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CHANGES IN THE LUNGS OF THE NEW-BORN LAMB

By G. S. DAWES, JOAN C. MOTT,
J. G. WIDDICOMBE AND D. G. WYATT

From the Nuffield Institute for Medical Research, University of Oxford

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In a previous series of experiments it was shown that artificial positive pressure ventilation of the lungs of foetal lambs caused an immediate fall of pulmonary and systemic arterial blood pressures (Ardran, Dawes, Prichard, Reynolds & Wyatt, 1952). In three lambs the systemic arterial pressure recovered, while the pulmonary arterial pressure continued to fall towards the level commonly found in adult animals. The observations of Reynolds, Ardran & Prichard (1953) on pulmonary circulation time in these newly delivered lambs also showed that on ventilation of the lungs pulmonary blood flow increased, on an average fourfold. These experiments led to the conclusion that ventilation of the lungs for the first time after birth leads to a decrease of pulmonary vascular resistance. This is an idea which has often been discussed during the last three hundred years but has not been tested by direct experiment. In order to obtain a direct estimate of pulmonary vascular resistance it is necessary to measure the quantity of blood flowing through a pulmonary artery per minute and also the pulmonary arterial and left atrial pressures. This paper gives an account of such measurements, from which it is concluded that positive pressure ventilation of the foetal lungs after birth causes an immediate and dramatic decrease of pulmonary vascular resistance, which must be one of the principal factors in the neonatal changes in the circulation. A brief report of some of these observations has already been given (Dawes, Mott, Widdicombe & Wyatt, 1952).

METHODS

Twenty Welsh ewes were used, whose duration of pregnancy was known, and three Hampshire-Clun Forest ewes (the maternal grandam of the lamb being Clun Forest) whose date of tupping was not known, but which were in a very advanced state of pregnancy. The weight of the Welsh ewes ranged from 22–33 kg and that of the Hampshire-Clun Forest ewes from 70–85 kg. They were anaesthetized by slow injection of 'dial-urethane' (diallyl-barbituric acid 0·1 g, urethane 0·4 g/ml.) into the external jugular vein. At first a dose of 0·5 ml./kg was used, but further experience showed that 0·2–0·35 ml./kg was sufficient to keep the ewe and lamb lightly anaesthetized.

The ewe was laid on its right side, the trachea was cannulated to provide a good airway, and the left carotid arterial blood pressure was recorded continuously with a mercury manometer on a kymograph. The uterus was then partially delivered through a lower abdominal midline incision and the head of the foetus located. A rubber bag filled with warm saline was pushed over the foetal head immediately after delivery, in order to prevent inspiration of air. The lamb was laid on its back on a metal plate 3½ in. above the level of the table on which the ewe rested, so that the lamb, the umbilical cord and the ewe's abdominal incision were as nearly as possible in the same horizontal plane. There was thus no tension on the umbilical cord, which was surrounded by warm moist saline pads. The metal plate was warmed and was slotted to take uprights which supported the condenser manometer gauge heads and the flowmeter.

The left femoral artery of the lamb was dissected at once after delivery and a short length of polythene tubing attached to a condenser manometer was introduced for a few centimetres. The systemic arterial blood pressure was thenceforward under continuous observation and was recorded intermittently until the end of the experiment. The trachea was dissected and a cannula filled with warm saline and having two closed side-arms was inserted without allowing air to enter. The chest was then opened by splitting the sternum along the midline, and by cutting between the fourth and fifth ribs on the left side. The pericardium was opened and tethered to either side of the chest wall. The left pulmonary artery was freed from surrounding tissue within the pericardium, and a loop of thick thread was placed around the ductus arteriosus. Heparin (10 mg/kg or more) was injected through a cannula in the left femoral vein. The left pulmonary artery was ligated and cannulae connected by a Portex tube filled with warm saline were tied into the peripheral and central ends in that order. Flow through the left pulmonary artery was restored within 2–5 min of tying it. A polythene tube connected to a condenser manometer was then introduced into the cavity of the left atrium through an incision in the tip of the left auricular appendage. Flow through the left pulmonary artery was interrupted again for a few moments to insert a flowmeter, and a third condenser manometer was attached to the polythene tube leading from the central end of the left pulmonary artery just where it entered the flowmeter (Fig. 1). Fine polythene tubes were passed into the central ends of the right femoral and left carotid arteries in order to take blood samples. Blood samples from the left pulmonary artery were taken from the tube leading to the flowmeter.

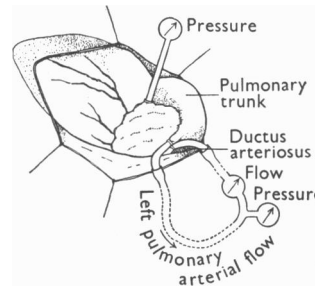

Fig. 1. Left lateral view of heart and great vessels when the preparation is completed. The aorta lies beneath and is concealed by the pulmonary trunk and ductus arteriosus.

The principal difficulty in the preparation was the insertion of the cannulae into the left pulmonary artery, of which there is only a short length between the main pulmonary trunk and the origin of the branch to the left upper lobe. In the foetus the virtual separation of the internal and external coats of the left pulmonary artery into two concentric tubes makes it difficult to insert a cannula without producing a valve; this was the main cause of failure in early experiments. An attempt was always made to use cannulae which were as wide as possible. We cannot exclude the possibility that the insertion of the peripheral cannula to some extent interfered with the flow of blood through those pulmonary arterial branches which leave the main trunk immediately beyond the pericardium, though this cannula was always orientated so as to obtain the greatest rate of flow.

The density flowmeter used was of the type described by Dawes, Mott & Vane (1953). The time required for a fixed volume of fluid to pass through was recorded intermittently by a Gaddum drop-timer (Gaddum & Kwiatkowski, 1938) on a kymograph. The flowmeter was filled with either saline or Dextran before insertion into the left pulmonary artery. The plastic connecting tubes were each from 15 to 20 cm long and of 3 mm internal diameter. The pressure drop across the flowmeter and tubes was not more than 3 mm Hg at a flow of 15 ml./min. The total volume of fluid required

to fill the flowmeter and tubes was 10 ml. In the majority of experiments no special precautions were taken to avoid heat loss in the flowmeter, other than the close proximity of a 100 W lamp bulb. In lambs nos. 6 and 14 a flowmeter was used in which the temperature of the surrounding air was thermostatically regulated to within 0·5° C; the temperature of the out-flowing blood was 38·5–39° C.

