Long-Lasting Effect of Prolonged Hypoxemia after Birth on the Immediate Ventilatory Response to Changes in Arterial Partial Pressure of Oxygen in Young Lambs¹

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ABSTRACT. The effect of prolonged hypoxemia (H) after birth on the evolution of the ventilatory response to changes in arterial partial pressure of O₂ was determined in unanesthetized, awake lambs. H was induced for 12 d after birth in seven lambs through exposure to 0.10 fraction of inspired O₂ (FiO₂). Five control (C) lambs were kept in 0.21 FiO₂. The ventilatory response (percent increase from baseline) to acute hypoxia was tested with 0.14 FiO₂ and 0.10 FiO₂. The tonic activity of the peripheral chemoreceptors was assessed by the transient pure oxygen inhalation test (Dejours' test). The occlusion technique was used to measure the baseline neuromuscular drive of breathing. A markedly decreased early ventilatory response to acute hypoxia persisted in the H lambs for at least 5 wk after termination of H compared with the C group. The second phase of the response was significantly lower only at 12 d (the end of H) and was thereafter comparable to that in the C lambs. The ventilatory response to hyperoxia was significantly lower in the H lambs only at the end of hypoxemia at 12 d and rapidly normalized after return to normoxia. H did not significantly affect resting neuromuscular drive. These results show that postnatal maturation of the ventilatory response to changes in arterial partial pressure of O₂ can be delayed by prolonged postnatal hypoxemia. The effect on the response to hyperoxia is transient, whereas the response to acute hypoxia is affected for an extended time. This study illustrates the importance of an adequate postnatal arterial partial pressure of O₂ for the development of the ventilatory response to acute hypoxia. (*Pediatr Res* 34: 821-828, 1993)

Abbreviations

C, control
CB, carotid body
H, prolonged hypoxemia (experimental group)
FiO₂, fraction of inspired oxygen
PaCO₂, arterial partial pressure of CO₂
PaO₂, arterial partial pressure of O₂
RR, respiratory rate
V_I, minute ventilation
V_T, tidal volume
P_{0.1}, airway pressure achieved at 0.1 s after the onset of inspiration

The immediate ventilatory response to hypoxia and hyperoxia is principally mediated by the peripheral chemoreceptors located in the CB (1-3). The magnitude of this response is proportional to the strength of O₂-sensitive chemoreceptors and is abolished by CB denervation (2-4). The role of CB in the ventilatory regulation *in utero*, at the time of relative hypoxemia and hypercapnia, still remains unresolved and controversial (5, 6). Recent studies have indicated that the peripheral chemoreceptors are responsive to changes in oxygen tension during fetal life (7-9), although the respiratory response to hypoxemia in the fetus is notably different from that after birth, because severe hypoxemia abolishes fetal breathing movements (10, 11). The CB response to hypoxic stimuli is overruled in the fetus by a central mechanism (8, 12) probably located at the upper lateral pons (13). It has recently been suggested that low PaO₂ stimulates a suprapontine center sensitive to hypoxemia that inhibits the medullary respiratory center rather than directly depresses fetal breathing at the medullary level (14). The mechanism of transition from a fetal to an adult response pattern has been a subject of much interest, and some evidence has been presented showing that the resetting is dependent, at least in part, on the increase in PaO₂ (8, 15). After birth, the chemoreceptors become silent, presumably because of the relative hyperoxia of the extrauterine milieu, and their tonic activity progressively resets to a higher oxygen level (7, 16, 17). This transition occurs slowly as the result of maturational processes occurring over the first 2 wk after birth (18-21).

Recently, there has been much interest in the study of peripheral chemoreceptor function in infancy because of a possible relationship between hypoxic exposure, CB malfunction, and the sudden infant death syndrome (22, 23). Inadequate respiratory control and failure to respond to acute hypoxemia may initiate a pattern of chronic hypoxemia. Furthermore, alternation in respiratory reflexes was postulated as a possible mechanism in sudden infant death syndrome (24). Contradictory results of the effect of prolonged hypoxemia on the chemoreceptor hypoxic sensitivity in adult cats have been presented. Barnard *et al.* (25) showed that 28 d of chronic hypoxemia in cats significantly increased the chemoreceptor response to acute hypoxia, whereas Tatsumi *et al.* (26) showed in cats that a decreased peripheral chemoreceptor responsiveness to hypoxemia is associated with an attenuated CNS translation of chemoreceptor input. A delayed maturation of the ventilatory response pattern to acute hypoxemia has been observed in newborn rats (27) and kittens (21) after exposure to chronic hypoxemia after birth.

The present study was designed to evaluate the effects of

Received January 19, 1993; accepted August 17, 1993.
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Supported by grants from the National Institutes of Health (HD22721 and HL14214).

¹ Presented in part at the annual meetings of the Society for Pediatric Research and the American Thoracic Society 1990.

prolonged hypoxemia after birth on the evolution of the ventilatory response to acute hypoxia and hyperoxia in term awake and unanesthetized lambs. It was of interest to determine whether prolonged hypoxemia merely delayed the maturational changes or had additional effects on respiratory control.

