Teocc during the occluded inflation was remarkably similar to that of the tidal EIO maneuver, both P0.1 and P10% were lower during the inflation maneuver than during EIO (Table 2). The relationship between Vocc and HBIR for the EIO, EEO, and inflation techniques is shown in Fig. 7A, in which it can be seen that HBIR was lowest for the EIO technique. An inverse relationship between Vocc and the value of P10% is suggested in Fig. 7B.

DISCUSSION

To our knowledge, this is the first published comparison of paired measurements of the EIO and EEO technique in infants. These findings suggest an important influence of the technique on results in anesthetized infants, with respect to both the respiratory timing and drive components of the HBIR. Results obtained from the EEO technique indicated the presence of an active, albeit weak, HBIR in the majority of anesthetized infants, whereas results obtained from the EIO technique suggested that there was no physiologically significant HBIR over the tidal range. Furthermore, there were marked differences in respiratory drive according to the technique used. These results are in marked contrast to those reported in sleeping infants of similar age and suggest differences in the central integration of stretch receptor activity during anesthesia compared with sleep.

Unpublished data (35) of paired EIO and EEO measurements from naturally sleeping newborns showed a mean prolongation in Teocc and Tiocc of 98 and 99%, respectively, suggesting that the two techniques give similar results when the strength of the HBIR is being assessed. More recently, these findings have been confirmed in 15 older infants (mean age 12 mo), in whom the strength of the HBIR was 48 and 44% during EIO and EEO, respectively (95% CI of difference: -14 and 22%; P. S. Rabbette, personal communication). The
reasons for these discrepancies are probably related to both specific effects of anesthetic agents on the control of breathing and to the reduction in both lung volume (9) and VT (4, 12) induced by inhalation of volatile anesthetics such as halothane (13). They might also reflect some interdependence between chemo- and mechanoreflexes because any degree of hypoventilation, such as commonly occurs in anesthetized subjects during spontaneous breathing (2), would be expected to inhibit HBIR activity (19, 20, 28). However, before the results can be interpreted more fully, it is necessary to consider factors that could have potentially influenced them.

Potentially Confounding Factors

Several aspects of the study design could have potentially influenced our findings. ANOVA suggested an effect of an anesthetic agent on the activity of the HBIREEI, such that HBIREEI was lower, and the relative increase in HBIR between the EIO and EEO techniques was greater, in those infants who received halothane. Rather than analyzing the two groups separately, which would have reduced the power of study, we have indicated which agent was used in all illustrations. Of importance, halothane affected the magnitude but not direction of the response (Figs. 3–5). No difference in HBIREEI activity was observed between halothane and sevoflurane, which agrees with findings in adults (21). Although infants were premedicated with atropine, an agent known to decrease vagal activity, the oral dose of 20 µg/kg is minimal compared with the effect of an anesthetic agent on the activity of the HBIREEI, such that HBIREEI was lower, and the relative increase in HBIR between the EIO and EEO techniques was greater, in those infants who received halothane. Rather than analyzing the two groups separately, which would have reduced the power of study, we have indicated which agent was used in all illustrations. Of importance, halothane affected the magnitude but not direction of the response (Figs. 3–5). No difference in HBIREEI activity was observed between halothane and sevoflurane, which agrees with findings in adults (21). Although infants were premedicated with atropine, an agent known to decrease vagal activity, the oral dose of 20 µg/kg is minimal compared with the

Table 2. Results of inflation technique, arranged in ascending order of TEocc during the inflation, and corresponding EIO data

