Small Preterm Infants (≤ 1500 g) Have Only a Sustained Decrease in Ventilation in Response to Hypoxia¹

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ABSTRACT. The classic "biphasic" ventilatory response to 15% O₂ was previously observed in preterm infants who were large compared with those in the intensive care nursery today. We hypothesized that in the smaller infant (≤ 1500 g) the response might be closer to that of the fetus, with no initial increase in ventilation. Thus, we studied 14 healthy preterm infants ≤ 1500 g [birth weight 1220 ± 63 g (mean $\pm$ SEM); gestational age 29 ± 0.4 wk; postnatal age 17 ± 3 d] during rapid eye movement and quiet sleep. Ventilation was measured using a nose-piece and a flow-through system. Sleep states were defined using EEG, electro-oculogram, and body movements. After a control period in 21% O₂ (3 min), infants breathed 15% O₂ for 5 min. In rapid eye movement sleep, minute ventilation decreased from 0.186 ± 0.020 (control) to 0.178 ± 0.021 (30 s), to 0.171 ± 0.017 (1 min; $p = 0.03$), to 0.145 ± 0.016 (3 min; $p = 0.002$), and to 0.129 ± 0.011 $1 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (5 min; $p = 0.004$). In quiet sleep, it decreased from 0.173 ± 0.019 (control) to 0.164 ± 0.019 (30 s), to 0.166 ± 0.019 (1 min), to 0.148 ± 0.013 (3 min; $p = 0.03$), and to 0.146 ± 0.012 $1 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (5 min; $p = 0.04$). These changes in ventilation were primarily related to a decrease in frequency in rapid eye movement [38 ± 2 (control) versus 28 ± 3 (5 min); $p = 0.01$] and in quiet sleep [36 ± 5 (control) versus 27 ± 3 (5 min); $p = 0.02$]. Changes in tidal volume were negligible. These findings suggest that the classic biphasic response to hypoxia is not observed in very small preterm infants. These infants show only a sustained decrease in ventilation with low O₂. We speculate that the response reflects a more pronounced inhibitory mechanism induced by hypoxia at this gestational age, representing an intermediate profile between that observed in the fetus and that present in larger neonates. (*Pediatr Res* 32: 403–406, 1992)

Abbreviations

REM, rapid eye movement
P_AO₂, alveolar PO₂
P_ACO₂, alveolar PCO₂

(30 s) increase followed by a late (5 min) decrease in ventilation. The immediate increase in ventilation has been traditionally accepted as a reflection of peripheral chemoreceptor activity. The late response, however, is poorly understood and has been attributed to such factors as central hypoxic depression, decreased metabolic rate, and decreased compliance of the lungs (1–6). However, the infants who have shown this response have been larger and more mature than those admitted to the nursery today. We thought that in smaller and less mature infants (≤ 1500 g) the response to low inspired O₂ may differ from that previously described. It might represent an intermediate response between the biphasic profile in larger preterm infants and the abrupt cessation of breathing in the fetus (7, 8).

We therefore designed this study to examine the ventilatory response to 15% inhaled O₂ in preterm infants ≤ 1500 g to test the hypothesis that these infants show only a sustained decrease in ventilation in response to hypoxia.

MATERIALS AND METHODS

Subjects. We studied 14 healthy preterm infants ≤ 1500 g. Birth weight was 1220 ± 63 g (mean $\pm$ SEM; range 785 to 1460 g), gestational age 29 ± 0.4 wk, postnatal age 17 ± 3 d, and study weight 1250 ± 78 g. The study was approved by the Faculty Committee for the Use of Human Subjects in Research, University of Manitoba, and written consent was obtained from at least one parent of each infant.

Methods. The system used to measure ventilation and alveolar gases has been described in detail previously (9–11). Briefly, we used a nose-piece and a screen flowmeter to measure respiratory minute volume and alveolar gases. We eliminated valves and reduced dead space by using a constant background flow (3 L $\cdot$ min⁻¹) which was electrically balanced to an artificial zero. The infant breathed through the nostril adapters and added to (expiration) or subtracted flow from (inspiration) the background flow. The flow signal was electrically integrated to give volume.