The dimensions of the stiff plastic tubes attached to the condenser manometers were such that the damped natural frequencies of the instruments were considerably higher than the fundamental frequencies of the pressure waves to be measured. In a typical experiment, the natural frequencies of the femoral, pulmonary, and left atrial manometers were, respectively, 125, 500 and 100 c/s. The left atrial manometer was insufficiently damped, with the result that free oscillations of appreciable amplitude occurred on some occasions. The selection of suitable cannulae was determined also by surgical considerations. The pressure records were displayed on two double-beam cathode-ray tubes of which short photographic records were taken at $\frac{1}{2}$, 1 or 2 min intervals, depending on the stage of the experiment. The time of each exposure was recorded on the kymograph tracing (see Fig. 2) for synchronization with the flow record, blood pressure of the ewe, blood samples and other experimental observations and procedures. Each pressure was also displayed on a meter reading directly in mm Hg. The periods of the meters were such that only the mean pressure was recorded in this way. The readings of these meters were plotted at $\frac{1}{2}$ min intervals in order to guide the conduct of the experiment. The sensitivity of the condenser manometers did not change perceptibly during experiments or even appreciably from week to week, but there was a substantial drift in base-line due to temperature changes in the electronic apparatus and in the gauge head. For this reason readings of atmospheric pressure were taken on each manometer at intervals of not more than 10 min throughout all experiments. The pressure records were measured with a travelling microscope and, with the necessary corrections applied, are estimated to have a possible absolute error of ± 4 mm Hg and a possible relative error (as between individual records in any one experiment) of ± 3 mm Hg in the pulmonary and femoral records, and of ± 2 and ± 1 mm Hg respectively in the left atrial record. The probable errors are approximately one-half these amounts.

When the preparation had been completed and an adequate time allowed for preliminary observations, the clips were removed from the side-tubes of the tracheal cannula, which was drained of saline and aspirated by a water pump. The lungs were ventilated by positive pressure from a Palmer respiration pump at a frequency of 18 per min, and the intratracheal pressure recorded by a critically damped mercury manometer on a kymograph. The tidal air was calculated from the intratracheal pressure, the stroke-volume of the respiration pump and the dimensions of the pump and connecting-tubes. The expansion of the rubber tubes in the system was measured at various pressures and due allowance made for this in calculating the tidal air. It is estimated that the maximal error is ± 4 ml., and this is borne out by a direct experiment in which the lungs were replaced by a rubber bag whose volume changes were measured by a plethysmograph. No allowance was made for the change in residual air with progressive expansion of the lungs, but as the total volume of the system, including the tracheal cannula, was approximately 1 l., an increase of 50 ml. in the residual air would only lead to an over-estimate in the tidal air of less than 5%.

At various times during an experiment blood samples of 0·5 ml. were withdrawn from one or more arteries as described above. The blood was mixed in the sampling syringe with a trace of heparin (20%) and sodium fluoride (4%) and the syringes immediately placed in an ice-water mixture in a vacuum flask. This procedure was effective in inhibiting aerobic respiration in the blood corpuscles, an important consideration with foetal blood since a high proportion of the red blood cells are nucleated. It was found that the blood could be stored for at least 24 hr without a measurable decrease in its oxygen content, although in practice all blood gas estimations were made within 12 hr of the experiment. Each sample was analysed for oxygen content using the micro-method of Roughton & Scholander (1943). Oxygen capacities were determined after saturating samples of blood with oxygen; the values obtained agreed well with those found by Barcroft (1946), and there was no appreciable change in the oxygen capacity of a lamb's blood

during the course of any experiment. Repeated determinations of oxygen content were made on most of the blood samples and an accuracy of ±0·1 ml. oxygen/100 ml. blood has been assumed in calculating the possible error in the estimations of percentage flow down the ductus arteriosus. Results have been expressed as the percentage saturation of the blood with oxygen. Oxygen tensions could have been measured only at the cost of taking considerably larger samples of blood.

RESULTS

Artificial positive pressure ventilation of the foetal lungs with air, oxygen or nitrogen always caused a great increase in the volume of blood flowing each minute through the left pulmonary artery. Before describing this change in detail an account must be given of the condition of the foetus.

The femoral arterial blood pressure was recorded from within 2 or 3 min of delivery for the duration of the experiment. The initial values of from 92/74 to 57/45 mm Hg lie within the range to be expected. During the dissection and insertion of cannulae and manometers, which lasted on an average 57 min from the time of delivery (51–65 min), there was a fall of femoral arterial blood pressure of 11% (2–24%). When the preparation had been completed we waited on an average 11 min (6–19 min) so that an adequate number of observations might be made before ventilation began. During this control period the femoral arterial pressure fell by 3%, the pulmonary arterial pressure by 8% and flow in the left pulmonary artery was reduced by 28% (means of all observations). Changes in left atrial pressure and heart rate varied considerably in either direction with no consistent deviation from the initial value. We had the impression that the lambs were in as good a condition as could be expected, and this was confirmed by the blood oxygen saturations given in Table 3. The carotid blood pressures of the ewes were between 130 and 90 mm Hg for the duration of the experiment except for nos. 4 and 7. These two sheep received injections of methedrine, saline and dextran in a moderately successful effort to sustain their blood pressure, which, however, fell occasionally as low as 35 mm Hg. This may account for the exceptionally low blood oxygen percentage saturation of lamb no. 4 before ventilation.

At the end of the control period the tracheal cannula was opened and the fluid therein aspirated through a thin polythene tube passed as far as possible down the trachea. In this way the fluid in the trachea and bronchi was replaced by air; this procedure had little or no effect on pulmonary arterial blood pressure or flow. The tracheal cannula was then connected to the respiration pump and manometer, and positive pressure ventilation was begun. Within the first two or three breaths there was a perceptible increase in the amount of blood flowing down the left pulmonary artery, sometimes as much as 20% (Fig. 2). The pulmonary blood flow increased very rapidly during the next minute, and then more slowly. It continued to increase in some lambs up to 20 min after ventilation had begun, though usually a steady state was reached after 5–10 min. The change was dramatic; the pulmonary blood flow

in those lambs which were 130 days old or more (full-term being about 147 days) became 3–10 times greater than that observed during the control period before ventilation. This was the more striking because in almost all lambs the flow down the left pulmonary artery had become less during the control period. This great increase in pulmonary blood flow was accompanied by a fall in pulmonary and femoral arterial pressures (Fig. 3), which usually did not exceed 10–15 mm Hg; this fall of pressure was usually somewhat greater in the pulmonary artery than in the femoral artery. At the same time

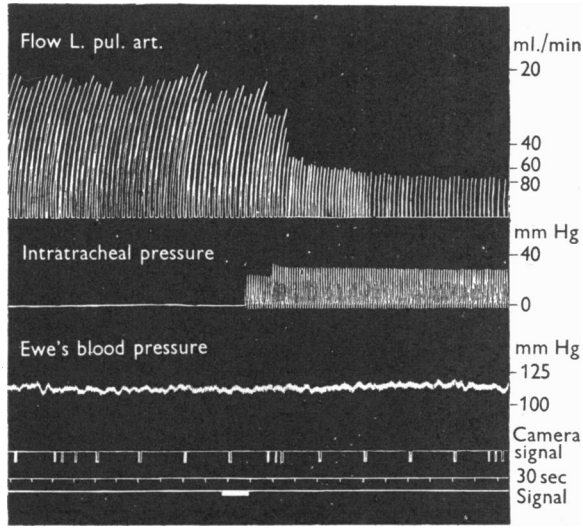

Fig. 2. Lamb no. 6, delivered by caesarian section. Records of the rate of blood flow through the left pulmonary artery and of intratracheal pressure in the lamb, and of maternal blood pressure. At the signal mark the trachea was drained of fluid and positive pressure artificial ventilation with air was begun. It caused a great increase in pulmonary blood flow.

there was a tendency for the left atrial pressure to rise; Fig. 3 shows a particularly striking example of this rise. Similar rises of 50–300% in left atrial pressure were seen in five other lambs in which a large increase of pulmonary blood flow occurred on ventilation. In the remainder of the lambs there was also a tendency for the left atrial pressure to rise but the change was not great. The left atrial pressure was recorded from a polythene tube introduced through the left auricular appendage, and the movements of the heart against this tube undoubtedly sometimes produced artifacts in the record. We would not like therefore to emphasize too strongly the correlation between increase in pulmonary blood flow and rise in left atrial pressure. The onset of ventilation was not accompanied by any consistent changes in heart rate.

