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THE EFFECT OF CHRONIC HYPOXIA UPON THE DEVELOPMENT OF RESPIRATORY CHEMOREFLEXES IN THE NEWBORN KITTEN

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SUMMARY

1. We have studied the reflex respiratory responses to two-breath alternations of fractional inspired oxygen ($F_{\mathrm{I,O_2}}$) in normoxic (reared in room air) and chronically hypoxic kittens (born into and reared in an $F_{\mathrm{I,O_2}}$ of 0·13–0·15) on post-natal days 1, 2–3, 4–8 and 9–14.

2. Respiration was measured non-invasively in the unanaesthetized kittens. Test runs (with alternations of $F_{\mathrm{I,O_2}}$ between 0·21 and 0·14) and control runs (with an $F_{\mathrm{I,O_2}}$ of 0·21) were carried out during quiet sleep.

3. The degree of alternation in tidal volume, inspiratory time, expiratory time, frequency, drive, timing and instantaneous ventilation components of the respiratory response was compared during control and test runs.

4. There was little response to control runs in either group at any post-natal age.

5. In normoxic kittens we found no significant reflex response in any respiratory variable to test runs before day 4. However significant alternation was found in expiratory time, frequency and ventilation at days 4–8 and in tidal volume at days 9–14.

6. In chronically hypoxic kittens there were no significant differences between control and test runs at any of the ages studied.

7. In the normoxic group increases in the response with post-natal age probably reflect post-natal increases in the sensitivity of the peripheral chemoreceptors. The lack of development in the chronically hypoxic group may indicate abnormal function or delayed maturation of the peripheral chemoreceptor sensitivity to hypoxia.

8. The results suggest that the method can be used to detect developmental and pathological changes in the arterial chemoreflex.

INTRODUCTION

The work of Black & Torrance (1971) and Nye, Hanson & Torrance (1981) described how a sudden change in chemoreceptor discharge in the cat had an effect on ventilation which depended on its timing in relation to that of the respiratory cycle. This is also true in man where, if alveolar $P_{\mathrm{CO_2}}$ or $P_{\mathrm{O_2}}$ is made to alternate on a breath-to-breath basis, a reflex alternation in at least one respiratory variable results (Ward, Drysdale, Cunningham & Petersen, 1979; Metias, Cunningham, Howson, Petersen & Wolff, 1981). The reflex involves the arterial chemoreceptors, as the responses to P_{CO_2} alternations are more pronounced in hypoxia (Marsh, Lyen, McPherson, Pearson & Cunningham, 1973; Metias *et al.* 1981) and are blocked by hyperoxia (Metias *et al.* 1981). Moreover, the latency of the response approximates to that of the lung-to-carotid body transit time (Ward *et al.* 1979). In adult cats, direct electrophysiological recordings have shown that the carotid chemoreceptor discharge oscillates as predicted from the alveolar P_{CO_2} (Kumar & Nye, 1983) or P_{O_2} (Kumar, Nye & Torrance, 1988) changes. Thus it is clear that it is these oscillations in chemoreceptor discharge which lead to alternations in respiratory variables.

However, such reflex studies have not been performed in the newborn animal or infant, where developmental changes in the chemical control of breathing are occurring. For instance, in the lamb both the aortic and the carotid chemoreceptor sensitivity to P_{a,O_2} has been shown to reset during the first two post-natal weeks, causing a shift to the right of the hyperbolic stimulus–response curve (Blanco, Dawes, Hanson & McCooke, 1984; Hanson, Kumar & McCooke, 1986; Kumar & Hanson, 1988). Thus a given oscillation of P_{a,O_2} would be expected to cause an increase in both the mean level and in the amplitude of chemoreceptor discharge, and hence in the respiratory response, as post-natal age increases.

We have chosen to study the respiratory response, in the kitten, to alternations in P_{a,O_2}, as it is a specific stimulus to the arterial chemoreceptors. Since kittens made chronically hypoxic from birth show a reduced carotid chemoreceptor sensitivity (Hanson, Eden, Nijhuis & Moore, 1988), we have also studied the effects of chronic hypoxia upon the development of the reflex responses to alternations of P_{O_2}.

A preliminary communication of some of our results has been published (Hanson, Kumar & Williams, 1987).