We measured breath-to-breath alveolar PO₂ and PCO₂ using Beckman analyzers. The 95% response times of the analyzers were 0.16 and 0.18 s for CO₂ and O₂, respectively. EEG was monitored using a single channel with an electrode placed in the right frontal position and referenced to the left mastoid. The electro-oculogram was recorded from eye electrodes referenced to the right ear. O₂ saturations and ECG were used to monitor the infant's well-being but were not considered end points of this study. Sleep states were monitored according to previous criteria (3). We characterized REM and quiet sleep according to previous recommendations (12). All signals were recorded on a polygraph (model 4221, Nihon Kohden, Tokyo, Japan). A representative tracing is shown in Figure 1.

Procedure. Infants were studied on the Ohio Neonatal Intensive Care Unit (Ohio Medical Instruments, Madison, WI) in our

Preterm infants have long been known to present a classic "biphasic" ventilatory response to 15% O₂ with an immediate

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Fig. 1. Representative tracing in one preterm infant (body weight 1400 g, gestational age 28 wk, postnatal age 17 d) during REM sleep. Note the decrease in ventilation since the 1st min of hypoxia. This decrease was related primarily to a decrease in respiratory frequency, with breathing becoming quite periodic during hypoxia.

Table 1. Physiologic responses to inhalation of 15% O₂ in preterm infants ≤ 1500 g*

	$\dot{V}_E$ (L·min ⁻¹ ·kg ⁻¹)		V_T (mL·kg ⁻¹)		f (breaths·min ⁻¹)		V_T/T_i (mL·kg ⁻¹ ·s ⁻¹)		T_i/T_{TOT}		P_{ACO_2} (kPa)		P_{AO_2} (kPa)	
	Quiet	REM	Quiet	REM	Quiet	REM	Quiet	REM	Quiet	REM	Quiet	REM	Quiet	REM
Control	0.173 ±0.019	0.186 ±0.020	5.2 ±0.6	5.0 ±0.5	36 ±5	38 ±2	9.0 ±1.2	9.0 ±1.0	0.354 ±0.042	0.350 ±0.018	5.28 ±0.16	5.20 ±0.15	12.49 ±0.36	13.29 ±0.44
15% O ₂ 30 s	0.164 ±0.019	0.178 ±0.021	5.4 ±0.7	4.8 ±0.6	33 ±3	38 ±3	9.5 ±1.3	8.8 ±1.2	0.311 ±0.029	0.351 ±0.028	5.23 ±0.19	5.07 ±0.16	8.29† ±0.37	8.45† ±0.44
1 min	0.166 ±0.019	0.171† ±0.017	5.6 ±0.7	4.9 ±0.5	32 ±3	37 ±3	9.4 ±1.4	8.8 ±1.1	0.326 ±0.030	0.345 ±0.025	5.20 ±0.16	5.13 ±0.16	7.91† ±0.44	8.24† ±0.48
2 min	0.161 ±0.013	0.153† ±0.017	6.1† ±0.8	5.4 ±0.7	29† ±3	32† ±4	10.3† ±1.3	10.0 ±1.4	0.293† ±0.035	0.289† ±0.035	5.29 ±0.21	5.05 ±0.19	7.32† ±0.48	7.21† ±0.49
3 min	0.148† ±0.013	0.145† ±0.016	6.2† ±0.9	5.7 ±0.7	28† ±3	30† ±2	11.2 ±2.0	11.0 ±1.7	0.266† ±0.030	0.268† ±0.022	5.28 ±0.16	5.04 ±0.19	7.23† ±0.51	7.32† ±0.45
4 min	0.146† ±0.017	0.133† ±0.010	6.1† ±0.7	5.6 ±0.7	26† ±3	27† ±3	11.1† ±1.7	10.0 ±1.3	0.252† ±0.038	0.250† ±0.025	5.36 ±0.16	5.33 ±0.16	6.49† ±0.63	7.57† ±0.41
5 min	0.146† ±0.012	0.129† ±0.011	6.1† ±0.8	5.1 ±0.7	27† ±3	28† ±3	10.2† ±1.3	9.2 ±1.4	0.267† ±0.037	0.258† ±0.028	5.44 ±0.19	5.25 ±0.25	7.08† ±0.53	7.24† ±0.51

* Values are mean $\pm$ SEM. $\dot{V}_E$, minute ventilation; V_T , tidal volume; f , respiratory frequency; V_T/T_i , inspiratory drive; T_i/T_{TOT} , duty cycle.

