HYPOXIC VENTILATORY RESPONSE IN THE NEWBORN MONKEY

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SUMMARY

The hypoxic ventilatory response was determined in twelve unanesthetized newborn monkeys, *Macaca nemestrina*. Measurements of blood gases and ventilation were made during normoxia and hypoxia at the postnatal ages of 2, 7, and 21 days. Data were collected during quiet sleep. The infant monkey demonstrated a definite but transient hyperventilatory response following exposure to a FiO_2 of 0.12 or 0.14 on the second day of life. Baseline ventilation increased 15% ($\text{FiO}_2=0.14$) and 28% ($\text{FiO}_2=0.12$) after 1 minute of hypoxia; $p<0.05$ in both instances. Return to baseline ventilation occurred between 3 and 5 minutes after hypoxic stimulus onset. This biphasic response to hypoxia converted to an adult-like, sustained hyperventilation during the ensuing three weeks of postnatal maturation. Episodes of periodic breathing and/or apnea were noted to occur during the induced hypoxemia. These data demonstrate that the infant subhuman primate has a ventilatory response to hypoxia that is similar to that of the human infant and is an excellent model for the study of the maturation of the respiratory control system.

SPECULATION

The mechanisms involved in the unique neonatal response to hypoxia have not been elucidated. In light of current evidence, direct suppression of respiratory center output by an inhibitor seems the most likely possibility. However, adverse alterations in pulmonary mechanics brought on by the hypoxia itself or fatigue of the carotid body remain viable alternatives.

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The human newborn responds to a reduced FiO_2 by a rapid increase in minute ventilation ($\dot{V}_E$). This response is not sustained and with continued low FiO_2 breathing the $\dot{V}_E$ returns to baseline or below prestimulus levels (7, 27, 38, 42). The ventilatory response of the more mature human differs from the newborn in that a sustained increase of $\dot{V}_E$ occurs during low FiO_2 breathing (36, 42). Mechanisms involved in the unique neonatal response are not known. It is reportedly affected by cold stress (the initial $\dot{V}_E$ increase is abolished), by maturation ($\dot{V}_E$ becomes adult-like during the first month of postnatal life), and by sleep state (7, 8, 38, 40).

Studies of the hypoxic ventilatory response of adult subprimate species provide data similar to that from adult humans (13), whereas there is confusion in the literature as to the ventilatory pattern of the hypoxic response in newborn subprimate animals. Some reports describe a pattern similar to that of the human neonate (15, 44). Others suggest that the response is sustained like that of the adult (1, 11, 35). The reasons for these contradictory results are unclear. Possible explanations include species differences, nonuniform anesthetic effects, and sleep state differences during data collection.

The primary goal of the current study was to develop a primate animal model for the study of hypoxic ventilatory control in the newborn. It was hypothesized that the unanesthetized newborn *Macaca nemestrina* would manifest a biphasic response to a reduction in the FiO_2 in the immediate newborn period during non rapid eye movement (nonREM) sleep and that this response would gradually convert to the more sustained type with advancing maturation.

METHODS AND MATERIALS

The hypoxic ventilatory response of 12 infant *Macaca nemestrina* was studied during the first three weeks of life. Animals were delivered by Cesarean section at 0.9 of term (150 $\pm$ 2 days gestation), $n=8$, and term (166 $\pm$ 2 days gestation), $n=4$. They were healthy and free from lung disease as determined by clinical criteria, chest roentgenogram, and arterial blood gas analysis.

Animals were unanesthetized and restrained in the supine position in an incubator (Air Shields Isolette) at environmental temperatures within the neutral thermal range for infant monkeys (14). The mean core temperature for study animals was 37.5 ± 0.5 degrees C.

Tidal volume (V_T) was measured using nasal prongs and a hot wire anemometer (19). The instrument was calibrated over the observed range of tidal volume of $1-10 \pm 0.1$ cc before each experimental trial.