<table>
<thead>
<tr>
<th>Infant</th>
<th>Inflation</th>
<th>Vocc, ml/kg</th>
<th>TEocc, s</th>
<th>HBIREEI, %</th>
<th>T1occ, s</th>
<th>P10%, kPa</th>
<th>P20%, kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.89</td>
<td>-3</td>
<td>0.42</td>
<td>0.15</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.69</td>
<td>-17</td>
<td>0.41</td>
<td>0.37</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>1.21</td>
<td>54</td>
<td>0.40</td>
<td>0.45</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.69</td>
<td>-12</td>
<td>0.36</td>
<td>0.73</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>1.61</td>
<td>82</td>
<td>0.25</td>
<td>0.74</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.90</td>
<td>-3</td>
<td>0.36</td>
<td>1.18</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>1.85</td>
<td>171</td>
<td>0.29</td>
<td>0.19</td>
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<tr>
<td></td>
<td>5</td>
<td>0.59</td>
<td>-16</td>
<td>0.31</td>
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<td>0.11</td>
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</tr>
<tr>
<td>5</td>
<td>23</td>
<td>2.66</td>
<td>44</td>
<td>0.59</td>
<td>0.26</td>
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</tr>
<tr>
<td></td>
<td>5</td>
<td>1.91</td>
<td>4</td>
<td>0.66</td>
<td>0.28</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>3.16</td>
<td>290</td>
<td>0.21</td>
<td>0.13</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.79</td>
<td>-4</td>
<td>0.34</td>
<td>0.34</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>3.71</td>
<td>310</td>
<td>0.33</td>
<td>0.08</td>
<td>0.03</td>
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</tr>
<tr>
<td></td>
<td>5</td>
<td>0.95</td>
<td>3</td>
<td>0.39</td>
<td>0.41</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

HBIREEI, relative prolongation of expiration during an EIO.

Fig. 4. Relative Hering-Breuer inflation reflex (HBIR) activity in individual infants. Mean effect of EIO on duration of expiration (HBIREEI) was significantly lower than effect of EEO on duration of inspiration (HBIREEE). Symbols are defined as in Fig. 2. Values are means ± SD. *P < 0.01.

Fig. 5. Relationship between age and HBIREEI. Infants under 12 mo of age had a shortening of TEocc relative to TE so that negative values for HBIREEI were obtained. Symbols are defined as in Fig. 2.

Fig. 6. Change in airway pressure during inspiratory effort against occlusion during fixed proportion (10%) of T1occ (P10%). P10% was significantly lower (P < 0.01) during EIO than EEO occlusions. Values are means ± SD. Symbols are defined as in Fig. 2. *P < 0.01.
intravenous dose required for ablation of a vagal response in dogs (1.5 mg/kg) (34).

The use of a laryngeal mask, positioned above the larynx, may have allowed vagally mediated volume-dependent modulation from the upper airway to influence the duration of inspiration (48). Weight-corrected VT was higher in this study than is usually reported during anesthesia (38), which probably reflects the lower resistive load imposed by a laryngeal mask compared with that by an endotracheal tube (39). As expected (30), the resistance of the occlusion devices changed the pattern of breathing compared with the unloaded pattern, resulting in an increase in VT and a slowing of respiration (Fig. 3). Nevertheless, VT remained lower than in nonanesthetized infants (37), which could have contributed to the diminished HBIR, as discussed below. Importantly, the need to use different devices for the EEO and EIO did not result in any detectable differences in the baseline ventilation between the two techniques (Table 1).

It has been suggested that, because stretch receptor activity is obviously dependent on volume changes, the magnitude of VT should be taken into account when the strength of the HBIR is being calculated (5, 15, 42). However, the model proposed by Grunstein et al. (15), which was developed from work in anesthetized cats, is not directly applicable to human infants, particularly when the relative strength of the HBIR at the extremes of VT is being investigated. While marked increases in VT do occur during early life, reflecting the rapid growth over this period, they are accompanied by parallel increases in respiratory compliance (37, 44). Consequently, elastic recoil of the respiratory system at end inspiration remains at ~1 kPa throughout the first year of life. This means that, under any given measurement conditions, a remarkably constant volume (and pressure) stimulus is presented to infants by occluding the airway at end inspiration, as indicated in this study by the consistency of the weight-corrected VT (Table 1).

