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HYPOXAEMIA AND AORTIC CHEMORECEPTOR FUNCTION IN FOETAL LAMBS

BY G. S. DAWES, SHEILA L. B. DUNCAN, B. V. LEWIS, CLAUDIE L. MERLET,* J. B. OWEN-THOMAS† AND J. T. REEVES‡

From the Nuffield Institute for Medical Research, University of Oxford

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SUMMARY

1. In foetal lambs the effect of raising and lowering arterial P_{O_2} (by varying the O_2 content of the maternal inspired gas mixture) was studied in order to determine whether the systemic arterial chemoreceptors regulated the circulation.

2. From 0·7 of term relative hypoxaemia (e.g. reducing carotid P_{O_2} from 40 to 20 mm Hg) caused a rise of arterial pressure and femoral vasoconstriction. These changes were unaffected or even increased by bilateral section of the nerves from the carotid sinus and body. They were abolished by section of the vagi or aortic nerves.

3. It is concluded that in foetal lambs during the last third of gestation the circulation is under reflex control by the aortic chemoreceptors.

INTRODUCTION

In a previous paper (Dawes, Lewis, Milligan, Roach & Talner, 1968) cyanide was used to provoke cardiovascular changes in foetal lambs. It was concluded that the aortic chemoreceptors were active, and that they might represent the first foetal line of defence in blood gas homoeostasis. The present experiments were designed to test this hypothesis, by examining the response of foetal lambs to hypoxaemia before and after section of the afferent nerves from the systemic arterial chemoreceptors. A brief account of some of these observations has appeared elsewhere (Dawes, Duncan, Lewis, Merlet, Owen-Thomas & Reeves, 1968).

* Attachée de Recherches à l' I.N.S.E.R.M., Paris.

† Nuffield Department of Anaesthetics, Oxford.

‡ Present address: Department of Medicine, University of Kentucky, Lexington, Kentucky, U.S.A.

METHODS

Twenty-two foetal lambs (of a Clun-Hampshire cross-breed) of 84–141 days gestation age (term is ~ 147 days), weighing 0·57–5·6 kg were studied under light chloralose anaesthesia administered to the maternal ewe (British Drug Houses; $23 \pm 1{\cdot}5$, S.E., mg/kg I.V. initially). Further small doses of chloralose were given at intervals of 1–2 hr; these caused no discernible changes in foetal arterial pressure, blood gas tensions or femoral flow.

In six lambs (123–137 days gestation) only the head, neck and one leg were delivered from the uterus through small amniotic incisions, so that a sleeve of amnion was drawn over the extremity. Loss of amniotic fluid was minimized by sewing the skin to the uterine wall. The remaining lambs were wholly delivered from the uterus and were placed on a warmed table alongside the mother. In both groups the umbilical cords were intact. Exposed surfaces were covered so far as possible with cellulose wadding (Cellosene B.P.), and a long saline-filled open-ended cannula was inserted into the trachea.

External flow circuits. A foetal femoral artery was exposed and divided and heparin (10 mg/kg) was injected intravenously. The peripheral end of the femoral artery was joined by an external circuit of plastic materials (polyvinyl, polyethylene and Perspex) either to its central end (five lambs), or to the central end of an axillary artery (eleven lambs) or common carotid (the six lambs still partly *in utero*). (Blood flow to the distal end of the tied carotid is ensured by the large occipito-vertebral and other anastomoses in lambs; Waites, 1960).