MATERIALS AND METHODS

Twelve full-term, vaginally delivered lambs of mixed breed were used in this study. Seven lambs, forming the H group, were continuously exposed to 0.10 FiO₂ in a 0.85-m³ normobaric chamber for 11 to 14 d (average 12 d) after birth except for 2–3 h after birth and for 15-min periods 5 times a day for feeding, catheter care, and cleaning of the chamber. The total gas flow introduced into the chamber was 21 L/min. The oxygen concentration of the mixture of air and nitrogen was monitored continuously with an oxygen analyzer (Ventronics model 5525, Hudson, Ventronics Division, Temecula, CA). A CO₂ absorber was placed in the chamber to avoid an appreciable increase in CO₂. The temperature was kept at 21–24°C. Duration of hypoxemia was based on the study of Hanson *et al.* (28), who established that, in lambs, the postnatal resetting of CB occurs over a 10-d period. Five lambs were used as a control (C) group and were kept in the chamber with 0.21 FiO₂ and total gas flow of 21 L/min for a comparable time period. Thereafter, all lambs were reared with the ewes in room air. Both groups were nursed *ad libitum*.

H lambs were studied at an age of 5 d, at the end of hypoxemia on d 11 to 14 (average age 12 d), 2 to 4 d after return to room air (average age 16 d), 6 to 7 d after return to room air (average age 19 d), and weekly thereafter until 5 wk after termination of hypoxemia. The C lambs were studied at comparable time points. The number of animals studied at each time point varied from 4 to 7 in the H group and from 2 to 5 in the C group. Two lambs died from the experimental manipulation. Some lambs could not be studied when they were older because they were too excitable.

The research protocol was approved by the Vanderbilt University Animal Care Committee.

Instrumentation. On the 3rd postnatal day and using aseptic technique and local anesthesia, the lambs were instrumented with placement of a low tracheostomy and catheters in the cranial tibial artery and lateral saphenous vein, respectively. During the surgical procedures, the H lambs were breathing 0.10 FiO₂ to ensure preservation of the effects of prolonged hypoxemia. To allow the lambs to breathe through the upper airway, except when being studied, a 2-inch segment of an endotracheal tube (Portex, Inc., Wilmington, MA) was inserted into the tracheostomy. Antibiotics (gentamicin 4 mg/kg and carbenicillin 100 mg/kg) were given daily from the time of the instrumentation until the last study. A postoperative 48-h recovery period was allowed before the first study was performed. At the time of each study, the tracheostomy prosthesis was removed and replaced by a downward directed tight-fitting endotracheal tube (Portex 4.5–8). A tracheostomy tube was used so that ventilation could be measured without leaks during the duration of the acute studies. A pneumotachograph (model 21070B, Hewlett-Packard, Waltham, MA) was interposed between the endotracheal tube and a Baby Bird respirator (Bird Corp., Palm Springs, CA). During the study, the lambs were breathing spontaneously. The inspiratory flow was 10 L/min and the gases were humidified at room temperature. To maintain functional residual capacity, a continuous positive airway pressure of 2–3 cm of water was applied to compensate for the effect of reduced upper airway tone due to endotracheal intubation.

Recordings. For ventilation measurements, the pneumotachograph flow signal was integrated to yield $\dot{V}_I$ or tidal volume V_T when needed. The pneumotachograph was connected to a differential pressure transducer (model 270, Hewlett-Packard) and a respiratory integrator (model 8815A, Hewlett-Packard). Statham

transducers (model P23ID, Gould-Statham, Oxnard, CA) were used for pressure measurements. All recordings were made with an eight-channel Hewlett-Packard 7758B recording system.

The lambs were monitored during the experimental period with continuous recordings of arterial pressure, heart rate, and serial blood gas analyses (Corning model 158 pH/Blood Gas Analyzer, Ciba Corning Diagnostics Corp., Medfield, MA).

Experimental protocol. The lambs were studied unanesthetized, lightly restrained in a sling (Alice King Chatham, Medical Arts, Los Angeles, CA) while they were awake and quiet (open eyes, regular breathing, and absence of body movement). The lambs were studied only if their rectal temperature was normal ($39 \pm 0.5^\circ\text{C}$) and if they had no sign of infection. The ambient temperature was maintained at 21–24°C. Before the onset of the study, the animals were allowed to become familiar with the equipment. At each determined age and within 2 h of breathing 0.21 FiO₂, all lambs were exposed to one set of measurements of respiratory output indices and hypoxic and hyperoxic challenges as described below. Each trial was begun when ventilation was judged to be stable, and measurements were always performed in the same order: respiratory output indices, 0.14 FiO₂ test, hyperoxia test, and 0.10 FiO₂ test. The lambs were allowed at least 20 min to recover between each test.

Respiratory drive and respiratory timing indices. The occlusion technique, which uses airway pressure at 0.1 s after the onset of an occluded inspiration as an index of central inspiratory drive, was used during resting conditions while the lambs were breathing 0.21 FiO₂ (29). To perform these measurements, the respirator was disconnected and a small polyethylene catheter (inner diameter = 0.71 mm) was inserted into the endotracheal tube for tracheal pressure recordings. The occlusions were performed at the end of expiration. $P_{0.1}$ and the maximal airway pressure value ($P_{\max}$) were calculated from the recordings using a recorder speed of 50 mm/s. A series of at least 10 occlusions were done, no more frequently than every 3rd breath. Occlusions that were not performed exactly at the end of expiration were excluded from analysis. $\dot{V}_I$ and V_T were obtained by electronic integration of the respiratory flow signal. The timing components, *i.e.* inspiratory time (T_i) and total cycle duration (T_{tot}), were measured using the flow signal from the unloaded breath immediately preceding the occluded inspiratory effort. The inspiratory “duty time” (T_i/T_{tot}) and mean inspiratory flow (V_T/T_i) were computed from the above variables. To detect changes in respiratory mechanics due to prolonged hypoxemia, effective impedance [$P_{0.1}/(V_T/T_i)$] and elastance ($P_{\max}/V_T$) were calculated. $P_{0.1}$ and T_i/T_{tot} are reported in absolute values and all volume data are normalized for body weight and expressed in mL per kg.