METHODS

Animals

Two groups of kittens from six litters were studied between post-natal days 1 and 14. The first group ($n = 7$) were born and reared in room air, fractional inspired oxygen (F_{I,O_2}) *ca* 0·21. The second group ($n = 6$) were born and reared in an hypoxic environment where F_{I,O_2} was maintained at *ca* 0·14. For analysis the study period was divided into four, namely post-natal days 1, 2–3, 4–8 and 9–14.

Exposure to chronic hypoxia

A normobaric environmental chamber as described by Eden & Hanson (1987) was used to maintain the F_{I,O_2} of the second group of kittens between 0·13 and 0·15. F_{I,O_2} and ambient temperature were read from an oxygen monitor (Beckman OM-15) and a thermocouple. Ambient temperature was maintained at 22–26 °C. Humidity (monitored by hair hygrometer, Fisher) remained between 40 and 60%. Samples of gas were taken twice daily from the chamber for P_{CO_2} measurement (Instrumentation Laboratories 1302 analyser) and an increase in P_{CO_2} was prevented by circulating gas from the chamber through a container of soda-lime.

Measurement of respiration

Respiration was measured non-invasively in the unanaesthetized kittens using the method of McCooke & Hanson (1985). Each kitten was placed in a Perspex plethysmograph with a loose seal around the neck, the head remaining outside the plethysmograph. Respiration was measured as

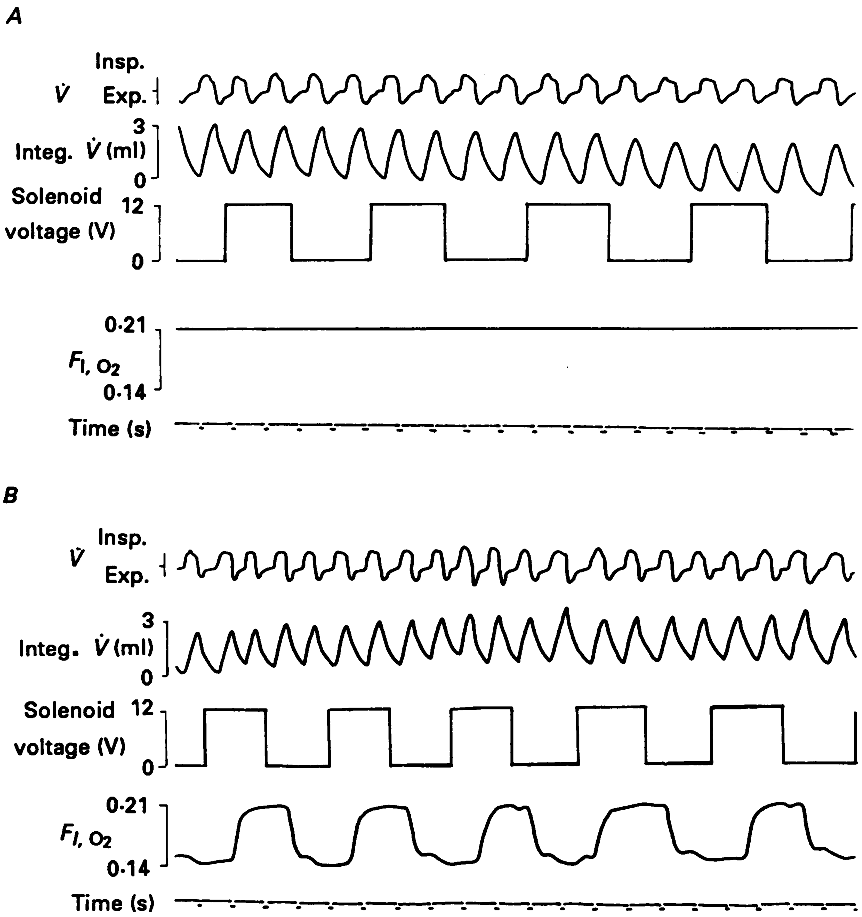

Fig. 1. Recordings made during a control run (*A*) with constant F_{I,O_2} of 0·21 and during a test run (*B*) with a two-breath alternation of F_{I,O_2} between 0·21 and 0·14. In each case traces from the top are respiratory airflow ($\dot{V}$), integrated airflow (Integ. $\dot{V}$), solenoid voltage (controlling the solenoid valves to switch the inspired gas between alternate pairs of breaths), fractional inspired oxygen (F_{I,O_2}) and time.

airflow into or out of the plethysmograph through a pneumotachometer head (Fleish No. 0). The airflow signal was electronically integrated to derive tidal volume. Airflow and the integrated signal were recorded onto magnetic tape (Racal Store 7DS). Tidal volume was calibrated by passing known volumes of air into and out of the plethysmograph using a calibrating syringe. Ambient temperature was maintained between 33 and 35 °C (i.e. thermoneutral, see Hill, 1959).

