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OXYGEN CONSUMPTION AND THE ARTERIAL OXYGEN SATURATION IN FOETAL AND NEW-BORN LAMBS

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Recently it has been shown that the oxygen consumption of new-born babies (Cross, Tizard & Trythall, 1955), puppies and kittens (Moore, 1956*a*, *b*) falls when they breathe gas mixtures of somewhat reduced oxygen content. Now the oxygen consumption of healthy adult mammals under ordinary conditions is independent of the oxygen tension of the circulating blood. Only when the oxygen pressure of the atmosphere is exceptionally low, as at great heights, is there evidence that oxygen tension may be a limiting factor to survival. The explanation of the observations on new-born animals is not therefore immediately obvious.

Three possibilities may be considered. First, it is known that the lungs of new-born animals are relatively inefficient. The oxygen tension of the circulating arterial blood may therefore have fallen greatly when the oxygen content of the inspired air has been reduced to 10–15%. Secondly, it is possible that a small reduction in the oxygen tension of the circulating blood may have reduced oxygen consumption by an action on the central nervous system (e.g. by reduction of muscle tone and inhibition of shivering). Thirdly, it may be that, in the new-born animal, the oxygen consumption of the tissues is directly limited by a comparatively small reduction in the arterial oxygen tension, smaller, that is, than in the adult animal. It is with the third of these possibilities that this paper is mainly concerned.

There is a further reason for interest in this problem. In the foetus the arterial blood is barely half saturated with oxygen, yet the relation between the arterial oxygen supply and oxygen consumption has never been studied. In the absence of this information it is impossible to assess the influence of foetal anoxaemia on survival.

We have therefore examined the relationship between arterial O_2 saturation and O_2 consumption in anaesthetized foetal and new-born lambs, under conditions in which shivering and muscular movements do not occur. A preliminary account has been given elsewhere (Acheson, Dawes & Mott, 1956).

METHODS

Foetal O_2 consumption was calculated from the umbilical blood flow and arteriovenous O_2 difference. Sixteen ewes (4 Suffolk, 1 Kerry Hill and the remainder Clun-Hampshire), 79–138 days pregnant, were anaesthetized by intravenous injection of 10 mg/kg sodium pentobarbitone; anaesthesia was maintained by an intravenous infusion of sodium pentobarbitone 10–20 mg/kg/hr. The foetus was delivered by Caesarean section and umbilical blood flow was measured in a venous occlusion plethysmograph, whose temperature was about 38° C (Dawes, Mott & Rennick, 1956), using a modification of the system described by Greenfield (1949) and Cooper & Greenfield (1949). Blood samples (0·8–1·0 ml.) were withdrawn from catheters in small cotyledonary branches of the umbilical arteries and veins. Four other Clun-Hampshire ewes, whose duration of pregnancy was not known, were anaesthetized and delivered in the same way; since the lambs weighed 3·47–6·63 kg they were probably within 2 weeks of term. Umbilical blood flow was measured by inserting a flow-meter into the abdominal umbilical vein (Dawes *et al.* 1956). Blood samples were withdrawn from a catheter in the femoral artery and from the tubing between the umbilical vein and the flow-meter. They were analysed for their O_2 content and capacity by a modification of the Barcroft–Haldane method, using Warburg manometers (Born, Dawes & Mott, 1955). The foetal arterial O_2 saturation was altered by supplying the ewe with gas mixtures of differing O_2 content through her tracheal cannula as described by Born, Dawes & Mott (1956).

The O_2 consumption of new-born lambs was measured by ventilating the lungs with positive pressure from a Starling Ideal pump, attached to a closed circuit filled with O_2, a soda-lime canister and a spirometer recording on a kymograph. Twelve lambs (2 Welsh and the remainder Clun-Hampshire) of 136–144 days gestation age were delivered by Caesarean section under pentobarbitone anaesthesia. Many of these lambs were placed in a bath warmer than 38° C to prevent shivering. Four lambs (Clun-Hampshire) born naturally 12 hr–3 days previously were anaesthetized by intravenous injection of 2–5 mg/kg sodium pentobarbitone, supplemented by a slow infusion of pentobarbitone. Body temperature was measured by a thermometer in the oesophagus. The temperature was raised by both radiant and conducted heat, and heat loss was reduced by wrapping the legs in cotton wool. Cooling was effected by removing external sources of heat, and, when necessary, by covering the lambs with wet muslin and placing ice in the axillae and groins. Blood samples were withdrawn for analysis of the O_2 content from a carotid arterial catheter. The lamb's arterial O_2 saturation was altered by varying the stroke of the respiration pump.

In nearly all experiments the blood pressure was recorded from a carotid or femoral artery with a condenser manometer, and the pulse wave was used to operate a heart rate meter (Wyatt, 1956*a*, *b*). These provided a valuable indication of the general condition of the lamb and of the depth of anaesthesia.

RESULTS

Oxygen tension and oxygen consumption

Foetal lambs. The O_2 saturation of the blood differs in different parts of the foetal arterial system; that in the carotid arteries is normally about 62%, in the umbilical arteries 58% and in the pulmonary trunk 52% under our experimental conditions (Dawes, Mott & Widdicombe, 1954). We have therefore selected, as the best single index of the tension of the O_2 supply to the foetal tissues, the O_2 saturation of the umbilical arterial blood.

Fig. 1 illustrates an experiment in which foetal O_2 consumption was determined at different levels of O_2 saturation in the umbilical artery. Anaesthesia was maintained at a steady level by means of a slow intravenous infusion of

sodium pentobarbitone into the ewe. After a period of equilibration, during which the ewe breathed air, blood samples were withdrawn simultaneously from the umbilical vein and artery. From the umbilical arteriovenous oxygen difference and the average of several measurements of umbilical blood flow made immediately before and after taking each pair of blood samples, the oxygen consumption of the foetus was calculated as follows:

$$O_2 \text{ consumption} = Q\ (v - a) \times C \text{ ml./min}, \qquad (1)$$

where Q = umbilical blood flow, ml./min,

v = umbilical venous O_2 saturation %,

a = umbilical arterial O_2 saturation %, and

C = O_2 carrying capacity of blood, ml./100 ml.

