Increased Peripheral Chemoreceptor Activity may be Critical in Destabilizing Breathing in Neonates

Abdulrahman Al-Matary, Ibrahim Kutbi, Mansour Qurashi, Mohammed Khalil, Ruben Alvaro, Kim Kwiatkowski, Don Cates, and Henrique Rigatto

Periodic breathing and apnea are common in neonates, yet the physiological mechanisms involved are not clear. A low arterial PO2 might magnify peripheral chemoreceptor contribution to breathing, with its baseline variability inducing major changes in ventilation, leading to instability of the respiratory control system. We hypothesized that neonates: (1) would depend much more on the peripheral chemoreceptor contribution to breathing than adult subjects and (2) their baseline arterial PO2 would sit on the steep portion of the ventilation/arterial PO2 relationship on the adult nomogram, making breathing prone to oscillate. We analyzed data from previous polygraphic recordings in four groups of subjects: small preterm infants [SPI; postconceptional age (PCA) 33 ± 2 weeks; n = 40], large preterm infants (LPI; PCA 36 ± 2 weeks; n = 34), term infants (TI; PCA 42 ± 1 week; n = 24), and adult subjects (AS; weight 63 ± 2 kg; age 29 ± 3 years, n = 16). Peripheral chemoreceptor activity was measured by: (1) the immediate decrease in ventilation and (2) apnea time during brief inhalation of 100% O2 (about 1 minute). We found that: (1) the immediate decrease in ventilation with 100% O2 was more pronounced in infants than in adult subjects (38 ± 2 versus 6 ± 5%), and in infants breathing periodically versus those breathing continuously; (2) the apnea time during 100% O2 was also significantly longer in periodic breathing infants; and (3) the TcPO2 was much lower in infants than in adult subjects (65 ± 1 versus 93 ± 1 Torr), and also lower in periodic versus continuously breathing infants. It was located significantly to the left of values for the adult subject, on the ventilation/arterial PO2 diagram. The data suggest that: (1) a substantial portion of baseline breathing activity early in life is maintained by increased peripheral chemoreceptor activity; and (2) neonates breathe irregularly with apneas due to the position of their arterial PO2 values on the ventilation/arterial PO2 diagram, in which a change in PO2 produces a more significant change in ventilation than that observed later in life.

From the Department of Pediatrics, Physiology, and Reproductive Medicine University of Manitoba, Winnipeg, MB Canada. Supported in part by the Canadian Institutes of Health Research, the Winnipeg Rh Institute Foundation, Inc., and the Children’s Hospital of Manitoba.

Address reprint requests to Henrique Rigatto, MD, WR-125, Women’s Hospital, 735 Notre Dame Avenue, Winnipeg, MB, R3E 0L8, Canada e-mail: hrigatto@cc.umanitoba.ca

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0146-0005/04/2804-0000$30.00/0
doi:10.1053/j.semperi.2004.08.003

Periodic breathing and apnea are common in neonates, particularly in preterm infants, but they are rare or absent in older children and adult subjects.1-15 Despite many efforts in the past to understand the physiologic mechanisms responsible for this respiratory pattern, we still do not know why some neonates breathe more periodically than others.10-12,16 In previous studies, we observed that infants breathing periodically hypoventilated, were hypoxic, and had increased peripheral chemoreceptor activity when compared with infants breathing continuously. We were not able at the time to adjust for the impact of gestational and postnatal age, nor were we able to integrate these data into a mechanistic hypothesis.11,12

Since these previous publications, new developments have occurred in the field of respiratory control, particularly regarding the importance of central versus peripheral chemoreceptor activity to maintain baseline breathing, and the crucial role of the PCO2 apneic threshold in inducing apnea.9,15,17,18 We hypothesized
that the degree to which maintenance of breathing was dependent on peripheral chemoreceptor activity might be a major destabilizing factor leading to apnea in term and preterm infants. If this were true, we should observe greater peripheral chemoreceptor activity early versus late in life, and in periodic breathers versus continuous breathers. Moreover, if peripheral chemoreceptor dependence was related to arterial hypoxemia, we should observe a leftward shift of the minute ventilation/transcutaneous PO$_2$ ($V_E$/TcPO$_2$) relationship in infants versus adult subjects, and in periodic versus continuous breathers.$^{19,20}$

We designed this study to examine respiratory pattern and ventilation in neonates of distinct gestational and postconceptional ages and in adult subjects, in parallel with measurements of transcutaneous gases and peripheral chemoreceptor activity. In addition, these measurements were also made in neonates with and without periodic breathing.

