A study of breathing pattern and ventilation in newborn infants and adult subjects

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Experimentally modified breathing pattern in human subjects, by varying the inspired gas mixture or administering different neuromodulators, has been studied extensively in the past, yet unmodified breathing has not. Moreover, most data refer to infants during sleep and adults during wakefulness. We studied the baseline breathing pattern of preterm infants \( n = 10; \text{GA} 30 \text{(27–34 wk (median, range)); term infants \( n = 10; \text{GA} 40 \text{(39–41 wk)}, \) and adult subjects \( n = 10; \text{age} 31 \text{(17–48 y)}) \) during quiet sleep. A flow-through system was used to measure ventilation. We found: (i) instantaneous ventilation was \( 0.273\pm0.006, 0.200\pm0.003, \) and \( 0.135\pm0.002 \text{ L min}^{-1} \text{kg}^{-1} \) in preterm, term infants, and adult subjects; the coefficients of variation were 39%, 25%, and 14% \( (p < 0.01) \). The greater coefficient of variation in neonates compared to adults related to increased variability in \( V_t \) (39% and 25% in preterm and term infants vs 14% in adults; \( p < 0.01 \)) and \( f \) (39% and 22% vs 9%; \( p < 0.01 \)). The major determinant of frequency in preterm infants was \( T_e \) (81% variability), \( T_i \) varying less (25% variability); (ii) \( V_t/T_i \) decreased and \( T_i/T_{tot} \) increased with age; (iii) the higher breath-to-breath variability in preterm infants was associated with larger changes in alveolar \( PCO_2 \) and a larger variability in \( O_2 \) saturation than later in life.

We conclude: (i) the high breath-to-breath variability in frequency in preterm infants closely relates to variation in \( T_e \); (ii) decreased effective inspiratory timing (\( T_i/T_{tot} \)) in preterm infants compared with adults likely reflects their high pulmonary impedance; and (iii) greater breath-to-breath variability in ventilation in neonates with large variations in alveolar \( PCO_2 \) and \( O_2 \) saturation remains when compared with values in the sleeping adult. We speculate that high variability in \( T_e \) early in life represents an effort to maintain lung volume through increased post-inspiratory diaphragmatic activity and increased upper airway resistance in an attempt to avoid collapse due to poor chest wall recoil.

**Key words:** Adults, control of breathing, preterm infant, respiration, term infant

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The experimentally modified breathing pattern in human subjects, through administration of various inspired gas mixtures or neuromodulators, has been extensively studied in the past, yet unmodified breathing pattern has not (1–7). Furthermore, most studies report findings in adults during wakefulness and in infants during sleep (1, 2, 8–11). Assessment of the variations in baseline breathing pattern in different age groups under similar experimental conditions would illustrate more clearly the maturation of breathing pattern in human subjects. Since quiet sleep represents more clearly the stage of sleep in which breathing pattern is determined by autonomic or metabolic factors, we chose this sleep stage to assess breathing (12). We designed this study, therefore, to examine the variability in breathing pattern during quiet sleep in preterm, term infants, and adult subjects.

**Subjects and methods**

**Subjects**

We examined the tracings of 30 subjects previously studied during sleep (13, 26). The original study was approved by the Faculty Committee for the Use of Human Subjects in Research at the University of Manitoba. Parental written consent was obtained. Of the 30 subjects, 10 were preterm infants [BW 1.3 (1.0–3.1) [median, range]; SW 1.3 (1.2–2.9) kg; GA 30 (27–34) wk; PNA 14 (11–27) d]; 10 term infants [BW 3.6
(2.9–4.1) kg; SW 3.8 (2.8–5.1) kg; GA 40 (39–41) wk; PNA 13 (7–33) d], and 10 were adult subjects [weight 60 (48–81) kg; age 35 (17–48) y]. All human subjects were breathing room air, were not on any medication and were not inhaling supplemental O\textsubscript{2} and were considered healthy at the time of the study. Preterm infants had only mild complications after birth, three presenting with wet lung or transient tachypnea and two presenting with mild RDS which resolved quickly after birth. By day 5, all infants were off medication and breathing spontaneously. Of the adult subjects, six were male and four were female and all were voluntary, non-smokers.