An estimate has been made of the change in pulmonary vascular resistance on ventilation. The mean pressure difference across the lungs was calculated by subtracting the mean left atrial pressure (average of systolic and diastolic) and the calculated pressure drop across the flowmeter from the mean left pulmonary arterial pressure. This mean pulmonary pressure difference

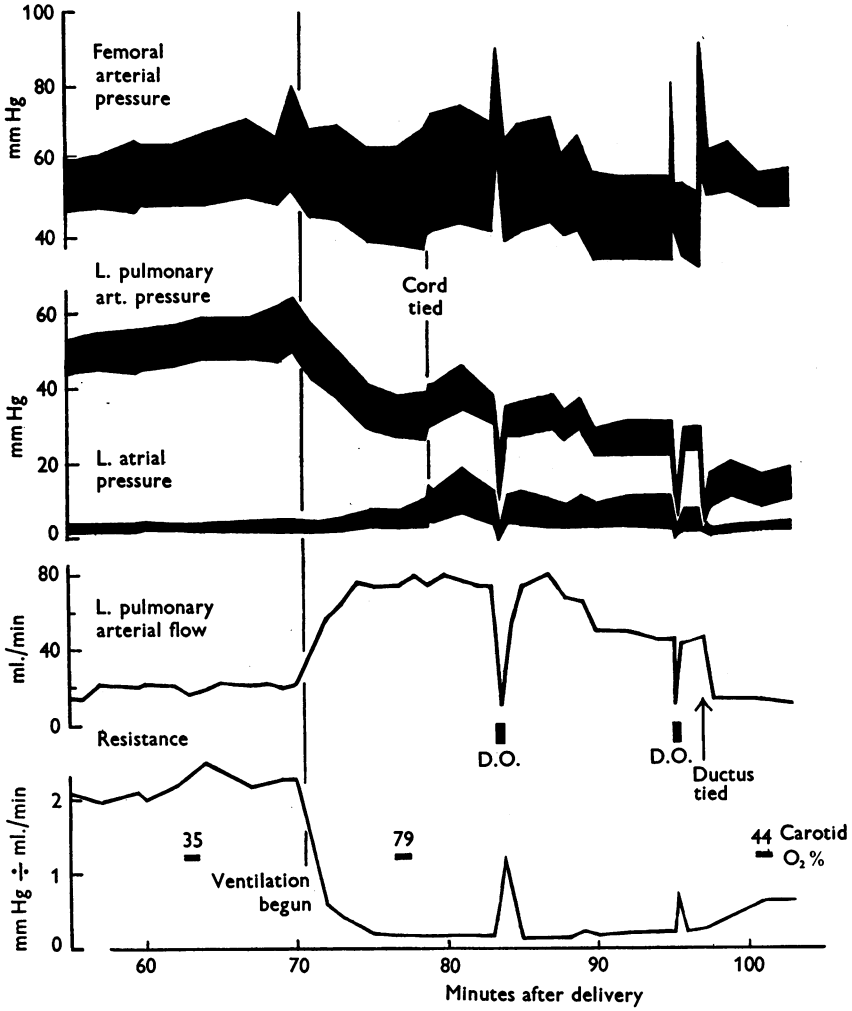

Fig. 3. Lamb no. 6, delivered by caesarian section (see also Fig. 6). Records of blood pressure, pulmonary blood flow, pulmonary vascular resistance, and oxygen saturation of carotid blood samples. Artificial positive pressure ventilation of the lungs caused a great decrease in pulmonary vascular resistance. Twelve minutes later temporary occlusion of the ductus arteriosus (D.O.) caused a rise in femoral pressure and a fall in pulmonary pressure and flow, showing that blood had been flowing from the aorta into the pulmonary trunk.

(mm Hg) was divided by the mean rate of left pulmonary arterial flow (ml./min) to give an index of vascular resistance. Table 1 shows that there is a very substantial reduction in pulmonary vascular resistance on ventilation with air, oxygen or nitrogen. In lambs weighing more than 2·3 kg (older than 130 days) this amounted to a decrease of from 50 to 91%. The number of animals was too small to allow any conclusion as to whether this decrease is greater in mature than in premature lambs. But it is perhaps worth noting that in the smallest lambs, nos. 11 and 12, the alterations in pulmonary vascular resistance were comparatively small. There is no correlation between weight and either the pulmonary blood flow or the resistance before ventilation, but on the whole the greater the initial flow (and so the lower the vascular resistance) the less is the percentage change in resistance on ventilation.

TABLE 1. Change of pulmonary vascular resistance on ventilation of foetal lambs

Lamb no.	Breed	Age (days)	Wt. (kg)	Ventilated with	Flow before ventilation (ml./min)	Pulmonary vascular resistance, mm Hg ÷ ml./min	
						Before ventilation	10 min later
1	H	—	5·7	O_2	17·2	3·0	0·70
2	W	137	3·05	N_2	19·4	1·7	0·44
3	W	135	3·0	N_2	16	3·3	0·8
4	W	141	2·9	Air: O_2 after 5 min	8·2	1·7	0·20
5	W	136	2·7	N_2	11	4·0	0·86
6	H	—	2·6	Air	21	2·3	0·13
7	W	134	2·35	Air, then O_2	31	1·5	0·75
8	W	130	2·3	O_2	9·3	3·1	0·29
9	W	122	2·1	O_2	16·1	2·5	0·20
10	W	120	1·9	O_2	8·1	4·1	0·76
11	W	121	1·5	O_2	31·5	0·9	0·57
12	W	111	1·1	Air, then O_2	28	1·2	0·97
13	W	134	2·95	O_2	22·5	1·6	0·88
14	H	—	2·9	Air	13·9	3·0	1·2
15	W	134	2·35	Air and O_2	12·0	2·3	3·3

The lambs are arranged in order of descending weight, apart from nos. 13–15 which had their lungs distended with saline before ventilation with a gas. Distension with saline *increased* pulmonary vascular resistance.

W, Welsh; H, Hampshire: maternal grandam Clun Forest.

The changes in pulmonary blood flow, pressure and vascular resistance appeared to be much the same whether the lamb was ventilated with air, oxygen or nitrogen (Table 1). In the latter instance, the fluid in the trachea was replaced by nitrogen and a closed circuit system was used, so that gaseous exchange between the lamb and the system would be reduced to a minimum. When a lamb was ventilated with nitrogen first and a steady state had been reached, subsequent ventilation with oxygen produced no further change in pulmonary blood flow or vascular resistance. Fig. 4 illustrates one of three experiments in which this observation was made. During inflation with

nitrogen, the placental circulation was intact and the animal was in good condition. From these observations it is clear that it is ventilation with a gas, rather than any particular gas mixture, which causes a reduction in pulmonary vascular resistance.