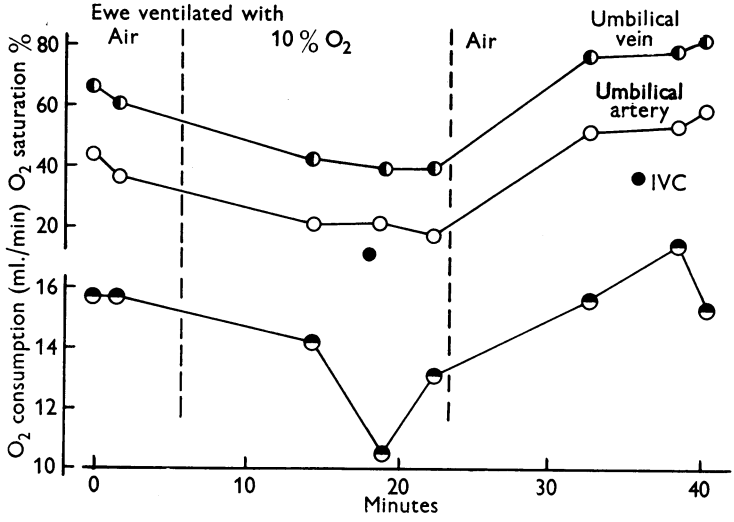

Fig. 1. Foetal lamb 611 B, 138 days gestation age, pentobarbitone anaesthesia. Blood samples from the umbilical vein (◑) and artery (○), and from the abdominal inferior vena cava below the entry of the hepatic veins (●) were analysed for O_2 content and capacity, while the ewe was ventilated with air or 10% O_2. The O_2 consumption (◓) was calculated from the umbilical blood flow and the arteriovenous O_2 difference.

When two or three such sets of observations had been completed, the oxygen saturation of the foetal blood was changed. In the instance depicted in Fig. 1, the ewe was given 10% oxygen in nitrogen to breathe and, after another period of equilibration, the umbilical blood flow and oxygen difference were measured. The observations were repeated when the ewe had been breathing air again for some time. Thus measurements of O_2 consumption at a low arterial oxygen saturation were bracketed between measurements made when the ewe was breathing air. The calculated O_2 consumption varied considerably,

even under equilibrium conditions. This variation was attributed to alterations in the estimated umbilical arteriovenous O_2 difference (which is small), resulting both from errors in measurement and from transient changes in the animal. Blood gas analyses were therefore duplicated and two or three sets of observations made at each level of arterial oxygen saturation. Fig. 1 shows that when the arterial saturation was reduced from a mean of about 48 to 20%, O_2 consumption fell. In this experiment there was no overlap between any of the values calculated for foetal O_2 consumption while the ewe was breathing 10% oxygen in nitrogen and those obtained when she breathed air.

Ten such experiments were performed in lambs of from 117 to 138 days gestation. They are summarized in the middle part of Table 1. The averages of the observations shown in Fig 1. are given near the foot of Table 1 (lamb 611B). Each figure in the table is the mean of several observations. Oxygen consumption varied considerably from one foetus to another. In order to relate oxygen consumption to umbilical arterial O_2 saturation in different lambs we have represented the O_2 consumption/kg of all foetal lambs as 100 when their umbilical arterial saturation was 48–60% (* in Table 1). The O_2 consumption of each animal at arterial O_2 saturations outside this range was then calculated and plotted against umbilical arterial saturation (Fig. 2). Oxygen consumption fell considerably when the arterial saturation was reduced below 35%.

Fig. 1 also shows that when the umbilical arterial O_2 saturation fell, the saturation in the abdominal inferior vena cava (below the entry of the hepatic veins, closed circles) also decreased to a low value. The systemic arteriovenous O_2 difference was reduced, as may be seen by comparing the O_2 saturation in the inferior vena cava (closed circles) with that in the umbilical artery (open circles). Similar observations were made in five foetal lambs, and are summarized in Fig. 3. As the O_2 saturation of umbilical arterial and venous blood was reduced, the saturation of inferior vena caval blood fell less rapidly (interrupted line of Fig. 3). The difference between the slope of the inferior vena caval regression line (0·71) and that of the umbilical arterial regression line (0·5) is highly significant ($P < 0{\cdot}01$). When the umbilical arterial O_2 saturation was less than 35%, the abdominal inferior vena caval saturation was less than 15%, corresponding to an O_2 partial pressure of, say, 10–13 mm Hg. It may be that the fall in O_2 consumption depends on a fall in the O_2 tension in the tissues below this level.

New-born lambs. The observations recorded in Fig. 2 suggested that O_2 consumption might rise even further if the arterial O_2 saturation were increased above 60%. However, the O_2 saturation of the umbilical arterial blood did not rise above 68% in the foetal lambs used in these experiments, even when the ewe was given 100% O_2 to breathe. We therefore separated lambs from their mothers and ventilated their lungs with 100% oxygen from a respiration

pump, to which were attached a spirometer and soda-lime canister. The O_2 content of the arterial blood was varied by changing the pump stroke. After allowing several minutes to elapse so that equilibrium was established, blood samples were withdrawn from the carotid artery and analysed to provide an index of the arterial O_2 tension.

Fig. 4 summarizes observations made on seven lambs newly delivered from their mothers (open circles) and on two lambs born naturally 1 and 3 days

TABLE 1. O_2 consumption of foetal lambs at different gestational ages and with different umbilical arterial O_2 saturations

