Influence of volume dependency and timing of airway occlusions on the Hering-Breuer reflex in infants

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Rabbette, Patricia S., and Janet Stocks. Influence of volume dependency and timing of airway occlusions on the Hering-Breuer reflex in infants. J. Appl. Physiol. 85(6): 2033–2039, 1998.—Both end-inspiratory (EIO) and end-expiratory (EEO) airway occlusions are used to calculate the strength of the Hering-Breuer inflation reflex (HBIR) in infants. However, the influence of the timing of such occlusions is unknown, as is the extent to which changes in volume within and above the tidal range affect this reflex. The purpose of this study was to compare both techniques and to evaluate the volume dependency of the HBIR in healthy, sleeping infants up to 1 yr of age. The strength of the HBIR was expressed as the ratio of expiratory or inspiratory time during EIO or EEO, respectively, to that recorded during spontaneous breathing, i.e., as the “inhibitory ratio” (IR). Paired measurements of the EIO and EEO in 26 naturally sleeping newborn and 15 lightly sedated infants at ~1 yr showed no statistically significant differences in the IR according to technique: mean (95% CI) of the difference (EIO − EEO) being −0.02 (−0.17, 0.13) during the first week of life and 0.04 (−0.14, 0.22) at 1 yr. During tidal breathing, a volume threshold of ~4 ml/kg was required to evoke the HBIR. Marked volume and age dependency were observed. In newborn infants, occlusions at ~10 ml/kg during sighs always resulted in an IR > 4, whereas a similar response was only evoked at 25 ml/kg in older infants. Age-related changes in the volume threshold may reflect maturational changes in the control of breathing and respiratory mechanics throughout the first year of life.

control of breathing; vagal reflexes; pulmonary stretch receptors; occlusion technique; sedation; non-rapid-eye-movement sleep

THE IMPORTANCE OF VOLUME-RELATED feedback in respiratory control has been recognized since Breuer and Hering first demonstrated that lung inflation effectively terminated inspiration and prolonged expiration, whereas sustained deflation of the lungs had the opposite effect (42). These two reflexes, known as the Hering-Breuer inflation reflex (HBIR) and Hering-Breuer deflation reflex, respectively, have subsequently been shown to be vagally mediated via pulmonary afferents (12, 19) and to be present in numerous mammalian species (10, 39, 44, 46).

The HBIR has been widely described in both human adults (16–18) and infants (8, 11, 15, 21, 22, 26, 29, 31, 45), with apparently marked maturational differences in its potential functional significance. In adults, in whom lung inflations of at least 1–1.5 liters are required before any significant prolongation of expiration occurs (18), the HBIR appears to have little or no influence during tidal breathing and may play a primarily protective role against overstretching of the lungs at high volumes. By contrast, human infants demonstrate a much lower volume threshold, with a potent reflex response within the tidal volume range, during at least the first year of life (29, 31, 36).

The strength of the HBIR has been assessed by using three major approaches in infants: 1) the inflation technique (3, 8) as used originally by Breuer and Hering; 2) respiratory loading by using elastic or resistive loads to prolong expiratory (TE) or inspiratory time (TI), respectively (21, 22); and 3) the airway-occlusion technique applied either at end expiration (EEO) (21, 45) or end inspiration (EIO) (29).

This variety of methods may have contributed to discrepancies in the literature regarding the strength, role, and developmental changes of HBIR activity in infants and young children. The inflation technique is now known to stimulate chemoreceptor activity during prolonged inflations (46) and is therefore not a pure stimulus for quantifying the HBIR, whereas respiratory loading will alter the time constant of the respiratory system (5), thereby altering the respiratory cycle time from which the HBIR is calculated. By contrast, the rapidity with which changes in respiratory timing occur during airway occlusions precludes chemical interaction, thereby making this the preferred option for assessment of HBIR activity in infants (21, 29).