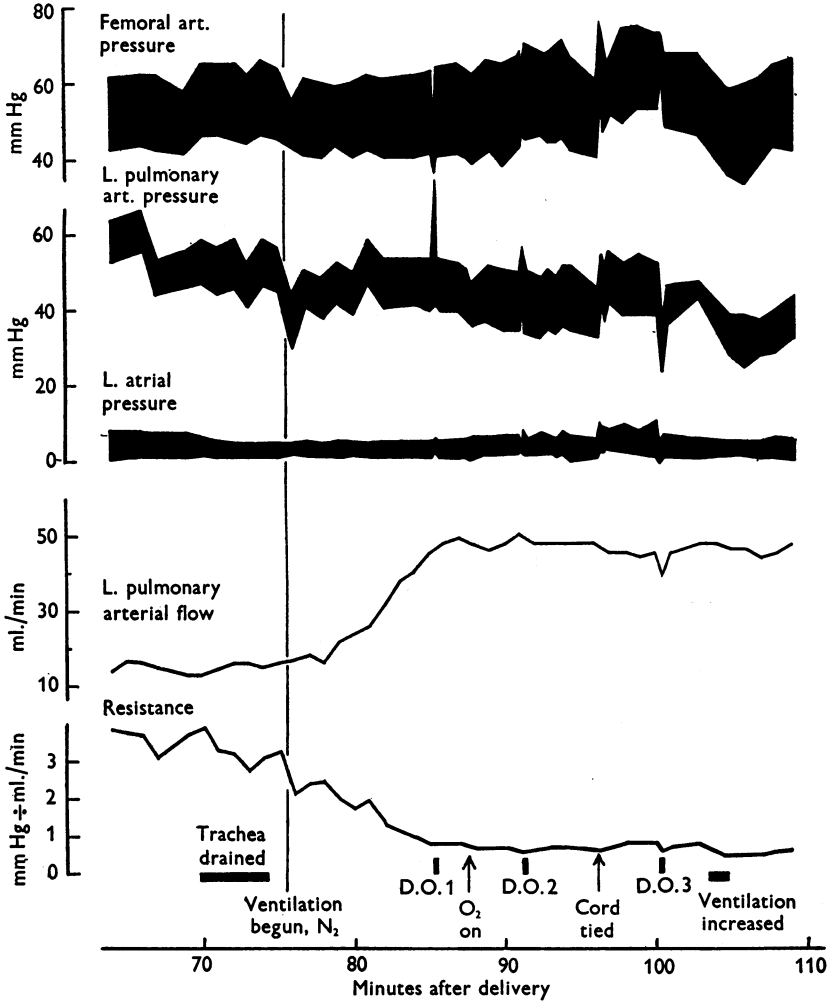

Fig. 4. Lamb no. 3, delivered by caesarian section. Records of blood pressure, pulmonary blood flow and pulmonary vascular resistance. Positive pressure ventilation with nitrogen caused a decrease in pulmonary vascular resistance. Subsequent ventilation with oxygen caused little or no further change. The first time the ductus arteriosus was occluded (D.O. 1), pulmonary arterial pressure rose and femoral pressure fell; blood was therefore flowing from pulmonary artery to aorta. The third time the ductus was occluded (D.O. 3), the pressure changes and the direction of flow were reversed. Late in the experiment an increase in the ventilation pump stroke from 75 to 125 ml. caused a substantial fall in femoral and pulmonary arterial pressures (the peak intratracheal pressure rose from 21 to 34 mm Hg).

In two experiments 30 ml. nitrogen were introduced through the trachea, from which the fluid had been removed under a stream of nitrogen, and were left there for a few minutes. There was a small increase of flow down the left pulmonary artery (up to about 15%), and a small fall in pulmonary arterial pressure. In one of these experiments, from which part of the kymograph

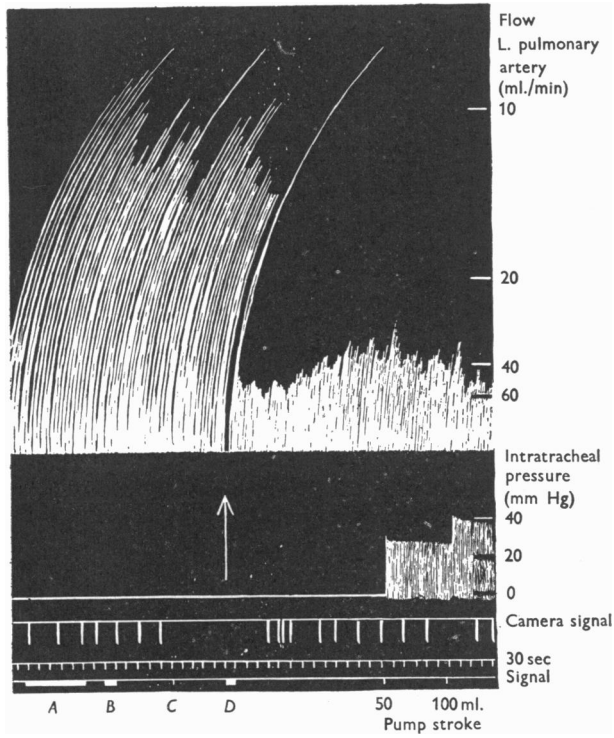

Fig. 5. Lamb no. 5, delivered by caesarian section. Records of left pulmonary arterial flow and intratracheal pressure. At *A* the trachea was drained of fluid in an atmosphere of nitrogen. At *B* and *C* 30 ml. nitrogen were introduced into the trachea for not more than 2 min on each occasion. At *D* the lungs were fully inflated with nitrogen under a high pressure and then immediately deflated to atmospheric pressure; there was a dramatic increase in pulmonary flow. Seven minutes later artificial positive pressure ventilation was begun using a closed circuit filled with nitrogen. The umbilical cord was intact throughout the experiment.

record is shown in Fig. 5, the lungs were then suddenly over-inflated with nitrogen. During this short period of distension pulmonary flow almost stopped. When the trachea was opened to atmospheric pressure and the lungs collapsed, flow instantly increased almost fourfold (from 13·4 to 48 ml./min), with an equivalent reduction in pulmonary vascular resistance. Nothing further was done to the lamb for another 6½ min; during this period the pulmonary flow reached a peak value of 63 ml./min and then slowly declined

to 33 ml./min, at which time closed circuit ventilation with nitrogen was begun and flow returned to the peak value. It is interesting that a single, admittedly excessive, inflation can produce such a dramatic and sustained reduction in pulmonary vascular resistance, from an initial value of 5·6 to a minimum of 0·9 mm Hg/ml./min.

Distension of the lungs with saline. In three lambs (nos. 13, 14 and 15) the lungs were distended with saline before aspiration of the trachea or ventilation with a gas. Introduction of 20–50 ml. of saline caused a decrease of pulmonary flow which was sometimes very considerable (50–100%). The intratracheal pressure was not raised by more than about 5 mm Hg. Pulmonary arterial pressure and femoral arterial pressure fell by 5–15 mm Hg and there was little change in left atrial pressure; pulmonary vascular resistance increased. These observations show that distension of the lungs by a liquid has the opposite effect to that seen with a gas.