Hypoxia tests. The lambs were subjected to mild (0.14 FiO₂) and severe (0.10 FiO₂) hypoxic challenges. After a 5-min period of baseline ventilation when they were breathing 0.21 FiO₂, without disturbing the animals, FiO₂ was abruptly changed to 0.14 and 0.10, respectively, using a Bird High Flow Oxygen Blender (model 2900, Bird Corp.). The first minute thereafter was considered a mixing time in the circuits and was disregarded. $\dot{V}_I$ was continuously recorded during baseline and the following 15 min of hypoxia. The ventilatory response to hypoxia was expressed as percent change in $\dot{V}_I$ from baseline during each of the first 5 min and the 10th and the 15th min after onset of hypoxia. Arterial pH, PaO₂, and PaCO₂ were determined before and after 1, 5, 10, and 15 min of each hypoxia test.

Hyperoxia test. The transient pure oxygen inhalation test based on Dejours’ original description (30) and the modification according to Purves and Biscoe (16) was used to determine the tonic CB activity. After 3–5 min of quiet breathing, the lamb was switched to 1.0 FiO₂ breathing for 1 min. After a lag time of 10 s, corresponding to the lung-peripheral circulation time, $\dot{V}_I$ was calculated during the next 10 s and the response to hyperoxia was expressed as percent change from baseline.

Tests were accepted as valid if the pretest baseline was stable

and free of visible oscillations and not interrupted by sighs or coughs.

Statistics. Results are presented as mean values $\pm$ SEM. Paired and unpaired *t* tests were used for single-point comparison within one group or between groups, respectively. Values of *p* < 0.05 were considered significant.

To assess whether prolonged hypoxemia merely delayed CB resetting or had an additional effect over this delay, we performed an overall analysis for $\dot{V}_I$ (dependent variable), using multiple regression (the GLM procedure in PC-SAS version 6.04, SAS Institute, Inc., Cary, NC). This analysis compared results after adjusting for the duration of hypoxemia. For example, if hypoxemia merely delayed the CB resetting, then we would expect the results on d 16 for an animal with hypoxemia for 12 d, *i.e.* 4 d after the end of hypoxemia, to be similar to those of a 5-d-old control animal. Thus, if the effect of hypoxemia is only to delay CB resetting, then the effect of treatment (hypoxemia or control) in this analysis should not be statistically significant. In addition to treatment, other independent variables in the model were the level of O_2 in the hypoxia test (0.10 or 0.14 FiO_2) treating O_2 level as a categorical variable and age (for C lambs) or duration of life after initial hypoxemia (for H lambs). Duration was treated both as a continuous variable, implying that the change in an outcome variable was linear over time, and as a categorical variable using study number. We required that both analyses should give similar results before concluding that treatment did have an effect in addition to delaying CB reset to avoid dependence on the assumption of a linear effect over calendar time. In this model, we allowed for the fact that observations within a lamb are related. Because we were not interested in estimating results for specific lambs, we included lamb as a random effect within treatment in the regression model.

RESULTS

Change in body weight and behavior. There was no significant difference in body weight at birth (C lambs, 4.9 ± 0.6 kg; H lambs, 5.1 ± 0.4 kg). The H lambs gained significantly less during the 12-d prolonged hypoxemia period compared with the C lambs (1.3 ± 0.2 kg *versus* 2.8 ± 0.4 kg, *p* < 0.05). The weight gain in the H lambs continued to be significantly less than that in the C lambs through the 5th study at 26 d of age. During the 12-d hypoxemia period, the H lambs were less active compared with the C lambs.

Baseline $\dot{V}_I$. Recorded in 0.21 FiO_2 before the first hypoxia test, baseline $\dot{V}_I$ decreased with increasing age and was similar in C and H lambs except at the age of 26 d, when it was higher in the H lambs (Table 1).

Respiratory center output indices. $P_{0.1}$ was significantly lower in the H lambs compared with the C lambs only at 16 d of age

(Table 2). Mean inspiratory flow was not significantly different between the two groups. Inspiratory duty cycle decreased with age, especially in the H lambs, and was significantly diminished in these lambs at 40 d of age compared with the C lambs.

Calculation of effective impedance and elastance of the respiratory system was performed to detect changes in respiratory mechanics (Table 2). Inspiratory impedance did not differ between the two groups, except during the first study, when the H lambs revealed a higher value than the C lambs. Effective elastance was comparable in the two groups.

P_{aO_2} and P_{aCO_2} . The average arterial blood gases in the lambs breathing different inspired oxygen concentrations are presented in Table 3. Baseline P_{aO_2} in 0.21 FiO_2 was significantly lower in the H group at 12 and 33 d of age before the 0.10 FiO_2 test and at 16 d of age before the 0.14 FiO_2 test. The abrupt change from 0.21 to 0.10 FiO_2 or from 0.21 to 0.14 FiO_2 resulted in a fall in P_{aO_2} as shown in Table 3. After 1 min of hypoxemia, P_{aO_2} was not significantly different between groups except for a lower mean P_{aO_2} in the H group at 16 and 33 d during 0.10 FiO_2 and at 16 d during 0.14 FiO_2 . After 15 min of hypoxemia, P_{aO_2} was similar in the two groups, except at 16 d during 0.10 FiO_2 and at 12 and 16 d during 0.14 FiO_2 when it was lower in the H group.