Materials and Methods

Subjects

We analyzed data from previous polygraphic recordings in 114 subjects: 98 neonates and 16 adults. We excluded tracings lacking recording of key variables or showing poor quality signals on the polygraphic recording. The subjects were growing preterm infants, normal term infants, and healthy adult subjects. The original studies were approved by the Faculty Committee for the Use of Human Subjects in Research. Informed consent was obtained from at least one of the parents of the neonates and from each adult subject. Neonates were further classified into three groups: small preterm infants [SPI, birth weight (BW) < 1500 g], large preterm infants (LPI, BW ≥ 1500), and term infants (TI). In each of these subgroups, half of the infants breathed predominantly periodic (>68% of sleep time) and half breathed predominantly continuous (>95%). Within each age/birth weight stratum, periodic breathers were matched 1:1 with continuous breathers. The subjects were not on any medication at the time of the study and were breathing room air.

Methods

Our system to measure breathing pattern and ventilation has been described.$^{3,7,21-23}$ Briefly, breathing was measured using a nosepiece and a flow-through system. The screen flowmeter was linear up to 6 L·min$^{-1}$. The resistance of the system was low (0.1 cm H$_2$O·L$^{-1}$·min$^{-1}$). The frequency response of the system was linear, varying less than 5% from 18 to 120 cycles·min$^{-1}$ with volumes of 5 to 30 mL. The infants breathed through nostril adaptors and added (expiration) or subtracted (inspiration) flow from the background flow. The flow signal was electronically integrated to give volume. Breath-to-breath alveolar PCO$_2$ (P$_a$CO$_2$) and PO$_2$ (P$_a$O$_2$) were measured using Beckman analyzers (LB-2 and OM11; Beckman Instruments Co., Fullerton, CA). The 95% rise time of the analyzers was 0.16 and 0.18 seconds for CO$_2$ and O$_2$, respectively. Alveolar gases are usually part of our polygraphic monitoring, and in this study, they were used primarily to monitor changes in inhaled O$_2$ during 100% O$_2$. Oxygen saturation (HbO$_2$) was monitored with a Nellcor Pulse Oximeter (model N-100C; Nellcor, Hayward, CA) and used as an index of infant well being. Transcutaneous O$_2$ (TcPO$_2$) and transcutaneous CO$_2$ (TcPCO$_2$) were measured with a model TCM 3 model (Radiometer, Copenhagen, Denmark). The 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. Respiratory efforts were determined using chest and abdominal displacements, which were measured using mercury strain gauges.$^{21}$ These strain gauges were placed at the level of the 4th intercostal space and just above the umbilicus. Heart rate was measured using conventional leads. All signals were recorded on a Nihon Kohden 21-channel recorder (Model 4221; Nihon, Kohden, Tokyo, Japan) and were also stored in a computer for further analysis. A representative tracing of pertinent variables in infants is shown in Fig 1.

Sleep states were classified as quiet, REM, transitional, and indeterminate. Quiet sleep was defined by the absence of rapid eye movement coupled with, in preterm infants, discontinuous EEG, or, in term infants, with “trace alter-
REM sleep was defined by the presence of rapid eye movements on the EOG and continuous, irregular, low-voltage on the EEG. Transitional states were short epochs lasting 1 to 3 minutes, which were usually observed during the transition from quiet to REM or vice versa. Indeterminate sleep was defined as that which could not be described by other definitions. All ventilatory measurements were made during quiet sleep, including the response to 100% O₂.

Apneas were classified as central or obstructive. Central apneas were those in which airflow and respiratory efforts (chest and abdominal displacement) were absent. Obstructive apneas were those in which absent airflow was associated with some respiratory efforts. This obstructive group therefore includes apneas traditionally classified as purely obstructive and mixed.