EIO uses the stimulus of lung expansion to maintain vagally mediated, slowly adapting pulmonary stretch receptor (PSR) input and inhibit subsequent inspiratory effort via negative feedback (19). 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 (i.e., TE). Alternatively, functional blockade of stretch receptor activity, by EEO to prevent lung inflation, causes prolongation of inspiratory time during occlusion (TIocc) proportional to the strength of the HBIR. The prolongation of TI during EEO [i.e., at functional residual capacity (FRC)] may reflect tonic changes induced by exotation of rapidly adapting irritant receptors, as well as the functional blockade of the slowly adapting stretch receptors (12). Given the marked volume dependence of the HBIR in animals and human adults above the tidal volume range, the choice of measurement technique may influence expression and interpretation of HBIR activity in infants. Indeed, during a recent
study of anesthetized infants, we found marked discrepancies in HBIR activity according to which technique was applied (4). To our knowledge, there is no information regarding the relative effects of stimulating or inhibiting PSR activity over the tidal range in naturally sleeping or sedated infants, nor on the existence of volume dependency of the HBIR beyond the first week of life, with which to clarify these issues.

The present study addresses the hypothesis that the HBIR is volume-dependent within and above the tidal range in infants throughout the first year of life. The primary purpose of the study was to compare the within-subject activity of the HBIR during inhibition (EEO) and stimulation (EIO) of the PSRs during tidal breathing. The second purpose was to investigate the volume dependency of the HBIR, both within and above the tidal range, by performing airway occlusions during expiration at different lung volumes, including those one complete respiratory effort against the occlusion. At least five breaths were recorded postocclusion to ensure no leak had occurred (38). Three to five such occlusions were performed in each infant at this lung volume, with an interval of at least 1 min between successive occlusions. HBIR activity during EIO has been reported from many of these infants previously (29, 31). The present protocol, involving the repeat measurements during EEO and sighs, was applied to those infants who remained asleep after completion of the standard protocol in the previous studies.

EEO. The strength of the HBIR was then assessed by performing three to five EEO in each infant, in accordance with the protocol outlined above for EIO.

Spontaneous occluded sighs. When spontaneous sighs occurred, airway occlusions were performed at as high a lung volume as possible and were held for one complete occluded respiratory effort. In infants in whom occlusion of sighs was successful, additional measurements of reflex activity at different volumes throughout tidal expiration were obtained by analyzing data that had originally been collected for assessment of respiratory compliance by using the multiple-occlusion technique (38).

Data analysis and statistical approach. For each occlusion, parameters of baseline spontaneous ventilation, including \( T_I \), \( T_E \), tidal volume, and respiratory rate were calculated as the mean of the five breaths immediately preceding each occlusion. The occluded volume \( V_{occ} \) was calculated as the volume excursion between the end-expiratory level and the plateau on the volume signal during occlusion (Fig. 1, A and B). Results were analyzed separately for EIO, EEO, and spontaneous sighs. During EIO and sighs, the strength of the HBIR was expressed as an inhibitory ratio (IR) by relating \( T_E \) during the occlusion \( T_{Eocc} \) to the mean \( T_E \) of the five breaths immediately preceding occlusion, whereby

\[
IR_{EIO} = \frac{T_{Eocc}}{T_E}
\]

\( T_{Eocc} \) was measured from the start of expiration, as seen on the volume trace, to the end of expiration, identified from the onset of the rapid negative deflection of pressure at the airway opening as inspiratory effort against the occlusion commenced (Fig. 1A).

During EEO, HBIR activity was expressed as the IR of \( T_I \) during the occlusion to that observed during spontaneous breathing, such that

\[
IR_{EEO} = \frac{T_{Iocc}}{T_I}
\]

As for EIO, \( T_I \) was calculated as the mean of five breaths preceding the occlusion. \( T_{Iocc} \) was measured from the initial to the maximum negative deflection of pressure at the airway opening (Fig. 1B).

