Inspired CO₂ and O₂ in sleeping infants rebreathing from bedding: relevance for sudden infant death syndrome

ALOKA L. PATEL, KATHY HARRIS, AND BRADLEY T. THACH
Edward Mallinckrodt Department of Pediatrics, Washington University
School of Medicine, St. Louis, Missouri 63110

Received 1 November 2000; accepted in final form 30 July 2001

Patel, Alok A., Kathy Harris, and Bradley T. Thach. Inspired CO₂ and O₂ in sleeping infants rebreathing from bedding: relevance for sudden infant death syndrome. J Appl Physiol 91: 2537–2545, 2001.—Some infants sleep facedown for long periods with no ill effects, whereas others become hypoxicemic. Rebreathing of expired air has been determined by CO₂ measurement; however, O₂ levels under such conditions have not been determined. To evaluate this and other factors influencing inspired gas concentrations, we studied 21 healthy infants during natural sleep while facedown on soft bedding. We measured gas exchange with the environment and bedding, ventilatory response to rebreathing, and concentrations of inspired CO₂ and O₂. Two important factors influencing inspired gas concentrations were 1) a variable seal between bedding and infants' faces and 2) gas gradients in the bedding beneath the infants, with O₂-poor and CO₂-rich air nearest to the face, fresher air distal to the face, and larger tidal volumes being associated with fresher inspired air. Minute ventilation increased significantly while rebreathing because of an increase in tidal volume, not frequency. The measured drop in inspired O₂ was significantly greater than the accompanying rise in inspired CO₂. This appears to be due to effects of the respiratory exchange ratio and differential tissue solubilities of CO₂ and O₂ during unsteady conditions.

Incidence of sudden infant death syndrome (SIDS) has decreased markedly over the past decade since recommendations were made in several countries to place infants in a nonprone position when sleeping (13, 16, 21, 32). However, SIDS remains the leading cause of infant death beyond the neonatal period in the United States, and 20% of US infants continue to sleep prone (21). Despite the established increased risk of SIDS with prone sleep, the mechanism of death is still debated (3, 16, 17, 19, 27, 33). One proposed mechanism for infants sleeping facedown involves “rebreathing” of expired air retained within soft porous bedding that covers an infant’s face (22). Prior studies of infant rebreathing models have measured inspired carbon dioxide (CO₂) levels of 1–6% (4, 6, 30). The rebreathing theory has been criticized because, although this degree of hypercarbia is biologically significant, it is unlikely to cause CO₂ narcosis or rapid death (19, 30, 38, 43). Hypoxemia has been noted in animal models of rebreathing (4, 24, 25); however, there has been no direct measurement of environmental oxygen (O₂) in animal or human models. O₂ content of inspired air during rebreathing has been assumed to reciprocate CO₂ levels, such that inspired O₂ = room air O₂ minus end-inspiration CO₂ (30); however, effects of factors such as the respiratory exchange ratio on CO₂ and O₂ are unknown (8). Preliminary work by Chiordini et al. (5) suggests that there may be additional factors that affect the degree of rebreathing in infants sleeping facedown. The authors noted gradients in CO₂ concentration in bedding beneath an infant’s face. They also noted the sporadic occurrence of otherwise occult air channels at the juncture of the bedding with the infant’s face, allowing partial exchange of fresh air with the external environment analogous to gas leaks that occur in a loosely fitting facemask, thus limiting gas exchange with the bedding (5). These observations suggest that complex interactions of several factors influencing gas exchange between infant and environment may influence the degree of hypercarbia and hypoxia that develop in inspired air. To further explore these several issues with regard to infants sleeping facedown on soft bedding, we have evaluated four aspects of gas exchange in our study: 1) infants’ gas exchange with the external environment through air-channel formation in bedding, 2) infants’ gas exchange with the bedding as affected by gas gradients, 3) infants’ ventilatory responses to hypercarbia and hypoxia during rebreathing and gas exchanging efficiency of different respiratory patterns, and 4) direct measurement of CO₂ and O₂ in the rebreathing environment during periods of rapid and slow change in the gas concentration of inspired air.