Arterial pressure in the flow loop, central venous pressure (from a catheter passed into the thoracic superior vena cava) and amniotic fluid pressure (in lambs partly *in utero*) were measured with calibrated strain-gauge transducers. Femoral blood flow was measured with a cannulated electromagnetic flowmeter (Wyatt, 1961) using a gauge head of 2 mm internal diameter, with a full scale meter deflexion (equivalent to an output of 42 μV r.m.s.) for a flow of 20 ml./min on the most sensitive range. The stability was good, neither base line nor sensitivity varying more than 2% over the period of an experiment, and resistance to flow in the external circuit was very low compared with that of the hind limb. Heart rate was recorded from the arterial pressure pulse (Wyatt, 1957). Pressures, femoral blood flow, heart rate and maternal end tidal P_{CO_2} (measured with a Beckman Medical Gas Analyser LB-1, calibrated with gases containing known percentages of CO_2) were recorded on a Schwarzer polygraph. A vertical tube was attached to the external flow loop. At intervals blood was drawn into this vertical tube, arterial inflow was arrested, and a femoral arterial pressure–flow curve was recorded during free flow from the vertical tube over the physiological range of pressures and flows (as already described; Dawes, Lewis, Milligan *et al.* 1968).

Blood samples. Arterial samples (0·3–0·5 ml.) were obtained anaerobically simultaneously from a medial plantar artery of the ewe and a branch (axillary or carotid) of the ascending aorta of the lamb. They were analysed at once for pH, P_{O_2} and P_{CO_2} using a Radiometer ultra-micro-electrode assembly. The observations were corrected for any difference between the temperatures of the electrodes and the rectal temperature of the lamb and ewe (usually 39·5–40·5° C). Maternal haematocrit averaged $27 \pm 1{\cdot}4$% (S.E.); it fell slightly on induction of anaesthesia, a little more than anticipated from the volume of fluid injected, but recovered within the next hour. Foetal haematocrit averaged $38 \pm 2{\cdot}1$% (S.E.).

Nerve section. The nerves from the carotid body and sinus, the cervical vagi or vago-sympathetic trunks, or the aortic nerves were prepared before heparin was given or the flow loop was inserted. The vagi were identified in the neck either before or after junction with the cervical sympathetic nerves. To expose the aortic nerves, the second to fourth ribs were removed, and the nerves were identified as they joined the main vagus trunk. On the left side the junction is just caudal to the left subclavian artery and the nerve runs medially to pierce the pericardium lateral to the origin of the brachiocephalic artery from the aorta; occasionally there is more than one branch. On the right side it arises from the vagus just

below the level of the first rib, between the superior vena cava and the brachiocephalic artery; it then runs along the brachiocephalic artery to pierce the pericardium with other vagal and sympathetic branches.

RESULTS

The effect of hypoxaemia in foetal lambs. The maternal ewe was given either 100% O_2 or an O_2-enriched air mixture initially to raise foetal arterial (ascending aorta) P_{O_2} above 30 mm Hg. Relative foetal hypoxaemia was then induced by giving the ewe lower oxygen mixtures to breathe for 6–10 min. The ewe then hyperventilated and her arterial P_{CO_2} fell, and hence that of the foetus also fell. Thus foetal hypoxaemia was accompanied by hypocapnia (e.g. Fig. 1). This was minimized (when the O_2 content of maternal inspired gas was reduced below 21%) by adding CO_2 to maintain the maternal end-tidal P_{CO_2} approximately constant. In seventeen foetal lambs of 121–141 days gestation during hypoxaemia arterial P_{CO_2} fell by a mean of 3 ± 1 mm Hg (S.E.); pH rose by $0{\cdot}04 \pm 0{\cdot}007$.

A reduction in foetal arterial P_{O_2} caused a considerable rise in arterial pressure, a fall in femoral blood flow due to vasoconstriction and, usually, tachycardia in lambs of 122–141 days gestation, $0{\cdot}82 - 0{\cdot}96$ of term (e.g. Fig. 1). Figure 2 shows the femoral arterial pressure–flow curves of the experiment illustrated in Fig. 1. Central venous pressure was measured in eleven lambs; the changes during hypoxaemia (usually a fall of not more than 1 mm Hg when the foetal arterial P_{O_2} was reduced to 20–25 mm Hg) were small. The heart rate rose when the foetal arterial P_{O_2} was reduced to 30 mm Hg, sometimes dramatically as in Fig. 1. When the P_{O_2} was reduced further, arterial pressure rose further and the heart rate fell. Hence the mean rise in rate when the P_{O_2} was lowered by 10 mm Hg in ten lambs near term (Table 1) was smaller than might otherwise have appeared.