The subsequent history of these three lambs is also interesting. After their lungs had been distended with saline, their tracheae were drained of fluid (all that which had been injected was recovered and more) and ventilation with air or oxygen was begun. In all three this caused some increase in left pulmonary arterial blood flow. In no. 15 there was no reduction of pulmonary vascular resistance and no. 13 showed a reduction smaller than was to be expected (Table 1). In no. 14 there was a considerable reduction in pulmonary vascular resistance, but this was less than that seen in its twin, no. 6. We have the impression that distension of the lungs with saline reduced the normal pulmonary vascular change on subsequent ventilation with air or oxygen.

Effect of tying the umbilical cord. The umbilical cord was not tied in any of these experiments until a mean of 7 min (range 2–14 min) after ventilation with air or oxygen had begun. Only a limited number of pregnant ewes were available, and to have tied the cord before ventilation had begun in some lambs would have introduced yet another variable in a series of experiments already sufficiently complicated. When the cord was tied there was a rise in mean femoral arterial pressure (in all the lambs) of 19% (4–46%, Figs. 3 and 4). The latter led to an increase in the pressure difference across the lungs and hence to an increase in left pulmonary arterial blood flow of 12% (0–28%). (Figs. 3 and 4 were chosen for other reasons and do not show the latter change, which was obvious in other lambs.) There was no significant change of pulmonary vascular resistance in any experiment.

Ventilation volumes and pressures

The intratracheal pressure was recorded directly during ventilation, and the tidal air calculated from the respiration pump-stroke and intratracheal pressure as described under Methods. At the beginning of these experiments we had no quantitative information to guide us as to the pressures required to

inflate the foetal lung with 'physiological' volumes of tidal air. We therefore increased the stroke of the respiration pump until the lungs were reasonably distended in the thoracic cage as judged by direct observation. We could then see on the surface of the lung areas which over the next few minutes gradually became filled with gas. The pressures required to produce this degree of inflation were very substantially greater than those required for adequate ventilation of adult mammalian lung.

It is impossible to give comprehensive figures for the relationship between pressure and volume of tidal air in the neonatal lamb, because first, as might be expected, the tidal air is greater for a given pressure in lambs of greater weight, and secondly because the relation between pressure and tidal air varied progressively in every lamb during the period of observation, up to an hour or more after beginning ventilation. Some representative figures for tidal air and intratracheal pressure (taken some 30–60 min after ventilation has begun) in lambs of different weights are given in Table 2. The low tidal air

TABLE 2. To show the relation between pressure and volume of inflation in lambs of different weights, after 30–60 min ventilation

Lamb no.	Weight (kg)	Intratracheal pressure (mm Hg)	Tidal air (ml.)	Intratracheal pressure (mm Hg)	Tidal air (ml.)
3	3·0	16	25	20	41
6	2·6	18	23	23	47
9	2·1	12	23	21	36
11	1·5	20	19	29	25
12	1·1	23	11	39	35
		Lamb born spontaneously 3–4 hr old			
—	1·6	12	21	18	35

and relatively high intratracheal pressure in a very premature lamb no. 12 (age 111 days) is particularly noticeable. In all the lambs, while the stroke volume of the respiration pump was unchanged, tidal air increased and intratracheal pressure diminished progressively. Fig. 6 illustrates this phenomenon for the first quarter of an hour after ventilation began in lamb no. 6, a fairly typical experiment in this respect. The change was usually greatest within the first 5–10 min of ventilation; thereafter it became progressively slower. Inflation with higher pressures in the early stages of ventilation accelerates this process. In most experiments, by varying the stroke of the respiration pump, we were able to examine the relationship between intratracheal pressure and tidal air, and found that this was approximately linear. If we assume that there is a direct relationship between inflating pressure and tidal air, the resistance to inflation of the lungs may be calculated. During the first quarter of an hour after ventilation the resistance to inflation in lamb no. 6 decreased nearly threefold, and this is the period over which the great decrease of pulmonary vascular resistance occurs.

We had two opportunities to examine the respiratory movements of lambs breathing naturally, as a basis for comparison with the artificial positive pressure ventilation used in these experiments. On one occasion a ewe died during anaesthesia and one of its twin lambs, delivered by immediate caesarian section, was induced to breathe spontaneously. The intrapleural pressure as measured by a condenser manometer fell to more than 30 mm Hg below atmospheric pressure during deep inspiration; the breathing of the lamb at this time, 10–20 min after delivery, was periodic in character. The second lamb had been born naturally some 3–4 hr before measurements were begun. Under local anaesthesia the intrapleural pressure at the peak of inspiration was less

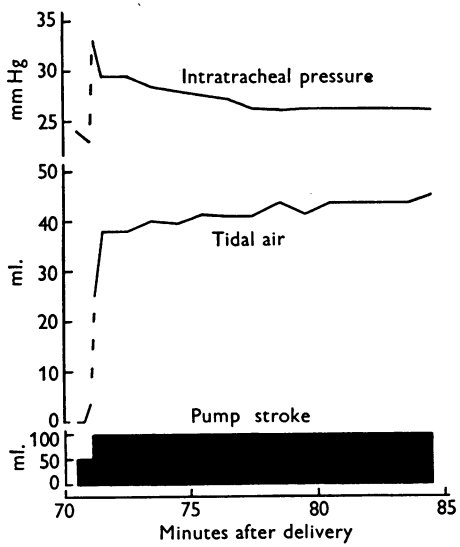

Fig. 6. Lamb no. 6 (see also Figs. 2 and 3). Records of intratracheal pressure, calculated tidal air and (positive pressure) respiration pump-stroke. The resistance to pulmonary inflation, begun 70½ min after delivery, decreases, at first very rapidly and then more slowly.

than 10 mm Hg below atmospheric pressure, and the respiratory rate 50 per min and regular. The lamb was then lightly anaesthetized with dial-urethane and its tidal air measured in a body plethysmograph (7½–9 ml., with a minute volume of 390–430 ml.). The chest was then opened under positive pressure ventilation, the intratracheal pressure measured, and the tidal air calculated; these figures are included in Table 2. They confirm the conclusion that there is a progressive diminution of the resistance to inflation after birth. The left pulmonary arterial blood flow in this lamb was 20–30 ml./min.

There are two further series of observations which show that the inflation volumes which we used were adequate but not excessive. On a number of occasions we raised the respiration pump-stroke volume substantially for a short while so that the lungs were over-inflated as judged by direct observa-

tion. This over-inflation caused a fall of femoral and pulmonary arterial blood pressure, usually accompanied by a decrease in pulmonary blood flow (Fig. 5). There was no consistent change in pulmonary vascular resistance. These effects were a useful guide to the upper limit to which the lungs might normally be inflated.