METHODS

Subjects. Twenty-one healthy infants younger than 6 mo old from the St. Louis community were enrolled between September and November 1999. Subjects were 5–24 wk old. There were 8 males and 13 females. Nineteen of the 21 were born at term. At home, 4 (19%) slept prone, 4 (19%) slept

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.jap.org 8750-7587/01 $5.00 Copyright © 2001 the American Physiological Society 2537
supine or on the side, and 13 (62%) slept supine. Seventeen infants (81%) received routine periods of prone positioning while awake and supervised. The Washington University Human Studies Committee approved the study, and informed consent was obtained from the parent(s).

Direct measurement of $O_2$ and $CO_2$ concentrations. Infants were studied during natural sleep during a morning or afternoon nap after a feeding. They were placed in a plastic crib. Bedding used in this study consisted of a corrugated foam pad (5) covered by a polyester-filled comforter folded double (thickness of doubled comforter = 3 cm). A shallow depression (12.5 x 12.5 cm at surface, 4.5 cm deep) was cut into the foam mattress directly beneath the infant’s head. This created an environment with high rebreathing potential closely similar to the partially filled air mattress covered by a comforter described by Kemp and Thach (26). Breath-by-breath $O_2$ and $CO_2$ were measured via an 8-Fr silastic catheter with two small holes attached to the upper lip under the nares. The catheter was connected to a laser-diode $O_2$ analyzer (Vacumed 17518C, Ventura, CA) at a low sampling rate (100–150 ml/min; response time <200 ms) and an infrared photometer $CO_2$ analyzer (Ohmeda 5200, Madison, WI) at a low sampling rate (150 ml/min; response time <200 ms), with both analyzers arranged in parallel. Before each study, the $O_2$ and $CO_2$ analyzers were calibrated with standard gas mixtures. A separate nasal catheter also positioned in front of the nares was attached to a differential pressure transducer, comparing pressure at the narial opening to room pressure (28). During periods in which there was no change in head position, the resistance to flow produced by the bedding was constant; thus narial pressure was proportional to flow. This relationship has been previously demonstrated to be linear over a range of 0–8 l/min (28), allowing us to measure relative changes in nasal airflow. Flow signal was integrated to give tidal volume (VT). The infant’s heart rate, respiratory rate (Respiritrace, Noninvasive Monitoring Systems, Miami Beach, FL), and $O_2$ saturation (Nellcor, Hayward, CA) were also monitored. All output data were continuously recorded on a polygraph (Beckman R611). Infant and polygraph tracings were recorded with an infrared video camera (Videonics, Campbell, CA) so as to allow correlation between infant behaviors and physiological recordings on analysis at a later date. After the infant fell asleep, baseline data were obtained. He or she was then turned prone, and rebreathing was detected by an elevation in the inspired $CO_2$ level. To augment the degree of rebreathing, we often applied silk cloths around the face on theory that these would decrease flow in occult air channels that might be present (28). However, we did not apply silk cloths in all infants, as those who slept facedown for relatively long periods achieved significant rebreathing on their own. In addition, not all infants underwent all protocols for evaluating their ventilatory responses or gas exchange with the environment and bedding due to either time constraints, nap duration, or the availability of the $O_2$ analyzer, which arrived after five infants had been studied (Table 1).

Evidence for occult air channel formation. Once the infant was asleep and rebreathing, additional studies were conducted to evaluate his or her air exchange with the bedding and the environment. Studies were done in three infants to detect air channels around the face. Once asleep and rebreathing, the $O_2$ and $CO_2$ analyzers were disconnected from the nose catheter and connected to a free catheter. This catheter was placed at various positions around the head just above the groove where the bedding contacts the infant’s face. Detection of an elevated $CO_2$ level in currents of air in phase with respiration defined an air channel.

Evidence for gas-gradient formation in bedding. Before the start of the study, two 21-gauge lumbar puncture needles with blunted tips were inserted into the bedding into the pocket beneath the face. After a period of rebreathing when inspired gas had reached relatively steady-state concentrations, the $O_2$ and $CO_2$ analyzers were disconnected from the nose catheter and connected to the bedding needle. The needle was slowly withdrawn at 0.5-cm intervals until it was out of the bedding. This was repeated as tolerated by the infant. This procedure was done in the 7 of 21 infants who remained asleep and rebreathed for long enough periods for the sampling procedure to be completed.