Lamb no.	Age (days)	Weight (kg)	Umbilical blood flow (ml./min), Q	% O_2 saturation in umbilical		O_2 capacity (ml./100 ml. blood), C	O_2 consumption (ml./kg/min)
				Vein, v	Artery, a		
603B	79	0·32	35	89·5	55	9·1	3·4
607B	80	0·31	36	75	35	9·0	4·2
610A	81	0·27	33	78	47	11·0	4·2
601B	81	0·33	36	80·5	55	11·0	3·1
609A	84	0·40	59	79	38	9·1	5·5
608A	87	0·52	86	52	37	13·5	3·3
608B	87	0·52	70	69	43	12·5	4·4
612	117	2·13	178	80·5	52	15·6	3·7*
			211	91	63·5	15·4	4·2
638	119	3·71	394	83·5	50	14·0	5·0*
			430	56	29·5	13·8	4·2
683	126	3·33	323	48	30·5	16·4	2·8
			259	22·5	8·5	16·8	1·8
			282	80·5	58·5	17·5	3·3*
643	130	4·11	429	58·5	39	17·7	3·6
			433	80·5	59	17·5	4·0*
			417	43·5	27	18·2	3·1
606	131	3·79	388	54	31·5	16·3	3·8
			446	89	68	16·0	4·0
			311	75·5	48	16·4	3·7*
			366	67	45·5	16·6	3·4
649	132	4·36	491	75·5	49·5	16·4	4·8*
			436	94	65	16·1	4·7
628A	133	3·30	219	82·5	59·5	14·9	2·3*
			177	76	46	15·2	2·4
			160	55	24·5	14·6	2·2
653B	134	4·27	429	21	7·5	20·9	2·8
			415	78	54·5	20·5	4·7*
647B	135	3·66	342	75·5	51	11·5	2·6*
			309	44	22	11·7	2·2
611B	138	5·23	457	72·5	48·5	14·7	3·1*
			413	40·5	20	14·6	2·4
4118	†	6·63	490	89	53	16·7	4·4
459	†	4·92	340	93	68	15·6	2·7
456	†	4·22	303	81	48	17·7	4·2
458B	†	3·47	312	84	55	15·0	3·9

* Values taken as 100 for Fig. 2.

† The gestation age of these lambs was not known accurately; they were believed to be within 2 weeks of term, as the foetal weight suggests.

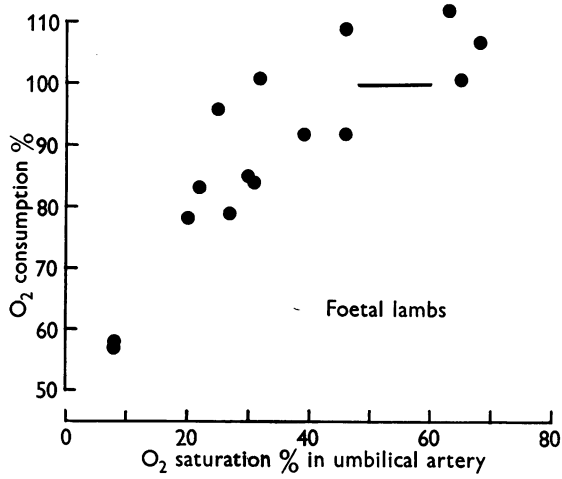

Fig. 2. Observations on ten foetal lambs, 117–138 days gestation age (see Table 1). The rate of O_2 consumption, expressed as a percentage of that observed when the umbilical arterial O_2 saturation was 48–60%, (—) has been plotted against the umbilical arterial O_2 saturation.

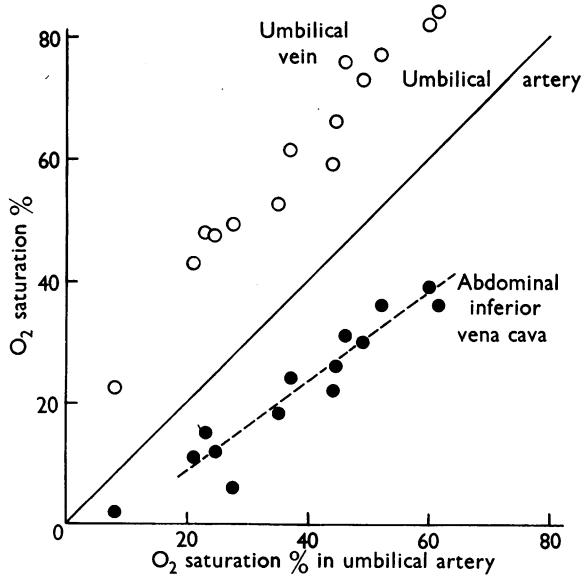

Fig. 3. Observations on five mature foetal lambs. As the oxygen saturation of blood in the umbilical artery is reduced, that in the abdominal inferior vena cava below the entry of the hepatic veins (●) also falls, but less rapidly, so that the systemic arteriovenous O_2 difference decreases. The difference between the O_2 saturation in the umbilical artery and that in the umbilical vein (○) does not alter significantly.

previously (closed circles). The figure includes only results obtained when the lambs were not obviously shivering, nor panting, nor making muscular movements. O_2 consumption has been expressed as a percentage of that observed when the carotid arterial O_2 saturation was 47–73% and each point is the mean of several observations. In new-born as in foetal lambs the oxygen consumption fell when the arterial saturation was reduced below 35%. There was no significant change in O_2 consumption when the arterial O_2 saturation was raised from 60 to 100%. The scatter of the observations was large, although

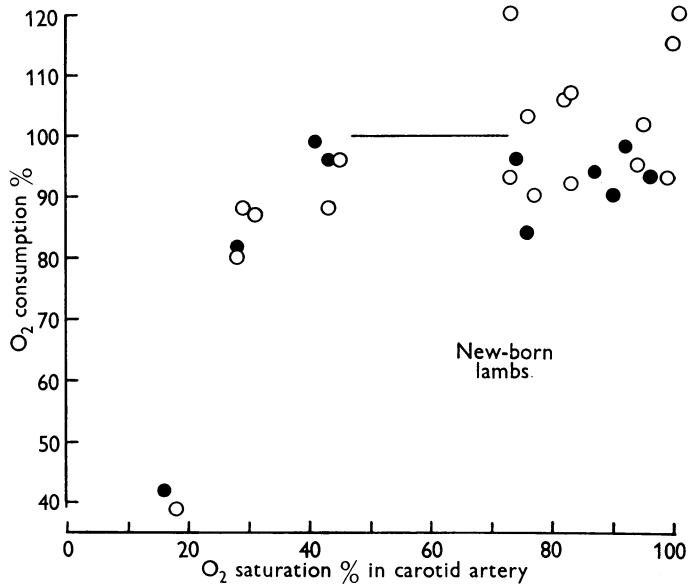

Fig. 4. Observations on seven new-born lambs, delivered by Caesarean section 1–2 hr previously (○), and on two lambs born naturally 1 and 3 days previously (●). The rate of O_2 consumption, measured by a spirometer attached to a closed circuit respiration pump, and expressed as a percentage of that observed when the arterial O_2 saturation was 47–73%, (—) has been plotted against the carotid arterial O_2 saturation.