Experimental protocol

The plethysmograph was placed within a nylon hood (volume = 120 cm^3) through which gas flowed via a baffle at about 5 l/min from one of two gas delivery lines. The composition of the gas in each delivery line was set by rotameters connected to cylinders of air and nitrogen. It was possible to switch rapidly between the two gas delivery lines using electrically controlled solenoid valves (Platon Flowbits). F_{I,O_2} was measured with a fast-gas analyser (Beckman OM-11) and this signal was also recorded onto magnetic tape.

Each animal was allowed 15 min to become accustomed to the apparatus before recordings were made. Experiments were only carried out when the kittens were asleep; when it was possible to distinguish different sleep states (non-REM, during which body and eye movements were absent, and REM, during which eye movements and intermittent body or limb movements were observed) measurements were made only during non-REM sleep. Electrocortical activity was not measured as it is not possible to identify sleep state from it in the kitten until after day 21 (Jouvet-Mounier, Astic & Lacote, 1969). For a test run alternations with a two-breath duration were made between air (F_{I,O_2}, 0·21) and hypoxia (F_{I,O_2}, 0·14) (see Fig. 1*B*). The switch between the two inspired gas mixtures was made at the start of the expiration of the second of each pair of breaths. In this way the kittens received two full inspirations of each gas mixture on an alternating basis. Control runs were carried out using air in both gas delivery lines (see Fig. 1*A*). Each test or control run lasted between 50 and 100 breaths.

Data analysis

The integrated airflow signal was digitized and tidal volume (V_T), inspiratory time (T_I) and expiratory time (T_E) for each breath were derived using a BASIC program, running on a BBC Master microcomputer. For each breath the frequency ($F = 1/(T_I + T_E)$) and the instantaneous ventilation ($\dot{V}_E = V_T F$) were then computed. Two other variables, the mean inspiratory flow (V_T/T_I) and the inspiratory duty cycle ($T_I/(T_I + T_E)$) were also calculated for each breath. These will be referred to as the drive (Dr) and timing (Tim) components respectively. Analysis always began with a pair of air breaths. For the second of each pair of breaths the values of each of the seven respiratory variables were compared with their values in the second breath of the previous pair using a method based on that of Metias *et al.* (1981).

Data were normalized by expressing the differences between successive values as a percentage change about the average of the two values. The degree of reflex alternation was found by summing the differences between successive values of a variable, the sign of alternate values being reversed. Figures 2 and 4 show examples of such data displayed graphically. The quantity $\overline{\Delta y}$ (i.e. $\Sigma \Delta y/n-1$) was derived as the mean of successive differences, where Δy is the breath-by-breath percentage change of a variable and n is the total number of breaths analysed. Thus for an alternating variable the quantity $\overline{\Delta y}$ is the mean amplitude of the alternation, tending to zero as the degree of breath-by-breath alternations in that variable becomes less.

The sign of $\overline{\Delta y}$ indicates the direction of the alternation. The significance of any alternation was tested using a paired t test to compare the value of $\overline{\Delta y}$ during alternations of F_{I,O_2} with that during control runs. For the t test the sign of $\overline{\Delta y}$ was ignored. An unpaired t test was used for comparisons between age groups and between normoxic and chronically hypoxic groups. A difference was taken to be significant if $P < 0·05$.

RESULTS

The body weights of both groups of kittens increased with post-natal age showing similar developmental changes to those reported by other workers (Parot, Bonora, Gautier & Marlot, 1984). As shown in Table 1, the body weights of the chronically hypoxic kittens were less at each post-natal age than those of the age-matched normoxic kittens but the differences were not significant.