† $p \leq 0.05$ in relation to control.

clinical research laboratory located adjacent to the Intermediate Care Nursery. A neutral thermal environment was maintained with skin abdominal temperature at $36.5 \pm 0.03^\circ\text{C}$ (10, 11). After appropriate placement of the various electrodes and nosepiece, we waited for the infants to fall asleep. Once they had been in quiet and REM sleep breathing 21% O₂ for 3 min each, 15% O₂ was given for 5 min. A given infant had to remain in the same sleep state during the 5 min of inhalation of 15% O₂ to be considered for analysis. Infants tolerated the procedure well and no complications were seen in any of the infants.

Data collection and analysis. We analyzed the records by hand and transferred the data to a computer for appropriate treatment. We measured minute ventilation, respiratory frequency, tidal volume, inspiratory time, total duration of the respiratory cycle, P_{AO_2} , and P_{ACO_2} for 30 s to 1 min during 21% and 15% O₂. Inspiratory drive (tidal volume/inspiratory time) and "duty cycle" (inspiratory time/total duration of respiratory cycle) were calculated.

Analysis of variance was used to test the significance of the differences between values during 15% O₂ and 21% O₂ and between sleep states. Values are expressed as mean $\pm$ SEM. A p value ≤ 0.05 was considered significant.

RESULTS

Results are summarized in Table 1 and illustrated in Figures 1 and 2. With administration of 15% O₂, there was an immediate and sustained decrease in ventilation in both sleep states, which was significant in REM sleep from the 1st min and in quiet sleep from the 3rd min of breathing low O₂. These changes in ventilation were primarily related to a decrease in frequency in both sleep states (Figs. 1 and 2, Table 1).

The sustained decrease in ventilation was more pronounced during REM sleep with a percentage of change in ventilation of $-33 \pm 5\%$ compared to $-11 \pm 5\%$ during quiet sleep at 5 min ($p = 0.005$). This difference between sleep states was related to a lack of increase in tidal volume in REM sleep ($-3 \pm 8\%$ in REM versus $23 \pm 7\%$ in quiet sleep; $p = 0.02$) (Fig. 2, Table 1).

The inspiratory drive increased in quiet sleep only, paralleling the changes in tidal volume. The duty cycle decreased in both sleep states, suggesting that the changes related to hypoxia were mediated primarily through a change in timing. P_{AO_2} decreased similarly in both sleep states and P_{ACO_2} was somewhat lower in REM than in quiet sleep, although the differences were not statistically significant (Fig. 2, Table 1).

Fig. 2. Changes in ventilatory variables in response to 15% O_2 . *Left*, Sustained decrease in ventilation occurred in both sleep states, mainly due to a decrease in frequency. *Right*, Percentages of change show that during REM sleep ventilation decreased significantly more than in quiet sleep as a result of a lack of increase in tidal volume. Values are mean $\pm$ SEM; *, $p \leq 0.05$ compared to control; †, $p \leq 0.05$ between sleep states.

DISCUSSION

We found that the classic biphasic response to hypoxia was not observed in very small preterm infants, these infants showing only a sustained decrease in ventilation with low inhaled O_2 . The decrease in ventilation was primarily related to a decrease in frequency in both sleep states, usually related to the appearance of periodic breathing, and occurred despite an increase in respiratory drive (tidal volume/inspiratory time) and tidal volume during quiet sleep. This type of response is entirely compatible with the central depressive effects of hypoxia. In preterm infants, the initial inhibition of ventilation during hypoxia is mediated by a decrease in frequency rather than tidal volume (1, 2, 4). Term infants and adult subjects change ventilation by primarily changing tidal volume. The absence of an immediate increase in ventilation in response to 15% O_2 was observed in both sleep states, although early hypoventilation (1st min) was significant only in REM sleep.

