THE RESPIRATORY RESPONSE OF THE NEW-BORN LAMB TO INHALED CO_2 WITH AND WITHOUT ACCOMPANYING HYPOXIA*

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(*Received* 16 *September* 1965)

SUMMARY

1. The respiratory response to inhaled CO_2 was measured in twenty unanaesthetized new-born lambs aged 4 hr–10 days. Measurement of resting arterial pH, P_{CO_2} and plasma bicarbonate showed a non-respiratory acidosis immediately after birth which was corrected in the first 24–28 hr: thereafter, the acid–base pattern was of a compensated respiratory alkalosis.

2. When CO_2 was added to the inspired gases and resting arterial oxygen tension (P_{a, O_2}) was controlled, the average increase in minute ventilation ($\dot{V}$) was $0.075 \, 1.min^{-1}.kg^{-1}.mm \, Hg$, P_{a, CO_2}^{-1} and duplicate responses in the same lamb differed by 6–22.5 %.

3. The slope of the $\dot{V}/P_{a, CO_2}$ line (S) varied inversely with P_{a, O_2}. In one lamb, severe hypoxia ($P_{a, O_2} = 21$ mm Hg) caused a marked depression of the slope.

4. Neither the slope S nor the horizontal intercept B of the lines was related to the age of the lamb. B was not related to pH_a and only slightly affected by acute hypoxia. B was related to arterial $[HCO_3^-]$ and values for both were reduced with the acid–base disturbances seen in the first 10 days after birth. Evidence was given which suggested that the response of the new-born lamb to inhaled CO_2 was similar to that of man acclimatized to a P_{a, O_2} of 70–75 mm Hg.

5. In the lightly anaesthetized lamb, bilateral section of the sinus nerves caused a small reduction in the sensitivity to inhaled 5 % CO_2 in air, an increase in the respiratory lag and a reduction in the rate at which $\dot{V}$ increased.

6. It was concluded that, in the new-born lamb, the carotid chemo-

receptors are involved in the response to inhaled CO_2 and that hypoxia potentiates this response.

INTRODUCTION

The sustained increase in arterial or alveolar P_{CO_2} (P_{a, CO_2} or P_{A, CO_2}) brought about by the inhalation of CO_2 cannot be considered to be a physiological stimulus. Nevertheless, the relation between P_{a, CO_2} (stimulus) and $\dot{V}$ (response) has been used to give an index of the sensitivity of the respiratory system under a number of conditions. Thus the effect of sleep has been measured by Oestergaard (1944), and Reed & Kellogg (1958); altitude acclimatization by Reed & Kellogg (1958); raised body temperature by Cunningham & O'Riordan (1957); noradrenaline infusion by Cunningham, Hey, Patrick & Lloyd (1963) and hypoxia by Lloyd, Jukes & Cunningham (1958).

The respiratory response of the new-born to inhaled CO_2 has been studied by Wilson, Long & Howard (1942), Howard & Bauer (1950), Cross, Hooper & Oppé (1953), Miller (1954), Stahlman (1961) and Avery, Chernick, Dutton & Permutt (1963). Some of the more recent studies have been concerned with specific points, e.g. the effect of progesterone (Stahlman, 1961) or a comparison with the response in the adult (Avery *et al.* 1963).

Cross, Hooper & Lord (1954) extended a previous study on the response of the new-born infant to hypoxia (Cross & Oppé, 1952) and showed that the increase in $\dot{V}$ induced by breathing 0·5 % CO_2 was reduced or abolished when the infant was also made hypoxic. These authors concluded that the potentiation of the respiratory response to inhaled CO_2 by hypoxia which had been demonstrated in adult man (Neilsen & Smith, 1952) did not occur in the new-born.

This problem has been re-examined in the new-born lamb and the study has been extended to assess the part played by the carotid body chemoreceptors in the response to CO_2 at this age.

METHODS

The methods used to measure $\dot{V}$, P_{A, CO_2}, P_{a, CO_2} and P_{a, O_2} in the unanaesthetized new-born lamb are those described in a previous paper (Purves, 1966a). In addition, arterial pH (Radiometer capillary electrode) and the CO_2 content of arterial plasma (Natelson–Kopp apparatus) were measured in duplicate from 0·6 ml. samples of arterial blood taken in the resting period.

Thirty-two unanaesthetized new-born lambs aged 4 hr–10 days after birth were studied but satisfactory records were obtained in only twenty. As previously described (Purves, 1966a), to be satisfactory, the records of minute ventilation had to show a variation of no more than 5 % during the control period while there had to be no obvious change in the state of wakefulness during the experimental period which followed. After the 5 min control period during which the lamb breathed an O_2/N_2 mixture at ambient P_{O_2}, CO_2 was added in four increments, approximately 1, 2, 4 and 6 %. A steady state, as judged by the respiratory