Infants’ ventilatory responses to rebreathing. The change in end-inspiration $CO_2$ that followed placement of cloths was evaluated in 31 episodes in 11 infants by comparing mean end-inspiration $CO_2$ for the 10 breaths that preceded and followed cloth placement. In a different subset of 11 infants, subjects’ responses to rebreathing were evaluated for 31 episodes of rising end-inspiration $CO_2$ and decreasing end-inspiration $O_2$. Episodes of changing inspired gas concentrations were selected, and each breath, including at baseline, was evaluated as the index breath until the gas concentrations reached a relative steady state. In each subject, we measured respiratory frequency (f) and relative VT after the index breath at varying sequential $CO_2$ and $O_2$ levels. We studied the effect of tidal volume size on inspired-gas ($CO_2$ and $O_2$) concentrations in five facedown infants who were chosen because they slept for relatively long periods with their faces straight down. The relative size of five sequential breaths, including a sigh or large breath, was compared with the inspired $CO_2$ and $O_2$ associated with each breath in each infant. Infants were studied for the duration of the nap, usually <2 h.

Effect of gas measurement technique on gas concentration in bedding. In this study, it became clear that gas concentrations in bedding during rebreathing are influenced by a number of factors. Clearly, withdrawing gas from the bedding for determining concentration could have had some effect, even though we used the smallest feasible flow rates. We sought to estimate the effect of this sampling by using a simplified model in which concentration is primarily determined by two factors: 1) the relatively rapid rate of flow of $CO_2$ (for example) into the bedding from the infant and 2) the relatively slow rate of flow of $CO_2$ out of the bedding as a result of simple diffusion.

To estimate the rate of flow out of the bedding, we introduced a mixture of $CO_2$, $N_2$, and $O_2$ (5% $CO_2$, 13% $O_2$, balance $N_2$) into the bedding until it was saturated. We then placed a water-filled container with a shape and mass approximating that of an

### Table 1. Distribution of subjects among multiple analyses

<table>
<thead>
<tr>
<th>Gas evaluation</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CO_2$</td>
<td>21</td>
</tr>
<tr>
<td>$O_2$</td>
<td>16</td>
</tr>
<tr>
<td>Protocols performed</td>
<td></td>
</tr>
<tr>
<td>Air channel</td>
<td>3</td>
</tr>
<tr>
<td>Rise in $CO_2$ after cloth</td>
<td>11</td>
</tr>
<tr>
<td>Gas gradient</td>
<td>7</td>
</tr>
<tr>
<td>Ventilatory response to rebreathing</td>
<td>11</td>
</tr>
<tr>
<td>Effect of VT size on i$CO_2$ and i$O_2$</td>
<td>5</td>
</tr>
<tr>
<td>Volume-averaged i$CO_2$ and i$O_2$</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
</tr>
</tbody>
</table>

$VT$, inspired tidal volume; i$CO_2$, inspired $CO_2$; i$O_2$, inspired $O_2$.
Next, the rate of CO₂ flow into the bedding was estimated by determining the maximum rates of rise of CO₂ when infants first assumed the facedown position. Half-life was calculated for this rate of rise. Knowing the rates of flow into and out of the bedding allowed us to mathematically determine the differences in gas concentration in the bedding for continuous vs. intermittent sampling.

**Data analysis.** O₂ and CO₂ concentrations were calculated by estimating to the nearest 0.25 mm on the output tracing and multiplying by the calibration constant (1 mm = 0.22% CO₂ or O₂). Relative inspired VT (in mm²) were calculated by integrating the flow curve during inspiration; f was calculated by counting the number of breaths in the preceding 10 s from the index breath and multiplying by six. Relative minute ventilation (V̇l) (units = 1 mm² box/min) was calculated by multiplying f and V̇r. The relationships between V̇l, V̇r, and f and inspired CO₂ and O₂ concentrations were evaluated by Student's two-tailed, unpaired t-test and multiple linear regression. The change in inspired CO₂ that followed cloth placement was analyzed by comparing mean inspired CO₂ before and after each cloth placement by Student's two-tailed, paired t-test. The significance of the relationship between VT size and inspired gas concentrations was evaluated by linear regression and Student's two-tailed, unpaired t-test (18).