Although the possible contribution of these methodological factors can be acknowledged, their potential influence seems too small to account for the magnitude of the difference in HBIR activity between EIO and EEO in anesthetized infants, with respect to both respiratory timing and drive components. Hence, other explanations need to be considered.

Respiratory Timing

Although stretch receptor activity is important in determining responses to both EIO and EEO, the actions at the level of central respiratory control differ. The lengthening of TE during an EIO is believed to be due to an inhibition of inspiratory neurons, whereas the lengthening of TI during an EEO is due to a lack of inhibition of inspiratory neurons during mid- to late inspiration. The pulmonary stretch receptors responsible for mediating the HBIR (10) are frequently separated into phasic and tonic components. The prolongation of TI during EEO may reflect tonic changes induced by excitation of rapidly adapting irritant receptors, as well as the functional blockade of the slowly adapting receptors. By contrast, during EIO, the phasic activity of slowly adapting receptors causes progressive increases in TE and hence inhibition of inspiration with progressive stretch receptor activity (20).

Experimental evidence suggests that lung volume is an important modulator of expiratory duration (45). In a canine model, a decrease in tonic lung volumes decreased expiratory duration (1). Alterations in end-expiratory lung volume also have a marked effect on expiratory duration in newborn infants (27), analogous to the vagally mediated control of TE with changes in FRC reported in anesthetized animals (1). Indeed, the shortening of TE and rise in respiratory rate associated with a reduction in end-expiratory lung volume has
been identified as an important mechanism to defend lung volume (22).

In this study, we found that although prolongation of TI did occur during EEO, as previously demonstrated in nonanesthetized infants (37), occlusion at end-tidal inspiration did not result in any inhibition of the inspiratory neurons and was frequently associated with a decrease in the duration of $T_{Eocc}$ relative to $T_E$ (Fig. 4), resulting in a negative mean value of HBIR$_{EI}$ of $-12\%$ (range $-53$ to $1\%$).

Potential Influence of Volume

Our results suggest that, during tidal breathing in anesthetized infants, a critical volume threshold sufficient to elicit the HBIR during EIO had not been attained. An HBIR$_{EI}$ of $~50\%$ (range $26$–$125\%$) has been reported in 1-yr-old sleeping infants (37), in whom the volume stimulus of $~10\,\text{ml/kg}$ was considerably greater than that observed in this study ($~6\,\text{ml/kg}$). In addition, inhalational anesthesia is accompanied by a reduction in lung volume (9, 17). The volume stimulus at EIO was therefore undoubtedly lower in our study than that presented by using the same technique in healthy, sleeping infants (37). Indeed, the absolute lung volume of an anesthetized infant during EIO (i.e., the sum of FRC and $V_t$) could well be lower than that at EEO in a nonanesthetized infant. It is of interest to note that, whereas in healthy infants the strength of the HBIR declines with increasing age (37, 44), in the present study the lowest levels of HBIR$_{EI}$ activity were observed in the youngest infants (Fig. 5). This may reflect the fact that the reduction in lung volume associated with anesthesia is inversely proportional to age (9). The prolongation of $T_{Eocc}$ relative to $T_E$ in all the infants in whom the airway could be occluded at volumes $>10\,\text{ml/kg}$ above FRC is consistent with the notion of a critical volume threshold to elicit the expiratory pause associated with the HBIR in infants.