and end-tidal CO_2 tracings, was attained at each stage, usually in 6–8 min. The hyperventilation so induced invariably caused an increase in P_{a, O_2}. The amount by which P_{a, O_2} increased varied considerably from lamb to lamb, possibly depending on the reduction of areas of uneven ventilation and perfusion and in the size of extra-pulmonary shunts. P_{a, O_2} was therefore controlled by increasing the proportion of inspired nitrogen and confirmed by measuring P_{a, O_2} (0·2 ml. samples) approximately every minute in the first 3 min after the gas mixture was changed during which period the major increase in ventilation occurred. A further sample was taken in the fifth or sixth minute in case further adjustment was necessary and further samples were taken in the eighth minute for duplicate determination of P_{a, O_2} and P_{a, CO_2}. With careful sampling, no more than 4–5 ml. of blood was removed for the measurements during each CO_2 response. In experiments where this was repeated at two or three levels of P_{a, O_2}, the total volume of blood removed was estimated at no more than 4 % of the blood volume in a 4–5 kg lamb. $\dot{V}$ was also measured over the eighth minute and the values for $\dot{V}$ and P_{a, CO_2} were used to construct $\dot{V}/P_{a, CO_2}$ lines for each experiment at each P_{a, O_2}.

In the first group of experiments, CO_2 responses were measured in thirteen lambs, P_{a, O_2} being controlled at resting levels, and to test the reproducibility of the responses the test was repeated in each lamb after an interval of not less than 1 hr. Satisfactory results were obtained in seven lambs. $\dot{V}/P_{a, CO_2}$ lines were constructed from points on the linear part of the CO_2 response curve as regression lines (least squares). The results from these seven lambs are given in Table 1. Where the CO_2 response curve contained an obvious inflexion (e.g. Fig. 3a, curve at $P_{a, O_2} = 76$ mm Hg; Fig. 3b, curve at $P_{a, O_2} = 47$ mm Hg), the lowest (resting) point was ignored.

In the second group of experiments, the respiratory response to inhaled CO_2 was measured in nineteen unanaesthetized lambs when the inspired oxygen tension was normal, high or low. Satisfactory records were obtained in thirteen lambs and in one lamb, the CO_2 response was successfully measured at two levels of hypoxia ($P_{a, O_2} = 43$ and 21 mm Hg). The sequence of tests was at ambient, then at high and, if possible, at low inspired oxygen tension. An interval of at least 1 hr was allowed between tests and the lamb breathed the new O_2/N_2 mixture for at least 10 min before CO_2 was added.

In the third group of experiments, eight lambs were lightly anaesthetized with sodium pentobarbitone, 7–10 mg/kg intraperitoneally. After tracheotomy the oesophagus and trachea were divided and reflected in the mid line and the sinus nerve was identified on each side. Each lamb then breathed 5 % CO_2 in air for 5 min after which the sinus nerves were cut. After a further 2–3 hr the same gas mixture was given and in both sets of tests, end-tidal P_{CO_2}, the respiratory lag after CO_2 was given, the rate at which $\dot{V}$ increased (measured in 5 or 10 sec intervals) and the maximum increase in $\dot{V}$ in the 6–8th min were recorded.

RESULTS

Control values

The values for resting $\dot{V}$, P_{a, O_2} and P_{a, CO_2} were within the ranges previously described in the unanaesthetized new-born lamb (Purves, 1966a). The relation between pH_a and the age of the lamb is shown in Fig. 1b and was significant; $r = 0·61$; $0·05 > P > 0·025$. The relation between arterial bicarbonate and age is shown in Fig. 1a and was not significant. For comparison, the measured values for pH and bicarbonate in arterial blood from carotid loops in eight trained unanaesthetized adult sheep are shown in both parts of Fig. 1. This shows that pH was substantially lower than in the adult mainly in the first 24–48 hr after birth.

On the other hand, arterial bicarbonate values of less than 18 m-equiv/l. were observed in lambs up to the ninth day. Buffer base varied between $-8\cdot5$ and -1 m-equiv/l. compared with the mean for the adults in the first 2 days of life and between -4 and $+1$ in the subsequent 8 days.
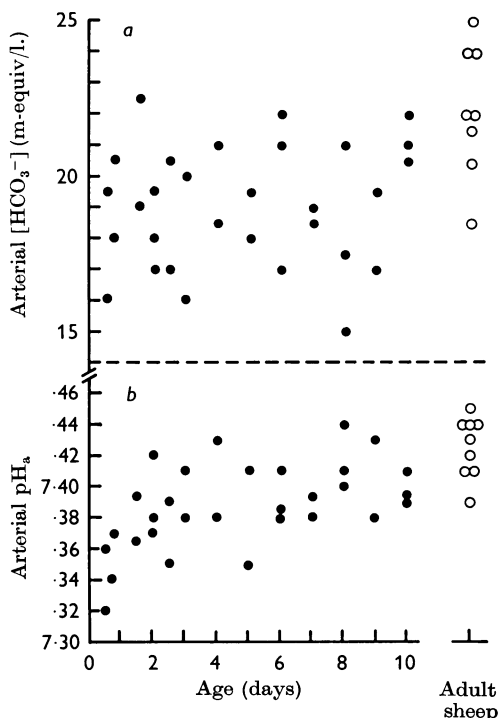

Fig. 1. The relation between arterial plasma HCO_3^- (*a*), pH_a (*b*) and age. Resting values from thirty unanaesthetized new-born lambs (filled circles) and eight unanaesthetized adult sheep (open circles). The relation between pH and age was significant, $r = 0\cdot61$; $0\cdot05 > P > 0\cdot025$.