The sustained decrease in ventilation in response to hypoxia has not been described previously in these infants. The mechanisms involved in this unique response are not completely clear. It is tempting to speculate that it is related to a decreased

peripheral chemoreceptor response and a predominantly central depressive effect of hypoxia. The decreased response of the peripheral chemoreceptors may be explained by their already high baseline activity related to the relatively low arterial PO_2 present in these infants. This would make the hypoxic stimulus unable to further increase the peripheral chemoreceptor firing, which is already very high. As a consequence, ventilation would decrease as a result of effects of hypoxia on the central chemoreceptors.

During the late response to hypoxia (5 min), the decrease in ventilation was observed in both sleep states, although it was significantly more pronounced in REM than in quiet sleep. This could have been explained by behavioral influences and the greater degree of hypoxemia already present at rest during REM sleep (13, 14). In quiet sleep, this response differed from that observed in larger preterm infants at 18 d of age, who present a more sustained hyperventilation (3). In REM sleep, the decrease in ventilation was about 33%, slightly more pronounced than the 20% decrease observed in larger preterm infants (2–4). It is interesting that the decrease in ventilation at 5 min of hypoxia observed in the present study was associated with only a mild increase in P_{ACO_2} , suggesting that some decrease in metabolism

bringing the $P_a\text{CO}_2$ down may also have occurred. This combined effect of central depression and decrease in metabolism has been reported previously (15).

Developmentally, this sustained decrease in ventilation mimics, although not fully, the inhibition of breathing present in the fetus (7, 8). In the fetus, hypoxia abruptly terminates breathing. We suspect that the degree of immaturity and the low arterial PO_2 of infants ≤ 1500 g makes them prone to a predominant respiratory inhibition during hypoxia. Experimental evidence suggests that hypoxemia acts by an indirect suprapontine mechanism, because after electrolytic lesions in the upper lateral pons (16) or after midbrain transection at mid collicular level (17), acute hypoxemia stimulates breathing without evidence of depression. This mechanism present in the fetus could still be predominant in small and very immature infants and could be part of a complex self-protective, energy saving mechanism of adaptation to episodes of decrease oxygenation *in utero*. This mechanism would progressively mature with an enhanced ventilatory response to hypoxia as the fetus and the preterm infant grow.

Brady and Ceruti (1) noticed that the term infant tends to sustain hyperventilation with hypoxia after the 1st wk of life. Rigatto *et al.* (4) found that preterm infants are better able to sustain ventilation after 18 d of life. In the present study, although we did not study specifically the effect of postnatal age on the ventilatory response to hypoxia, small preterm infants were unable to sustain ventilation in the first 3 wk of life.

Our findings and those reported previously (3) suggest that the initial response to hypoxia, reflecting peripheral chemoreceptor activity, matures after 31 wk of gestational age together with the late response in quiet sleep. In our previous study, though, the infants enrolled were older than 3 wk of age and at a later postconceptional age, possibly explaining the sustained hyperventilation in quiet sleep. The late response in REM sleep seems to be more dependent on postnatal age, although further studies are needed to define when the small preterm infant begins sustaining ventilation more efficiently in response to hypoxia. We now know that hyperventilation is not well sustained in response to hypoxia even in adult subjects, although in the adult ventilation remains above control values during late hypoxia (18).

In summary, we studied the response to 15% O_2 in small preterm infants ≤ 1500 g. We found that these infants show only a sustained decrease in ventilation with low O_2 that was primarily related to a decrease in frequency in both sleep states. An initial increase in ventilation reflecting peripheral chemoreceptor activity was never observed. We speculate that the sustained decrease in ventilation at this gestational age reflects a more pronounced

inhibitory mechanism in response to hypoxia, approaching the situation in the fetus, in which low O_2 abolishes breathing. Maturation of the CNS parallels the development of a mature response to hypoxia in these infants, in which susceptibility to inhibition by hypoxia disappears.

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