Normoxic kittens

Figure 2 shows three experimental runs taken on days 1, 5 and 11 from one normoxic kitten, illustrating the development of the response. The mean results from all normoxic kittens are shown in Fig. 3. No significant difference was found between control and alternating runs for $\overline{\Delta y}$ for any respiratory variable on post-natal day 1 or days 2–3. On post-natal days 4–8 significant alternation was found in T_E, the $\overline{\Delta y}$ value being *ca* three times greater during test than control runs. F and $\dot{V}_E$ also showed significant alternation at this age, this being primarily due to the alternation in T_E. Whilst large alternations in at least one of the respiratory variables were observed in all animals on post-natal days 9–14 (e.g. V_T and $\dot{V}_E$ in Fig. 2), for the

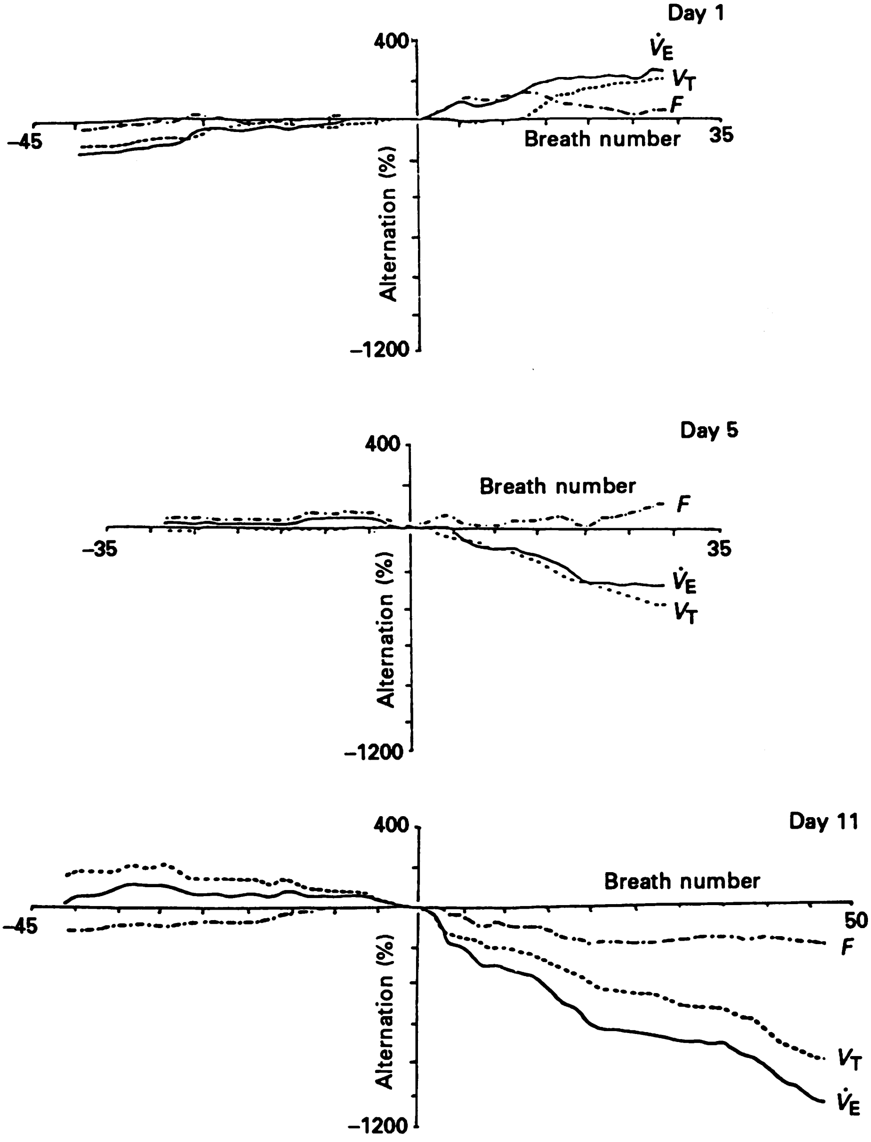

Fig. 2. Cumulative percentage alternation plots from one normoxic kitten on post-natal days 1, 5 and 11. The responses to control and test runs are plotted from the origin to the left and to the right, respectively. Plots are shown for tidal volume (V_T), frequency (F) and instantaneous ventilation ($\dot{V}_E$).