Calculation of $P_{a,\,CO_2}$ from these data confirm that $P_{a,\,CO_2}$ is low by adult standards in the first 10 days after birth and that the acid–base pattern which emerges is of a mixed non-respiratory acidosis, most pronounced in the first 24 hr after birth and a respiratory alkalosis which is almost completely compensated from the fourth day onwards.

CO₂ responses at ambient P_{O_2}

Figure 2 shows portions of the record of a 30 hr old lamb which successively breathed air, 1·9, 4·1 and 5·9 % CO_2 and air again. It shows that both the frequency and depth of respiration increased and, with 5·9 % CO_2, this increase was so great that the sensitivity of the amplifier had to

be halved. This sequence was repeated in seven lambs with resting P_{a, O_2} controlled. Table 1 shows the values for S for the duplicate studies in these lambs. S varied between 0·045 and 0·078 l./min^{-1}.kg^{-1} mm Hg P_{a, CO_2}^{-1}, average, 0·062. Duplicate slopes in the same lamb differed by 6–22·5 %. This difference is greater than that reported by Anderton, Harris & Slawson (1964) in adult man and probably reflects the number of variables, e.g. the degree of wakefulness, which it was not possible to control completely.
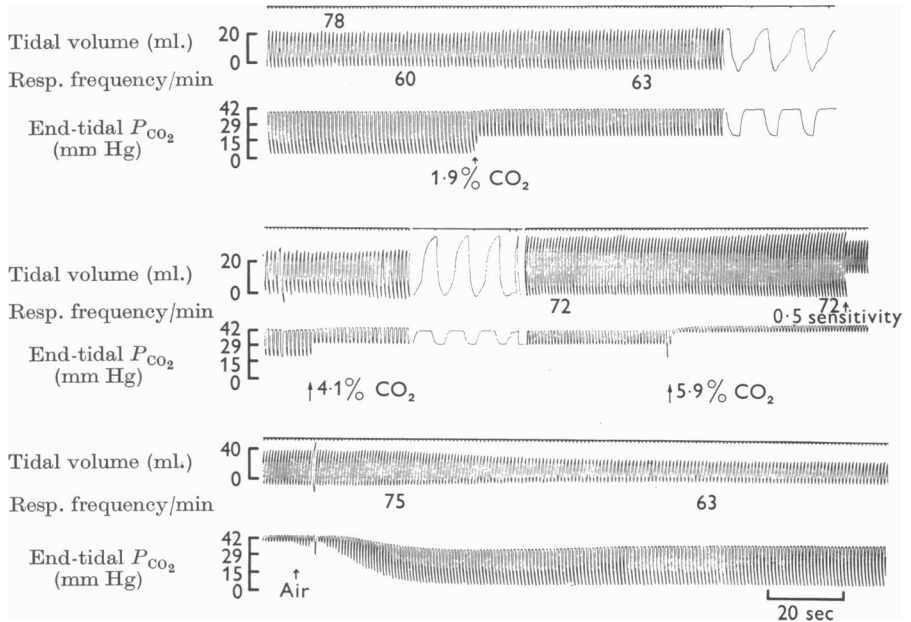

Fig. 2. Portions of a tracing from a 20 hr old lamb showing the effect of inhaling CO_2 on tidal volume, respiratory frequency and end-tidal P_{CO_2}. The lamb breathed successively air, 1·9, 4·1 and 5·9 % CO_2 and air again. P_{a, O_2} was controlled at 78 mm Hg.

TABLE 1. Results of duplicate CO_2 response curves in seven new-born lambs at ambient P_{a, O_2}

Lamb		l.kg^{-1} min^{-1} mm Hg P_{a, CO_2}		Difference (%)
No.	Age	1st slope	2nd slope	
17	4 hr	0·078	0·071	8·5
24	6 hr	0·056	0·068	22·5
12	2 days	0·045	0·048	6·0
54	4 days	0·086	0·073	13·5
35	6 days	0·067	0·060	11·5
53	9 days	0·046	0·049	6·5
11	9 days	0·058	0·064	10·5

CO_2 responses at varying P_{a,O_2}

The results of those experiments in which the respiratory response to inhaled CO_2 was satisfactorily tested at high, ambient and low P_{O_2} are summarized in Table 2. Satisfactory responses were measured in thirteen unanaesthetized lambs. The mean value for S at ambient P_{O_2} was 0·075 l. min^{-1}.kg^{-1} mm Hg P_{a,CO_2}^{-1}, at high P_{O_2}, 0·051 and at low P_{O_2} (P_{a,O_2} = 35–50 mm Hg), 0·145. Using the $\dot{V}$ and P_{a,CO_2} relation described by Lloyd *et al.* (1958), the parameter B was obtained by extrapolating S to the

TABLE 2. Values for S and B with varying P_{a,O_2}. Thirteen unanaesthetized new-born lambs*