Adults were studied in a fully equipped sleep laboratory. The method used was similar to that of infants, consisting of a face mask connected to a flow transducer. The flow signal was electrically integrated to give volume. EEG (C4-A1 and C3-A2) and EOG were recorded from surface electrodes. Breath-to-breath PₐO₂ and PₐCO₂ were measured at the nose with a CO₂ analyzer (Dole 223; Puritan-Bennett Corp, Wilmington, MA). All variables were continuously recorded at 10 mm/s using a 15-channel polygraph (Model 78; Grass Instruments Co, Quincy, MA). All measurements were made in stage 2 sleep, a physiologic stage comparable to quiet sleep in preterm infants.

**Experimental Procedures**

Infants were studied on the Ohio Neonatal Intensive Care Unit (Ohio Medical Instrument, Madison, WI) in a neutral thermal environment with skin abdominal temperature at 36.5 ± 0.03°C. After appropriate placement of the various electrodes and nosepiece, we waited for the infant to fall asleep. When the infant did not settle, a feeding was offered. If infants woke during the study, they were fed and the study was continued. Once in quiet sleep and breathing 21% O₂, the infants were exposed to 100% O₂ for about 1 minute. Recording was long enough to allow for a good representation of breathing pattern. At least one epoch of quiet and REM sleep were always observed. Adults slept overnight in the sleep laboratory and polygraphic tracings were obtained. Administration of 100% O₂ was given when the subjects were breathing quietly in stage 2 sleep.

**Data Collection and Analysis**

Respiratory minute ventilation (\(\dot{V}_E\)), frequency (f), tidal volume (\(V_T\)), PₐO₂, PₐCO₂, TcPO₂, TcPCO₂, HbO₂ saturation (HbO₂), heart rate (HR), EEG, EOG, chest and abdominal displacements, length and type of apneas were measured in all subjects. Apneas were defined as pauses equal to or greater than 3 seconds in infants, and equal or greater than 5 seconds in adults, as to avoid calling a prolonged expiration apnea. Peripheral chemoreceptor activity was assessed by the decrease in ventilation and by the apnea time during the brief inhalation of 100% O₂.

The data were measured by hand from the polygraphic tracings and transferred to a computer for analysis. To test the significance of differences between continuous variables, we used two-tailed one-way analysis of variance. Tukey’s Honest Significant Difference test was used for post hoc tests. Values are expressed as mean ± SEM. A probability value ≤0.05 was considered significant.
Results

General Observations

We were able to examine the polygraphic recordings of four groups of subjects: (1) small preterm infants [SPI, BW 1.2 ± 0.04 kg (mean ± SEM); gestational age (GA) 29 ± 0.3 week; postnatal age (PNA) 28 ± 3 days; postconceptional age (PCA) 33 ± 2 weeks; n = 40]; (2) large preterm infants [LPI, BW 2.0 ± 0.06 kg; GA 33 ± 0.3 week; PNA 23 ± 3 days; PCA 36 ± 2 weeks; n = 34]; (3) term infants [TI, BW 3.4 ± 0.1 kg, GA 39 ± 0.2 week, PNA 20 ± 4 days; PCA 42 ± 1 week, n = 24]; and (4) adult subjects [AS, weight 63 ± 3 kg, 29 ± 3 years, n = 16]. The percentage of periodic breathing was 68% in infants breathing periodically and 5% in infants breathing continuously. There was a trend for minute ventilation values for periodic breathing infants to be lower than those for continuously breathing infants, also due to a decrease in frequency. Values are expressed as mean ± SEM. *, P ≤ 0.05 in relation to adult subjects.

Ventilatory Measurements

Minute ventilation per unit body weight decreased significantly from early life to adulthood (Fig 2). This decrease was mediated primarily by a decrease in f, since VT actually increased to adulthood. In newborn infants VE was lower in the periodic group than in the continuously breathing group, although significance was present only for small preterm infants. This change in ventilation related primarily to a greater decrease in f in infants breathing periodically.