O_2 consumption was measured by a simple and direct method. The causes of this variation are interesting, and probably include both imperceptible shivering and small temperature changes (although the lambs were in a warm bath in many of these experiments).

Shortly after delivery from the ewe on to a heated table, most new-born lambs began to shiver. This shivering had a respiratory rhythm but was not affected by vagotomy; it greatly increased O_2 consumption. In order to obtain results comparable with those in foetuses it was necessary to find out how to abolish shivering. In three lambs additional intravenous injection of sodium pentobarbitone (7–10 mg/kg) greatly reduced or abolished shivering, but in other experiments this drug also lowered O_2 consumption in the absence

of noticeable shivering. In one lamb administration of 7 % CO_2 in the ventilating gas decreased but did not abolish shivering. A large decrease in arterial O_2 saturation abolished shivering in five lambs, but the most certain way was to keep the (anaesthetized) lamb's temperature at not less than 38° C.

The effect of temperature on O_2 consumption was also studied, independently, in three new-born lambs which were sufficiently deeply anaesthetized to abolish shivering. Fig. 5 illustrates a representative experiment, which shows that O_2 consumption may increase by as much as 50 % when the body temperature is raised from 35–40° C.

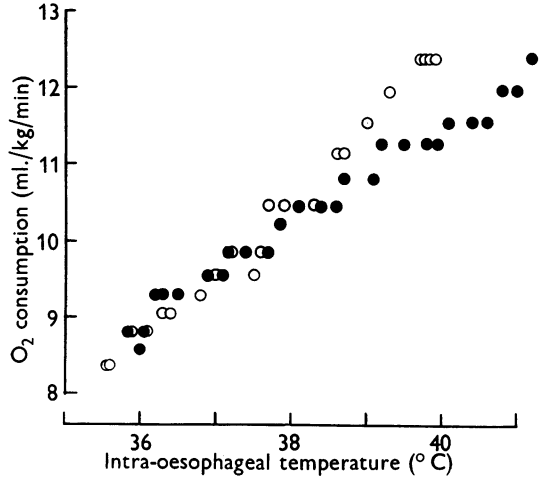

Fig. 5. New-born lamb, 3 days old, ventilated by a pump, under pentobarbitone anaesthesia. The O_2 consumption is plotted against intra-oesophageal temperature during cooling (○) and warming (●).

Cardiovascular changes. A general description has already been given of the cardiovascular response to oxygen lack in the mature foetal lamb (Born, Dawes & Mott, 1956). The foetal lambs used in the present experiments mostly reacted in the same way, with a rise of blood pressure and heart rate. In no experiment was there a fall of heart rate during the period of anoxaemia, even though the umbilical arterial saturation was sometimes less than 10 %. In only one lamb was there an unequivocal fall of blood pressure, and this did not exceed 10 mm Hg.

The new-born lambs also reacted with a rise of blood pressure and heart rate, often of considerable magnitude. Only in one experiment was there evidence of impending circulatory failure, when the blood pressure fell from 60 to 35 mm Hg in less than a minute, and the rate of O_2 consumption was halved, at an arterial O_2 saturation of 14 %; the heart was still beating at about 250/min, however.

Oxygen consumption and gestation age

We may now consider the oxygen consumption of lambs during the second half of gestation and the early neonatal period. As Table 1 shows, the O_2 consumption per kg of foetus does not change significantly during the latter half of gestation, provided that due account is taken of the umbilical arterial O_2 saturation at which the observations are made. Thus in seven lambs of 79–87 days gestation the mean O_2 consumption was $4{\cdot}0 \pm 0{\cdot}8$ (S.D.) ml./kg/min, while in fourteen lambs of 117–138 days gestation it was $3{\cdot}7 \pm 0{\cdot}9$ ml./kg/min (using from the middle part of Table 1 only those values marked with an asterisk).

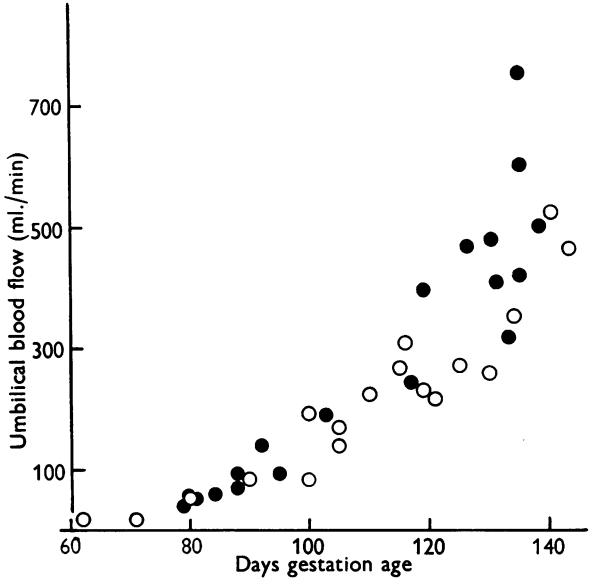

Fig. 6. Foetal lambs. Umbilical blood flow, measured by venous occlusion plethysmograph, has been plotted against gestation age, to compare the observations of Cooper, Greenfield & Huggett (1949) on Welsh lambs (○) with ours on lambs of other breeds (●).

The O_2 consumption of new-born lambs delivered by Caesarean section, separated from the mother and artificially ventilated for 1–2 hr, was in the same range as that of foetal lambs. In twelve lambs of 136–144 days gestation age the O_2 consumption was $4{\cdot}5 \pm 1{\cdot}2$ ml./kg/min. This provides a useful check between the methods of measuring O_2 consumption in foetal and new-born lambs. In lambs which are more than 12 hr old, however, there is evidence that O_2 consumption is much increased, a phenomenon which will require further investigation.