Lamb		S (l.min^{-1}.kg^{-1}.mm Hg P_{a,CO_2}^{-1})			B (mm Hg P_{a,CO_2})
No.	Age	High	Ambient	Low P_{a,O_2}	
28	4 hr	0·032	0·041	—	29
		0·033	0·037	—	
56	4 hr	0·053	0·087	—	29
21	4 hr	0·079	0·014	0·170	28·5
27	10 hr	0·115	0·120	0·308	35
			0·132		
16	18 hr	0·058	0·069	0·177	29
17	20 hr	0·062	0·134	0·264*	29·5
				0·017**	
51	30 hr	0·024	0·035	0·086	32·5
24	2 days	0·054	0·074	—	34·5
		0·046	0·063		
31	4 days	0·033	0·043	0·124	33
38	6 days	0·046	0·065	0·088	33
44	8 days	0·054	0·085	0·117	30
19	9 days	0·035	0·048	—	30
			0·050		
72	9 days	0·039	0·051	0·060	34
Mean		0·051	0·075	0·155	31·6
		S.D.	± 0·026		
		S.E.	± 0·006		

*P_{a,O_2} 43 mm Hg; **P_{a,O_2} 21 mm Hg.

The full data, summarized in Table 1, have been deposited in the Library, National Institute for Medical Research, the Ridgeway, London N.W. 7.

P_{a,CO_2} axis. The values for B given in Table 2 are the means for each family of $\dot{V}/P_{a,CO_2}$ lines, and representative examples of the latter are shown in Fig. 3. In each panel, filled circles represent CO_2 responses at ambient P_{O_2}, filled triangles at high P_{O_2} and filled squares at low P_{O_2}. Open symbols represent duplicate curves at that P_{O_2} while the numerals refer to the average P_{a,O_2} which was maintained throughout the experiment. The lambs whose responses are shown varied in age from 4 hr to 9 days. There was no evidence that S at ambient P_{O_2} varied with age. B tended to increase with age but the series was too small for this relation to be significant.

The mean value for B in the thirteen lambs varied between 29 and 34·5 mm Hg P_{a,CO_2}. This range is low by standards in adult man (e.g. data

given by Lambertsen, Hall, Wollman & Goodman, 1963). The value for B
was 1–4 mm Hg P_{a, CO_2} lower than resting and, of the various factors in
arterial blood which affect B, the only significant relation was with arterial
bicarbonate, Fig. 4: $r = 0.78$, $0.025 > P > 0.01$. The possible reasons for
the shift of the CO_2 response curves to the left are discussed in a later
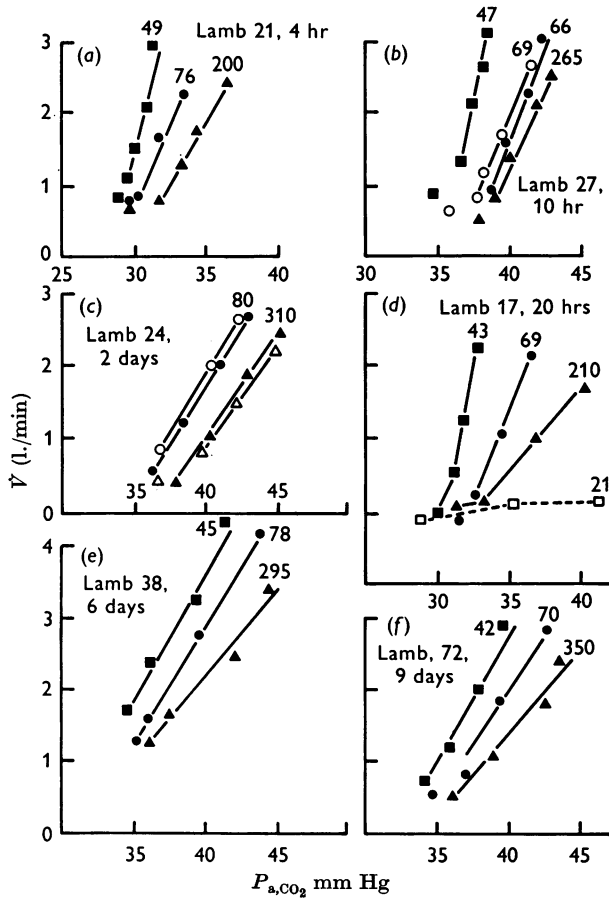section.

Fig. 3. Representative families of $\dot{V}/P_{a, CO_2}$ curves. Filled circles, steady-state
points at resting P_{a, O_2}; filled triangles, at high P_{a, O_2}; filled squares at low P_{a, O_2}.
Open symbols refer to duplicate response curves at the respective P_{a, O_2}. The number
and age of each lamb is indicated in each panel while the numerals refer to P_{a, O_2}
(mm Hg) at which the test was carried out. Six unanaesthetized lambs, 4 hr–9 days.