The effects of hypoxaemia were the same whether the foetus was only partly (head, neck and one leg) or wholly delivered from the uterus, and whether the external femoral flow circuit was constructed between the peripheral end of a femoral artery and its central end or that of an axillary or carotid artery. All results have, therefore, been combined. Episodes of hypoxaemia, repeated at intervals of 20–30 min, caused responses which were similar, though foetal arterial P_{O_2} and femoral flow tended to decline gradually over a period of 2–3 hr from completion of the preparation.

Figure 3 illustrates the change in response to hypoxaemia with age. The responses were invariably large at 132–141 and at 121–127 days gestation. Also in both of two lambs of 104 and 110 days gestation, 0·71–0·75 of term (not shown in Fig. 3) hypoxaemia caused a clear, but small, rise of blood pressure and heart rate accompanied by femoral vasoconstriction.

In two twin lambs of 84 days gestation, 0·57 of term (Fig. 3), arterial pressure fell slightly during hypoxaemia (P_{O_2} range 36–21 mm Hg) and there was evidence of femoral vasodilatation, but this was accompanied by a small rise in heart rate.

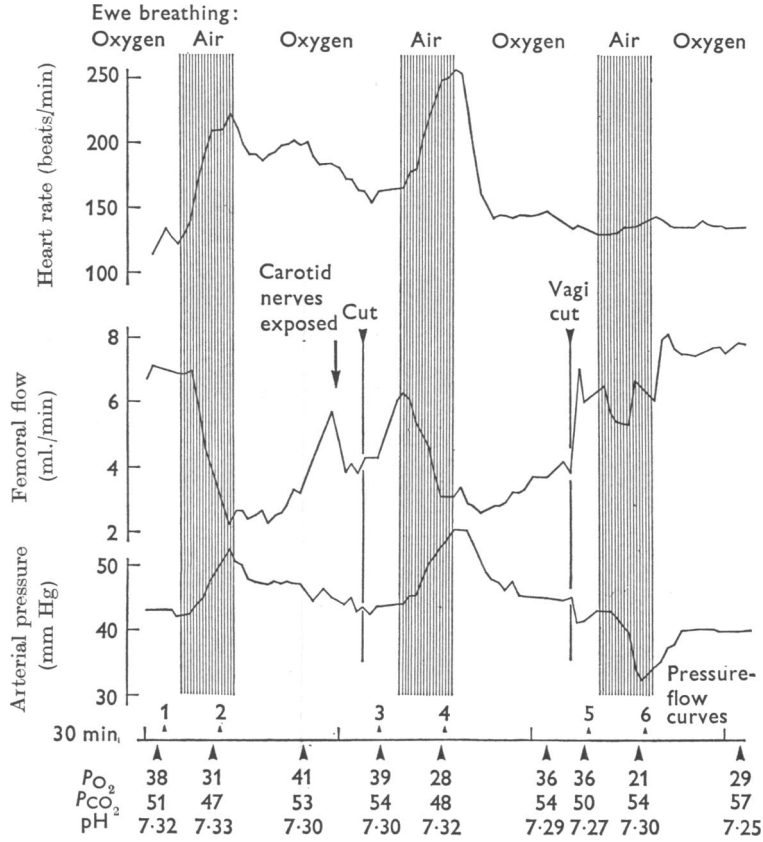

Fig. 1. Foetal lamb 127 days gestation age, 2·2 kg body weight, 225 g hind-limb weight, head and leg only delivered from the uterus. Relative hypoxaemia, by giving the maternal ewe air in place of 100% O_2 to breathe, caused tachycardia and femoral vasoconstriction, which persisted after carotid denervation but was abolished by cutting the vagi. The corresponding femoral pressure–flow curves taken as indicated by the small numbered arrows are shown in Fig. 2. The large arrows below the abscissa show the times at which blood samples were taken.