Arterial blood gases were sampled from a catheter placed in the umbilical (day 2 studies) or femoral (day 7-8 or 19-21 studies) artery under local anesthesia.

Sleep state was determined from simultaneous recording of electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), heart rate, and respiratory pattern on a Beckman Accutrace. The EEG was recorded from FP2-CZ, CZ-A2 and FP2-A2 (time constant 0.3 sec.) using Beckman disc electrodes. EOG was recorded from disc electrodes placed diagonally over the outer canthus of each eye. EMG was recorded from bipolar electrodes placed over posterior neck muscles. Sleep state was scored according to standard criteria for primate infants (2, 22, 32).

Animals were studied at postnatal ages 2, 7 to 8, and 19 to 21 days. The experimental protocol included waiting for the establishment of a nonREM state, and then switching the inspired gas from 21% oxygen/79% nitrogen to 14 or 12 percent oxygen in nitrogen. The study gases were maintained for 20 minutes or until arousal or state change occurred. Arterial blood gas samples were drawn at 1, 2, 3-6, 7-10, and 17 to 20 minutes during hypoxic gas breathing. Tidal volume and ventilatory frequency were determined over a 30 second interval while blood gas samples were being withdrawn. Records in which erratic ventilatory patterns or apnea lasting greater than 15 seconds occurred were not accepted for analysis.

Forty-four successful individual experimental 20 minute trials were done in an FiO_2 of 0.14 and 27 successful individual experimental 20 minute trials were done in an FiO_2 of 0.12. The incidence of arousal increased with postnatal maturation, and occurred too frequently to obtain sufficient data for analysis at the 17-20 minute time in the 7-8 day 0.12 FiO_2 exposures, at the 17-20 minute time in the 19-21 day 0.14 FiO_2 exposures, and at all study points in the 19-21 day 0.12 FiO_2 exposures. Data collected during individual experimental trials at each postnatal age were averaged to obtain a single data point for each study animal at the specific time intervals noted above during hypoxic gas breathing. The Student's t-test was utilized for statistical comparisons and regression analysis was employed to determine potential relationships between independent and dependent variables.

RESULTS

Minute ventilation ($\dot{V}_E$), Tidal Volume (V_T), frequency (f), arterial blood gases and ventilatory response to a reduced FiO_2 were not significantly different when prematurely delivered animals were compared to term animals at comparable postdelivery dates. Therefore, data from both premature and term animals have been pooled for presentation. (Tables I, II, and III).

Effect of Hypoxic Gas Breathing on Arterial Oxygen Tension, Ventilation and Arterial Carbon Dioxide Tension.

The major decrement in arterial oxygen tension occurred during the first minute of low FiO_2 breathing in all postnatal age groups studied. (Figure 1) The baseline PaO_2 increased and absolute magnitude of arterial hypoxemia during low FiO_2 breathing decreased with postnatal maturation (Figure 1, Tables I, II, and III).

Ventilation increased rapidly following the onset of low FiO_2 breathing, in all instances attaining a 1 minute level that was significantly elevated over baseline. The duration of time that $\dot{V}_E$ remained significantly elevated above baseline increased with postnatal maturation (Figure 2, Tables I, II, and III). Group mean PaCO_2 values varied inversely with changes in $\dot{V}_E$ (Fig. 3, Tables I, II, and III).

Effect of Hypoxic Gas Breathing on Respiratory Frequency, Tidal Volume and/or Pattern.

The ventilatory response that occurred with low FiO_2 breathing was mediated by changes in both respiratory frequency and tidal volume (Tables I, II, and III). Both periodic breathing of a Cheyne Stokes nature and apneic episodes (greater than 5 seconds in duration) were noted to occur at times during hypoxic gas breathing. (See Figure 4 for an example of this phenomenon.) The frequency with which these patterns occurred is quantitated in Table IV. There was no relationship between the tendency to have periodic breathing and the tendency to have apnea. Periodic breathing occurred exclusively in 2 animals, apnea occurred exclusively in 3 animals, both periodic breathing and apnea occurred in 4 animals and neither occurred in 3 animals. There was also no obvious relationship between either the degree of hypoxemia or hypocapnia and the occurrence of these episodes.