A physiologically significant reflex was defined as an IR > 1.25, that is, when \( T_I \) or \( T_E \) increased by at least 25% during EEO and EIO, respectively. This value was chosen to represent the upper 95% confidence limits (i.e., mean + 2 SD) for within-subject variability of \( T_I \) or \( T_E \) in infants (29). The relative activity of the HBIR during EEO and EIO was compared by paired t-tests by using the method of Bland and Altman (2). Data from newborn and 1-year-old infants were analyzed separately to allow for the developmental changes in reflex strength over this period (31). In those infants in whom sighs were successfully occluded, the measured reflex response was plotted against weight-corrected \( V_{occ} \), together with data available from the same infants during occlusions over the tidal range, so that a stimulus-response curve could be created for each individual.

METHODS

Infant population. Healthy, full-term infants (≥36 wk gestational age) were recruited shortly after birth from the maternity ward at Homerton Hospital, London (29, 31), or from a local community health center in East London as part of ongoing epidemiological studies (9). Those recruited at birth from the maternity ward at Homerton Hospital were studied during the first 3 days of life, whereas those recruited from the local community were studied at ~1 yr of age. Approval for this study was granted by the local research ethics committee. Written consent to participate was obtained from the parents, who were usually present throughout the measurements.

HBIR activity was measured as described previously (29, 31, 38). Changes in flow and volume during tidal breathing were recorded while the sleeping infant breathed through a transparent face mask attached to a pneumotachograph (PT). Changes in pressure at the airway opening during airway occlusions were detected at a manually operated shutter, placed proximal to the PT. Data acquisition and analysis were performed by using previously validated software (RASP, Physiologic, Newbury, Berks, UK). The size of the face mask and PT was adjusted according to the age of the child to maintain the dead space of the apparatus at ~2 ml/kg body weight and the resistance at <0.47 kPa·l\(^{-1}\)·s at a flow of 100 ml/s.

The newborn infants were allowed to settle to sleep naturally after a feeding, whereas in older infants sleep was induced by 75 mg/kg of triclofos sodium sedation (equivalent to 45 mg/kg chloral hydrate) administered orally. It has previously been shown that this level of sedation does not influence HBIR activity (30), respiratory mechanics (41), or timing (20). In both groups of infants, measurements were confined to periods when the infant appeared to be in non-rapid-eye-movement sleep (i.e., posture was stable, respiration was regular, and no eye movements were seen) (28). Once the infant was asleep, a thin ring of therapeutic putty was placed around the nose and mouth. The mask and recording apparatus were then attached to the putty seal, and the system was checked for leaks (38). Real-time signals were displayed on the computer, and airway occlusions were timed from the display of tidal volume.

EIO. After a minimum of six regular breaths with a stable end-expiratory level, an EIO was made and held for at least one complete respiratory effort against the occlusion. At least
RESULTS

EIO vs. EEO. Of the 61 infants in whom measurements during EIO were originally performed, paired measurements of EIO and EEO were obtained in 26 infants during the first 3 days of life and in 15 infants at 1 yr of age. Details about the infants are presented in Table 1. A physiologically significant reflex, i.e., an IR > 1.25, was observed during every occlusion in all the younger infants, at both levels of occlusion. Mean (±SD) HBIR activity was 1.99 ± 0.23 during stimulation of the PSRs by EIO and 1.97 ± 0.29 when there was functional blockade of the PSRs during EEO [mean (95% CI) of the difference (EIO - EEO) being -0.02 (-0.17, 0.13)]. Similarly, among the 1 yr olds, there was no significant difference in reflex activity according to technique, mean (±SD) HBIR activity being 1.48 ± 0.25 using the EIO and 1.44 ± 0.28 with the EEO [mean (95% CI) of the difference being 0.04 (-0.14, 0.22)]. However, the IR was < 1.25 in three of the 1 yr olds during EEO (individual values being 1.03, 1.06, and 1.22) and in one infant when EIO was used (IR of 1.24).