The effect of carotid denervation, vagotomy and aortic nerve section on the response to hypoxaemia. Section of the carotid nerves (the nerves of Hering) bilaterally in six lambs did not alter arterial pressure significantly; there was usually a rise in hind-limb vascular resistance. After carotid nerve section the rise in arterial pressure during hypoxaemia was on average greater, and the rise in hind-limb vascular resistance as great as with the

nerves intact. These results are illustrated in Figs. 1 and 2 for a lamb of 127 days gestation. (The fall in femoral flow just before section of the carotid nerves in Fig. 1 was associated with manipulations to expose them.) Figure 4 summarizes the effect of carotid nerve section on arterial pressure in lambs of 132–141 days gestation; and Table 2 shows the statistical data on hind-limb vascular resistances, which are depicted graphically in Fig. 5. Hypoxaemia caused a highly significant ($P < 0{\cdot}001$) increase in resistance

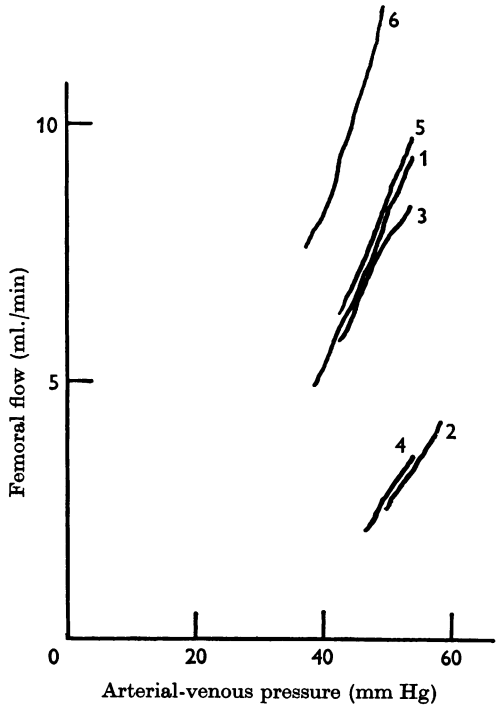

Fig. 2. Femoral pressure–flow curves from the experiment illustrated in Fig. 1, at a P_{O_2} of 36-39 (1, 3, 5) and at a P_{O_2} of 21–31 before nerve section (2), after carotid nerve section (4) and after vagotomy (6).

TABLE 1. Effect of relative hypoxaemia in ten lambs of 132–141 days gestation

	Ewe breathing	
	O_2 or O_2-enriched air	Air or low O_2 mixture
Foetal arterial		
P_{O_2} (mm Hg)	37·8 ± 0·5	28·4 ± 0·9
P_{CO_2} (mm Hg)	48·7 ± 1·5	47·9 ± 1·1
Pressure (mm Hg)	50·8 ± 2·3	59·8 ± 2·7
Heart rate (beats/min)	196 ± 13	215 ± 13
Increase in heart rate	—	18·3 ± 8·1

Means ± S.E.

(shown by a fall in the slope of the pressure–flow curve), which still persisted after carotid nerve section.

Bilateral section of the cervical vagi or vago-sympathetic trunks in lambs near term always caused a fall in arterial pressure (which averaged