Mean inspired gas concentration (volume-averaged) for each breath was calculated by weighting the gas concentration by the corresponding portion of VT for each millimeter subdivision (1 mm = 0.1 s) of inspiration divided by the VT. This method is depicted by the following formula, where i = each 0.1-s subdivision of inspiration and there are n total subdivisions: \[ \frac{\sum (\text{gas concentration}_i \times \text{volume}_i)}{\text{VT}} \] (Fig. 1). Volume-averaged inspired CO₂ and O₂ concentrations were calculated by estimating to the nearest 0.25 mm on the output tracing and multiplying by the calibration constant (1 mm = 0.22% CO₂ or O₂). Relative inspired VT (in mm²) were calculated by integrating the flow curve during inspiration; f was calculated by counting the number of breaths in the preceding 10 s from the index breath and multiplying by six. Relative minute ventilation (V̇l) (units = 1 mm² box/min) was calculated by multiplying f and V̇r. The relationships between V̇l, V̇r, and f and inspired CO₂ and O₂ concentrations were evaluated by Student's two-tailed, unpaired t-test and multiple linear regression. The change in inspired CO₂ that followed cloth placement was analyzed by comparing mean inspired CO₂ before and after each cloth placement by Student's two-tailed, paired t-test. The significance of the relationship between VT size and inspired gas concentrations was evaluated by linear regression and Student's two-tailed, unpaired t-test (18).

**Data analysis.** O₂ and CO₂ concentrations were calculated by estimating to the nearest 0.25 mm on the output tracing and multiplying by the calibration constant (1 mm = 0.22% CO₂ or O₂). Relative inspired VT (in mm²) were calculated by integrating the flow curve during inspiration; f was calculated by counting the number of breaths in the preceding 10 s from the index breath and multiplying by six. Relative minute ventilation (V̇l) (units = 1 mm² box/min) was calculated by multiplying f and V̇r. The relationships between V̇l, V̇r, and f and inspired CO₂ and O₂ concentrations were evaluated by Student's two-tailed, unpaired t-test and multiple linear regression. The change in inspired CO₂ that followed cloth placement was analyzed by comparing mean inspired CO₂ before and after each cloth placement by Student's two-tailed, paired t-test. The significance of the relationship between VT size and inspired gas concentrations was evaluated by linear regression and Student's two-tailed, unpaired t-test (18).

Mean inspired gas concentration (volume-averaged) for each breath was calculated by weighting the gas concentration by the corresponding portion of VT for each millimeter subdivision (1 mm = 0.1 s) of inspiration divided by the VT. This method is depicted by the following formula, where i = each 0.1-s subdivision of inspiration and there are n total subdivisions: \[ \frac{\sum (\text{gas concentration}_i \times \text{volume}_i)}{\text{VT}} \] (Fig. 1). Volume-averaged inspired CO₂ and O₂ concentrations were calculated by estimating to the nearest 0.25 mm on the output tracing and multiplying by the calibration constant (1 mm = 0.22% CO₂ or O₂). Relative inspired VT (in mm²) were calculated by integrating the flow curve during inspiration; f was calculated by counting the number of breaths in the preceding 10 s from the index breath and multiplying by six. Relative minute ventilation (V̇l) (units = 1 mm² box/min) was calculated by multiplying f and V̇r. The relationships between V̇l, V̇r, and f and inspired CO₂ and O₂ concentrations were evaluated by Student's two-tailed, unpaired t-test and multiple linear regression. The change in inspired CO₂ that followed cloth placement was analyzed by comparing mean inspired CO₂ before and after each cloth placement by Student's two-tailed, paired t-test. The significance of the relationship between VT size and inspired gas concentrations was evaluated by linear regression and Student's two-tailed, unpaired t-test (18).

Mean inspired gas concentration (volume-averaged) for each breath was calculated by weighting the gas concentration by the corresponding portion of VT for each millimeter subdivision (1 mm = 0.1 s) of inspiration divided by the VT. This method is depicted by the following formula, where i = each 0.1-s subdivision of inspiration and there are n total subdivisions: \[ \frac{\sum (\text{gas concentration}_i \times \text{volume}_i)}{\text{VT}} \] (Fig. 1). Volume-averaged inspired CO₂ and O₂ concentrations were calculated by estimating to the nearest 0.25 mm on the output tracing and multiplying by the calibration constant (1 mm = 0.22% CO₂ or O₂). Relative inspired VT (in mm²) were calculated by integrating the flow curve during inspiration; f was calculated by counting the number of breaths in the preceding 10 s from the index breath and multiplying by six. Relative minute ventilation (V̇l) (units = 1 mm² box/min) was calculated by multiplying f and V̇r. The relationships between V̇l, V̇r, and f and inspired CO₂ and O₂ concentrations were evaluated by Student's two-tailed, unpaired t-test and multiple linear regression. The change in inspired CO₂ that followed cloth placement was analyzed by comparing mean inspired CO₂ before and after each cloth placement by Student's two-tailed, paired t-test. The significance of the relationship between VT size and inspired gas concentrations was evaluated by linear regression and Student's two-tailed, unpaired t-test (18).