The effect of altering P_{a, O_2} upon S is shown in Fig. 5. S at ambient P_{O_2}
has been plotted for each lamb against S at low P_{O_2} (above the line of
equality) and against S at high P_{O_2} (below the line of equality). This
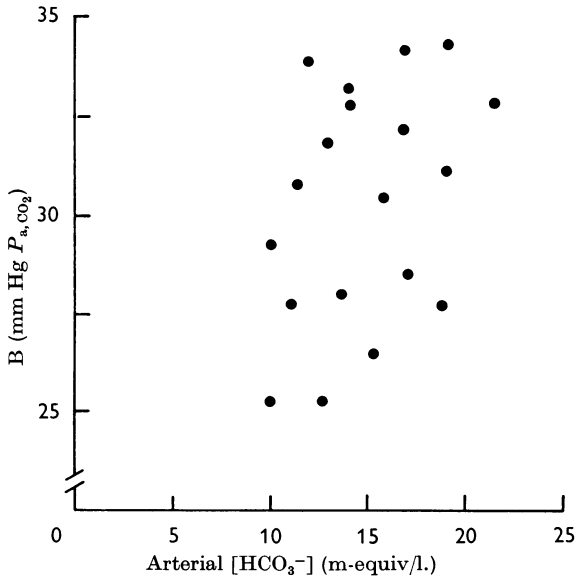figure shows clearly that in the new-born lamb, S increases as P_{O_2} falls.

Fig. 4. The relation between mean B and arterial plasma $[HCO_3^-]$ in thirteen unanaesthetized lambs. $r = 0.78$; $0.025 > P > 0.01$.
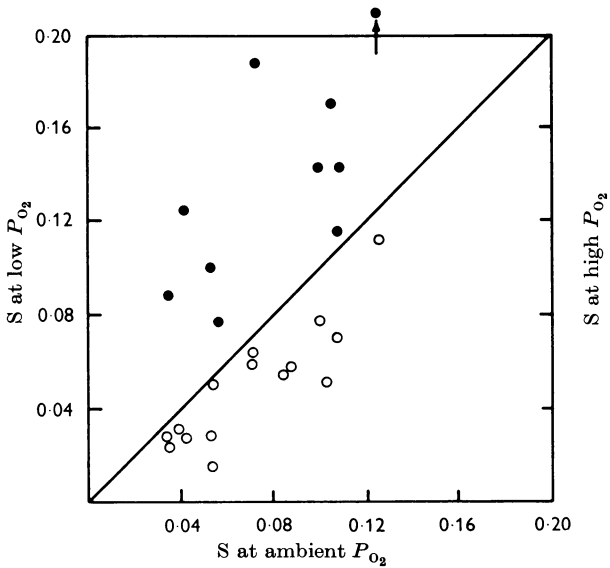

Fig. 5. The relation between P_{a,O_2} and S in thirteen unanaesthetized new-born lambs aged 4 hr–10 days. S at ambient P_{a,O_2} has been plotted against S at high P_{a,O_2} (below the line of equality) and against S at low P_{a,O_2} (above the line of equality).

In Fig. 6 the relation between S and P_{a,O_2} has been plotted for the group of thirteen lambs (filled circles represent S at low P_{a,O_2}, open circles, S at resting P_{a,O_2} and filled squares, S at high P_{a,O_2}). The continuous line joins the average value for S at each level of P_{a,O_2} and this line is similar in shape and position to that relating $\dot{V}$ and P_{a,O_2} at raised P_{A,CO_2} in the new-born lamb (Purves, 1966b) and to those relating $\dot{V}$ and P_{A,O_2} in adult man (Cormack, Cunningham & Gee, 1957).
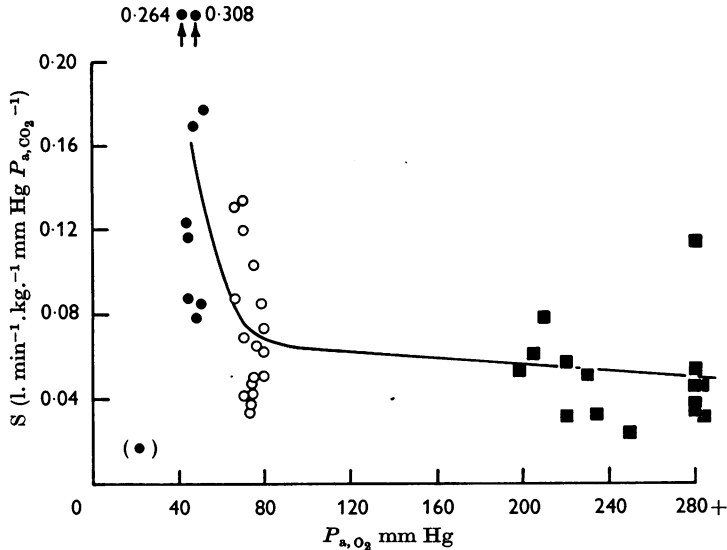

Fig. 6. The relation between S and P_{a,O_2}; thirteen unanaesthetized new-born lambs. The filled circles indicate S at low P_{a,O_2}, open circles, S at normal P_{a,O_2} and filled squares, S at high P_{a,O_2}. The continuous line joins the average values of S and P_{a,O_2} in each group of points. S at P_{a,O_2} of 21 mm Hg was not included.