TABLE 1. Mean body weight ± S.E.M. (g) for normoxic and chronically hypoxic kittens at increasing post-natal ages

Post-natal age (days):	1	2–3	4–8	9–14
Normoxic kittens ($n = 7$)	131·3 ± 5·6	135·8 ± 4·2	171·4 ± 9·5	272·1 ± 7·2
Chronically hypoxic kittens ($n = 6$)	128·6 ± 2·6	130·4 ± 3·0	168·3 ± 9·6	257·8 ± 7·6

No significant differences were found between the body weights of normoxic and chronically hypoxic kittens at each age.

group as a whole only the alternation in V_T was significantly greater in test than in control runs.

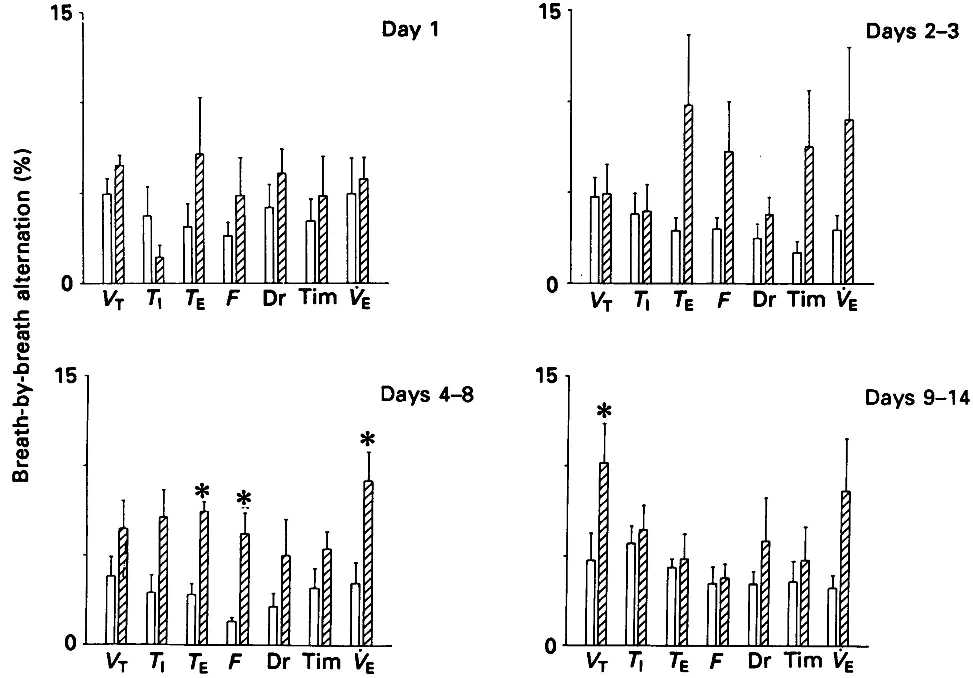

Fig. 3. The mean percentage breath-by-breath alternation for normoxic kittens on post-natal days 1 ($n = 6$) 2–3 ($n = 8$), 4–8 ($n = 9$) and 9–14 ($n = 8$). Mean responses ± S.E.M. are shown during control (open bars) and test runs (hatched bars) for tidal volume (V_T), inspiratory time (T_I), expiratory time (T_E), frequency (F), inspiratory drive (Dr), timing (Tim) and instantaneous ventilation ($\dot{V}_E$). Asterisks show significant differences between control and test runs ($P < 0{\cdot}05$) by Student's paired t test.

Chronically hypoxic kittens

Figure 4 shows experimental runs carried out on post-natal days 1, 4 and 14 from one chronically hypoxic kitten, illustrating a relative lack of development of the response. The mean results from all hypoxic kittens are shown in Fig. 5. No significant difference was found between the values of $\overline{\Delta y}$ during control and test runs for any of the respiratory variables at any age.