Volume dependence of the HBIR. It was extremely difficult to effect occlusions during sighs because of their rapidity and spontaneity. Nevertheless, such occlusions were obtained in seven of the infants, two of whom had recordings during three sighs each. An example is shown in Fig. 2. Characteristics of these infants are shown in Table 2. A stimulus-response curve relating magnitude of response to Vocc is shown in Fig. 1. Measurement of relative changes in respiratory cycle time for assessment of Hering-Breuer inflation reflex (HBIR) by using end-inspiratory occlusions (EIO; A) and end-expiratory occlusions (EEO; B) in a 3.4-kg, 2-day-old female infant. Vocc, volume above functional residual capacity (FRC; i.e., end-expiratory level) at which airway occlusion was performed, i.e., 28 ml (8.2 ml/kg) during EIO and 4 ml (1.2 ml/kg) during EEO. TE, expiratory time; TI, inspiratory time; TEOocc and TIOocc, occluded expiratory and inspiratory time, respectively.

Table 1. Characteristics and ventilatory parameters of newborn and 1-yr-old infants in whom paired measurements were obtained

<table>
<thead>
<tr>
<th></th>
<th>Newborn</th>
<th>1-Yr Old</th>
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<tbody>
<tr>
<td>n</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Male:female</td>
<td>12:14</td>
<td>8:7</td>
</tr>
<tr>
<td>Age</td>
<td>35±5.6 h</td>
<td>12.7±0.6 mo</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>3.4±0.38</td>
<td>10.4±1.3</td>
</tr>
<tr>
<td>Length, cm</td>
<td>50.7±1.7</td>
<td>77.7±2.5</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>47.6±12.6</td>
<td>30.5±4.8</td>
</tr>
<tr>
<td>Tidal volume, ml</td>
<td>25.2±6.4</td>
<td>113.8±13.3</td>
</tr>
<tr>
<td>Inspiratory time, s</td>
<td>0.56±0.14</td>
<td>0.83±0.10</td>
</tr>
<tr>
<td>Expiratory time, s</td>
<td>0.67±0.19</td>
<td>1.17±0.19</td>
</tr>
<tr>
<td>TI/Ttot</td>
<td>0.45</td>
<td>0.42</td>
</tr>
<tr>
<td>HBIR - IR_EIO</td>
<td>1.99±0.23</td>
<td>1.48±0.25</td>
</tr>
<tr>
<td>HBIR - IR_EEO</td>
<td>1.97±0.29</td>
<td>1.44±0.28</td>
</tr>
</tbody>
</table>

Values are means ± SD. n, No. of infants; RR, respiratory rate; TI/Ttot, ratio of inspiratory (TI) to total respiratory cycle time (Ttot); HBIR, Hering-Breuer inflation reflex; IR_EIO, inhibitory ratio (IR) calculated by using end-inspiratory occlusions (EIO); IR_EEO, IR calculated using end-expiratory occlusions (EEO).