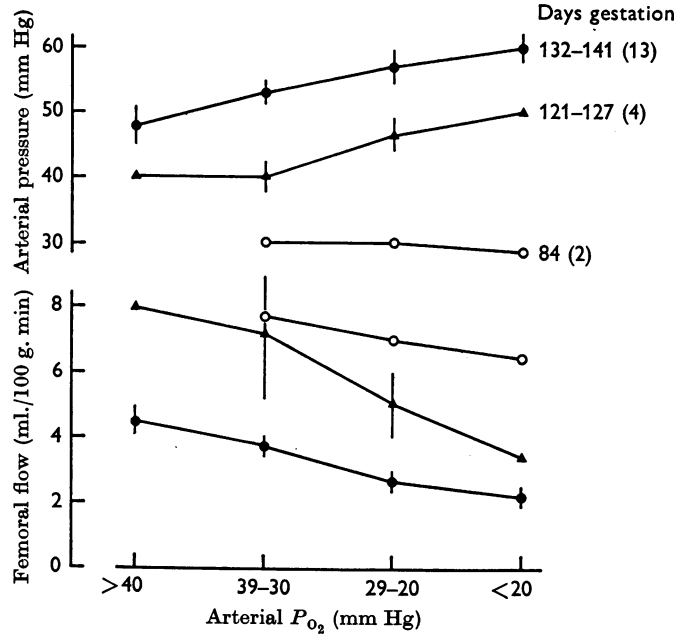

Fig. 3. Changes in systemic arterial pressure and femoral blood flow with variations of ascending aortic P_{O_2} in lambs of different gestation ages. The figures in brackets indicate the numbers of lambs, and the vertical lines ±S.E.

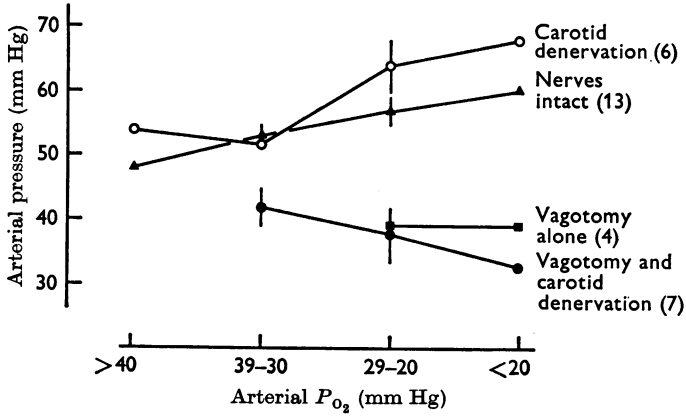

Fig. 4. Changes in systemic arterial pressure with variations in ascending aortic P_{O_2} in lambs of 132–141 days gestation before and after nerve section. The figures in brackets indicate the numbers of lambs, and the vertical lines ±S.E.

22 %, Table 3) and a considerable fall in heart rate accompanied by an increase in femoral blood flow (average 20 %). In younger lambs, of 122–127 days, the initial arterial pressure was less and femoral flow per 100 g hind limb was more than double; the arterial pH and P_{CO_2} values were rather better on average, but the mean P_{O_2} was less (Table 3). On vagotomy the mean fall in arterial pressure (9 %) and rise in femoral flow (9 %) were less, but the fall in heart rate was of similar size. The results of vagotomy in lambs near term were quantitatively similar whether or not the carotid nerves were already cut.

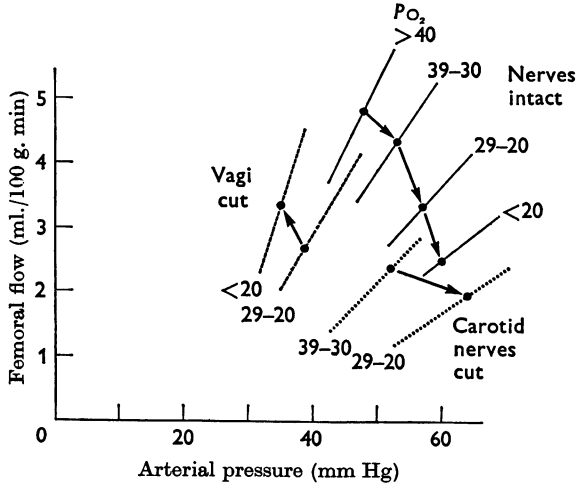

Fig. 5. Arterial pressure–femoral flow (per 100 g leg weight) diagram to illustrate the mean variations in the pressure–flow curves of mature lambs subjected to relative hypoxaemia before (continuous line) and after section of the carotid nerves (dotted line) or vagi (interrupted line), from the data of Table 2. The filled circle indicates the mean arterial pressure in each group.