Normoxic versus chronically hypoxic kittens

During control runs, the values of $\overline{\Delta y}$ were not significantly different for any of the respiratory variables when the normoxic and the chronically hypoxic kittens were compared at each age group. Nor were there significant differences in the $\overline{\Delta y}$ values of any respiratory variable during test runs between normoxic and chronically hypoxic kittens on post-natal days 1, 2–3 or 4–8. However, on post-natal days 4–8 the mean values of $\overline{\Delta y}$ were greater for most of the variables in the normoxic kittens. Significant differences ($P < 0{\cdot}05$) were found in the responses of the kittens on post-

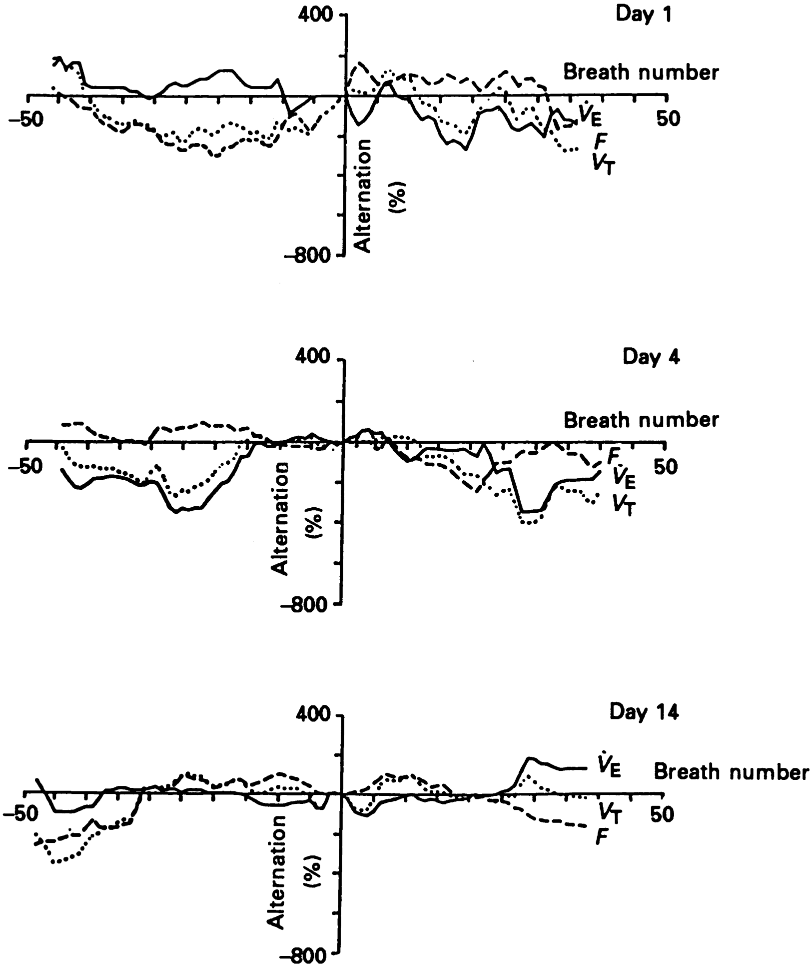

Fig. 4. Cumulative percentage alternation plots from one chronically hypoxic kitten on post-natal days 1, 4 and 14. The responses to control and test runs are plotted from the origin to the left and to the right, respectively. Plots are shown for tidal volume (V_T), frequency (F) and instantaneous ventilation ($\dot{V}_E$).

natal days 9–14, when the values of $\overline{\Delta y}$ for V_T and F were *ca* three times greater during test runs in the normoxic kittens than in the chronically hypoxic kittens.

DISCUSSION

Our results show that there is a reflex respiratory response to alternations of F_{I,O_2} in the normoxic kitten after day 3. No single pattern of alternating response was observed and if consecutive test runs were examined the pattern of response could be different in each run. However the value of $\overline{\Delta y}$ for at least one respiratory variable was significantly greater during test runs as compared to control runs in each age group. These differences in response may in part be explained according to

Cunningham, Howson, Metias & Petersen (1986) who studied the respiratory responses to alternating alveolar P_{CO_2} in man. They concluded that the arterial chemoreceptor pathway affected predominantly only certain parts of the cycle of the respiratory pattern generator; thus the varied responses resulted from changes in the timing of the alternating stimulus at the carotid body in relation to that of the respiratory cycle.