Table 3 shows the percentage saturation of the carotid blood with oxygen before and after ventilation with air or oxygen. It will be seen that except for lambs nos. 11 and 15 there was a rise, often very great, in blood oxygen saturation. No. 11 was one of the smallest lambs, with a weight of only 1·5 kg. The change in its pulmonary vascular resistance on ventilation was small (Table 1). When its umbilical cord was tied its condition began to deteriorate rapidly, both

TABLE 3. Effect of ventilation on percentage saturation with O_2 of carotid arterial blood

Lamb no.	Carotid % O_2 saturation: Before ventilation	Carotid % O_2 saturation: After ventilation	Duration in minutes, and type of ventilation
1	34	77	18, O_2
2	61	89	4–5, air and O_2
3	87	93	15, O_2
4	19	61	26, O_2
5	54	86	7, O_2
6	35	79	7, air
8	39	77	4, O_2
9	56	77	7, O_2
10	34	69	2½, O_2
11	33	34	2, air
13	33	93	12, O_2
14	37	56	7, air
15*	82	24	10½, O_2

* This lamb had been 'ventilated' with saline (as had 13 and 14); it was the only animal in which the pulmonary vascular resistance did not decrease (Table 1).

femoral and pulmonary arterial pressures diminished and the carotid oxygen percentage saturation 3½ min later had fallen to less than 10%. These observations suggest that the lamb was principally dependent on its placental circulation for oxygenated blood, and that in spite of ventilation its lungs were not functioning adequately. The smallest lamb (no. 12, wt. 1·1 kg) behaved in the same way. On ventilation there was no significant change in pulmonary blood flow, and on tying the umbilical cord the percentage oxygen saturation of the pulmonary arterial blood fell within 2 min from 49 to 16% (carotid samples were not taken from this lamb).

Blood flow through the ductus arteriosus

Before ventilation was begun or the umbilical cord tied blood samples were taken simultaneously from the carotid, femoral and pulmonary arteries. The values observed are given in Table 4, which shows, in confirmation of earlier observations by Barcroft (1946), that the femoral arterial oxygen saturation is significantly lower than that of the carotid artery. In addition, the deter-

mination of the pulmonary arterial oxygen saturation, which, as expected, is lower still, allowed us to calculate that about half (29–80%) of the total aortic blood flow comes directly from the right side of the heart and passes through the ductus arteriosus. As these estimations are based on the determination of the quantity of oxygen contained in three samples of blood, each with its own error of assay, the final figure has sometimes rather a large possible error.

During the dissection a loop of string had been passed around the ductus. This loop was carefully pulled tight through a soft polythene tube to occlude the ductus on various occasions during many experiments. Temporary occlusion of the ductus before ventilation was begun caused a fall in femoral arterial pressure (as much as 30%, systolic and diastolic), with no change or a slight diminution of pulse pressure and a reduction in the rate of rise of the pulse pressure wave. The pulmonary arterial pressure was much increased

TABLE 4. Simultaneous determination of percentage saturation with oxygen of carotid, femoral and pulmonary arterial blood

Lamb no.	% O_2 saturation in Carotid artery	Femoral artery	Pulmonary artery	Deduced percentage of total aortic flow coming through ductus arteriosus
1	34	26	21	62± 9
2	61	51	36	40± 5
3	87	82	70	29± 9
5	54	45	41	70± 9
6	35	26	18	53± 7
8	39	37	33	33±20
9	56	52	45	44±11
13	33	31	27	33± 7
14	37	29	27	80±12·5
15	82	68	53	48± 5

(systolic 50–75%, diastolic 10–40%), the pulse pressure increased, and the rate of rise of the pulse pressure wave also increased (Fig. 7). There was as a result a large rise in pulmonary blood flow (Fig. 8), and a small rise in left atrial pressure. All these observations are consistent with a large volume flow of blood from the pulmonary trunk through the ductus.

Occlusion of the ductus arteriosus after ventilation in these experiments caused different effects according to the time which had elapsed since ventilation was begun. In the first few minutes it was usual to find that occlusion caused a similar series of changes to those seen before ventilation, but reduced in size. Next we encountered on two occasions an intermediate stage in which occlusion had no effect on pulmonary blood flow, caused an increase in pulmonary arterial pulse pressure, but no change in mean pulmonary or femoral arterial pressures. In the same experiments, occlusion of the ductus a few minutes later caused a reduction in pulmonary blood flow, a fall in pulmonary arterial pressure (the pulse pressure being unchanged or somewhat increased)

and a rise in femoral arterial pressure (Figs. 7 and 8). The implication of the latter observations is that flow is proceeding through the ductus arteriosus, from thoracic aorta to pulmonary trunk, in a direction opposite to that obtaining in the foetal state, before ventilation.

That this is the correct interpretation is shown by the observations assembled in Table 5. This table records the oxygen saturation of the carotid blood, and that of the pulmonary blood before, during and after occlusion of the ductus over a period of up to 1 min. There is a striking fall in the oxygen saturation of the pulmonary blood during occlusion of the ductus, and in fact on the first occasion on which we observed this phenomenon, the change in

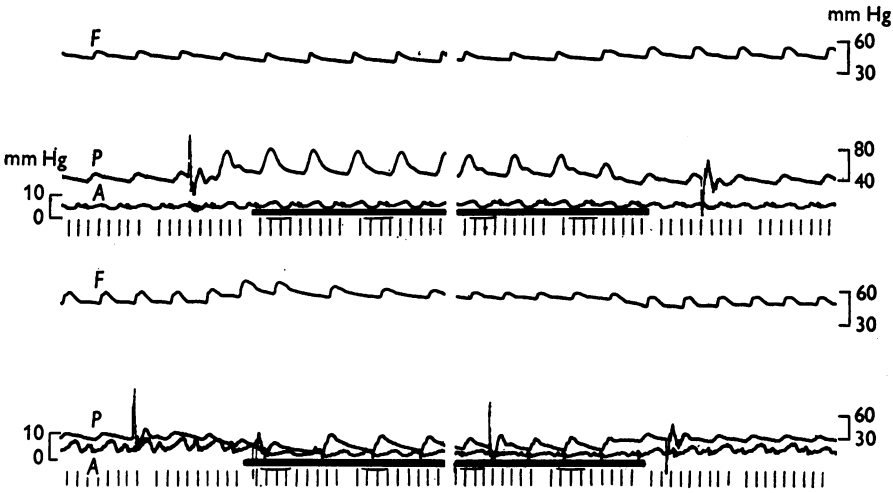

Fig. 7. Lamb no. 9. Condenser manometer records of blood pressure in the left femoral artery (*F*), left pulmonary artery (*P*) and left atrium (*A*). Time marks are $\frac{1}{10}$ sec with a gap once a second. The upper record shows the effect on the pulse contours of temporary occlusion of the ductus arteriosus (during the signal mark) before ventilation of the lungs. The lower record shows the effect of occluding the ductus arteriosus 15½ min after ventilation was begun. The abrupt oscillations in the pulmonary arterial pressure records are caused by the operation of the flowmeter.

colour of the blood in the polythene tube leading from the central end of the left pulmonary artery to the flowmeter was arresting. We then confirmed the conclusion that retrograde flow was taking place through the ductus by injecting indian ink into the cavity of the left ventricle, whence it was at once carried down the thoracic aorta and into the lungs in less than 2 sec. Table 5 shows that on the four occasions on which we carried out the necessary estimations 40–68 % of the total pulmonary blood flow was derived from the left heart, passing down the thoracic aorta and through the ductus arteriosus.