Inspection of equation (1) shows that there are three variables to which the foetal oxygen consumption is related, the umbilical arteriovenous O_2

difference, the O_2 capacity of the blood and umbilical blood flow. The arterio-venous O_2 difference does not change appreciably during the latter half of gestation (Table 1). The oxygen capacity of the blood rises by about 30% (Born, Dawes & Mott, 1956). However, total umbilical blood flow increases greatly. Fig. 6 combines our observations on umbilical flow, made soon after delivery, on lambs of large breeds (14 Hampshire, 4 Suffolk and 1 Kerry Hill) with those of Cooper, Greenfield & Huggett (1949) on eighteen Welsh lambs

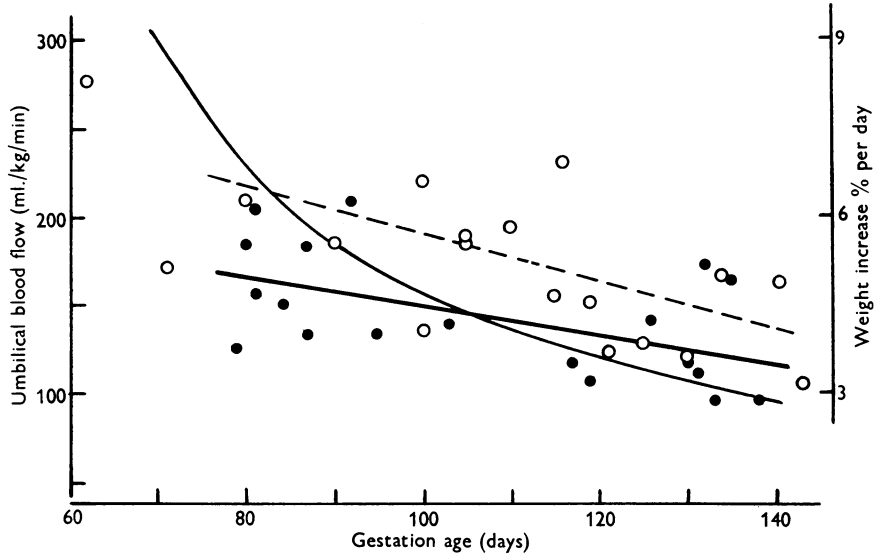

Fig. 7. Foetal lambs. Umbilical blood flow per kg body weight (ordinates on the left) has been plotted against gestation age using the data of Cooper, Greenfield & Huggett, 1949 (○, - - -) and our observations (●, —). The thin continuous curved line indicates the weight increase % per day (ordinates on the right), calculated as described in the text.

which were in good condition. The agreement between the two groups of observations is good, a fact which is no doubt related to the similarity between the growth rate of Welsh lambs and those of the other breeds (Dawes, 1956). There is a greater scatter in the range of observations during the last 2 weeks of gestation, which is partly due to the greater variation in weight at this period. There was a reduction of umbilical blood flow *per kg body weight*, between 80 days gestation and term, of 37% according to Cooper *et al.* (1949) and of 30% according to our measurements (Fig. 7). This reduction of umbilical blood flow approximately counterbalances the small increase in oxygen capacity of the blood.

DISCUSSION

Oxygen consumption and arterial Oxygen tension

In the experiments on foetal lambs the supply of oxygen was reduced, whereas the new-born lambs were underventilated. Thus in the latter carbon dioxide must have accumulated. However, in neither foetal nor new-born did the O_2 consumption fall until the arterial O_2 saturation was reduced below 35%. This corresponds to an arterial O_2 tension of about 20 mm Hg, according to the published foetal and new-born dissociation curves at 38° C and a pCO_2 of 50 mm Hg (Barcroft, 1946; Barron & Meschia, 1954; Born, Dawes, Mott & Rennick, 1956). Hypoxia causes a movement of the dissociation curve to the right *in vivo*, even in the presence of a constant pCO_2; the pCO_2 may also have varied. Therefore the estimate of arterial O_2 tension given above can only be very rough.

Muscular activity increases oxygen consumption and, in the form of shivering, makes an important contribution to heat production. In these experiments muscular movements, and particularly shivering, were deliberately reduced to a minimum to avoid this variable factor, and in order that it should be the O_2 supply to the tissues, rather than an effect on the central nervous control of muscle tone, which was the limiting factor. In the absence of shivering, a fall in body temperature lowers oxygen consumption (Fig. 5). In the experiments on hypoxaemia the reduction of O_2 consumption was not due to a fall in body temperature because the lambs were immersed in a bath at approximately their deep body temperature.

Acclimatized adult man. Barcroft (1946) compared foetal life to adult life at great altitudes, since both involved survival at a low partial pressure of oxygen. The foetal circulation also has some analogies with that in children with congenital cardiac malformations and central cyanosis.

It has generally been believed that the O_2 consumption of man does not decrease at low partial pressures of oxygen. In the experiments on which this view is based, however, survival was naturally of paramount importance. Houston & Riley (1947) found no reduction of oxygen consumption in four men acclimatized to an altitude of 20,000 ft. in whom the arterial O_2 saturation fell to 52%, corresponding to an O_2 tension of 29 mm Hg. The data of Lilienthal, Riley, Proemmel & Franke (1946) indicate some fall of O_2 consumption in six men from 0·285 l./min at a mean arterial O_2 tension of 94·2 mm Hg to 0·25 l./min at 36·3 mm Hg. Only one subject had a higher O_2 consumption at the lower tension, and their results suggest that these men were on the verge of having their O_2 consumption limited by the O_2 tension of their arterial blood. This is perhaps the more likely since the energy consumption of their cardiovascular and respiratory systems was almost certainly greater at high altitude than at sea level. It is common knowledge that the problems of

mountaineering become more acute above 20,000 ft, at which Houston & Riley (1947) found an arterial O_2 tension of 29 mm Hg.

Several groups of workers have measured the O_2 consumption of patients suffering from cyanotic heart disease. Neither Burchell, Taylor, Knutson & Wood (1950), Ernsting & Shephard (1951), nor Davison, Armitage & Arnott (1953) found any such patients whose basal metabolism was outside the normal range for their physique. However, in very few of these patients was the arterial O_2 tension less than 40 mm Hg. Bing, Vandam, Handelsman, Campbell, Spencer & Griswold (1948) claimed that the basal metabolic rate was reduced in twenty-eight of thirty such patients. There was, however, no correlation between arterial O_2 tension and metabolic rate, and their conclusions have been criticized because of the difficulty in referring the estimated basal O_2 consumption of these patients to normal standards.