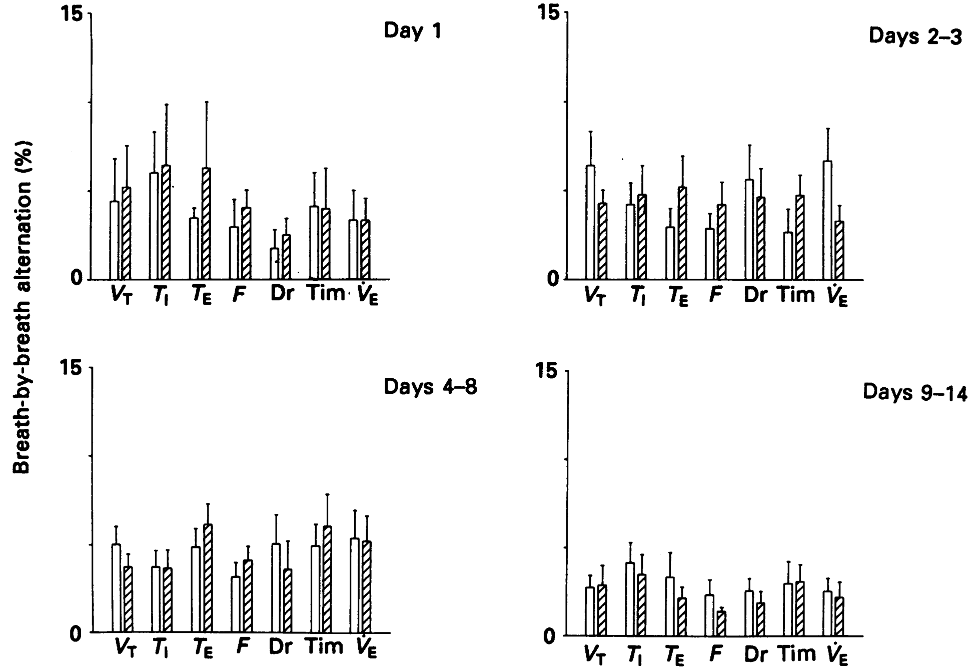

Fig. 5. The mean percentage breath-by-breath alternation for chronically hypoxic kittens on post-natal days 1 ($n = 5$), 2–3 ($n = 6$), 4–8 ($n = 9$) and 9–14 ($n = 5$). Mean responses ± s.e.m. are shown during control (open bars) and test runs (hatched bars) for tidal volume (V_T), inspiratory time (T_I), expiratory time (T_E), frequency (F), inspiratory drive (Dr), timing (Tim) and instantaneous ventilation ($\dot{V}_E$). There were no significant differences between control and test by Student's paired t test.

A large value of $\overline{\Delta y}$ does not mean that a variable alternated continuously throughout an experimental period. It indicates that if the alternation is lost and then starts again some breaths later, then the alternation is more likely to be resumed in the same phase as before. Metias *et al.* (1981) described such 'turning points' and showed that the incidence of the resumption of alternation in the same phase during experimental runs was high.

Metias *et al.* (1981) compared their values for $\overline{\Delta y}$ with zero using a t test based on the null hypothesis that no alternation would occur. We have preferred to use a paired t test to compare control and test values of $\overline{\Delta y}$. We observed small alternations in respiratory variables during control runs. These probably resulted from random changes in the breathing pattern. Although with our method of analysis any degree of control alternation will reduce the chance of finding significant alternation during test runs, we feel that we have applied a more rigorous analysis.

As F_{I,O_2} was the alternating stimulus and the respiratory responses occurred rapidly it is likely that the arterial chemoreceptors were responsible for mediating the effects. Support for this idea comes from our observation (B. A. Williams & M. A. Hanson, unpublished observations) that there is little respiratory response to an alternation in F_{I,O_2} in lambs aged 5 days in which the carotid sinus nerves had been sectioned on the day of birth. In the normoxic kittens a development of the respiratory responses was observed, with an increase in the degree of alternation between post-natal days 1 and 14. These changes may reflect a maturation of arterial chemoreceptor sensitivity to hypoxia as has been observed by direct recordings of carotid sinus nerve afferent activity in the neonatal lamb (Hanson *et al.* 1986).

We examined relative changes in the responses in order to exclude any effect of the increase in V_T and in $\dot{V}_E$ with increasing post-natal age. However it is possible that developmental changes in the response resulted from post-natal improvements in gas exchange at the lungs, increasing the amplitude of the alternating stimulus. Ideally, arterial blood gases would have been monitored throughout the experiment; however the kittens did not have arterial catheters, as we wanted to make developmental studies of the responses in each animal under as near to normal conditions as possible. Due to the small size of our experimental animals we were unable to measure end-tidal gases and thereby estimate the size of the oscillation in the arterial stimulus.