DISCUSSION

The data from this investigation demonstrate that in the subhuman primate *M. nemestrina* during nonREM sleep: (1) there is a definite but transient ventilatory response to a hypoxic stimulus in the immediate neonatal period; (2) this response develops a more sustained nature with postnatal maturation; and (3) hypoxia stimulates in the infant monkey episodes of apnea and/or periodic breathing some of the time. The data confirms previous studies that describe the effect of postnatal maturation on the pattern of hypoxic ventilatory response and the effect of hypoxia on the predisposition for the occurrence of apnea and/or periodic breathing (37, 38). They contradict data, reported in abstract form, that suggests the biphasic hypoxic ventilatory response of the neonate is absent in nonREM sleep (40).

Numerous recent studies suggest that the output of the respiratory center represents a summation of both facilitative and inhibitory factors (9, 17, 31, 40, 41, 48). Structures reported as having a positive effect on output include the carotid body (31, 41) and diencephalon (48). Negative or inhibitory effects are said to be exerted by the cerebral cortex (48). During low FiO_2 breathing there is a direct depressant effect of hypoxia on respiratory center neuronal function (41) and, during conditions of increased cerebral blood flow, a depressant effect may be exerted by alkalization of CSF pH secondary to CO_2 washout (31, 49). It is important to note that in mature study subjects, whether human or experimental animal, the usual net effect of the facilitatory and inhibitory factors is positive, and a sustained increase in ventilation occurs during a hypoxic stimulus. Depression of ventilation occurs only with severe hypoxemia (9, 33). In contrast, our immature subjects when studied shortly after birth all demonstrated a rather uniform pattern of response that included a secondary ventilatory depression in the face of modest hypoxic stimuli. A diminution in this depressant effect was noted to occur in the studies done on older animals. Further speculative support of either diminished suppression or increased facilitation of ventilation with maturation may be noted by plotting interactions between $\dot{V}_E/\text{Kg}$ and arterial PaO_2 at the various postnatal ages. Figure 5 is a simplified plot of group mean arterial PaO_2 values versus simultaneous $\dot{V}_E$ during hypoxic study periods. Note that for a given level of arterial oxygen tension, whether during room air or hypoxic gas breathing, $\dot{V}_E/\text{Kg}$ increases with postnatal maturation. It therefore seems reasonable to speculate that a maturational process might be responsible for the more robust response in the older animals.

Potential mechanisms that might be involved in this phenomenon include alterations in: (1) lung, chest wall, or diaphragmatic response to efferent stimuli; (2) carotid body function; or (3) the respiratory center in the brain stem.

Attempts to limit the role of inefficient effector organ (chest wall, intercostal muscles, diaphragm and lung) function from playing a role in the ventilatory response patterns observed in the current study included: delay of initial studies for 24 hours to minimize effects of alterations in pulmonary mechanics that are known to occur in the first hours following birth (23), and collection of data only during nonREM sleep - eliminating potential variability in chest wall stability (24) and inspiratory limiting reflexes (25). Previous studies conducted in our laboratory have demonstrated that there is a two fold increase in dynamic lung compliance between postnatal day 2 and 21 in the infant *M. nemestrina*, and also that the potential for a sustained response to a ventilatory stimulus is present by the second day of postnatal life (22). Thus, the maturational increase in the magnitude of hypoxic ventilatory response might be explained by an improvement in mechanical characteristics of the lung. It is not possible, however, to explain the secondary depression in ventilation that occurred in the younger age group as a function of the same

process. Several investigators (20, 34, 43, 46, 47) have demonstrated that increased airway resistance occurs during hypoxic gas breathing in both adult human and animal study subjects. It is possible that a similar phenomenon occurred in our infant animals at all of the study ages. If load compensatory mechanisms were ineffective or lacking in the younger age group, then a depression of $\dot{V}_E$ might be expected to occur as the increase in pulmonary resistance occurred in response to the hypoxic stimulus itself.