Methods

We measured minute ventilation (\(V_E\)), respiratory frequency (f), tidal volume (\(V_T\)), inspiratory time (Ti), expiratory time (Te), alveolar PCO\textsubscript{2} (P\textsubscript{A}CO\textsubscript{2}), O\textsubscript{2} saturation, electroencephalogram (EEG), electrooculogram (EOG), and heart rate (HR). The system to measure ventilation and alveolar gases has been described previously (4, 7, 9, 15). Briefly, breathing pattern and ventilation were measured using a nosepiece and a flow-through system (4, 7, 9). The screen flowmeter was linear up to 6 L/min. The resistance of the system was low (0.1 cmH\textsubscript{2}O·L\textsuperscript{-1}·min\textsuperscript{-1}). The dead space, when measuring ventilation with the flow-through system and nasal adaptors, is negligible. The background flow was 3.8 L·min\textsuperscript{-1}. End tidal alveolar PCO\textsubscript{2} was measured using Beckman carbon dioxide analyzer (Model LB-2, Beckman Instruments Co., Fullerton, CA) (14). A 75 cm long catheter was used to sample the inspired and expired gas from one of the nostrils. A vacuum pump drew gas through this catheter at a rate of 54 ml·min\textsuperscript{-1} such that the 95% response time for CO\textsubscript{2} was 0.14 sec. The end tidal plateaus were good for measurements, with the top ‘ramp’ being less than 10% of the total CO\textsubscript{2} deflection for each breath. Heart rate was measured using conventional leads and O\textsubscript{2} saturation was measured using a Nellcor Oximeter (Model N-100C, Nellcor, Hayward, CA). Electroencephalogram (EEG) was recorded with electrodes placed in the C4-A1 positions. The electrooculogram (EOG) was recorded from the upper outer canthus of the left eye and the lower outer canthus of the right eye and referred to the right ear lobe (15). All signals were recorded on a 21 channel recorder (Model 4221, Nihon Kohden, Tokyo, Japan) and were also taped for subsequent analysis.

Adults were studied in a fully equipped sleep laboratory. The method used was similar to that used with infants and consisted of a nasal mask connected to a flow transducer (13). Adults had a “chin strap” around the lower jaw in order to keep their mouth closed. The bias flow was 2 L·sec\textsuperscript{-1}. The electroencephalogram (C4-A1 and C3-A2) and electrooculogram were recorded from surface electrodes. Breath-to-breath P\textsubscript{A}CO\textsubscript{2} was measured at the nose with the CO\textsubscript{2} analyzer (DOLE 233; Puritan-Bennett Corp., Willmington, MA). All variables were continuously recorded at 10 mm·s\textsuperscript{-1} using a 15 channel polygraph (Model 78, Grass Instruments Co., Quincy, MA). Sleep states were monitored according to criteria previously reported (1, 16). Briefly, quiet sleep was defined by the absence of rapid eye movements coupled with, in preterm infants, discontinuous EEG, or, in term infants, with “trace alternans” (1, 17, 18). In adults, studies were performed in stage 2 sleep (3).

Procedure

Infants were studied on the Ohio neonatal intensive care unit (Ohio Medical Instruments, Madison, WI). Babies were fed before or during the study as required by the usual feeding schedule, but never during quiet sleep. A neutral environment was maintained with abdominal skin temperature 36.5 ± 0.03°C. Similarly, adults were allowed to sleep in quiet conditions in the adult sleep laboratory during night time. After appropriate placement of various electrodes and nosepiece, we waited for the subjects to fall asleep. Only those experiments during which infants remained in quiet sleep and adults in stage 2 sleep were analyzed.