TABLE 2. Effect of hypoxaemia on hind-limb vascular resistance in foetal lambs of 132–141 days gestation before and after section of the carotid nerves and/or vagi

	No. of observations	Arterial P_{O_2} (mm Hg) Range	Arterial P_{O_2} (mm Hg) Mean	Pressure intercept (mm Hg)	Slope of pressure–flow curve (ml./min 100 g per mm Hg)
Nerves intact (12 lambs)	10	40–44	41	24 ± 2·2	0·204 ± 0·027
	39	39–30	35	24 ± 1·2	0·153 ± 0·022
	22	29–20	27	27 ± 1·8	0·112 ± 0·014
	5	< 20	15	29 ± 5·1	0·081 ± 0·018
Carotid nerves cut (5 lambs)	12	39–30	34	30 ± 2·6	0·106 ± 0·012
	6	29–20	26	35 ± 6·0	0·069 ± 0·008
Vagi and/or aortic nerves cut (10 lambs)	23	29–20	25	22 ± 1·5	0·160 ± 0·015
	17	< 20	16	25 ± 2·0	0·326 ± 0 051

Means ± S.E.

In five additional lambs of 134–140 days gestation the aortic nerves were cut either bilaterally (three lambs) or unilaterally after section of the contralateral vagus. The range of initial blood gas values was similar to that in the mature lambs of Table 3. When the nerves were cut arterial pressure and heart rate fell and femoral flow rose; these changes were as great or greater than those observed on bilateral vagotomy in lambs of the same age. When the remaining vagi or vagus was then cut there was no further fall in arterial pressure or rise in femoral flow, but heart rate increased (presumably because the efferent inhibitory fibres to the heart

TABLE 3. Immediate effect of bilateral section of the cervical vago-sympathetic trunks of foetal lambs on blood gas values and the circulation

	pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	Arterial pressure (mm Hg)	Femoral flow (ml./100 g. min)	Heart rate (beats/min)
9 lambs of 122–141 days						
Initial values	7·28	53	33	55	1·87	194
	±0·01	±2	±2	±3	±0·21	±18
Change on vagotomy	−0·04	+2	−3	−12	+0·37	−34
	±0·01	±2	±1	±3	±0·02	±15
4 lambs of 122–127 days						
Initial values	7·34	47	29	44	4·62	219
Change on vagotomy	−0·01	0	0	−4	+0·40	−48

Means (±S.E. where relevant); measurements were made before and 5–10 min after vagotomy.

were cut). This evidence suggests that the immediate effect of vagal section on arterial pressure and hind-limb vascular resistance can be attributed wholly to interruption of afferent fibres in the aortic nerves.

Section of the cervical vago-sympathetic trunks and/or aortic nerves abolished the rise in arterial pressure and hind-limb vasoconstriction during hypoxaemia in all twenty lambs from 104 to 141 days gestation. Indeed after nerve section hypoxaemia caused a fall of arterial pressure and femoral vasodilatation (Figs. 1, 2 and 5). In lambs in which the initial heart rate was low, and in which hypoxaemia had caused a large increase, this increase was abolished by vagotomy (e.g. Fig. 1). In the majority initial heart rate was already relatively high, and the changes in heart rate with hypoxaemia were complex; after vagotomy hypoxaemia was often accompanied by a small rise in heart rate from a lower level.

In six of nine lambs near term, whose cervical vagi were cut, arterial pressure fell 21–55 %. The pressure fell further during the next bout of hypoxaemia and did not fully recover; their condition deteriorated as evidenced by a continued fall in arterial P_{O_2} and pH and rise in P_{CO_2} during the next 30–40 min. The starting condition of this group of lambs (Table 3)

was reasonably satisfactory, and there was no reason to suppose that they would have deteriorated so rapidly in the absence of vagotomy.