Effects of cutting both sinus nerves

The immediate effects of cutting both sinus nerves were hypertension and a fall in $\dot{V}$ with periods of irregular respiration. Respiratory minute volume and blood pressure had usually returned to control levels after 2 or 3 hr but in three of the eight lambs studied respiration was either unstable or depressed after this period or blood pressure was still elevated. The records from these lambs were discarded. The results from the remaining five lambs are given in Table 3. This shows that resting minute ventilation did not greatly vary between the tests and that the maximum increase in minute ventilation while breathing 5 % CO_2 was similar before and after section of the sinus nerves. There were, however, three points of difference in the response after both sinus nerves had been cut. First, in each lamb the same increase in $\dot{V}$ was achieved with a greater increase in

P_{a, CO_2}, i.e. assuming that the respiratory response was linear over this range, S. With the number of lambs involved, this difference was not significant, $P > 0.1$. This effect has also been described by Mitchell (1965) in the adult dog after chemoreceptor denervation. Secondly, there was a consistent increase in the respiratory lag before $\dot{V}$ started to increase in response to CO_2. The interval approximately doubled. Thirdly, the rate at which $\dot{V}$ increased in response to inhaled CO_2 was obviously more sluggish after carotid chemoreceptor denervation, the time constant approximately doubling.

TABLE 3. The effect of inhaling 5 % CO_2 in air on $\dot{V}, P_{A, CO_2}$, respiratory lag and time constant of the rate of increase of $\dot{V}$ (T_c) before and after section of both sinus nerves. Five lambs; sodium pentobarbitone, 7–10 mg/kg

Lamb		Control $\dot{V}$	$\Delta \dot{V}$ %	$\Delta P_{A,CO_2}$	Lag	T_c
No.	Age	(l./min)	of control	(mm Hg)	(sec)	(sec)
		Sinus nerves intact				
56	8 hr	0·724	120	3·5	4·0	45
48	2 days	0·816	185	7·0	3·5	35
39	2 days	0·782	146	8·0	3·5	50
62	4 days	1·026	216	6·5	4·0	45
47	7 days	0·880	196	8·0	4·25	38
		Mean 172		6·6	3·85	42
		Sinus nerves cut				
56	8 hr	0·802	124	7·0	9·5	95
48	2 days	0·774	206	9·5	9·0	85
39	2 days	0·842	150	9·0	10·0	120
62	4 days	0·980	204	9·0	8·75	60
47	7 days	0·764	218	10·5	9·0	82
		Mean 180·4		9·4	7·45	88·4

It has been calculated (M. J. Purves, unpublished) that the lung to carotid circulation time in the lamb is approximately 2·5–3 sec and the measured lag in the gas delivery system was just over 1 sec. The fact that the average respiratory lag in the group of five lambs with intact sinus nerves was 3·85 sec suggests that the carotid body chemoreceptors were involved in the response to CO_2. Similarly, the fact that this interval increased and the rate at which $\dot{V}$ increased diminished after section of the sinus nerves suggests that other H^+ or P_{CO_2} sensitive receptors having different response times function at this age. These may well be the medullary chemoreceptors.

There was no relation between any of these responses and the age of the lamb.

DISCUSSION

There are relatively little data on the respiratory response of the new-born to inhaled CO_2. Stahlman (1961) used a steady-state method and when her results are replotted, it appears that the new-born infant

increases $\dot{V}$ in response to inhaling up to 4 % CO_2 by between 0·04 and 0·11 l. min^{-1} kg^{-1}mm Hg P_{A, CO_2}^{-1}. Avery *et al.* (1963) found an average increase in $\dot{V}$ of 0·045 l. min^{-1}.kg^{-1} mm Hg P_{A, CO_2}^{-1} and though this is a lower figure than the average for new-born lambs, the results may be more comparable when it is remembered that Avery *et al.* (1963) used a non-steady state method and that the infants breathed high oxygen. Both these factors would diminish the respiratory response to inhaled CO_2 (Tenney, 1963).
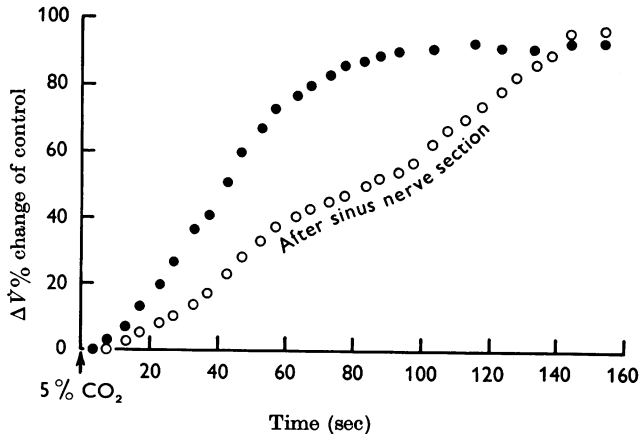

Fig. 7. The time course of $\Delta \dot{V}$ (% of control) before (filled circles) and after (open circles) bilateral section of the sinus nerves. 5 % CO_2 in air given, t = 0. Lamb, 4 hr after birth; pentobarbitone sodium.