Mean inspired gas concentration (volume-averaged) for each breath was calculated by weighting the gas concentration by the corresponding portion of VT for each millimeter subdivision (1 mm = 0.1 s) of inspiration divided by the VT. This method is depicted by the following formula, where i = each 0.1-s subdivision of inspiration and there are n total subdivisions: \[ \frac{\sum (\text{gas concentration}_i \times \text{volume}_i)}{\text{VT}} \] (Fig. 1). Volume-averaged inspired CO₂ and O₂ concentrations were calculated by estimating to the nearest 0.25 mm on the output tracing and multiplying by the calibration constant (1 mm = 0.22% CO₂ or O₂). Relative inspired VT (in mm²) were calculated by integrating the flow curve during inspiration; f was calculated by counting the number of breaths in the preceding 10 s from the index breath and multiplying by six. Relative minute ventilation (V̇l) (units = 1 mm² box/min) was calculated by multiplying f and V̇r. The relationships between V̇l, V̇r, and f and inspired CO₂ and O₂ concentrations were evaluated by Student's two-tailed, unpaired t-test and multiple linear regression. The change in inspired CO₂ that followed cloth placement was analyzed by comparing mean inspired CO₂ before and after each cloth placement by Student's two-tailed, paired t-test. The significance of the relationship between VT size and inspired gas concentrations was evaluated by linear regression and Student's two-tailed, unpaired t-test (18).
concentrations were compared with prior methods of estimating inspired gas concentrations (end-inspiration CO$_2$ and O$_2$ = room-air O$_2$ – end-inspiration CO$_2$) by Student’s two-tailed, paired t-test for each breath (30). Forty-five breaths during both rapidly changing and relatively steady-state conditions while rebreathing were analyzed in this manner in five infants who slept facedown for long periods. Results are expressed as means ± SE. Results for all statistical analyses were considered significant if $P < 0.05$.

RESULTS

Evidence for occult air channel formation. Gas exchange with the environment while facedown via air channels not apparent to visual inspection was demonstrated by a rise in CO$_2$ to 1.5% at certain positions around the infant’s face in the three infants tested, with gas changes in phase with respiration usually detected at one or more sites (Fig. 2, example of one infant). Location of channels and size of the CO$_2$ signal often changed with changes in the infant’s head position.

End-inspiration CO$_2$ rose by an average of 28.7% after placement of a silk cloth (1.34 ± 0.19 and 1.73 ± 0.17% before and after cloth placement, respectively) around the face in 11 prone infants ($P < 0.005$). Figure 3 shows a representative tracing from one infant.

Evidence for gas-gradient formation in bedding. As the needle was pulled from deep in the bedding into the pocket immediately beneath the face in seven infants, CO$_2$ levels gradually rose and O$_2$ levels fell. CO$_2$ levels rose to 3.96% and O$_2$ levels fell to 12.4% in the bedding beneath the face in a representative subject (Fig. 4). In addition, a rise and fall in gas concentration in phase with breathing was detected beneath the face in zones A and B, suggestive of bulk air movement.

Infants’ ventilatory responses to rebreathing. Larger $V_t$ was associated with a decrease in end-inspiration CO$_2$ (52.8 ± 8.93% lower) and an increase in end-inspiration O$_2$ (10.8 ± 0.53% higher) in the five facedown infants. These trends were significant with $P < 0.05$ for each of the five facedown infants studied (Fig. 5).