Data collection and analysis

We analyzed the records by hand and transferred the data to a computer for appropriate analysis. Epochs of quiet sleep were first identified. A 10-min portion of it per subject was then randomly selected for measurements. Therefore \(n = 10\) means 10 experiments in 10 subjects, one in each. Heart rate was recorded to monitor infants’ condition and not as an endpoint of the study. We used ANOVA to measure the between-subject and within-group differences for each group. Bartlett’s test for homogeneity of variance was used to determine differences in variance between the groups for each variable. For those variables with the same variance, ANOVA was used for further analysis and Fisher’s least significant difference test used for individual comparisons. For those variables with difference variance, the Kruskal-Wallis non-parametric test was used and the Wilcoxon rank sum test test for individual companies. The reported values are mean ± SEM of the average in each subject of all values from the 10 min periods measured. Values are also reported as median and range when indicated. The coefficient of variation reported is an average of a single coefficient of variation calculated for each subject. A \(p\) value ≤ 0.05 was considered significant.

Results

The duration of individual studies was 150 ± 14 min. After carefully defining the epochs of quiet sleep, a 10 min interval was randomly selected for calculations.
A total of 8275 breaths were analyzed, 3558 in preterm, 2979 in term, and 1738 in adults. A representative tracing of respiratory pattern at various ages is given in Fig. 1.

Instantaneous ventilation decreased from preterm to term and to adult subjects \( (p < 0.01 \text{ between groups}; \text{Table}) \). These changes corresponded to adjustments in tidal volume and respiratory frequency with age, tidal volume increasing towards adulthood and frequency decreasing \( (\text{Table}) \). The corresponding coefficients of variation also decreased with age \( (p < 0.01 \text{ between groups}; \text{Fig. 2}) \). The greater coefficient of variation for minute ventilation in neonates compared to adult subjects related to increased variability of tidal volume \( (39\% \text{ and } 25\% \text{ in term and preterm vs } 14\% \text{ in adults}, \ p < 0.01) \) and respiratory frequency \( (39\% \text{ and } 22\% \text{ vs } 9\% \text{ respectively}; \ p < 0.01) \).

The changes in respiratory frequency with age related to adjustments in Ti and Te, Ti increasing almost threefold from preterm to adulthood and Te increasing only twofold \( (\text{Table, Fig. 3}) \). These changes allowed for a restructuring of the average individual breath such that in the preterm infant Ti occupied only 34\% of the total breath duration and in adults it represented 45\% \( (\text{Fig. 4}) \). Ti/Ttot, therefore, was significantly less in the preterm infant \( (p < 0.01) \). Furthermore, the decrease in variability of frequency with age corresponded primarily to a decrease in variability of Te \( (81\% \text{ and } 32\% \text{ in preterm and term infants vs } 13\% \text{ in adults}; \ p < 0.01) \); variability of Ti changed much less. \( V_T/Ti \) and the corresponding coefficients of variation decreased with advancing age \( (\text{Table}) \).

Values for alveolar PCO\(_2\) were lower in preterm infants \( (35 \text{ Torr in preterm and vs } 39 \text{ Torr in adults}; \ p < 0.01) \), but the coefficients of variation were higher early in life \( (\text{Table}) \). Oxygen saturation was also lower in preterm infants \( (97 \text{ and } 96\% \text{ in preterm and term infants vs } 98\% \text{ in adults}; \ p < 0.01) \), but the variability was greater early than later in life \( (\text{Table}) \).