There was no difference in P_{aCO_2} except for a lower baseline P_{aCO_2} before the 0.14 FiO_2 test in the H group at d 5 and a higher P_{aCO_2} in the H group after 15 min at d 16 (both 0.10 and 0.14 FiO_2) and d 19 (0.10 FiO_2) and after 1 min at d 47 (0.14 FiO_2) as presented in Table 4.

Ventilatory response to acute hypoxic challenges. Both C and H lambs responded to 0.10 FiO_2 and 0.14 FiO_2 with an immediate increase in ventilation followed by a decline toward baseline. The stronger stimulus triggered the stronger response in both groups. The first phase of the ventilatory response was described by the peak response. It was defined as the single minute during which the change in $\dot{V}_I$ was the greatest and usually occurred during the 1st to 3rd min of hypoxemia. The peak ventilatory response to 0.10 FiO_2 in the C group was lowest at 5 d of age and increased thereafter (Fig. 1). The response at 5 d was significantly lower compared with the response at 12, 16, 19, 33, and 40 d. In the H group, the lowest peak ventilatory response to 0.10 FiO_2 occurred at 12 d, at the end of prolonged hypoxemia. The responses at 5 d and at 16–19 d were of similar magnitude in this group and increased thereafter. Comparison between groups showed significantly lower ventilatory response to 0.10 FiO_2 at 12 d of age (last day of prolonged hypoxemia) and at 16, 19, 33, and 47 d of age, which corresponds to 4, 7, 21, and 35 d after completed prolonged hypoxemia. The peak ventilatory response to 0.14 FiO_2 was significantly less in the H group compared with the C group when the lambs were 12, 19, and 26 d old, which corresponds with the last day of prolonged hypoxemia and until 14 d after completed hypoxemia.

The peak response to 0.10 FiO_2 at 5 d of age was seen at 2.6 ± 0.8 min after the onset of acute hypoxemia for the C lambs and at 2.0 ± 0.4 min for the H lambs, but this difference was not statistically significant (Fig. 2). At 16 d of age, 4 d after prolonged hypoxemia, the peak response to 0.10 FiO_2 was significantly delayed in the H group compared with the C group (3.3 ± 0.4 *versus* 1.0 ± 0.0 min) and the difference was statistically significant (*p* < 0.05). There were no significant differences in the time for peak response during the last five studies. The time for the peak response to 0.14 FiO_2 was similar in both groups.

The ventilatory response to 0.10 and 0.14 FiO_2 for the two groups at peak response, 5, 10, and 15 min of hypoxemia performed at 5, 12, 16, and 47 d of age is presented in Figure 2. The response remained biphasic in both groups throughout the study period with a marked reduction in the response at 5, 10, and 15 min (second phase) compared with the peak response. The ventilatory response to 0.10 FiO_2 in the H group was considerably reduced during the first 5 min of the acute hypoxia

Table 1. $\dot{V}_I$ ($mL \cdot min^{-1} \cdot kg^{-1}$) at baseline (0.21 FiO_2) before hypoxia tests*

Age (d)	Time after prolonged hypoxemia (d)	Control	Prolonged hypoxia
5		512 $\pm$ 56	466 $\pm$ 19
12		453 $\pm$ 36	450 $\pm$ 31
16	4	430 $\pm$ 28	376 $\pm$ 31
19	7	381 $\pm$ 32	368 $\pm$ 36
26	14	249 $\pm$ 11	349 $\pm$ 9†
33	21	242 $\pm$ 27	296 $\pm$ 17
40	28	295 $\pm$ 20	266 $\pm$ 16
47	35	237 $\pm$ 1	268 $\pm$ 36

* Values are mean $\pm$ SEM.

† Statistically significant difference between the groups at *p* < 0.001.

Table 2. Respiratory data in 0.21 FiO₂*

	Group	Age				
		5 d	12 d	16 d	40 d	47 d
P _{0.1} (cm H ₂ O)	C	3.4 ± 0.2	5.0 ± 0.6	4.5 ± 0.4	4.0 ± 0.4	3.2 ± 0.1
	H	4.3 ± 0.4	4.3 ± 0.5	3.1 ± 0.3†	3.8 ± 0.2	4.4 ± 0.4
V _T /T _i (mL·kg ⁻¹ ·s ⁻¹)	C	24.5 ± 0.7	26.9 ± 2.5	25.2 ± 2.7	17.6 ± 0.9	16.3 ± 0.3
	H	24.7 ± 4.5	25.5 ± 2.0	21.1 ± 2.5	21.1 ± 1.7	18.7 ± 2.2
T _i /T _{tot} (s·s ⁻¹)	C	0.40 ± 0.03	0.38 ± 0.02	0.36 ± 0.03	0.36 ± 0.03	0.36 ± 0.01
	H	0.40 ± 0.03	0.38 ± 0.02	0.38 ± 0.02	0.27 ± 0.02†	0.30 ± 0.03
P _{0.1} /(V _T /T _i) (cm H ₂ O·mL ⁻¹ ·kg·s)	C	0.14 ± 0.01	0.19 ± 0.02	0.19 ± 0.02	0.23 ± 0.03	0.20 ± 0.01
	H	0.18 ± 0.01†	0.17 ± 0.01	0.15 ± 0.01	0.18 ± 0.01	0.25 ± 0.02
P _{max} /V _T (cm H ₂ O/mL)	C	1.4 ± 0.1	1.7 ± 0.1	1.8 ± 0.2	2.4 ± 0.2	2.3 ± 0.3
	H	1.8 ± 0.1	1.9 ± 0.1	1.7 ± 0.1	2.0 ± 0.2	2.5 ± 0.2