Cross *et al.* (1954) observed that new-born infants responded to the inhalation of CO_2 with an increase in respiratory minute volume, but these authors were not in a position to measure the sensitivity of this response. They observed that, when the infants inhaled 0·5 % CO_2 and also a low oxygen mixture, the increase in $\dot{V}$ was reduced or abolished. They concluded that interaction between hypoxia and CO_2 did not take place in the new-born as it had been shown to occur in adult man (Neilsen & Smith, 1952). Further, this response of the new-born apparently afforded further confirmation of their previously expressed hypothesis that the fall in $\dot{V}$ observed when infants inhaled low oxygen mixtures was due to medullary depression. It is probable that the explanation for this phenomenon is more complex than the straightforward effects of hypoxia since Dawes & Mott (1959) and Adamsons (1959) subsequently showed that the respiratory response of the new-born to hypoxia was critically dependent on the environmental temperature at which the experiments were carried out. When the temperature was in the neutral range, i.e. where metabolism was basal, the respiratory response was as in the adult; and this has been

confirmed in the new-born lamb (Purves, 1966*b*). The results from this present paper show clearly that the respiratory responses to CO_2 is enhanced by hypoxia until very low oxygen tensions are reached. Thus, there was a clear distinction between the response in lamb 17, aged 20 hr (Fig. 3*d*) at P_{a, O_2} of 43 and of 21 mm Hg. The latter response in which S was severely reduced must be considered as an example of a genuine and probably central depression of respiration.

The resting values for P_{a, CO_2}, pH_a and arterial $[HCO_3^-]$ in the new-born lamb in this and the two previous papers (Purves, 1966*a, b*) show that the new-born lamb resembles the new-born infant and both differ from the adult in a number of important respects. Thus in both the new-born lamb and infant there is a non-respiratory acidosis shortly after birth which follows birth asphyxia. In both species, this is corrected in 24–48 hr (Graham & Wilson, 1954; Weisbrot, James, Prince, Holaday & Apgar, 1958; Reardon, Baumann & Haddad, 1960). Most of these and other studies on the new-born infant have concentrated on the changes which occur in the first 2 or 3 days after birth but the data of Reardon *et al.* (1960) show that the non-respiratory acidosis is followed by a compensated respiratory alkalosis where the pH_a is normal and both the arterial P_{CO_2} and HCO_3^- are markedly reduced. A similar acid–base pattern was found in the lamb up to the tenth day after birth.

What is the nature of the excess stimulus to ventilation? Measurement of P_{a, O_2} in normal new-born infants after the third day has been scanty. Reardon *et al.* (1960) found that six out of the thirteen infants studied had a P_{a, O_2} of less than 78 mm Hg between the second and sixth days. A low mean P_{a, O_2} (70–75 mm Hg) was more obvious in the new-born lamb up to the tenth day after birth. The respiratory response to this, as judged by the level of P_{a, CO_2} would be consistent with that of adult man acclimatized to this P_{a, O_2} (e.g. Fitzgerald, 1913). It will require more complete measurement of the P_{a, O_2} of normal new-born infants to show whether the low P_{a, CO_2} observed by the authors cited above can be similarly explained.

It was unfortunately not possible to measure the respiratory response of the unanaesthetized adult sheep to CO_2. They were reluctant to lie quietly even with training and preliminary CO_2 response curves showed such a wide scatter that it was clear that steady-state points were unlikely to be achieved. However, comparison of the results of the CO_2 response of the new-born lamb to that of adult man has thrown some light on the nature of the respiratory drive and of the participation of the peripheral chemoreceptors in this.

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<div align="center">

The $\dot{V}/P_{a,CO_2}$ slope, S

</div>

Figure 6 shows that the relation between S and P_{a,O_2} is described by a rectangular hyperbola whose shape and position is similar to that relating chemoreceptor discharge and P_{a,O_2} in the anaesthetized cat (Eyzaguirre & Lewin, 1961); $\dot{V}$ and P_{A,O_2} in adult man (Cormack *et al.* 1957) and in the new-born lamb whose level of P_{A,CO_2} has been raised above control (Purves, 1966*b*). The relation between S and P_{a,O_2} is expressed in the equation

$$S = D\{(1 + A/(P_{a,O_2} - C)\} \quad \text{(Lloyd *et al.* 1958).}$$

The values for the parameters A, C and D have been calculated from the average of the values for S and P_{a,O_2} for the experiments listed in Table 1 and have been found to be

$$A = 16 \cdot 8 \text{ mm Hg } P_{a,O_2},$$
$$C = 38 \text{ mm Hg } P_{a,O_2},$$
$$D = 0 \cdot 054 \text{ l. min}^{-1}.\text{kg}^{-1}.\text{mm Hg } P_{a,CO_2}^{-1}.$$

The line *b* (of slope AD and intercept D) for the lambs has been plotted (Fig. 8*a*) on the same axes for S and $1/(P_{a,O_2} - C)$ as similarly constructed slopes from the data of Milledge (1963) for man at sea level (slope *c*) and
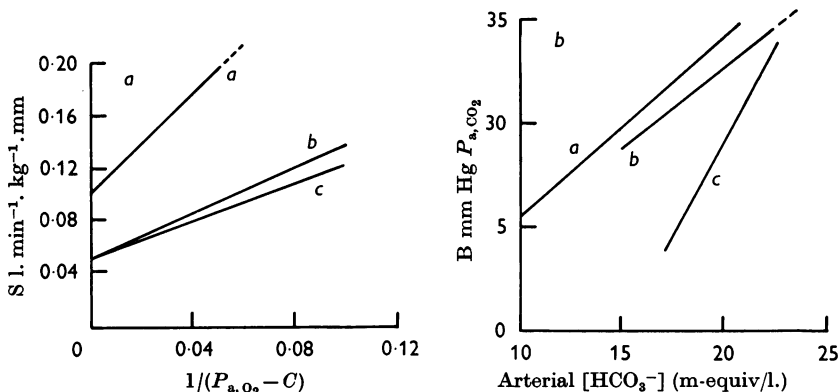