Respiratory response to rebreathing was evaluated in 11 infants (represented by subject IA in Fig. 6). All demonstrated an increase in $V_t$ (average of 332%) and $V_t$ (average of 319%) as infants were exposed to an increasingly asphyxial environment. $f$ Varied irregularly with regard to O$_2$ and CO$_2$. Slopes of $V_t$ and $V_t$ vs. end-inspiration O$_2$ and end-inspiration CO$_2$ were significantly different from zero by t-test for all patients ($P = 0.01$ and $P < 0.01$, respectively). In contrast, the slope of $f$ vs. end-inspiration O$_2$ and end-inspiration CO$_2$ was not statistically significantly different from zero ($P = 0.57$). The high level of correlation between CO$_2$ and O$_2$ ($r = -0.9$) precluded use of multiple-regression analysis.

Direct measurement of O$_2$ and CO$_2$ concentrations. Inspired-gas concentrations were analyzed from five infants who rebreathed while sleeping in a facedown position without requiring additional cloths around the face. These infants were similar to the entire study group with regard to age and sex. Of these five, two (40%) slept prone at home. Volume-averaged inspired CO$_2$ concentration was 3.43 ± 0.19%, range 5.78–5.75%. Volume-averaged inspired O$_2$ concentration was 15.94 ± 0.23, range = 13.32–19.65%. Linear regression of the change in CO$_2$ on the change in O$_2$ concentration from room air did not reveal an equal relationship, as the slope was <1 for each subject. The
decrease in O₂ was significantly greater in magnitude than the increase in CO₂ (P < 0.01 for each infant; Fig. 7).

Analysis of the 45 breaths showed the volume-averaged inspired CO₂ concentration was significantly higher than the end-inspiration CO₂ concentration for each subject (18.2–122.2% higher; P < 0.005). In each subject, volume-averaged inspired O₂ concentration was significantly lower than prior estimates (inspired O₂ = room air O₂ – end-inspiration CO₂) of O₂ levels (6.7–17.2% lower, P < 0.005; Fig. 8). Two of our subjects who showed the most pronounced differences in O₂ concentrations (16.1 and 17.2% lower) also experienced rapid desaturations to 84–85%. Concurrently, volume-averaged O₂ concentration decreased to 13% over 20–30 s with a much slower accompanying rise in CO₂ (Fig. 9). Figure 10 shows the relationship between change in CO₂ and change in O₂ in both expired and inspired air during this rapid desaturation, which is best fit by a curve. One of these infants failed to arouse on his own and required our intervention when his O₂ saturation reached 85%.

Effect of gas measurement technique on gas concentration in bedding. The intermittent method of gas sampling approximated the natural time course of diffusion of gas out of the bedding, as minimal flow was directed to the gas analyzers. Average half-life of flow of CO₂ out of the bedding for intermittent sampling was 125 vs. 88 s for continuous sampling, which had an effect of increasing flow of gas out of the bedding. Similar results were obtained for O₂. Half-life of flow of gas into the bedding was 10.4 s for CO₂ and 10.5 s for O₂. Thus, although the continuous method changed gas concentration faster than the intermittent method by a factor of 1.4, the rate of change in inflow was still roughly 10 times faster than the rate of outflow, irrespective of the method of sampling. The ratio of gas-concentration equations showed that the effect of continuous sampling was to lower measured values of CO₂ and raise measured values of O₂ by 5%, compared with our estimates of gas concentrations if no sampling had occurred.

DISCUSSION

We verified preliminary data that there are often air channels around the infant’s face, while sleeping facedown, which allow gas exchange with the environment and that they are occult, in that direct inspection does not suggest their presence. In addition, we noted that slight movements of the infant’s head could increase or decrease flow through these channels. This principle was also demonstrated by the significant rise in CO₂ after the placement of clothes near infants’ faces, thus increasing the bedding’s effect on rebreathing. When the infant has the ability to exchange air via air channels, the degree of rebreathing may be limited (5). However, this also highlights the subtleties of infant and bedding positioning, which are not immediately visible and may allow some infants to sleep facedown, whereas others who do so may experience dangerous asphyxia. Although we investigated only one type of bedding, it is conceivable that certain characteristics of the composition of the bedding influence the occurrence and size of channels and thereby would be relevant to its safety for infants (26).

We evaluated the effect of our method of continuously sampling gas for analysis by comparing it to intermittent sampling. We estimated that the continuous withdrawal of gas in the bedding altered gas values by ~5% compared with actual values that would have been present during rebreathing in the absence of sampling. Thus we slightly underestimated the asphyxial challenge to the infant during rebreathing. Because the overall effect of continuous sampling was to cause an apparent increase in the background diffusion of gas out of the bedding and because CO₂ and O₂ were affected equally, our findings regarding proportional differences in gas concentrations and gradients in bedding were unaffected.