Arterial pressure and gestational age. The foregoing results show that foetal arterial pressure is dependent on arterial P_{O_2} over a wider range than hitherto supposed, and this relationship is variable with age. Figure 6 (●) shows the relation between arterial pressure and age in thirty-one lambs under light chloralose anaesthesia (sixteen from the present paper and the

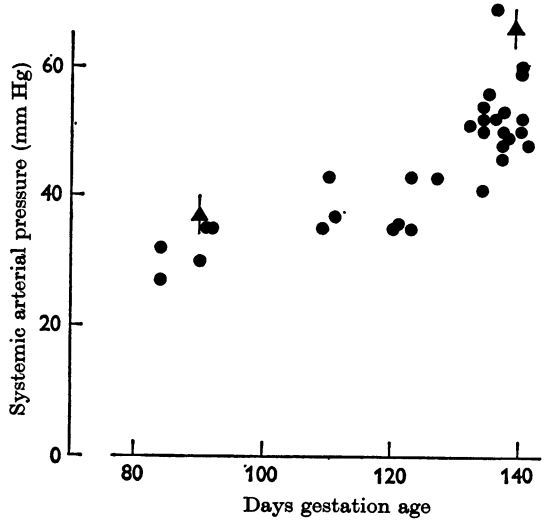

Fig. 6. Systemic arterial pressure in lambs of different gestational ages under light chloralose anaesthesia at an arterial P_{O_2} (35 ± 3 mm Hg, ●) elevated by giving the mother O_2-enriched air to breathe, for comparison with previous observations when the mother breathed air only (▲, ±S.E. from Dawes & Mott, 1964).

remainder from experiments under similar conditions) whose carotid arterial P_{O_2} had been raised to 35 ± 3 mm Hg, with P_{CO_2} $48 \pm 0{\cdot}8$ (S.E.) mm Hg. For comparison the mean and S.E. are shown of previous observations on twenty-two lambs ~ 90 days and ten lambs ~ 140 days gestation, delivered under chloralose anaesthesia from ewes breathing air (▲; Dawes & Mott, 1964).

In thirty-four lambs of 140 ± 2 days gestation delivered from ewes breathing air, there was a highly significant correlation between arterial blood pressure and foetal weight (Dawes, 1968; p. 178 and Fig. 80). But when the arterial P_{O_2} was raised, as in the eighteen lambs of 132–141 days gestation of Fig. 6, this correlation was not significant ($r = 0{\cdot}17$). This suggests that the higher arterial pressure of heavier lambs near term delivered from mothers breathing air is a consequence of a relatively lower arterial P_{O_2}.

DISCUSSION

The results add support to the hypothesis that, during the latter part of gestation in foetal lambs, the circulation is under reflex control by the aortic chemoreceptors. Section of the vagi abolished the response to hypoxaemia. The conclusion that this was due to interruption of afferent nerves from the aortic bodies, rather than other vagal afferents, depends mainly on the fact that cutting the aortic nerves abolished the response. Also in both foetal lambs and adult animals subjected to haemorrhage, the fall of arterial pressure on cervical vagotomy is attributed to interruption of tonic activity from the aortic chemoreceptors (Dawes, Lewis, Milligan *et al.* 1968). The aortic nerves were identified in lambs by their anatomical location, by following their course to the periphery with the aid of a dissecting microscope, and by recording multifibre activity with a prominent systolic peak frequency, characteristic of aortic depressor fibres. The aortic nerves gave branches to the aortic arch and to a network between the pulmonary trunk and the aorta. A more detailed histological investigation of this area and of its blood supply is needed, together with better records of the impulse traffic in foetal aortic nerves.

The facts at present available suggest that the range of arterial P_{O_2} values over which the aortic chemoreceptors are active in mature foetal lambs is high, up to 40 mm Hg. It is possible that they might still be active at even higher P_{O_2} values, but to raise the foetal P_{O_2} further would require either a hyperbaric oxygen chamber or some form of cross-circulation. It would appear that the range of P_{O_2} values over which the foetal aortic chemoreceptors operate is not very different from that in adult animals, even though the normal P_{O_2} in the ascending aorta of mature foetal lambs is only 20–25 mm Hg when the mothers breathe air. The factors which determine the range of aortic chemoreceptors before birth are unexplored. No systematic study of the effect of variations in arterial pH or P_{CO_2} has been undertaken, though limited observation suggests that changes in P_{CO_2} upwards from 40 mm Hg have little effect.