Animal studies have established that the immediate hypoxic response in the newborn is mediated by the carotid body (5, 6, 35, 44). However, the ability of the carotid body of the newborn animal to mount a sustained neural output in response to a hypoxic challenge has not been well established. Moreover, certain deficits in carotid body function - notably a delayed response time to induced hypoxia - have been observed to be present in the immediate newborn period and not 2 weeks later (5). Thus, a lack of facilitative input from the carotid body to the brain stem in early postnatal life either because of anatomic or biochemical immaturity is another possible explanation for the unique neonatal hypoxic ventilatory response.

Studies involving human infants have demonstrated that in contrast to adults (30) CO_2 responsiveness is depressed in the early neonatal period by low FIO_2 breathing (12, 39). These studies, as well as more direct evaluation of the effects of hypoxia on brain stem respiratory output in adult experimental animals (9, 41) suggest that primary failure of the respiratory center may play a role in the neonatal hypoxic ventilatory response. Potential mechanisms that might be involved include: one, brain stem interstitial fluid alkalosis, secondary to increased cerebral blood flow and CO_2 washout, and/or two, a direct depressant effect of hypoxemia on brain stem neuronal metabolism and/or function (41, 49). Recent work suggests a third possible mechanism for a direct inhibition of brain stem afferent neural output. This work includes studies involving newborn rabbits and suggests that naloxone, an opiate receptor antagonist, blocks the hypoxic respiratory depression that occurs following the initial hyperventilatory phase (21) and shortens the duration of primary apnea following severe hypoxia and/or asphyxia (10). Further studies have demonstrated that endogenous opiates are found in increased concentrations in the monkey fetal brain (45) and in adult rat brain stem areas directly contiguous to components of the respiratory center (3, 4). Moreover, endogenous opiates have been shown to inhibit neuronal output of the respiratory center (16, 18, 28). Thus, the induction of a hypoxemic state in the immediate newborn period could result in the release or enhancement of a transmitter like endorphin that is capable of an overwhelming inhibitory effect on the respiratory center. The potential for this phenomenon to occur in older infants may be diminished and/or facilitative factors developed to the point where the net effect of a hypoxic stimulus is that of a sustained increase in ventilatory drive.

Finally, it should be noted that during low FIO_2 breathing, the infant M. nemestrina will develop both periodic breathing and/or apnea. The relationship between this and the ventilatory response to hypoxia, if any, is unclear. However, that both phenomena occur in the infant M. nemestrina provides further support for this model as an important tool for the study of respiratory control in early life.

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TABLE I: DATA SUMMARY FOR ANIMALS STUDIED ON POSTNATAL DAY 2

	Baseline (8)	1 min (8)	2 min (8)	3-6 min (8)	7-10 min (7)	17-20 min (6)
0.14 FiO ₂ Studies V _E /Kg	342±20	*392±36	348±20	339±15	349±22	323±21
PaCO ₂	35±2	33±2	33±2	34±2	35±2	35±2
PaO ₂	63±4	47±3	36±2	38±2	36±3	38±3
V _T /Kg	4.63±.29	5.03±.32	4.67±0.27	4.74±.40	4.77±.45	4.23±.41
F/min	75±5	78±5	79±6	74±6	74±3	78±5
0.12 FiO ₂ Studies V _E /Kg	(8)	(7)	(8)	(7)	(4)	(7)
PaCO ₂	346±18	*441±33	414±27	351±22	357±32	318±19
PaO ₂	34±2	32±1	29±1	36±2	37±2	37±3
V _T /Kg	63±5	34±3	26±3	21±2	21±3	18±2
F/min	4.69±.30	5.29±.32	5.02±.32	4.38±.35	4.27±.35	4.27±.37
	76±5	82±4	78±4	85±6	83±7	88±10

All values are mean ± SE.