Fig. 8. (*a*). The relation between S and $1/(P_{a,O_2} - C)$ for the group of thirteen unanaesthetized new-born lambs (slope *b*), man at sea level (slope *c*) and man at 19,000 ft (5791 m) (slope *a*). The slope $AD + D$ of line *b* for the lambs was calculated from the average of values for S and P_{a,O_2} (given in Table 1) using the equation $S = D(1 + A/(P_{a,O_2} - C))$. The slopes for man were drawn from the data of Milledge (1963).

(*b*). The relation between B and arterial plasma $[HCO_3^-]$. Slope *a* is the regression line of B upon $[HCO_3^-]$ for thirteen unanaesthetized new-born lambs. Slope *b* was drawn from the data of Cunningham, Shaw, Lahiri & Lloyd (1961) for man during ingestion of NH_4Cl and recovery and slope *c* is the mean slope for three subjects 90 and 4340 m above sea level (Kellogg, 1963).

at 19,000 ft (5791 m) (slope a). Although the comparison is not intended to be more than qualitative, the similarity of the slopes for the lambs and for man at sea level is remarkable and if further studies, particularly on the new-born infant, can demonstrate that this similarity is not a mere coincidence, these results would provide further evidence that the new-born lamb responds to inhaled CO_2 as man does at or slightly above sea level.

For the reasons fully discussed by Lloyd *et al.* (1958) and by Lloyd & Cunningham (1963) the similarity of the curves is strong evidence that the respiratory response of the new-born lamb to the combination of hypoxic and CO_2 stimuli is mature in the lamb and that the peripheral chemo-receptors function at or shortly after birth.

The relation between B and arterial [HCO₃⁻]

Values for B were found to be 2–4 mm Hg lower than resting P_{a, CO_2}, i.e. when the lambs were at ambient P_{O_2}. B was only slightly affected by acute hypoxia; it was not related to the age of the lamb or to the level of arterial pH. It was significantly related to arterial [HCO₃⁻] (Fig. 4) and, as is shown in Fig. 1, arterial [HCO₃⁻] was reduced below adult levels up to the tenth day after birth. It is therefore probable that B was significantly reduced by comparison to the adult, Such a reduction in the value for B has been found after ingestion of NH_4Cl (Lerche, Katsaros, Lerche & Loeschcke, 1959; Cunningham *et al.* 1961), during exercise while breathing air (Asmussen & Neilsen, 1957), during pregnancy and after the administration of progesterone (Döring & Loeschcke, 1947), during sustained exposure to altitude (Reed & Kellogg, 1958; Kellogg, 1963). Of these factors, the effects of progesterone have been virtually excluded by Stahlmann (1961). A low arterial pH cannot explain the low values for B since this was only seen in the first day or two after birth.

The regression line of the relation between B and arterial [HCO₃⁻] in new-born lambs has been plotted (Fig. 8b, slope a) on the same axes as comparable lines obtained from the data of Cunningham *et al.* (1961) on man before, during and after ingestion of NH_4Cl (slope b) and from the data of Reed & Kellogg (1958) and Kellogg (1963) on adult man at 90 m and at altitude (4340 m) above sea level (slope c). This shows that the slope for the lambs was shifted to the left of the others and this was due to the mixed respiratory acidosis and a compensated respiratory alkalosis present in lambs, particularly shortly after birth. The slope is slightly greater than that of Cunningham *et al.* (1961) and less than that of Reed & Kellogg (1958). Thus, in this respect also, the values obtained for the lamb are consistent with those in man adapted to a mild reduction in P_{a, O_2}.

The possible role of the carotid body chemoreceptors in the response to CO_2

In early experiments (Hemyans, Bouckaert & Dautrebande, 1930; Sella-durai & Wright, 1932; von Euler & Lilljestrand, 1936), it was concluded that the peripheral chemoreceptors were not essential in the response to inhaled CO_2 since the respiratory response was unchanged before and after vagotomy and carotid chemoreceptor denervation. More recently, and with more refined techniques, it has become clear that the peripheral chemoreceptor contribution to the response to CO_2 cannot be ignored. Thus Fitzgerald, Zajtchuck, Penman & Perkins (1964) have shown that the respiratory response to the intracarotid injection of hypercapnoeic blood is abolished after sinus nerve section. Leitner, Pages, Puccinelli & Dejours (1965) have also shown that in the adult cat, the respiratory response to inhaled CO_2 is more sluggish after section of the sinus nerves.

The results in the present paper confirm this view. Thus, although the numbers were few, there was a consistent change in response after bilateral section of the sinus nerves; the sensitivity to CO_2 was reduced, the respiratory lag and time constant of the rate of increase in $\dot{V}$ were approximately doubled. It is therefore probable that future experiments will reveal that the dynamic response to inhaled CO_2 in the new-born is composed of a variety of components with differing response times as has been shown in the adult (Lambertsen, Gelfand & Kemp, 1965).

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