Presence of CO₂ and O₂ gradients in the bedding, with high CO₂ and low O₂ just beneath the nose and low CO₂ and high O₂ furthest from the nose, demonstrates that the infant exchanges gas with bedding during rebreathing as well. These findings confirm preliminary observations made earlier by this laboratory (5). Reasons for formation of gradients are not clearly identified. We theorize that the microstructure of the bedding (23, 24, 26) allows airflow with minimal turbulence and consequently little air mixing. Also, exchange of gases at the interface between the bedding and the environment must be occurring by diffusion. As air is exhaled, end-expired air, which is of highest CO₂ and lowest O₂ content, is trapped closest to the face. Although convection does occur, as demonstrated
by the pulsatile flow detected in the bedding nearest the face, it diminishes further out from the infant's face and thus limits mixing. In effect, the bedding expands the dead space in series with the infant's dead space. Due to the relatively large nature of this space, the infant inspires end-expiratory gas before accessing fresher air that is further away in the bedding (Fig. 4). This is confirmed by the effect of VT on inspired-gas concentrations, with larger VT allowing access to fresher air, in the facedown infants seen in this study.

Fig. 7. Mean change in CO₂ from room air (RA) vs. mean change in O₂ from room air in 5 facedown rebreathing infants (modified conventional POCO₂ and PPO₂ diagram) (37). Note that each infant's regression line has a slope of <1, which is shown by the line of identity. Therefore, for each infant, the absolute decrease in O₂ is larger in magnitude than the absolute increase in CO₂ (P < 0.01 for each regression line). ●, TA; x, BM; ○, MD; ●, IA; △, RM.

Fig. 8. Measured volume-averaged inspired O₂ (black bars) vs. estimated O₂ (gray bars) from previous method (inspired O₂ = room air O₂ - end-i CO₂) (30) in 5 facedown, rebreathing infants (mean ± SE). Note that, for each infant, measured O₂ is significantly lower than previously theorized. *P < 0.005.
The relationship between $V_t$ size and inspired-air composition highlights the importance of volume averaging inspired-gas concentrations. Nunn (34) reviews a method for determining the composition of gas rebreathed from apparatus dead space. Because inspired rebreathed gas is of changing composition, as shown by Fig. 1, the true effective mean concentration is volume based (2). When facedown and breathing from a relatively large reservoir of exhaled air in the bedding, true inspired-gas concentration depends on the volume and corresponding concentration of air breathed early as well as late in inspiration. For example, at the beginning of inspiration, the infant breathes in end-expiratory gas near the nose. As the inspiratory volume increases, more air is drawn from distant, fresher areas of the bedding. Thus the volume-averaged concentration reflects the various sources of gas inhaled during the entire inspiration.

Subjects demonstrated appropriate ventilatory responses to an asphyxial environment. Of note, our subjects were exposed to a hypercarbic and hypoxic stimulus, depending on the degree of rebreathing achieved by each infant. Although the usual ventilatory response to hypoxia is hyperbolic in shape, the responses of these infants fit a linear model best (11). Hypercarbia normally results in a linear increase in $V_i$ (29). The observed response likely reflects the dual stimuli as the ventilatory response to asphyxia is greater than that to the individual stimuli of the rise in CO$_2$ and the fall in O$_2$ (9, 29). Our subjects increased $V_i$ primarily by increasing $V_T$, with inconsistent changes in $f$. It has been shown that humans, unlike other animals, primarily change $V_T$ to affect ventilation (1, 5, 7, 11, 15). In a facedown rebreathing environment, the increase in $V_T$ is beneficial as it allows access to fresher air in the bedding. If the primary response consisted of shallow, rapid breathing, then the infant would be exposed to a more threatening environment. This may explain the greater increased risk of SIDS associated with prone positioning in infants with infectious respiratory illness as opposed to well infants (36). Such illnesses tend to be associated with stimuli that increase $f$.