Table 2. Characteristics of infants in whom sighs were successfully occluded

<table>
<thead>
<tr>
<th>Subject</th>
<th>No.</th>
<th>Gender</th>
<th>Age</th>
<th>Wt, kg</th>
<th>Length, cm</th>
<th>Vt, ml</th>
<th>RR, breaths/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>2 days</td>
<td>3.3</td>
<td>50.1</td>
<td>20.1±1.8</td>
<td>63±2.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1 day</td>
<td>3.7</td>
<td>52.2</td>
<td>21.8±1.1</td>
<td>56±3.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>3 days</td>
<td>4.1</td>
<td>52.9</td>
<td>20.3±2.4</td>
<td>58±3.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>2 days</td>
<td>3.0</td>
<td>51.4</td>
<td>19.6±1.3</td>
<td>59±1.6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>13.0 mo</td>
<td>9.8</td>
<td>79.0</td>
<td>102.6±6.7</td>
<td>30±0.9</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>12.8 mo</td>
<td>10.3</td>
<td>77.1</td>
<td>103.0±5.4</td>
<td>25±1.1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>11.0 mo</td>
<td>13.4</td>
<td>81.0</td>
<td>111.6±4.0</td>
<td>32±1.4</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD for tidal volume (Vt) and RR. M, male; F, female.
Fig. 3. It can be seen that, when expiratory occlusions were performed throughout the tidal range, a relatively weak response was observed, especially during the lower-volume occlusions, whereas a much greater response was elicited in all the infants when lung volume was elevated above the tidal range during a sigh (Fig. 3). Thus, whereas an EIO at end-tidal inspiration (7 ml/kg) caused an approximate doubling of Tₑ in newborn infants, a further increase by as little as 3 ml/kg (i.e., Vₒc = 10 ml/kg) resulted in at least a fourfold increase in Tₑ in all of the youngest infants. Further increases in Vₒc produced proportional increases in measured reflex response, with two newborn infants demonstrating an IR₁₀ when lung volume was maintained at 13–16 ml/kg above the end-expiratory level (equivalent to doubling the resting tidal volume). A similar volume dependency was apparent in the 1-yr-old infants (Fig. 3), although the volume threshold at which marked prolongation of Tₑ above that noted at end inspiration occurred increased to ~25 ml/kg (i.e., 2–3 times the resting tidal volume).

DISCUSSION

To our knowledge, this is the first within-infant comparison of the relative effects of EIO and EEO in healthy, sleeping infants throughout the first year of life. By performing paired measurements in each subject, we have been able to demonstrate that, during tidal breathing, the calculated strength of the HBIR is very similar whether the PSRs are stimulated during EIO or receive no excitation during EEO. Clear evidence of volume dependency of the HBIR beyond the neonatal period has not been reported previously. In this study, a volume stimulus of as little as 4 ml/kg above FRC (equivalent to one-half a tidal volume) was sufficient to induce a physiologically significant HBIR at end inspiration in all infants during the first week of life and in all except one infant at 1 yr of age. When additional occlusions were performed throughout tidal expiration, a graded reflex response occurred, with the strength of the HBIR increasing as Vₒc increased (Figs. 2 and 3). However, when lung volume was increased naturally above the tidal range during a spontaneous sigh, more marked volume dependency of reflex response was observed (Figs. 2 and 3). These findings provide clear evidence for a volume-dependent, vagally mediated HBIR within and above the tidal volume range in infants throughout the first year of life.

EIO vs. EEO. The present findings suggest that, in healthy, sleeping infants, there is a very careful balance of PSR activity over the tidal range. Prolongation of inspiration, when phasic vagal activity is blocked by preventing lung inflation, is virtually identical to the prolongation of expiration that occurs when lung volume is maintained at end-tidal inspiration, thus stimulating the PSRs. This suggests that either approach may be used to assess the HBIR in healthy infants during tidal breathing and that the HBIR probably plays an important physiological role in maintaining a regular tidal volume and assisting in minimizing the work of breathing in infants (21). However, from a practical point of view, the EIO technique is generally preferable in that it is less likely to disturb the infant or induce glottic closure (29).

These observations in healthy, sleeping infants are in marked contrast to a recent study of anesthetized infants of similar age (4), in whom HBIR activity could not be elicited during EIO, whereas some weak activity (equivalent to a mean IR of 1.2) was found during EEO. These discrepancies may be related to the reduction in both tidal volume and FRC induced by inhalation of volatile anesthetics such as halothane (13) such that the volume threshold for stimulation of the phasic PSRs may not have been reached at end-tidal inspiration in these infants. They may also reflect some interdependence between chemo- and mechanoreflexes because most of the anesthetized infants showed some hypoventilation, with elevated CO₂ levels, which would be expected to inhibit HBIR activity (18, 19, 24).