* P_{0.1}, occlusion pressure; V_T/T_i, mean inspiratory flow; T_i/T_{tot} inspiratory duty time; P_{0.1}/(V_T/T_i), effective impedance; P_{max}/V_T effective elastance. Values are mean ± SEM.

† Different from control at $p < 0.05$.

Table 3. Effect of acute hypoxia on Pao₂ (kPa)*

Age (d)	Time after H (d)	Group	n	Response to 0.10 FiO ₂			Response to 0.14 FiO ₂		
				0 min	1 min	15 min	0 min	1 min	15 min
5		C	5	13.2 ± 0.6	5.0 ± 0.2	3.9 ± 0.2	12.7 ± 0.5	6.6 ± 0.3	5.7 ± 0.5
		H	5	11.4 ± 0.8	4.5 ± 0.3	3.2 ± 0.1	11.4 ± 0.4	6.5 ± 0.4	5.1 ± 0.1
12		C	5	13.6 ± 0.6	5.1 ± 0.1	3.6 ± 0.1	11.9 ± 0.5	7.7 ± 0.6	6.2 ± 0.5
		H	7	11.4 ± 0.4†	4.8 ± 0.2	3.1 ± 0.2	11.1 ± 0.4	6.2 ± 0.4	4.7 ± 0.4†
16	4	C	4	13.0 ± 0.4	5.3 ± 0.2	4.2 ± 0.1	12.7 ± 0.3	7.0 ± 0.3	6.0 ± 0.3
		H	6	11.5 ± 0.5	4.4 ± 0.1†	3.1 ± 0.1†	10.9 ± 0.5†	5.9 ± 0.2†	4.7 ± 0.2†
19	7	C	4	12.7 ± 0.1	5.1 ± 0.1	4.0 ± 0.3	12.3 ± 0.5	7.2 ± 0.2	5.7 ± 0.3
		H	6	11.9 ± 0.3	5.1 ± 0.1	3.5 ± 0.1	11.5 ± 0.4	6.8 ± 0.1	5.4 ± 0.1
26	14	C	4	12.4 ± 0.6	5.4 ± 0.2	4.1 ± 0.3	12.7 ± 0.5	7.3 ± 0.2	5.9 ± 0.6
		H	4	12.6 ± 0.2	4.9 ± 0.2	3.5 ± 0.1	11.9 ± 0.1	6.7 ± 0.3	5.3 ± 0.4
33	21	C	4	13.0 ± 0.3	5.6 ± 0.2	4.0 ± 0.2	12.0 ± 0.3	6.8 ± 0.2	5.4 ± 0.3
		H	5	11.4 ± 0.5†	4.5 ± 0.2†	3.5 ± 0.2	11.6 ± 0.3	6.6 ± 0.3	5.2 ± 0.3
40	28	C	3	12.8 ± 0.7	5.3 ± 0.2	4.3 ± 0.5	11.9 ± 0.2	7.0 ± 0.2	5.8 ± 0.4
		H	4	11.5 ± 0.2	5.3 ± 0.3	3.9 ± 0.2	11.5 ± 0.3	6.7 ± 0.2	5.4 ± 0.3
47	35	C	2	12.2 ± 0.1	5.3 ± 0.0	3.8 ± 0.3	12.3 ± 0.3	7.2 ± 0.2	5.7 ± 0.5
		H	5	11.9 ± 0.6	5.2 ± 0.2	3.9 ± 0.2	11.9 ± 0.4	7.3 ± 0.3	5.7 ± 0.3

* Values are mean ± SEM.

† Different from control at $p < 0.05$.