Retrograde flow from aorta to pulmonary trunk through the ductus arteriosus was observed on each of the ten lambs in which it was sought, some time

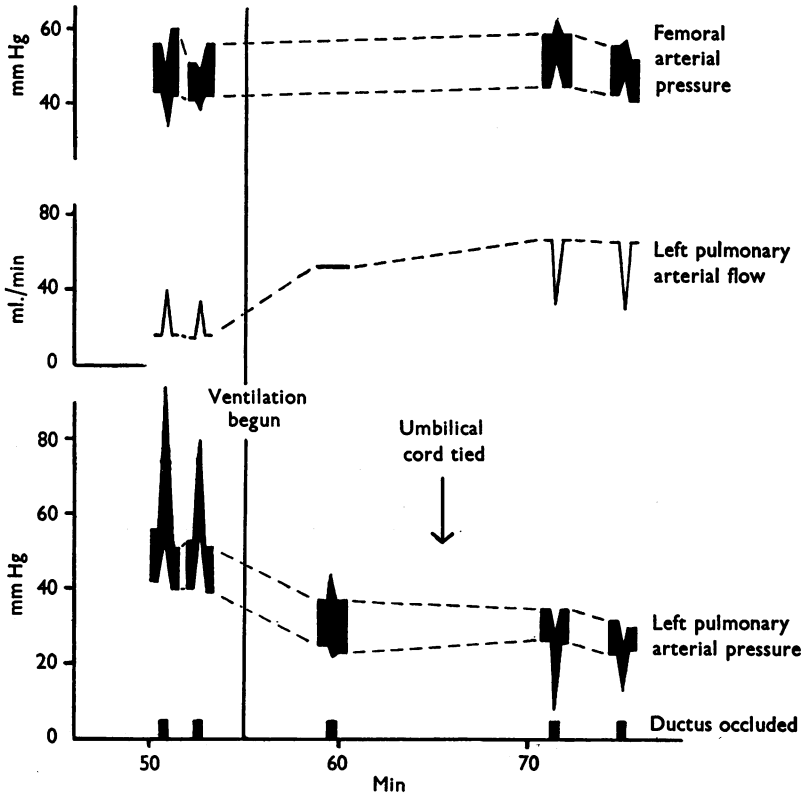

Fig. 8. Lamb no. 9. Chart to show the relative changes in left femoral and pulmonary arterial pressures, and in left pulmonary arterial blood flow, during temporary occlusion of the ductus arteriosus before and after ventilation of the lungs. These changes show that a short while after ventilation has begun, blood begins to flow from the aorta to the pulmonary trunk through the ductus arteriosus.

TABLE 5. Flow from aorta to pulmonary artery through the ductus arteriosus as indicated by changes in blood oxygen saturation

		% O_2 saturation of blood from				Deduced % of total pulmonary arterial flow which comes from aorta	
			Pulmonary artery				
Lamb no.	Time after ventilation (min)	Carotid artery	Before temporary occlusion	During temporary occlusion	After temporary occlusion	Before occlusion	After occlusion
3	24	93	71	51	68	48±5	40±5
5	36	86	77	65	74	57±5	43±5
8	25	70	65	57·5	—	60±9	—
13	20	93	81	56	76	68±3	54±3

after ventilation was begun. Table 6 gives a summary of these observations. It should perhaps be explained that the experiments were not primarily designed to find the time at which reversal occurred, which accounts for the rather scattered observations on this point. Nevertheless, this table does suggest that reversal normally occurred in these experiments from 5 to 15 min after ventilation had begun. There are a number of other points which a closer scrutiny of individual experiments reveals. Reversal of flow down the ductus arteriosus occurred in lamb no. 2 during ventilation with nitrogen only. In lambs nos. 2, 5 and 8 reversal of flow occurred before the umbilical cord had been tied, in lambs nos. 3 and 9 it is probable that it did so; in the remainder there is not sufficient evidence on which to judge.

In none of these experiments was there any evidence of closure of the ductus arteriosus. It might at first be thought that closure had occurred at those two points indicated in Table 6 at which occlusion of the ductus caused no alteration in pulmonary blood flow. This is not, however, the correct conclusion. On these occasions tightening the loop around the ductus arteriosus gave the usual sensation of compressing a patent vessel against a resistance, and subsequently there was no doubt that voluminous flow proceeded in a retrograde direction.

TABLE 6. Reversal of flow through the ductus arteriosus as indicated by changes in pressure and flow on temporary occlusion

	Minutes after ventilation was begun			
Lamb no.	Flow P.A.→aorta	No flow either way	Flow aorta→P.A.	Cord tied
2	—	—	16–33	23
3	10	16	25–40	20
5	—	—	27	30
6	—	—	13–27	9
7	1¼	—	17½–39	2
8	4	—	5½–19	7½
9	—	4½	15½–20	10
13	5	—	9–18	6½
14	—	—	10–13	9½
15	—	—	9	7

It will perhaps not have escaped notice in Figs. 3 and 4 that the pressure measured in the femoral artery was always higher than that in the left pulmonary artery, even before ventilation, when blood was flowing down the ductus arteriosus from pulmonary artery to aorta. This difference is partly but not entirely explained by the pressure drop along the polythene tube between the origin of the left pulmonary artery and the point at which the lateral pressure was measured, a distance of some 15–20 cm. When the rate of blood flow was 10–15 ml./min the pressure drop was about 1 mm Hg. This is not sufficient to explain the discrepancy, nor indeed would we expect it to do so since a similar discrepancy was observed when the lateral pressure was measured in the pulmonary trunk itself (Ardran *et al.* 1952). It may be

due to the presence of reflected waves in the femoral pulse (Hamilton & Dow, 1939; Hamilton, 1944).

After ventilation the difference between the left pulmonary and femoral arterial pressures as we measured them increased in most experiments. Part of this increase can certainly be ascribed to the increased pressure drop between pulmonary trunk and left pulmonary arterial manometer. The remainder may be due to a change in the pulse shape as measured by the femoral manometer.

DISCUSSION

The experimental observations which have been described confirm the hypothesis that expansion of the foetal lungs by positive pressure ventilation caused a great decrease in the resistance to blood flow through the lungs. The figures given in Table 1 show that pulmonary vascular resistance in eight lambs of from 130 to 141 days old fell to 21·5% (9–50%) of the initial value. We have taken as an arbitrary index of vascular resistance the quotient of the pressure difference and flow. We do not know if there is a linear relationship between pressure and flow through the neonatal lung. It is likely that this relationship is not linear, since when the ductus arteriosus is temporarily occluded before ventilation has begun the pulmonary arterial pressure rises, but the left pulmonary arterial flow increases more in proportion, and the pulmonary vascular resistance as calculated above appears to decrease (as much as 15–35%). Such a decrease would be expected if the vascular tissue of the lung behaved in an elastic fashion. The converse has occasionally been seen; Fig. 3 shows an example of an increase in pulmonary vascular resistance as the pulmonary arterial pressure falls on temporary occlusion of the ductus arteriosus after ventilation. Under the conditions of our experiments, when ventilation was begun, the pulmonary blood flow increased at a time when the pressure across the lungs was reduced, therefore if the pulmonary vessels do behave in an elastic manner, the use of our index of vascular resistance leads to an underestimate of the relative change.

There are two further questions which suggest themselves. What is the mechanism responsible for this change, and does it also occur in unanaesthetized animals which are breathing normally and which have not been submitted to a fairly severe surgical operation? These questions have not yet been answered by direct experiment.

It is evident that the decrease in pulmonary vascular resistance is due to distension of the lungs with a gas, rather than any particular gas, since the same change was observed whether air, oxygen or nitrogen was used. Distension of the lungs with saline actually increased the pulmonary vascular resistance, which shows that the operative factor is expansion of the lungs with a gas, rather than expansion *per se*. It also suggests that the explanation

of the decrease in pulmonary vascular resistance is more likely to be a direct mechanical effect upon the lung vessels, rather than through a nervous mechanism, which would presumably be equally excited by expansion of the lungs with saline.