The general conclusions to be drawn from these, and many other, observations on man acclimatized to low oxygen tension is that no reduction of oxygen consumption has been observed when the arterial O_2 tension exceeded 40 mm Hg. As arterial O_2 tensions of 30 mm Hg and below were approached, there may have been some decrease of O_2 consumption. As far as the experiments go, therefore, they agree with the results here reported in lambs.

Acute experiments on adult animals. In adult animals there is clear evidence that O_2 consumption falls when the oxygen content of the inspired air is much reduced (to 6% or below). Harrison & Blalock (1927) used dogs and concluded that 'when the arterial O_2 saturation was less than 40%, a definite diminution in oxygen consumption was found, the degree of diminution being roughly proportional to the severity of the anoxaemia'. Cordier & Mayer (1935), Lewis & Gorlin (1952) and Gorlin & Lewis (1954) confirmed these observations on dogs. Observations from the published tables of the last two authors have been plotted in Fig. 8 to show the general similarity between their findings and those on foetal and new-born lambs (Figs. 2 and 4). Harrison & Blalock (1927) and Gollwitzer-Meier (1928) showed that there was at first a large increase in cardiac output, as well as in blood pressure, pulse rate and ventilation, as the arterial saturation fell; it is not therefore surprising that O_2 consumption was somewhat increased at an arterial O_2 saturation of 60–70% (Fig. 8). As the arterial O_2 saturation fell below 40%, corresponding to less than 6% O_2 in the inspired air, there was evidence of progressive circulatory and respiratory failure with a large rise in venous pressure, bradycardia (Greene & Gilbert, 1922; Sands & DeGraff, 1925; Gollwitzer-Meier, 1928) and dilatation of the heart (heart-lung preparation; Gremels & Starling, 1926).

Lewis & Gorlin ventilated their dogs with 10% O_2 for up to six hours; the arterial O_2 saturation (73–93% on air) fell to 44–79%. On ventilation with 2·5–4·7% O_2 the arterial O_2 saturation fell to very low values within a few

minutes, and O_2 consumption then decreased as indicated in Fig. 8. It is only fair to add that the dogs might then have been in acute circulatory failure, and not in an equilibrium condition. Cordier, Magne & Mayer (1930) stated that dogs tend to die suddenly before their O_2 consumption is much reduced, whereas rabbits will withstand 4% O_2 fairly readily. Indeed Hamon, Kolodny & Mayer (1935) have succeeded in keeping unanaesthetized rabbits for 24 hr in

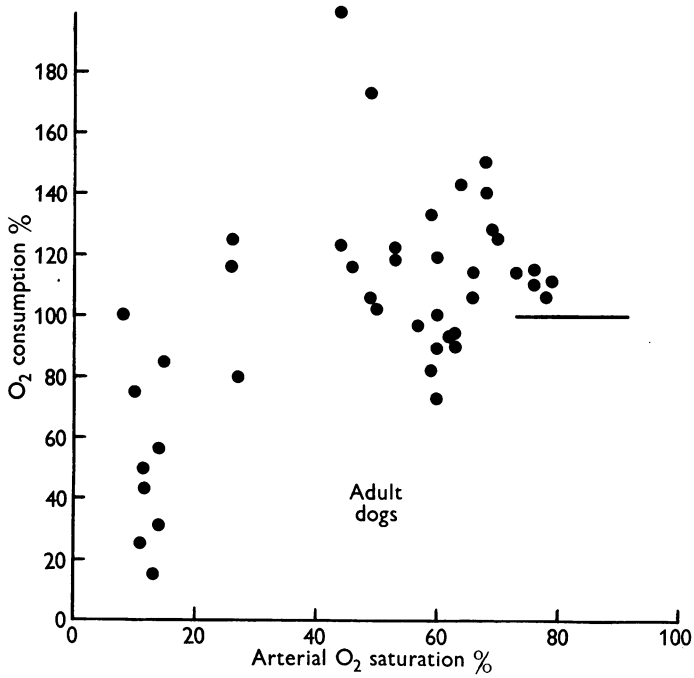

Fig. 8. Observations on adult dogs by Lewis & Gorlin (1952) and Gorlin & Lewis (1954). The rate of O_2 consumption, expressed as a percentage of that observed when the dogs were breathing air with an arterial O_2 saturation 73–93% (——), has been plotted against arterial O_2 saturation when breathing low O_2:N_2 mixtures.

an atmosphere of 3–5% oxygen, with survival; oxygen consumption was reduced by about 20% and there was a considerable fall in body temperature (to 29·7° C in one rabbit). This is the more remarkable in view of Jarisch & Wastl's (1926) observation of circulatory failure in rabbits, with dilatation of the heart at an arterial O_2 saturation of 40–50% (6% O_2 in the inspired air), albeit with the chest open and a cardiometer applied to the heart.

Some illuminating experiments have also been performed on cats. There was no change in O_2 consumption when the O_2 content of the inspired air was reduced to 13·3% (Doi, 1921). Rather more severe hypoxia temporarily diminished shivering (Burton & Bronk, 1955; Hemingway & Birzis, 1956; as in dogs, Hemingway & Nahas, 1952), but also, when shivering was abolished

by decerebration or deep anaesthesia, there was a further diminution of O_2 consumption in cats given 6% or less oxygen to breathe.

These short-term experiments in animals show that O_2 consumption may be (temporarily) diminished at quite high arterial O_2 saturations by inhibition of shivering, and that a fall in O_2 consumption at lower arterial saturations is associated with circulatory failure.

Mice, in contrast to larger mammals, show a fall of O_2 consumption and of temperature on inhalation of even 13·6–14·7% O_2 (Chevillard & Mayer, 1935). Similarly, the oxygen consumption of rats is reduced by as much as 30% when they are given 10% oxygen to breathe (Lintzel, 1931; Flückiger, 1956) provided that the environmental temperature is less than 35–37° C (Blood, Glover, Henderson & D'Amour, 1949). This difference may be related to the mechanism for maintenance of a high metabolic rate in these small animals.