Number of individual animals studied are in parenthesis.

*=p<.05, significantly different from baseline data.

TABLE II: DATA SUMMARY FOR ANIMALS STUDIED ON POSTNATAL DAY 7-8

	Baseline (8)	1 min (7)	2 min (7)	3-6 min (7)	7-10 min (8)	17-20 min (5)
0.14 FiO ₂ Studies V _E (ml/Kg)	357±22	*410±33	*413±30	372±25	371±32	323±8
PaCO ₂ (Torr)	34±1	31±1	31±1	32±1	32±2	33±2
PaO ₂ (Torr)	95±3	57±4	56±3	51±4	49±3	50±4
V _T (ml/Kg)	6.97±.50	7.18±.62	8.44±.73	7.15±.65	7.34±.80	6.75±.96
F/min	54±5	59±6	52±6	54±5	53±5	49±2
0.12 FiO ₂ Studies V _E (ml/Kg)	(8)	(7)	(4)	(5)	(4)	
PaCO ₂ (Torr)	376±15	*502±12	*447±30	*428±36	414±47	
PaO ₂ (Torr)	34±1	29±1	29±2	31±2	32±2	
V _T (ml/Kg)	89±4	41±2	38±2	31±1	29±2	
F/min.	7.26±.42	8.63±.46	8.32±.52	8.31±.53	7.58±.59	
	54±4	59±3	54±4	52±4	56±7	

All values are mean ± SE

Number of individual animals studied are in parenthesis

*=p<.05, significantly different from baseline data.

TABLE III: DATA SUMMARY FOR ANIMALS STUDIED ON POSTNATAL DAY 19-21

	Baseline (6)	1 min (6)	2 min (5)	3-6 min (5)	7-10 min (4)
0.14 FiO ₂ Studies V _E (ml/Kg)	459±32	*610±43	537±18	*546±22	*559±15
PaCO ₂ (Torr)	31±1	26±2	---	24±1	26±2
PaO ₂ (Torr)	97±3	69±6	---	59±5	58±8
V _T (ml/Kg)	9.85±1.11	12.72±1.29	12.22±1.29	12.07±1.15	11.95±1.71
F/min.	49±5	51±7	46±5	47±5	49±6

All values are mean ± SE

Number of individual animals studied are in parenthesis

*=p<.05, significantly different from baseline data.

TABLE IV: PERCENT OCCURRENCE OF APNEIC EPISODES AND PERIODIC BREATHING DURING HYPOXIC GAS BREATHING

FiO ₂	0.14	% Occurrence		0.12	% Occurrence	
		Apnea	Periodic Breathing		Apnea	Periodic Breathing
Total # of experimental trials accepted for analysis	44	23	16	27	22	22
day 2	18	28	22	16	19	19
day 7-8	15	27	6	11	27	27
day 19-21	11	9	18	---	--	--

Figure 1
Changes in arterial PaO_2 during low FiO_2 breathing.
Values are mean $\pm$ S.E.

Figure 2
Percent change in $\dot{V}_t/\text{Kg}$ during low FiO_2 breathing.
* = $p < .05$ difference from baseline.

Figure 3
 PaCO_2 levels during room air and low FiO_2 breathing.
Values are mean $\pm$ S.E.

Figure 4
Example of periodic breathing and apnea during low FiO_2 breathing.
Ventilation flow rate (± 2 l/min) is illustrated and 1 mm marks represent 1 second.

Figure 5
Relationship between arterial oxygen tension, minute ventilation and postnatal age. Data are mean values for 0.14 FiO_2 studies and points reflect baseline, 1, 2, 3-6, 7-10, and 17-21 minute samples. Data points are circled to facilitate postnatal grouping (i.e., day 2 vs. day 7-8). PaCO_2 was 33-35 mm on day 2, 31-34 mm on day 7-8, and 24-31 mm on day 19-21.