Although the notion of a volume dependence for inspiratory-inhibitory activity in infants is consistent with present concepts of ventilatory control (37, 44, 47), additional mechanisms may have contributed to the shortening of $T_{Eocc}$ during EIO, such as activation of expiratory muscles during halothane anesthesia (41). During this study, we noticed that Pao waveforms often showed an upward convexity during airway occlusions, consistent with active expiratory efforts. Anesthesia is known to be associated with a blunting of HBIR activity when measured by EEO (3, 21). The response of other pulmonary reflexes has also been shown to depend on the depth of anesthesia. The cough reflex, excited by laryngeal stimulation, is easily depressed, whereas the apneic reflex to an identical stimulus is not (31). Therefore, the reflex arcs that mediate the inspiratory-inhibitory activity of the HBIR measured by EIO or EEO may also exhibit a differential sensitivity to the anesthesia. During EEO, the intercostal-phrenic inhibitory reflex (16) may have decreased the relative prolongation of $T_{Iocc}$ resulting in a diminished HBIR$_{EE}$. Although this reflex has usually been observed only in preterm infants, the loss of intercostal tone and rise in chest wall compliance associated with inhalational anesthesia could potentially have activated this reflex in at least some of the infants.

Respiratory Drive

Respiratory drive was lower when measured with the EIO technique than with the EEO technique. Controversy has arisen regarding the validity of the occluded pressure waveform in infants because they are predisposed to chest wall retraction during an inspiratory effort, so that the contraction against the occluded airway may not be truly isometric (5). Analysis of the Pao, a mechanical transform of neural output, is therefore an imperfect method of assessing respiratory drive in infants.

The use of $P_{0.1}$, i.e., Pao at the fixed interval of 100 ms, has been used to minimize the behavioral and reflex modulation of the occlusion pressure (49). However, for any given respiratory drive, if the duration of inspiration were to shorten, the rate of change in pressure, and hence $P_{0.1}$, would have to increase (5). Because the mean duration of $T_{Iocc}$ was $0.7\,\text{s}$ for the EEO compared with $0.4\,\text{s}$ for the EIO, the potential influence of inspiratory duration on $P_{0.1}$ must be considered. Furthermore, whereas a fixed interval of $100\,\text{ms}$ represents $<10\%$ of $T_I$ in an adult breathing at 12 breaths/min, it will be $>30\%$ of $T_I$ in an infant breathing at 30 breaths/min. Therefore, the use of a fixed proportion might better reflect breath drive in situations where $T_{Iocc}$ is variable and deviates appreciably from 1 s.

In this study, $P_{10\%}$ was higher during EEO than EIO (Fig. 7, Table 2). Although the duration of occlusion preceding the EIO inspiratory effort was longer than that of the EEO, it is improbable that chemoreceptive modulation of respiratory drive was an important influence because $P_{10\%}$ and indeed all other indexes of respiratory drive and timing were remarkably similar during the first and second respiratory efforts.

Potential influence of lung volume on respiratory drive. Lung volume may influence $P_{10\%}$ in two ways. First, it may alter the conformation of the diaphragm and thereby its resting length. However, studies in adult men are have shown either no (25) or minimal (29) effect of $P_{0.1}$ with relatively large changes in lung volume. Furthermore, although configurational change in the curvature of the diaphragm may have occurred at the higher volumes achieved during inflations, this is less likely to have occurred with the relatively small $V_{occ}$ of $~6\,\text{ml/kg}$ during the EIO. This suggests that, unlike in the adult, the resting length of the infant’s diaphragm may be affected by even small changes in lung volume, or that other mechanisms are involved. Lung volume may also affect the performance of the diaphragm through vagal and nonvagal pulmonary reflex arcs (1, 18, 34, 40). Reflex-enhanced contractility of the diaphragm at the low lung volume associated with EEO in an anesthetized infant is equally plausible.
Conclusions

During this comparison of HBIR activity by using the EIO and EEO techniques in 22 anesthetized infants, we found that both the drive and timing components of the HBIR depended on which technique was used. The EIO method suggested an inactive HBIR and lower respiratory drive compared with the EEO method. The EIO method extended to the Departments of Orthopaedic, Urologic, and Plastic Surgery and to the Theatre and Ward staff at the Great Ormond Street Hospital for Sick Children (London), National Health Service Trust, for their support of the study protocol. Address for reprint requests: K. Brown, Dept. of Anaesthesia, Montreal Children's Hospital, 2300 Tupper St., Montreal, PQ, Canada H3H 1P3.

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