The relatively high mean value of foetal arterial P_{CO_2} (e.g. Table 1) calls for comment. In the anaesthetized lamb foetal arterial P_{CO_2} is greater than that of the mother by 9 mm Hg on average (Dawes, 1968). We chose to conduct the experiments with the ewes breathing spontaneously under chloralose anaesthesia. Their mean arterial P_{CO_2} was $36{\cdot}4 \pm 1{\cdot}1$ mm Hg; this rose to $40{\cdot}5 \pm 1{\cdot}3$ mm Hg when they were given high oxygen mixtures to breathe, as a result of hypoventilation when their arterial P_{O_2} rose from $\sim$ 90 to $>$ 150 mm Hg.

Section of the aortic nerves interrupts not only chemoreceptor afferent nerves, but also afferents from aortic baroreceptors whose activity must

limit the rise in arterial pressure on chemoreceptor stimulation. When arterial pressure rises during hypoxaemia, baroreceptor activity will introduce a second order reflex fall in heart rate and systemic vascular resistance. Section of the cervical vagi will, in addition, cut afferents from the pulmonary baroreceptors and left ventricle which probably have the same action as the aortic depressor nerves. After section of the vagi or aortic nerves, hypoxaemia causes a fall in arterial pressure and femoral vasodilatation (Fig. 5), presumably due to a direct effect on the blood vessels and possibly on the heart also. Therefore, the rise in arterial pressure and femoral vasoconstriction during hypoxaemia are even more striking than at first appears.

Section of the carotid nerves, when the vagi are intact, somewhat increases the response to hypoxaemia. The carotid nerves carry baroreceptor (as well as chemoreceptor) afferents, and the increased activity of the baroreceptor afferents when arterial pressure rises during hypoxaemia must limit the response. This consideration also must induce some caution before too readily concluding that the foetal carotid bodies are wholly inactive over the P_{O_2} range 40–20 mm Hg. A small degree of activity at P_{O_2}, say, 15–20 mm Hg might be effective synergistically with that of the aortic bodies, but not appear in the present experiments because nerve section cuts the baroreceptors at the same time. The observations in the succeeding paper (Dawes *et al.* 1969) demonstrate that foetal carotid chemoreceptors can be excited by injection of cyanide, and thus may be brought into action at a relatively lower arterial P_{O_2} (< 15 mm Hg).

The gestational age at which the effects of hypoxaemia on the circulation are first seen depends on the criteria employed. Born, Dawes & Mott (1956) found that the rise of arterial pressure during moderate hypoxaemia was insignificant at 90 days, but an increase in heart rate was still perceptible at ~ 75 days gestation; the present results agree. Reflex regulation of femoral flow is present at $\sim$ 90 days gestation, but is less than in older lambs (Dawes, Lewis, Milligan *et al.* 1968). The tachycardia observed during hypoxaemia in lambs of 75–90 days gestation could be due to the activity of some mechanism other than activity of the aortic chemoreceptors (e.g. direct liberation of catecholamines from the adrenals; Comline, Silver & Silver, 1965). We cannot determine from the information available whether the failure to observe a rise in arterial pressure and femoral vasoconstriction during hypoxaemia at 84 days gestation is due to inactivity of the aortic bodies, or to immaturity of the central nervous system or the efferent autonomic pathways or from all three in combination.

The results support the contention that, during the latter part of gestation in lambs, the maintenance of a relatively elevated arterial pressure, and hence of a high umbilical flow, depends on tonic aortic chemoreceptor

activity. In the extreme case of lambs delivered partly or wholly from the uterus, under general anaesthesia, and after manipulation and operation there is evidence to suggest that survival is dependent upon the proper operation of this mechanism. Section of the vagi or aortic nerves can lead to a rapid deterioration in physiological state. It remains to be seen whether in utero, without anaesthesia, towards term or during birth this mechanism offers an advantage. If it does we may suggest that the phylogenetic development of the aortic bodies in mammals may have resulted from their efficacy in regulating the foetal circulation in species with a relatively long period of gestation, rather than from any biological advantage in adult life.

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