Volume dependency of HBIR. Because PSR activity increases in a graded fashion with lung inflation (19),
prolongation of expiration has been ascribed to volume-dependent activity of the stretch receptors and has therefore been used as a measure of reflex strength. It should be noted that elastic recoil pressure at end inspiration remains relatively constant in healthy infants at ~1 kPa (10 cmH2O) throughout the first year of life because of the parallel increases in tidal volume and respiratory compliance with weight over this period (31). Relating PSR activity to a weight-corrected volume stimulus, rather than the less easily measured changes in transpulmonary pressure, was therefore felt to be justified.

Although Stark and Frantz (34) concluded that phasic vagal influences on inspiration are at a maximum in neonates during the normal tidal range, our data show the curvilinear relationship between Vocc and IR in the present study probably reflects increased PSR activity by recruitment of additional fibers at higher lung volumes, e.g., during sighs (19, 47). The findings of this study suggest that, while volume is an important determinant of respiratory timing in infants as in adults, there are critical differences in the volume threshold and magnitude of response, particularly during the first few months of life.

Most studies in adults report a volume threshold of 1–1.5 liters above FRC (i.e., 2–3 times the normal resting tidal volume of 0.5 liter) before lung inflation will prolong expiration (17, 18), with a maximum IR (~2–3) being reported in response to inflations up to 2.5 liters (17, 44). It is possible that, in contrast to findings in infants (30), state of consciousness plays an important role in the ability to evoke this response in adult humans. Most studies of HBIR activity in adults have been in awake or naturally sleeping subjects. However, a recent study in six healthy, sedated adults reported a volume threshold similar to that previously reported in adults but IR that were consistently higher, being greater than four at a lung inflation of 2 liters (18). When corrected for weight, these values are similar to those observed in the 1-yr-old sedated infants in this study. By contrast, during the first week of life, infants achieved a fourfold increase in TE at significantly lower thresholds (i.e., 10 ml/kg). During the first week of life, the magnitude of response at all lung volumes was considerably greater than that seen in the older infants in this study but similar to that reported previously in newborns by Cross et al. (8). It is possible that a relatively weaker hypercapnic response, and hence delayed onset of inspiration during airway occlusions after a sigh, could have contributed to the enhanced stretch receptor response found in the newborn infants (24). To our knowledge, there has been no previous documentation of the volume dependence of the HBIR in infants beyond the first week of life.

Physiological significance of findings. Although there is no doubt that EIO will evoke an expiratory pause in infants, this being the basis of measurements of passive respiratory mechanics by using the occlusion technique during the first 2 yr of life (38), considerable controversy remains regarding the physiological significance of the HBIR during tidal breathing. In contrast to adults, infants have a highly compliant chest wall that offers relatively little outward recoil with which to maintain an adequate FRC (27). Selection of a particular pattern of breathing and end-expiratory level is a critical factor in achieving overall efficiency of respiration. Although tidal volume remains remarkably constant throughout life when corrected for body size (38), there is marked variability in respiratory rate, particularly during the first few months of life (11, 31, 36, 37). Respiratory timing, specifically TE, has been identified as the most critical factor in determining FRC in young infants, although this may be accompanied by modulation of expiratory airflow and hence time constant, to dynamically elevate FRC above that passively determined by the mechanics of the lungs and chest wall (11, 33, 35).

Alterations in end-expiratory lung volume significantly affect expiratory duration in newborn infants (23), analogous to the vagally mediated control of TE with changes in FRC reported in anesthetized animals (1). The HBIR may therefore play a vital role in determining the optimal breathing strategy in infants to prevent alveolar collapse until the chest wall stiffens with maturity (21, 22). In contrast to phasic input, the tonic component of the HBIR can be assessed by measuring the response to a sustained change in FRC, induced by either continuous positive airway pressure or continuous negative extrathoracic pressure (14, 23, 34). Under these circumstances, a small increase in FRC will cause significant reductions in respiratory rate, primarily because of marked prolongation of TE, with virtually no impact on Ti, tidal volume, or the measured strength of the phasic component of the HBIR (14).