Table 4. Effect of acute hypoxia on Paco₂ (kPa)*

Age (d)	Time after H (d)	Group	Response to 0.10 FiO ₂			Response to 0.14 FiO ₂		
			0 min	1 min	15 min	0 min	1 min	15 min
5		C	4.9 ± 0.2	4.0 ± 0.2	4.1 ± 0.1	5.2 ± 0.1	4.4 ± 0.2	4.5 ± 0.1
		H	4.5 ± 0.2	3.9 ± 0.2	4.2 ± 0.2	4.5 ± 0.3†	4.2 ± 0.2	4.4 ± 0.1
12		C	5.0 ± 0.3	3.7 ± 0.2	3.8 ± 0.1	5.0 ± 0.2	4.5 ± 0.1	4.7 ± 0.2
		H	4.8 ± 0.2	4.2 ± 0.1	4.0 ± 0.1	4.7 ± 0.2	4.3 ± 0.1	4.5 ± 0.1
16	4	C	5.0 ± 0.1	3.9 ± 0.0	3.6 ± 0.1	5.5 ± 0.4	4.8 ± 0.2	4.5 ± 0.2
		H	5.6 ± 0.3	4.6 ± 0.3	4.4 ± 0.2†	5.6 ± 0.3	5.1 ± 0.2	5.2 ± 0.2†
19	7	C	5.0 ± 0.3	3.8 ± 0.2	3.6 ± 0.1	5.1 ± 0.3	4.7 ± 0.2	4.7 ± 0.3
		H	5.0 ± 0.1	3.9 ± 0.2	4.2 ± 0.1†	5.4 ± 0.1	4.9 ± 0.1	4.9 ± 0.1
26	14	C	5.2 ± 0.3	3.9 ± 0.2	3.7 ± 0.1	5.2 ± 0.2	4.6 ± 0.2	4.4 ± 0.1
		H	4.6 ± 0.3	3.8 ± 0.2	3.8 ± 0.1	5.0 ± 0.2	4.4 ± 0.2	4.4 ± 0.1
33	21	C	4.8 ± 0.3	3.7 ± 0.1	3.8 ± 0.1	5.2 ± 0.1	4.3 ± 0.2	4.3 ± 0.3
		H	4.8 ± 0.2	3.8 ± 0.1	3.7 ± 0.1	5.0 ± 0.2	4.7 ± 0.1	4.3 ± 0.2
40	28	C	5.1 ± 0.2	3.8 ± 0.1	3.6 ± 0.2	5.1 ± 0.3	4.5 ± 0.1	4.5 ± 0.1
		H	4.8 ± 0.3	4.0 ± 0.1	3.8 ± 0.2	4.9 ± 0.3	4.7 ± 0.1	4.7 ± 0.1
47	35	C	4.9 ± 0.1	3.5 ± 0.1	3.7 ± 0.1	5.1 ± 0.0	4.1 ± 0.0	4.3 ± 0.1
		H	4.8 ± 0.1	3.9 ± 0.2	3.8 ± 0.1	5.3 ± 0.1	4.6 ± 0.1†	4.7 ± 0.1

* Values are mean ± SEM.

† Different from control at $p < 0.05$.

Fig. 1. Peak ventilatory response to hypoxia after a change in FiO_2 from 0.21 to 0.14 or from 0.21 to 0.10 expressed as percent increase in $\dot{V}_I$ in seven lambs that experienced prolonged hypoxemia (0.10 FiO_2) during the first 12 postnatal days and five C lambs (mean $\pm$ SEM). *, Statistically significant difference between the groups at $p < 0.05$.

test at 12 d of age (the last day of prolonged hypoxemia). The ventilatory response at 10 and 15 min was not significantly different between the two groups during any of the study sessions. The ventilatory response never dropped below the baseline level in either group.

A similar, although less pronounced, response pattern was seen when 0.14 FiO_2 was used as an acute hypoxia test (Fig. 2).

Changes in $\dot{V}_T$ and RR during acute hypoxemia. To further analyze the ventilatory response to acute hypoxemia, the changes in $\dot{V}_T$ and RR were calculated during the 0.10 FiO_2 test at 12 d, when the effect of prolonged hypoxemia was most pronounced. A significant decrease from the peak $\dot{V}_T$ value was observed at 10 and 15 min in the C lambs, when the average $\dot{V}_T$ was below baseline (Fig. 3). There was no significant change in $\dot{V}_T$ from the peak value in the H lambs. There was no statistically significant difference in $\dot{V}_T$ response between the groups. A significant decrease from the peak RR value was observed at 5, 10, and 15

min in the C lambs, but no significant change in RR from the peak value was observed in the H lambs. The RR response was significantly lower in the H lambs compared with the C lambs at peak time and at 5 min.

Timed-shifted result analysis. A multiple regression model was used to assess whether prolonged hypoxemia merely delayed CB resetting with a time corresponding to the duration of hypoxemia or whether it had an additional effect on this delay.

There was a highly significant difference in baseline $\dot{V}_I$ ($p < 0.05$), percent change in ventilation at 1 min ($p < 0.001$), and percent change at peak ventilation ($p < 0.01$). There was no consistent evidence for differences between groups in percent change in ventilation at 5, 10, or 15 min.

Ventilatory response to hyperoxia. Ventilatory response to an abrupt change from 0.21 FiO_2 to 1.0 FiO_2 was characterized by an immediate fall in ventilation in all animals (Fig. 4). The response to hyperoxia increased gradually during the first 19 d after birth in the C group. In contrast, the ventilatory response to hyperoxia remained essentially unchanged between 5 and 12 d of age in the H group. The response to hyperoxia was significantly lower in the H group compared with the C group on the last day of hypoxemia, when the lambs were 12 d old. The response to hyperoxia was similar in the two groups at 16 d of age (4 d after completed hypoxemia) and thereafter.

DISCUSSION

This study shows that the ventilatory response to acute hypoxia can be markedly attenuated if newborn lambs are exposed to a hypoxic environment for a prolonged time after birth. This effect was extended and did not merely represent an offset corresponding to the time spent in hypoxia. In contrast, the ventilatory response to hyperoxia was only attenuated at the end of the hypoxemia period and was similar in the two groups thereafter.

Fig. 2. Ventilatory response to a change in FiO_2 from 0.21 to 0.14 and from 0.21 to 0.10 expressed as percent increase in $\dot{V}_I$ at the time of peak response, 5, 10, and 15 min of hypoxemia in seven lambs that experienced prolonged hypoxemia (0.10 FiO_2) during the first 12 postnatal days and five C lambs. Studies shown were performed at 5 d of age; 12 d of age, last day of prolonged hypoxemia; 16 d of age, 4 d after completed prolonged hypoxemia; and 47 d of age, 35 d after completed prolonged hypoxemia (mean $\pm$ SEM). *, Statistically significant differences between the groups at $p < 0.05$. +, Statistically significant difference compared with peak value within the group at $p < 0.05$.