Transcutaneous PO₂ and PCO₂

TcPO₂ and TcPCO₂ increased significantly from small preterm to term infants, and increased further to adult subjects (Fig 3). The TcPO₂ was much lower in infants than in adult subjects (65 ± 1 versus 93 ± 1 Torr), and also lower in periodic breathing infants than those breathing continuously (54 ± 2 versus 70 ± 2 Torr in SPI; 57 ± 1 versus 73 ± 3 Torr in LPI; and 63 ± 2 versus 74 ± 2 Torr in TI, P < 0.001). Values for TcPCO₂ were lower in the continuously breathing than in the periodic breathing groups. When the TcPO₂ was plotted on the Vₖ/Trace regression curve, values for neonates were located to the left of those for adult subjects, and the periodic breathing group was uniformly located to the left of the continuous breathing group, in-

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Figure 2. Minute ventilation and its components, frequency and tidal volume in the various groups. Note that minute ventilation per unit body weight gradually decreased from the small preterm infant to the adult subject; this was related primarily to a decrease in frequency, tidal volume increasing with postnatal age. There was a trend for minute ventilation values for periodic breathing infants to be lower than those for continuously breathing infants, also due to a decrease in frequency. Values are expressed as mean ± SEM. *, P ≤ 0.05 in relation to adult subjects.
indicating an increase contribution of hypoxia to ventilatory drive in the periodic group (Fig 4).

**Peripheral Chemoreceptor Activity**

Corresponding to the significantly lower TcPO₂ early in life, there was a pronounced increase in peripheral chemoreceptor activity at this age, as reflected by a greater percent decrease in ventilation with inhalation of 100% O₂ in neonates compared with adult subjects (38 ± 2 versus 6 ± 5%; Fig 5). The decrease in the various groups was 45 ± 3% (SPI), 35 ± 3% (LPI), 30 ± 5% (TI), and 6 ± 4% (AS), being more pronounced...
in periodic than in continuously breathing infants (53 ± 5 versus 38 ± 5% in SPI; 41 ± 5 versus 31 ± 5% in LPI; and 45 ± 5 versus 17 ± 6% in TI, P < 0.002). An additional index of this more pronounced peripheral chemoreceptor activity was reflected by the more prolonged apnea time with O2 inhalation in all three groups of neonates compared with adult subjects (Fig 6). These apneas were all central in term neonates and were 24% mixed in preterm infants. Only two adults had a brief apnea (<10 seconds). The periodic group showed a longer apnea with inhalation of 100% O2 than the continuously breathing group at all ages.

**Discussion**

We measured peripheral chemoreceptor activity in four groups of subjects, from small preterm infants to adulthood, to improve our knowledge
of the mechanisms responsible for the unstable breathing of newborn infants. We found that (1) peripheral chemoreceptor activity was significantly increased in early life versus adulthood and in infants breathing periodically versus those breathing continuously; (2) the TcPO$_2$ values of neonates were significantly lower than and located to the left of those in adult subjects on the $V'_\text{E}/\text{TcPO}_2$ nomogram; similarly, values for infants breathing periodically were to the left of those breathing continuously; and (3) apneas were more prolonged and more frequent in neonates than in adult subjects. The findings are supportive of the hypothesis that the drive to breathe early in life is dependent on increased peripheral chemoreceptor activity, and that this heightened peripheral chemoreceptor activity may play a role in disturbing the respiratory control system, leading to periodic breathing and apnea.

Although we previously found that preterm infants breathing periodically had lower arterial PO$_2$ than those breathing continuously, we did not explore the possible role of low PO$_2$ in destabilizing breathing. The present study of newborn infants and adult subjects provides some interesting clues to potential mechanisms. Today, it is well accepted that respiratory periodicity generated by low arterial O$_2$ relates to a decrease in arterial PCO$_2$ below the apneic threshold (ie, the PCO$_2$ level below which breathing ceases). This scenario was clearly present in the present study, in which infants breathing periodically manifested lower TcPO$_2$ values. We previously showed that neonates have a baseline $P_A CO_2$ which is only 1.3 Torr above the apneic threshold, and this difference may become even smaller with a decrease in metabolism associated with low PO$_2$. In contrast, adults have a difference of about 4 Torr between baseline and threshold PCO$_2$, making it more difficult for PCO$_2$ to dive below threshold and destabilize breathing. Thus, small decreases in PCO$_2$, such as changes in sleep state or stretching, can easily result in apnea. The low TcPO$_2$ levels early in life also lead to increased peripheral chemoreceptor activity and more instability of breathing, since minor changes in arterial PO$_2$ would greatly alter baseline ventilation. Therefore, this low arterial PO$_2$ early in life represents a major handicap for preterm infants.