Discussion

We found that (1) the high breath-to-breath variability in respiratory frequency observed in preterm infants was closely related to variation in Te; (2) effective inspiratory timing \( (Ti/T_{tot}) \) increased significantly from preterm infants to adult subjects, likely reflecting the high pulmonary impedance present early in life; and (3) greater variability in breath-to-breath instantaneous ventilation in neonates paralleled large variations in alveolar PCO\(_2\) and O\(_2\) saturation, reflecting a highly unstable chemical control of breathing in these infants. These findings suggest a significant variability in breathing pattern in the neonate, particularly in the preterm infant, in comparison with the adult subject, even when the latter is studied during sleep. Major components of the inter-individual variability likely
### Table 1. Respiratory measurements in preterm, term infants and adult subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$V_{in}^{\text{inst}}$ L·min$^{-1}$·kg$^{-1}$</th>
<th>$V_T$ ml·kg$^{-1}$</th>
<th>$f$ breaths·min$^{-1}$</th>
<th>Te s</th>
<th>Ttot s</th>
<th>$V_T/Te$ ml·s$^{-1}$·kg$^{-1}$</th>
<th>Ti/Ttot</th>
<th>$P_{\text{aCO}_2}$ Torr</th>
<th>$O_2$ Sat %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm infants</td>
<td>0.273 ± 0.006‡</td>
<td>7.5 ± 0.2</td>
<td>40 ± 1</td>
<td>0.55 ± 0.01</td>
<td>1.28 ± 0.06</td>
<td>1.03 ± 0.01</td>
<td>13.7 ± 0.2</td>
<td>0.34 ± 0.01</td>
<td>35.1 ± 0.1</td>
</tr>
<tr>
<td>Term infants</td>
<td>0.200 ± 0.03</td>
<td>6.8 ± 0.1</td>
<td>31 ± 1</td>
<td>0.70 ± 0.01</td>
<td>1.40 ± 0.03</td>
<td>2.11 ± 0.03</td>
<td>9.9 ± 0.1</td>
<td>0.36 ± 0.01</td>
<td>39.4 ± 0.1</td>
</tr>
<tr>
<td>Adult subjects</td>
<td>0.135 ± 0.002</td>
<td>8.3 ± 0.1</td>
<td>16 ± 1</td>
<td>1.68 ± 0.01</td>
<td>2.05 ± 0.02</td>
<td>3.73 ± 0.02</td>
<td>5.1 ± 0.1</td>
<td>0.45 ± 0.01</td>
<td>39.0 ± 0.1</td>
</tr>
</tbody>
</table>

† Values are mean ± SEM.
Values in parentheses are coefficients of variation.
Bartlett's test for homogeneity of variance is highly significant for all variables.
Kruskal-Wallis test for several groups is highly significant for all variables.
$p \leq 0.01$ for all paired comparisons using the Mann-Whitney two-sample test.

![Diagram of respiratory measurements](image)

**Fig. 3.** Breath duration and its components. Duration of the average breath increased with postnatal age and this was related increases in $V_T$ and $Te$. Note the high coefficient of variation for $Te$ in preterm infants. Coefficients of variation decreased with age. Differences between groups are all significant at $P < 0.05$. In adults, differences in tidal volumes of 6–8 ml·kg$^{-1}$ in the neonate and adult groups were not used in the analysis due to the small number of subjects in the adult group.

Additional description: The data presented here include changes in $Te$ and mechanical impairment due to increased stiffness of the lungs and a very compliant chest wall. Our ability to compare the results of previous studies with our own is limited by differences in methodology and the use of standardized values in neonates versus adult subjects. Sleep state was not a factor in the current study, which was done. The reported values for minute ventilation, using data published by Smith et al. (21), were based on the reported values for minute ventilation, using data published by Smith et al. (21). Central nervous system immaturity with decreased autonomic control likely plays a major role in intra-individual instability (20).
and 7 ml·kg⁻¹ in adults. Our values suggest that tidal volumes for adults are higher, at least in quiet sleep. Variability has not been assessed previously but in this study it decreased significantly with age (2, 13).

Inspiratory time, expiratory time, and total respiratory durations were less in preterm than in term infants, and those in the latter were less than those in adult subjects. The values are close to those obtained previously in infants (10, 22) and adult subjects (23, 24). The coefficient of variation of these measurements, however, decreased with age. The decreased Ti/Ttot in infants related primarily to a disproportionately long expiratory time. The values for inspiratory flow and Ti/Ttot are comparable to those we and others observed previously in term infants and adult subjects (10, 13, 24–26). The lower values for alveolar PCO₂ in infants compared with adults during sleep probably relate to a lower bicarbonate in small infants (4, 27). The increased variability in alveolar PCO₂ and O₂ saturation in early life again reflects the highly unstable pattern of breathing at this age (9, 10, 15, 22).