Small increases in lung volume (less than one-half a tidal volume) are also associated with less marked modulation (braking) of expiratory flow, and hence less dynamic elevation of lung volume, demonstrating that infants modulate both expiratory flow and timing to control their end-expiratory level (14). By contrast, any decrease in FRC is frequently associated with a decreased TE, increased respiratory rate, and increased modulation of expiratory flow, resulting in compensatory dynamic elevation of end-expiratory level (35, 36). The significance of vagal input to the modulation of breathing patterns and expiratory flow has been emphasized by recent work in animals (43).

The interrelationship between Ti and TE proposed by Clark and von Euler (6) does not appear to apply in infants, in whom a much more complex relationship occurs. As discussed above, increases in end-expiratory lung volume in infants prolong expiration with minimal effect on Ti. Our results in infants differ from the volume-time relationship reported in adult humans because infants clearly exhibited "range 2" behavior within the eupneic breathing range. It may be that more of the PSRs are tonically active in young infants and that some are subsequently converted to phasic activity in response to maturational changes in the size and stability of the chest wall.
Maturational changes in reflex response. Although the HBIR has been extensively studied, its functional importance in different species and at different levels of maturity remains an issue of debate. Despite the increased level of HBIR during infancy, the vagus nerve appears relatively immature at birth, with fewer myelinated fibers, a lower discharge frequency, and a smaller percentage of active, slowly adapting PSRs than in adults of the same species (10, 12). Thus the effect of the same stimulus on medullary control is more pronounced in the youngest infants, with respect to both amplitude and duration of response. This represents a changing threshold for reflex evocation with age, with older infants requiring volumes closer to two to three tidal volumes, as in adults, to produce a threefold increase in TE, whereas this occurs during the first week of life as soon as the normal tidal volume range is exceeded. The findings of the present study are therefore in agreement with our previous reports of maturational changes in reflex response during the first year of life (31, 36) and support the concept that respiratory control, and hence alterations in the rate at which afferent input to the stretch receptors decreases, plays an important role in the central regulation of breathing pattern and maintenance of an adequate FRC in the young infant. The possible interaction of any age-related changes in chemosensitivity with the strength of the HBIR (24) has yet to be elucidated in human infants. Because the activity of PSRs, which mediate the HBIR, increases gradually with lung expansion (19), volume-related feedback may be a more critical determinant of respiratory control during early life when end-expiratory lung volume is relatively unstable (21, 22, 34, 35). The transition from a dynamically elevated to passively determined FRC is thought to occur in the second half of the first year of life (7). Our present findings support this hypothesis and suggest a firm physiological role for the HBIR in infants during tidal breathing.

Because the lung inflation reflex is a simple, negative-feedback control system, it may function as a temporary controller, being superseded by the development of cortical control (25, 32, 40) with increasing maturity. The disparity between infant and adult studies may thus reflect an absence of well-developed higher centers that, in adults, may inhibit the effect of volume-related feedback (17). The findings of the present study may thus indicate the onset of increased stability and control of breathing by higher respiratory centers during the first year of life. This might coincide with the development of speech and other volitional acts that require precise control of expiration (25).

Conclusions. In conclusion, these data have defined the magnitude and threshold of the HBIR in healthy infants shortly after birth and at ~1 yr of age and suggest that vagal afferent inputs play a significant role in eugeneic breathing at both these ages. The HBIR may be evoked within the tidal volume range by using either the EIO or EEO techniques and, in this group of healthy infants, the choice of measurement technique did not influence the measured strength of the HBIR.

The primary effect of an increase in lung volume above FRC during sighs was a curvilinear increase in TE during occlusion, suggesting that the volume-time profile in infants is critically dependent on the HBIR. The regulation of breathing pattern and the interrelationship between TI and TE is particularly complex in infants. In contrast to those in adults, present findings indicate that the process by which the HBIR modulates eupneic respiratory timing involves both tonic and phasic vagal afferent information. It is probable that tonic and phasic inputs, and, indeed, the inflation and deflation reflexes, play complementary roles in determining the duration of expiration to depend lung volume in infants, particularly during the first 6 mo of life.

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