New-born man and animals. Cross *et al.* (1955) observed a fall in the O_2 consumption of new-born babies when given 15% O_2. Moore (1956*a*, *b*) found a similar fall in new-born puppies and kittens breathing 7–12% O_2. These are all higher than the values observed for adult animals of the same species. In the new-born mouse, however, oxygen consumption was unaffected until the O_2 tension of the atmosphere was 65–80 mm Hg (Fitzgerald, 1953) which corresponds to about 9–11% O_2 at atmospheric pressure, and is thus *less* than the value observed in the adult mouse (Chevillard & Mayer, 1935).

There may be a number of reasons why it is comparatively easy to demonstrate, in new-born animals, a progressive limitation of O_2 consumption when the supply of oxygen is reduced. An adult cat or dog whose arterial O_2 saturation is 30% or less is liable to sudden death, but the heart of the new-born animal will continue to work for a surprising length of time with almost no oxygen in the circulating blood. Moreover, in the adult, cardiac output may increase fourfold as arterial O_2 saturation is reduced, and the systemic arteriovenous O_2 difference will then decrease 75%. A large fall in arterial O_2 saturation may thus occur with only a small reduction in venous saturation, and hence with no restriction on O_2 supply to the tissues. Indeed at this stage O_2 consumption is raised, because of the increased work of the heart and respiratory muscles. If cardiac output were not increased (and autonomic nervous control of the circulation is believed to be poorly developed in many species at birth), then venous O_2 saturation would fall in proportion as arterial saturation fell and O_2 consumption would become limited at a higher arterial saturation. It is therefore interesting that MacKay Sawyer, Schlossberg & Bright (1933) found that sympathectomized cats were less well able to resist oxygen lack than normal cats.

There are other difficulties of interpretation. The O_2 tension or saturation of the arterial blood was not measured in the babies, puppies or kittens, and cannot be deduced from the available data. It is known that the lungs of

new-born animals function imperfectly; the O_2 content of the inspired air is therefore an unreliable guide to that of the circulating blood. The latter may have fallen so low as to limit the consumption of oxygen either by abolishing shivering and normal muscle tone (through an action on the central nervous system), or by reducing the partial pressure gradient of oxygen to the tissues themselves.

In lambs the patency of the ductus arteriosus for some while after birth enables arterial blood which is not fully saturated with O_2 to flow from the aorta through the lungs. The systemic arterial O_2 saturation is thus raised above the value observed when the ductus is artificially occluded (Dawes *et al.* 1955; Born, Dawes, Mott & Rennick, 1955). In three instances the carotid arterial O_2 saturation fell from 50–60% to 20–30% when the ductus was occluded. The observations recorded in the present paper suggest that a fall of this magnitude would reduce the O_2 consumption of the lambs, perhaps to dangerously low levels, and thereby compromise survival. This reinforces the hypothesis that the patency of the ductus arteriosus after birth may be of value until the lungs are functioning well.

Foetal lambs and babies. These experiments also provide some indication of the effects which may be expected from a reduction in the oxygen supply to the foetus. In the lamb the umbilical arterial O_2 saturation normally exceeds 50% (> 25 mm Hg tension). There is therefore some margin before it reaches 35%, and O_2 consumption of the foetal tissues begins to fall. In the mature foetal lamb, in which the autonomic nervous system is functional, there will be an increase of heart rate and blood pressure, and therefore of umbilical blood flow, before the oxygen saturation falls very far (Born, Dawes & Mott, 1956). Whether a foetal lamb accumulates an oxygen debt during anoxaemia, or whether the intermediary products of metabolism may be transferred across the placenta to the mother, is as yet unknown.

In the human infant at normal spontaneous vertex delivery, or at elective Caesarean section, the average O_2 saturation of umbilical arterial blood is lower than that of the lamb at term. The mean figure given by a number of authors under a wide variety of operative conditions varies from 9·8 to 33%, corresponding to an O_2 tension of about 8–16 mm Hg (Eastman, 1930; Haselhorst & Stromberger, 1930; Smith, 1939; Clemetson & Churchman, 1953; Walker, 1954; Beer, Bartels & Raczkowski, 1955; Rooth & Sjöstedt, 1955). The cineangiographic evidence of Lind & Wegelius (1954) suggests that the foetal circulation in the baby resembles that in the lamb; it is therefore the umbilical arterial O_2 tension (and not the umbilical venous) which is representative of the blood supply to the foetal tissues. If the O_2 tension of cord blood on delivery is similar to that *in utero*, then the average baby may be considered grossly asphyxiated at term. Alternatively, and more probably, the conditions under which the blood samples were taken, although excellent by

ordinary obstetrical standards, may have been such as to give a false impression of the conditions of intra-uterine life. That this is so is suggested by the very wide range of umbilical arterial O_2 saturations observed in babies on delivery; a small proportion have an umbilical arterial O_2 saturation which exceeds 50%.

Oxygen consumption during the latter half of gestation

Our observations showed no significant change in the O_2 consumption of foetal lambs per kg body weight during the latter half of gestation, under similar conditions of anaesthesia. Other workers measured the O_2 consumption of foetal lambs by different methods. The observations of Cohnstein & Zuntz (1884) are clearly not comparable, because as Barcroft (1946) has pointed out, the insertion of a flow-meter into an umbilical artery in their experiments had greatly reduced umbilical flow. Barcroft, Kennedy & Mason (1939) tied the umbilical cord in seven lambs delivered from ewes under spinal block, measured the rate of decrease of arterial O_2 content, and used an estimate of foetal blood volume to calculate O_2 consumption. Barcroft & Elsden (1946) computed O_2 consumption by multiplying the umbilical arteriovenous O_2 difference by half the cardiac output, as determined by Barcroft & Torrens (1946); the latter used a cardiometer and added 15% to their measurement to allow for coronary blood flow in six lambs (the anaesthetic was not recorded). Carlyle (1948) measured the O_2 uptake of tissue slices from the major organs, multiplied these by organ weights, and hence arrived indirectly at an estimate of basal O_2 consumption in six pairs of lambs. All these observations, together with our own, are assembled in Fig. 9. Considering the different methods employed, there is good agreement between the various observations on foetal lambs from 110 days gestation onwards. The largest discrepancies are the three estimates of O_2 consumption made by Barcroft & Elsden (1946) in lambs of 95–108 days gestation. Few details of these experiments are available but the method used may involve large errors. This is the more likely because although there is some justification for the assumption that *on the average* half the foetal cardiac output flows through the lamb's placenta *at term* (Dawes *et al.* 1954), there is no information as to the reliability of this assumption earlier in gestation. There are also insufficient observations either in Barcroft & Elsden's series or in Carlyle's, at any one period of gestation, to estimate the variation in the O_2 consumption between individual lambs as calculated by these methods.