We have elected to compare variables in these three age groups in quiet sleep only. The rationale for this was that this sleep state is the so called “metabolic state”, one which responds primarily to chemical stimuli, without the interference of impulses from cortical and forebrain structures (28). It is a more stable state in which comparisons are easier to make (12). We do not believe that measurements made during REM sleep would have added much to our findings. It is known that in REM sleep, total minute ventilation is greater than in quiet sleep. This is related primarily to an increase in frequency during REM, with no appreciable change in tidal volume. Alveolar ventilation is also greater, with lower alveolar PCO₂. This is true for preterm and term infants, and also adult subjects (8, 9, 10, 13, 24–26). Because breathing becomes somewhat irregular during REM sleep in adults, it is likely that the clear differences between the three groups might have been less distinct in this sleep state (26). However, from selective studies in infants and adults during REM sleep, it seems that the differences observed in quiet sleep would still be easily detectable in REM sleep (9, 10, 13, 15, 25). These are hypothetical considerations and a final answer to the question of whether REM sleep will show unique changes between groups will have to be determined in future studies.

There are at least three new observations in the present study. First, to the best of our knowledge this is the first study trying to compare respiratory values in these three groups of human subjects using similar methodology, with standardization for sleep state. Second, our findings indicate that the breathing pattern of preterm infants remains highly variable and unstable, and critically distinct from that of the adult subject even when the latter is studied during sleep (7, 14). Third, the high variability in the expiratory time seen in this study supports our previous observation, that the regularization of respiratory pattern in response to increased inspired O₂ concentration in these infants was related to a decrease in the variance of expiratory time (29). It is interesting to speculate that such a pattern may in fact be adaptive, since the neonatal respiratory apparatus is characterized by poor chest wall recoil, the neonatal lung functioning at or near closing volume, leading to excessive atelectasis. The increased post-inspiratory activity of the diaphragm and upper airway resistance, leading to a prolonged expiratory time, would help keep lung volume more stable and prevent further collapse (6, 22).

Our decision to study breathing at rest in humans was stimulated by the paucity of information related to the variability of breathing under baseline conditions. It is likely that some of the abnormal responsiveness to clinical stimuli in infants is based on inherent instability of the respiratory system. For example, we have observed previously that the breathing response to inhaled CO₂ is less in the preterm than in the term infant (1, 29). This is, at least in part, related to the stiffness of the lungs in these small infants. “Healthy” preterm infants have an unusually stiff lung when compared with term infants and adult subjects (2). They have a much lower alveolar/interstitial ratio than term infants and adult subjects (19). The term “healthy” applied to preterm infants is misleading because they are not healthy. They are premature, their lungs are not entirely formed yet, and the respiratory apparatus is not ready to cope well with the respiratory demands of extra uterine life. As a consequence, these infants have a barely sustainable respiratory activity, which is prone to variation. This instability accounts for the high variability in breathing early in life.

In summary, we studied the changes in breathing

![Fig. 4. Diagram of the shape of a breath in the 3 groups of subjects. Note that the average breath is restructured with postnatal development, the “effective” respiratory timing (Ti/Ttot) being low in preterm and increasing towards adulthood.](image-url)
pattern during development by examining polygraphic records in three groups of human subjects: preterm, term, and adult subjects. We found a high breath-to-breath variability, particularly in preterm infants, when compared with other groups. This greater variability resided primarily in respiratory frequency. Of the components affecting respiratory frequency, variability in expiratory time was highest and had a fundamental role in the overall breath-to-breath variation in breathing in these infants. We speculate that high variability in Te early in life is a consequence of increased post-inspiratory activity of the diaphragm and increased upper airway resistance, factors which tend to maintain lung volume and prevent collapse due to poor chest wall recoil (6, 22).

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References


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