In chronically hypoxic kittens the reflex respiratory responses were small in comparison to those seen in normoxic kittens. It is possible to explain these observations in two ways. First, it may be that by limiting the rise in P_{a,O_2} at birth the resetting of the arterial chemoreceptors is delayed. Secondly, it is possible that the suprapontine mechanism which inhibits breathing movements in the fetus (see Dawes, 1984) persists in the neonate and that the rate at which this inhibition disappears depends upon the level of P_{a,O_2} obtained post-natally.

With respect to the first possibility, there is evidence that the sensitivity of the carotid chemoreceptors in chronically hypoxic kittens is much less than that of age-matched normoxic kittens (Hanson *et al.* 1988). However, although Eden & Hanson (1987) found that chronic hypoxia delayed the maturation of the respiratory response to acute hypoxia in the neonatal rat, they found no difference in the afferent chemoreceptor sensitivity to hypoxia between normoxic and chronically hypoxic rats. It is possible that the different recording methods used in these studies influenced the results; in the rat whole-nerve recordings were made whereas in the kitten it was possible to record from single- or few-fibre chemoreceptor afferent preparations. While whole-nerve preparations give an indication of relative increases in activity they are not well suited to making comparisons between animals. Furthermore, in the rats recordings were made at 5–10 weeks of age, so that if chronic hypoxia merely delayed resetting, mature responses would have been observed in both groups.

There are also other reports that the effect of chronic hypoxia differs between species. Bisgard, Ruiz, Grover & Will (1974) have reported that the ventilatory responses to hypoxia were not different in calves born at altitude (about 3100 m) as compared to those born at sea level. However in infants born at altitude Lahiri, Brody, Motoyama & Velasquez (1978) showed a blunting of the ventilatory response to hypoxia. There are also reports that in children who are hypoxic for many years as a result of tetralogy of Fallot the hypoxic response is blunted, even after surgical correction of the syndrome (Sorensen & Severinghaus, 1968).

We have far less evidence regarding the second possibility, that the reduced responses to alternations of $F_{\mathrm{I,O_2}}$ in the chronically hypoxic kittens may represent the persistence of suprapontine mechanisms which inhibit breathing in the fetus during hypoxia. The proposed suprapontine fetal mechanism (Dawes, Gardner, Johnston & Walker, 1983; Gluckman & Johnston, 1987) can operate in the immediate post-natal period (Blanco, Martin, Hanson & McCooke, 1987). Evidence that it persists into neonatal life comes from the observations of Martin-Body & Johnston (1988) that pre-collicular brain stem transection in neonatal rabbits reduces the fall in ventilation occurring during hypoxia. It may be that the maturation of the adult response to hypoxia consists in part of a reduction in the extent to which the fetal mechanism operates, or even a disappearance of it. This maturation may depend on the $P_{\mathrm{a,O_2}}$. In chronically hypoxic rats, our preliminary results (Williams & Hanson, 1988) suggest that part of the reduced response to hypoxia is indeed removed by pre-collicular brain stem transection but not by decortication.

Despite our relative ignorance of the mechanisms involved in these reflexes, the method we have used shows that the neonate can detect small, rapid changes in $F_{\mathrm{I,O_2}}$, presumably via the arterial chemoreceptors. The development of the response in the normoxic kitten appears to reflect resetting of the chemoreceptor hypoxic sensitivity. The greatly reduced response of the chronically hypoxic kittens indicates that the test can be used to detect pathological changes in the arterial chemoreflex. There is histological evidence from sudden infant death syndrome (SIDS) infants indicating carotid body abnormalities (Naeye, Fisher, Ryser & Whelen, 1976) and reports that near-miss SIDS infants show reduced ventilatory responses to hypercapnia (Shannon, Kelly & O'Connell, 1977) or delayed arousal to hypoxia during sleep (Hunt, McCulloch & Brouillette, 1981). This evidence indicates the possible clinical importance of a simple non-invasive test of peripheral chemoreceptor sensitivity. Our preliminary studies indicate that the method can indeed be applied to the newborn infant (Blanco, Degraeuwe, Hanson, Kumar & Williams, 1988).

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