Fig. 3. V_T and RR response to a change in FiO_2 from 0.21 to 0.10 expressed as percent change from baseline in seven lambs that experienced prolonged hypoxemia (0.10 FiO_2) during the first 12 postnatal days and five C lambs (mean $\pm$ SEM). *, Statistically significant difference between the groups at $p < 0.05$. +, Statistically significant difference compared with peak value within the group at $p < 0.05$.

Fig. 4. Ventilatory response to hyperoxia expressed as percent decrease in $\dot{V}_I$ after a change from 0.21 to 1.0 FiO_2 in seven lambs that experienced prolonged hypoxemia (0.10 FiO_2) during the first 12 postnatal days and five C lambs (mean $\pm$ SEM). *, Statistically significant difference between the groups at $p < 0.05$.

The peak ventilatory response to acute hypoxia was both delayed and depressed after prolonged hypoxemia. The magnitude of the immediate ventilatory response to acute hypoxia is considered to be a reflection of the chemoreceptor strength (3, 31). The response of the CB receptors to acute hypoxemia undergoes a period of resetting during the first 1–2 postnatal weeks (2, 4, 17, 20). In this study, there was a marked increase between d 5 and d 12 in the peak ventilatory response to 0.10 FiO_2 , whereas the response to 0.14 FiO_2 was already well developed at d 5. The difference in developmental change in the response to mild or severe acute hypoxia may indicate that the

arterial chemoreceptors undergo a progressive resetting to different levels of P_{aO_2} .

A delayed development of a mature ventilatory response beyond the age when normoxic animals have developed an adult response has previously been shown after prolonged hypoxemia in newborn rats (27) and kittens (21). Eden and Hanson (27) proposed that ventilation during acute hypoxemia in the neonate can be discussed in terms of two opposing components: 1) the peripheral arterial chemoreceptors that stimulate ventilation (3, 31) and 2) a CNS component that inhibits ventilation, e.g. persistence of the suprapontine mechanism, which suppresses ventilation during hypoxemia in the fetus (12, 32). Based on whole carotid sinus nerve recordings, they concluded that the suppressed ventilatory response to acute hypoxia in the chronically hypoxic rats was caused by a shift in the balance to the central inhibition. However, this group later demonstrated that the single- or few-fiber carotid chemoreceptor response to acute hypoxemia was markedly attenuated in chronically hypoxic kittens kept hypoxic for 2 wk compared with age-matched controls (33). Further support for an abnormal function or delayed maturation of the peripheral chemoreceptor sensitivity to acute hypoxemia after chronic hypoxemia comes from studies by Hanson *et al.* (21), who used a two-breath alteration of FiO_2 method in chronically hypoxic kittens. In adult cats, however, prolonged hypoxemia decreases the peripheral chemoreceptor responsiveness to a decrease in P_{aO_2} and also attenuates the CNS translation of chemoreceptor input (26).

As previously shown by Bureau *et al.* (31), the ventilatory response to acute hypoxia consisted of an increase in both V_T and RR. In the control lambs, the increase in RR was larger and more sustained compared with the increase in V_T . After 12 d of prolonged hypoxemia, the increase in RR in response to 0.10 FiO_2 was significantly attenuated during the first phase of the response compared with that in the C lambs. However, the increases in V_T and RR in the H lambs were more sustained during the test compared with those in the C lambs.

Newborn infants and animals characteristically have a biphasic ventilatory response to acute hypoxia (31) that is characterized by transient hyperventilation followed by ventilatory depression. Such a biphasic response is related to postnatal maturity and is replaced by a more sustained ventilatory response in adults (31). The reason for the roll-off from the peak value has not been definitely delineated but is generally believed to be caused by a central mechanism (34–36) rather than a failure of the peripheral chemoreceptors to sustain afferent input (37).

In our study, the roll-off from the peak (5 to 15 min) was more pronounced during stimulation with 0.10 FiO_2 than with 0.14 FiO_2 . There was a significant difference between the groups only at the age of 12 d, at the end of prolonged hypoxemia. At that time, the reduced second phase was probably mostly related to low afferent input from the peripheral chemoreceptors rather than from a central influence, inasmuch as both the peak response to hypoxemia and the response to hyperoxemia were blunted. Already 4 d later, the magnitude of the second phase was similar in the two groups, indicating that prolonged hypoxemia mostly influences the first phase of the ventilatory response, which is mainly considered to be a reflection of peripheral chemoreceptor function.

We did not find marked changes in the neuromuscular drive during baseline conditions, which would indicate that the reduced response to acute hypoxia is most likely dependent on altered peripheral chemoreceptor function and/or the central mechanism that integrates their afferent signal rather than a generalized depressive effect on the respiratory center. Changes in metabolism induced by prolonged hypoxemia that could be reflected in diminished activity of the neuronal networks responsible for integrated functions such as breathing should also be considered. However, we did not find a significant difference between the groups in baseline $\dot{V}_I$ or P_{aCO_2} . Baseline oxygen consumption was only significantly different at 5 d of age, when

it was lower in the H group, yet the ventilatory response to acute hypoxia was not different (data not shown).