As to the second question, we think it is very probable that pulmonary vascular resistance does decrease in a normal new-born animal on spontaneous breathing. The decrease seen in our experiments was large, the lambs were in satisfactory condition and it is difficult to see how the absence of light anaesthesia and the thoracic operation would have modified the result. It would of course have been desirable also to have used negative pressure ventilation, but in view of the additional difficulties involved in applying the method to a foetal lamb which is still connected to its mother by the umbilical cord, it was thought unwise to attempt so much at this stage of the investigation. The observations of Barclay, Barcroft, Barron, Franklin & Prichard (1941) showed that in spontaneously breathing lambs, the pulmonary circulation time was much reduced below that observed before respiratory movements began. This change is certainly compatible with a decrease in pulmonary vascular resistance. Nevertheless, direct proof of the latter in a spontaneously breathing animal is still required.

Pulmonary inflation pressures and tidal air

It has already been explained that when we began these experiments we had no information available as a guide to the inflation pressures and volumes of tidal air which could reasonably be expected in the new-born lamb. We therefore used the following criteria in deciding whether the lungs were adequately but not excessively inflated: (1) The naked eye appearance of the lungs and the extent to which they filled the thoracic cage. (A mature new-born lamb is about the same weight and shape as an adult cat.) (2) The oxygen saturation of the carotid arterial blood. (3) The level of the systemic arterial blood pressure. During the course of the experiments we also had the opportunity of making measurements on two lambs which were breathing spontaneously. These measurements are in agreement with conclusions derived from observations on lambs which were ventilated by positive pressure, that the pressure required to produce a given tidal air in the new-born is much greater than that in the adult animal, and that the resistance to inflation of the lungs rapidly falls towards the adult level during the first few hours after delivery. It will also be apparent that a systematic investigation of the phenomenon in a much larger series of spontaneously breathing animals will be required to give an accurate description of the normal time-course and magnitude of this change.

There are several hypotheses, not mutually exclusive, which may be advanced to explain these findings. The alveoli, which are collapsed in the foetal state, may require a critical pressure to be applied before they will open.

Another explanation depends on the fact that when ventilation was begun the bronchioles and parts of the main bronchi were still full of fluid. This fluid offers a resistance to phasic inflation because of inertia, viscosity and surface tension forces acting at the air-liquid interface. As the fluid is removed by evaporation or absorption the resistance to inflation due to its presence will also vanish.

There are many other factors which may contribute to the change in resistance to inflation of the foetal lung. For instance we cannot ignore the possibility that the tone of the bronchial muscles may alter. We also cannot predict the quantitative effect of a change in the vascular capacity of the lung. An increase in pulmonary blood volume will not make much difference to the inertia of the lung tissue if we consider that the extra amount of blood is simply replacing amniotic fluid which formerly occupied the air-passages, but it might alter the elasticity of the lung. All these and perhaps many other changes will have to be considered before a complete explanation of the phenomenon is found.

Reversal of flow through the ductus arteriosus

In no lamb was the ductus arteriosus observed to close, during the period of observation of up to 1½ hr after ventilation was begun and the umbilical cord tied. In all ten lambs in which the requisite observations were made it was found that some minutes after ventilation was begun, blood began to flow *backwards* through the ductus arteriosus, backwards that is to say from the foetal point of view, from aorta to pulmonary artery. It seems very likely that the fall in pulmonary vascular resistance is the principal cause of this alteration in the course of the neonatal circulation, but we have no quantitative information about the systemic arterial resistance, or the relative output of the right and left ventricles at this time. It may be observed that tying the umbilical cord will much increase the systemic arterial resistance and hence favour what we have arbitrarily described as a reversal of flow through the ductus arteriosus. But as can be seen from Table 6, reversal certainly occurred in three lambs before the cord was tied.

The observation of reversal of spontaneous flow through the ductus arteriosus reinforces the conclusion drawn by Barclay, Franklin & Prichard (1944) that there is in the lamb no functional valve at the aortic end of the ductus arteriosus. The volume of this retrograde flow may be very large. It has been shown to constitute between 40 and 68% of the total pulmonary blood flow in four lambs at a time from 20 to 36 min after ventilation was begun. This blood travels in a short path between left ventricle, aorta, ductus arteriosus, lungs, left atrium and left ventricle again. The effect of this is to increase both the pulmonary blood flow and the left cardiac output very substantially. If the transfer of oxygen and carbon dioxide across the alveolar

walls is relatively inefficient, as it may well be in a lung which has only been partially expanded, the greater volume of blood flow may improve the rate of exchange, to such an extent that the increased work of the left heart is more than offset.

The observation that blood started to flow backwards through the ductus arteriosus some minutes after ventilation had begun was surprising. The work of Barclay *et al.* (1944) and of Barcroft (1946) using cineangiographic methods had not led us to expect this. Both published the same cineradiograms (taken at a speed of 2–3 frames per sec) from which they inferred that backflow did not occur. The limits of accuracy of negative observations using this method are not known.

In a previous series of experiments (Ardran *et al.* 1952) cineradiograms were taken at a speed of 25 frames per sec on nine lambs. These films have been re-examined in the light of our latest experiments and it was found that in two lambs of this series (nos. 5 and 8) retrograde flow certainly occurred. In lamb 5 the chest was closed throughout the experiment, and in lamb 8 when reversed flow occurred the lateral pressure in the thoracic aorta (51/43) was greater than that in the pulmonary trunk (46/34).

More evidence is required to determine the natural history of closure of the ductus arteriosus in the new-born lamb, and the effect on this process of operative procedures and anaesthesia. What has been demonstrated is that under certain conditions the ductus arteriosus does not close immediately after birth, and that, probably as a result of the profound decrease of pulmonary vascular resistance on expansion of the lungs, the direction of blood flow through the ductus arteriosus may be reversed.

SUMMARY

1. Lambs were delivered by caesarian section and the volume of blood flowing per minute through the left pulmonary artery was measured, together with the left pulmonary arterial pressure, the left atrial pressure and the femoral arterial pressure.

2. Artificial positive pressure ventilation caused an immediate increase in the rate of left pulmonary arterial blood flow, due to a reduction of pulmonary vascular resistance of as much as 90%. Even this change is probably underestimated in some experiments. A large decrease of pulmonary vascular resistance was observed when the lungs were expanded with air, oxygen or nitrogen, but not when they were expanded with saline.

3. With the circulation in the foetal condition, before ventilation was begun, simultaneous determinations of oxygen percentage saturation in the carotid, femoral and pulmonary arterial blood showed that from 29 to 80% of the aortic blood was derived from the pulmonary trunk through the ductus arteriosus.

4. Within a few minutes after ventilation was begun, when the pulmonary vascular resistance had decreased, the direction of blood flow through the ductus arteriosus reversed. Under these circumstances 40–68% of the total pulmonary blood flow was derived from the descending aorta through the ductus arteriosus, as shown by simultaneous blood oxygen determinations. The ductus arteriosus was not observed to close during the course of any of these experiments.

5. The resistance of the lungs of the new-born lamb to positive pressure ventilation is much greater than expected. The resistance to inflation rapidly and continuously decreases after birth.

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