There are a few new findings in the present study worth emphasizing. First, methodical and comprehensive studies of changes in ventilation at different gestational and postconceptional ages, including adult subjects, are limited. Second, an analysis of the differences in peripheral chemoreceptor activity, particularly at different postconceptional ages, has not been done, although reports on the overall responsiveness of neonates and adults to high O$_2$ has been documented previously. Finally, the pronounced shift to the left of the TcPO$_2$ values of infants breathing periodically versus infants breathing continuously, on the $V'_\text{E}/\text{TcPO}_2$ plot, is novel and supports the idea that low O$_2$ and its effect on the peripheral chemoreceptor control of breathing may be crucial to destabilize respiration in these tiny infants. Such instability generated by low O$_2$ is also seen in adult subjects climbing to altitudes, in whom low O$_2$ induces periodic breathing and apnea. The fact that an increase in inspired O$_2$, even a very small one, will reduce or eliminate apneas in these infants is further evidence that low O$_2$ is central to this disturbance of the control of breathing.

Our study focused on physiologic measurements likely to disturb breathing in infants breathing periodically as opposed to those breathing continuously. Adult subjects very rarely breathe periodically. In the infants studied, there was a gradual increase in TcPO$_2$ and TcPCO$_2$ from the small to the large preterm group. This occurred both in the subgroups breathing periodically and continuously, although TcPO$_2$ values for the periodic group were uniformly lower than those for the continuous breathing group. Why is the arterial PO$_2$ low in these infants as a group, and why is it even lower in the subgroup breathing periodically? The reason is likely the presence of intrapulmonary shunt. The more immature the infant, the greater the shunt and the lower the arterialized PO$_2$. Infants breathing periodically would supposedly have more lung immaturity and more shunt than those breathing continuously. Intrapulmonary shunt is also likely to be involved in some term infants, although in this group some degree of pulmonary hypertension may be present. Lower TcPO$_2$ values may also result from a greater decrease in functional residual capacity (FRC) in infants breathing periodically which is in general associated with the stiffer...
lungs. In previous studies, we demonstrated that term infants with excessive periodic breathing (≥50% of the sleeping time) were more likely to develop Apparent Life Threatening Events (ALTE).

The present data suggest that infants breathing periodically are more hypoxic than those breathing continuously, at any age. Their baseline TcPO2 levels being low indicates that, during prolonged apneic pauses (≥20 seconds), their saturation may decrease to low levels. Indeed, previously we found that infants ≤1500 g had a significant decrease in V̇E, accompanied by a decrease in HbO2 from 92 to 80% during the apneic period. Although speculative, this decrease in saturation may represent a more damaging insult than we have so far appreciated. Unfortunately, studies trying to unravel the role of these hypoxic events on late outcome have used developmental markers such as the Bayley test, which does not have the necessary discriminating power. These conventional markers are affected by so many other variables that they are unable to accurately assess the effect of one single event. New strategies are needed to assess the effects of these events on the ultimate outcome, but prevention of apnea by adjusting inspired O2 or distending the chest seems a reasonable thing to do.

In conclusion, we have measured ventilatory variables, transcutaneous gases, and peripheral chemoreceptor activity at distinct ages in neonates and adult subjects. We found that ventilation per unit body weight decreases with age, that the increased values early in life correspond to lower TcPO2 and greater peripheral chemoreceptor activity. The lower TcPO2 in infants sits on the steep portion of the ventilation/arterial PO2 regression line, suggesting major changes in ventilation with minor alterations in arterial PO2. In addition, we found that neonates breathing periodically have lower PO2 values than those breathing regularly and therefore may be subject to greater oscillations in breathing. We suggest that this dependency of respiratory pattern on peripheral chemoreceptor activity early in life is likely to offer greater instability to the respiratory control system, making it prone to oscillate and induce apnea.

Acknowledgments

We thank Marie Meunier Jackson for helping in the preparation of this manuscript.

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