High resistance to airflow associated with covering the nose and mouth has been associated with respiratory failure and/or death (40, 41). Although the facedown infants in our study did have their mouths and noses covered, the resistance of our bedding has been previously shown to be well below the level of resistive load associated with development of hypercapnia in infants (24, 41). High resistive loads in infants have been associated with hypoventilation, effected primarily through changes in $f$ instead of $V_T$ (41). Thus the ventilatory changes seen in our study reflect a response to an asphyxial environment due to rebreathing, not to a high resistive load.

Previously, estimates of the CO$_2$ concentrations in infants’ environments have used the end-inspiration point (6, 30). Actual inspired-O$_2$ concentration while rebreathing has not been measured, but it has been assumed to reciprocate elevated CO$_2$ levels (30). We attempted to find a more accurate estimate of the inspired gases by continuously measuring both CO$_2$ and O$_2$ and calculating the volume-averaged mean concentrations. Our data showed that the decrease in actual O$_2$ concentration does not reciprocate the elevation in CO$_2$ but is of significantly greater magnitude. During quasi-steady-state conditions, the inequality

\[ \text{Change in } CO_2 (\% \text{ from RA}) \]

\[ \text{Change in } O_2 (\% \text{ from RA}) \]

Fig. 10. Scatter diagram of simultaneous changes in CO$_2$ and O$_2$ concentrations from room air during a period of rapid desaturation in one subject. Note nonlinear shape of best-fit lines for both expired (●) and inspired (○) gas concentrations, which is suggestive of an unsteady state.
between changes in $O_2$ and $CO_2$ is partially due to the respiratory quotient, reflecting the relatively larger consumption of $O_2$ than $CO_2$ production. The respiratory quotient remains relatively constant as the data best fit a line for each subject (Fig. 7).

Additionally, the measured $O_2$ inspired by rebreathing infants was significantly lower than predicted when rapid change in inspired gas composition occurred soon after assuming the facedown position. This was most evident in the two infants who experienced rapid desaturations to 84–85%. The time course of these episodes was notable in that, although the $O_2$ concentration fell rapidly, the $CO_2$ concentration changed minimally. The relationship of change in $CO_2$ and change in $O_2$ is best fit by a curve during these rapidly changing episodes (Fig. 10), as opposed to a linear relationship during quasi-steady-state conditions. This likely reflects the body’s ability to store $CO_2$ 100-fold more than $O_2$ (34). Before reaching steady-state conditions, the respiratory exchange ratio temporarily changes, making the difference between $O_2$ and $CO_2$ even larger (34). The larger decrease in $O_2$ vs. increase in $CO_2$ while sleeping and rebreathing may have a deleterious effect on an infant’s ability to respond to an asphyxiating environment. The inspired $O_2$ reached a nadir of 13.3%, which is below the level of inspired $O_2$ generally considered safe for infants during prolonged exposure (35, 39, 42). Thus, although infants are exposed to both hypoxic and hypercapnic stimuli, hypoxic exposure approaches a level considered to be dangerous when prolonged. Ventilatory response to hypoxia is strongly influenced by other factors: 1) the accompanying $P_{CO_2}$, with hypocapnia reducing the response; 2) state of consciousness, with depressed consciousness states such as sleep or sedation reducing the response; and 3) central nervous system (CNS) hypoxia, which reduces respiratory drive (11, 14). A perhaps more important consideration is that several investigators have shown hypoxia to be a poor stimulus for arousal, especially in contrast to hypercarbia (10, 14, 20, 31). Potentially relevant is that the hypoxic arousal response has been shown to be even more depressed in siblings of SIDS infants and near-miss SIDS infants (12, 31). Rapidly advancing CNS hypoxia in infants, as in others, is associated with rapid onset of coma. Once coma occurs, an arousal-related change in head position is not possible and death would presumably eventually occur as in animal models of rebreathing (22, 24, 25). Therefore, the current findings further advance the concept that hypoxemia, rather than hypercarbia, may be the more important factor when death occurs in infants sleeping with their faces covered by soft porous bedding.

We thank Betsy Grant of the Washington University Department of Biostatistics for help with statistical analyses. This research was funded by National Institute of Child Health and Human Development Grant HD-10993. A. L. Patel was supported by National Heart, Lung, and Blood Institute Grant T32-HL-07873.

REFERENCES

22. Kemp JS, Kowalski RM, Burch PM, Graham MA, and Thach BT. Unintentional suffocation by rebreathing: a death