Barcroft (1946), Barcroft & Torrens (1946) and Carlyle (1948) all concluded that O_2 consumption fell with increasing gestation age in the lamb. However, this is in contrast to the results of earlier experiments on goats (Barcroft, Flexner & McClurkin, 1934). The balance of evidence now seems to suggest that there is little change in O_2 consumption per kg body weight during the latter half of gestation.

Umbilical blood flow. It is clear that the most influential variable in foetal oxygen transport is the umbilical blood flow. Our estimates of umbilical blood flow at different gestational ages agree very well with those of Cooper *et al.* (1949). This is particularly satisfactory because although we both used a venous occlusion plethysmograph, Cooper *et al.* compressed the whole umbilical cord while we occluded the abdominal umbilical vein alone. Moreover, our observations were made mainly on Hampshire lambs delivered under barbiturate anaesthesia on an operating table, while they used Welsh lambs delivered under spinal block into a saline bath.

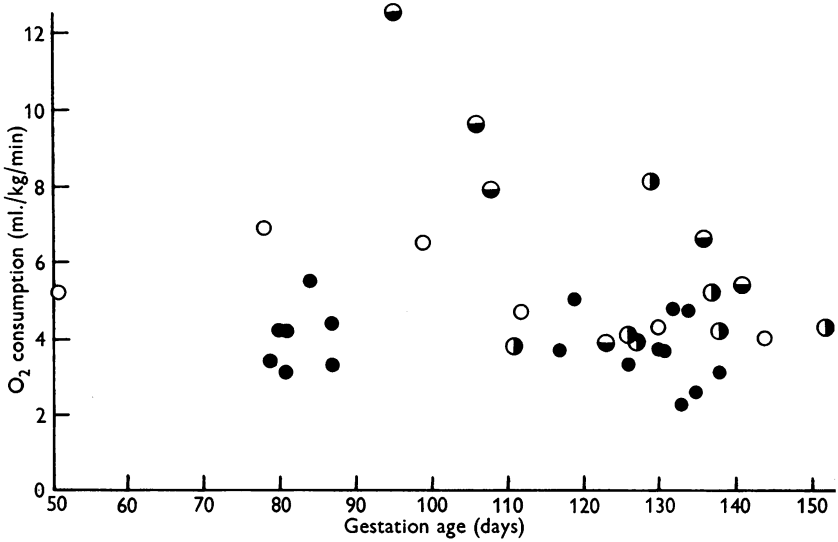

Fig. 9. Foetal lambs. Observations on O_2 consumption per kg body weight with increasing gestation age, according to Barcroft *et al.* 1939 (◑); Barcroft & Elsden, 1946 (◒); Carlyle, 1948 (○); and this paper (●).

The maintenance of the foetal O_2 consumption at a steady rate per kg body weight is accounted for by the great increase of umbilical blood flow, which occurs as the animal grows. This is the more remarkable because in the sheep the placenta reaches its greatest weight at 80–90 days gestation. The volume of blood in the placenta also scarcely increases after this period, although the blood volume of the foetus increases fourfold between then and term (Barcroft, 1946).

Although total umbilical flow increases steadily, the flow per kg of foetal body weight falls slightly with increasing gestation age. Cooper *et al.* (1949) related this fall to the percentage weight increase per day, which likewise decreased towards term. Huggett & Widdas (1951) found the relation between foetal weight (W, g) and age (t, days) was given by $W^{\frac{1}{3}} = a(t-b)$ where $a = 0{\cdot}149$ and $b = 38{\cdot}6$. Our own observations conform well with this equation (Dawes, 1956).

Now growth rate

$$\frac{dW}{dt} = a^3.3(t-b)^2$$

and

$$\% \text{ weight increase/day} = \frac{dW}{dt} \times \frac{100}{W} = \frac{300}{t-b}.$$

This tends to infinity at $t = 38{\cdot}6$ days and is not a linear function. The additional data assembled in Fig. 7, and particularly those between 80 and 100 days gestation, do not support the suggested correlation between the umbilical flow/kg and the % weight increase/day.

The small fall in umbilical blood flow/kg is just about offset by the rise in the O_2 capacity of the blood during the second half of gestation, so that both O_2 consumption/kg and the systemic arterial O_2 saturation (Born, Dawes & Mott, 1955) remain approximately constant. This suggests that umbilical blood flow may be indirectly controlled by the oxygen tension of the arterial blood. There is some evidence for this view. In the mature lamb, in which autonomic nervous control is well established, moderate anoxaemia causes a rise of heart rate, blood pressure and umbilical blood flow (Born, Dawes & Mott, 1956). Injection of hexamethonium causes a fall of blood pressure and of umbilical blood flow. The blood pressure rises during the latter half of gestation, and umbilical blood flow increases concomitantly. These observations support the hypothesis that umbilical blood flow is mainly regulated by the level of the arterial blood pressure, which is dependent on the integrity of the autonomic nervous system, and is thereby increased during anoxaemia.

SUMMARY

1. The rate of O_2 consumption has been calculated in foetal lambs from measurements of umbilical blood flow and arteriovenous O_2 difference. The rate of O_2 consumption has also been measured in newly delivered lambs by a spirometer connected to a closed-circuit respiration pump. In anaesthetized foetal and new-born lambs, in which shivering was avoided, O_2 consumption decreased when the arterial O_2 saturation fell below 35%.

2. These observations are discussed in relation to the effect of changes in the O_2 content of the inspired air on O_2 consumption in new-born and adult animals, and to the conditions of intra-uterine life.

3. The rate of O_2 consumption per kg body weight did not alter significantly during the last half of gestation in lambs, in spite of a great increase in foetal weight. This is mainly due to a large rise in umbilical blood flow. Since arterial O_2 saturation does not alter appreciably over this period, and since anoxaemia causes an increase in blood pressure and umbilical flow in mature lambs, it is suggested that the oxygen tension of the arterial blood may be one of the principal determinants of umbilical flow towards the end of gestation.

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