Respiratory output during the acute hypoxia tests was expressed as $\dot{V}_I$, which may be affected by factors other than respiratory drive, e.g. changes in respiratory mechanics. The H lambs showed decreased gain of body weight during the prolonged hypoxemia period. Lung growth and muscle development may have been affected as well, which could have modified the linkage between neural and mechanical output. It has been suggested that an increase in effective impedance and elastance reflects a decrease in dynamic compliance and/or an increase in airway resistance (38–40). Although we can not exclude the possibility that changes in pulmonary mechanics were present in the H lambs, absence of significant differences in baseline effective impedance and elastance during the studies performed at an age of 12 to 47 d may indicate that marked changes in pulmonary mechanics were not a major cause of the attenuated ventilatory response to acute hypoxia.

The upper airway was bypassed in these studies, because a tracheostomy tube was used to monitor ventilation. In tracheostomized lambs during hypoxia, Johnson *et al.* (41) have shown that respiratory reflexes may influence patency of the larynx and may alter the pattern of breathing. However, they also showed that applying positive airway pressure—as performed in this study—restored a normal response to acute hypoxia.

The differences found in the ventilatory response to acute hypoxia cannot be explained by differences in P_{aCO_2} , because in general P_{aCO_2} was not significantly different between the groups. While breathing room air, lambs exposed to prolonged hypoxemia had significantly lower P_{aO_2} at baseline compared with controls, which probably was not related to a decreased function of the peripheral chemoreceptors, inasmuch as ventilation was unaffected, but which might have been a result of ventilation-perfusion mismatching secondary to marked pulmonary hypertension (data not shown).

Our study and that of Mortola *et al.* (42) showed that prolonged hypoxemia after birth has a long-lasting effect on the response to acute hypoxemia, but in contrast to them we did not observe persistent hyperventilation after return to room air. The probable cause of desensitization is that the low level of P_{aO_2} from birth alters the development of the peripheral chemoreceptors and/or the neural centers responding to their impulses. There may be a critical maturational time after birth when the sensitivity of the peripheral chemoreceptors is determined and when hypoxemia permanently alters CB sensitivity. The study of Sorensen and Severinghaus (43) showed that the weak response to acute hypoxia in natives of high altitude remains even if they move to sea level. These authors also reported that in children who have been hypoxemic for many years, as a result of tetralogy of Fallot, response to acute hypoxia is blunted even after surgical correction (44).

Arterial chemoreceptor tonic input during normoxic breathing can be evaluated by the short hyperoxia test (29), and it has been widely used to assess peripheral chemoreceptor function in the newborn period (17, 45). The basic principal is that the decrease in ventilation, evoked by a withdrawal of the stimulus from the arterial chemoreceptors, can be regarded as an index of the tonic influence of the receptors. The immediate depression of ventilation during hyperoxemia is, therefore proportional to the chemoreceptor influence before the oxygen inhalation. In agreement with Bureau *et al.* (17), we found a significant increase with age in the response to pure oxygen in the control lambs that corresponded to an increasing response to acute hypoxia.

The response to hyperoxia in the H lambs remained small during the 12 d of prolonged hypoxemia but had already normalized within 4 d of normoxic breathing, which is in contrast to the prolonged depression of the immediate ventilatory response to acute hypoxia. This divergence of effects further raises the possibility that central inhibitory effects modified the response to acute hypoxia. The other possible explanation of our

results could be that different mechanisms are examined when oxygen sensitivity of the peripheral chemoreceptors is tested with acute hypoxia or acute hyperoxia. The hyperoxia test examines the tonic drive from the receptor, whereas the acute hypoxemia test determines the gain of the peripheral chemoreceptors.

Studies by Hertzberg *et al.* (45) have shown that the emergence of chemoreceptor sensitivity to hyperoxia in newborn rats was preceded by a prompt drop in dopamine turnover rate, suggesting that a high dopamine release keeps the chemoreceptor sensitivity low in the immediate newborn period. This concept was supported by the finding that rats born and reared in hypoxia showed an attenuated chemoreflex response that coincided with a maintained turnover of CB dopamine (46). During the postnatal period, the CB may undergo a gradual release from a dopamine-mediated inhibition governed by the prevailing arterial oxygenation, which modulates the sensitivity of the arterial chemoreceptor. This process may be inhibited by prolonged hypoxemia.

In conclusion, this study has shown that postnatal maturation of the ventilatory response to acute hypoxia or hyperoxia can be delayed by prolonged postnatal hypoxemia. As indicated by the response to hyperoxia, the tonic activity of the peripheral chemoreceptors is rapidly normalized after return to normoxia. The early ventilatory response to acute hypoxia is affected for an extended time, whereas the second phase is comparable to that in controls shortly after discontinued prolonged hypoxemia. These results indicate that prolonged hypoxemia in newborn lambs causes a delay in the postnatal reset of the sensitivity of the peripheral chemoreceptors and/or alters the development of the neural centers responding to their impulses. This study illustrates the importance of an adequate postnatal P_{aO_2} for the development of the ventilatory response to acute hypoxia. We speculate that a reduced ability to generate a forceful hyperventilatory response to acute hypoxia may be clinically relevant in infants who have experienced prolonged or intermittent hypoxemia after birth.

Acknowledgments. The authors thank Dr. Mildred T. Stahlman for her support and advice; Stanley Poole, MS, Patricia Minton, RN, and Rao Gaddipati, MS, for their skilled technical assistance; and Donna Staed for typing the manuscript.

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