A REDUCED supply of oxygen, such as that experienced at high altitude, sometimes induces pulmonary edema in the absence of heart failure. Pulmonary edema at high altitude is more common in infants and children than it is in adult humans (Hultgren et al., 1961; Scoggin et al., 1977), suggesting that lung maturation may be an important element in the adaptive response to hypoxia.

Bland et al. (1977) reported that alveolar hypoxia had no effect on pulmonary lymph flow or the concentration of protein in lymph of eight awake sheep breathing 10% oxygen for 4 hours compared to measurements made during a 2-hour control period in which the sheep breathed air. Even when hypoxia was sustained for 2 days in three of the sheep, lymph flow did not increase.

To see if the pulmonary microcirculation of lambs and sheep might react differently to hypoxia, we assessed lung fluid balance in 14 unanesthetized lambs, 1–3 weeks old, breathing 10–12% oxygen for 3–6 hours after a 2-hour steady state period in air. Contrary to results with sheep, pulmonary lymph flow increased and the concentration of protein in lymph decreased significantly in the lambs, suggesting that hypoxia caused an increase in the pulmonary transvascular pressure gradient, thereby increasing filtration of fluid into the lungs of the lambs. As in previous studies, there was no evidence of altered pulmonary microvascular permeability to protein during hypoxia.

Methods

Preparation of Lambs for Experiments

Using methods previously described (Staub et al., 1975; Bland and McMillan, 1977), we surgically prepared 14 newborn lambs (average birth weight, 3.7 ± 0.3 kg) to collect lung lymph and measure average pulmonary arterial, left atrial, and aortic blood pressures. Each lamb had two thoracotomies, the first at 1–2 days of age and the second 3–7 days later. We use halothane and nitrous oxide anesthesia and ventilated the animals with a piston-type respirator (model 607, Harvard Apparatus Co., Inc.) during surgery. Before and after surgery, and between experiments, the lambs remained with their ewes for feeding and warmth.

In the first operation we placed polyvinyl cathe-
ters (Tygon Tubing) in the thoracic aorta, pulmonary artery, and both atria. In the second operation we resected the systemic contribution to the caudal mediastinal lymph node and inserted a heparin-coated (TDMAC Processing, Polyscience Inc.) polyvinyl catheter (internal diameter, 0.38 mm) into the efferent duct of that node for collection of nearly pure pulmonary lymph. Previous studies showed that this fluid is not contaminated by lymph of systemic origin (Staub et al., 1975). We tunneled the catheter beneath the pleura and through the chest wall, securing it to the skin with a suture and protecting it with a canvas pouch. In addition, we placed a 4 x 2 cm silicone (Silastic, Dow Corning Corp.) balloon and a polyvinyl catheter in the pleural space for subsequent measurement of pleural pressures and postoperative drainage of fluid and air. The lambs had at least 3 days to recover from surgery, and experiments did not begin until the lymph was free of visible blood and flowing at a steady rate.

**Description of Experiments**

The average weight of the lambs at the time of experiments was 6.5 ± 0.5 kg; their average age was 14 ± 1 days. During studies, the lambs were awake and unmedicated, resting on a canvas sling that did not interfere with respiratory movements. We administered gas mixtures through a plastic bag around the lamb's head. Each lamb received isotonic saline, approximately 5 ml/hr per kg body weight, intravenously during experiments, an amount that yielded no significant change in body weight, vascular pressures, or concentrations of protein in plasma. The design of the 17 experiments was similar to that of the previous studies performed with sheep (Bland et al., 1977): after a 2-hour control period in air, the lambs breathed 10-12% oxygen in nitrogen during a steady state period lasting 3 or 6 hours. In 11 experiments the lambs were hypoxic for 3 hours; in six experiments we extended the study period to 6 hours.

During all experiments we measured pressures continuously in the pulmonary artery, left atrium, thoracic aorta, and pleural space, using calibrated pressure transducers (Statham P23 DC, Statham Instruments, Inc.) and a six-channel amplifier-recorder (Grass model 7B, Grass Instruments Co.). Zero reference level for measurement of vascular pressures was a line drawn on the lamb's skin at the level of the left atrium at the time of surgery; for measurement of pleural pressure, zero reference was atmospheric pressure.

We measured the flow of lymph to the nearest 0.01 ml at 30-minute intervals for at least 2 hours during a steady state baseline period, and then for 3 or 6 hours with the lamb breathing 10-12% oxygen in nitrogen. The change in the inspired oxygen concentration was sufficient to keep the partial pressure of oxygen in arterial blood at 30-35 torr. We collected samples of lymph and blood in heparinized test tubes every 30 minutes, taking blood at the midpoint of each lymph collection period. During control and experimental periods we measured respiratory frequency, heart rate, and rectal temperature, and obtained samples of arterial blood at frequent intervals for measurement of packed cell volume (hematocrit), pH, and blood gas tensions. We measured pulmonary blood flow (cardiac output) by indicator dilution (Rudolph, 1974) using cardiogreen dye (Hynson, Wescott, and Dunning, Inc.) and calculated pulmonary vascular resistance as (pulmonary arterial pressure — left atrial pressure)/pulmonary blood flow.

**Postmortem Studies**

At the conclusion of experiments on each lamb, we injected pentobarbital sodium, 20 mg/kg, into the right atrium, placed the lamb supine, ventilated the lungs with 10% oxygen in nitrogen via the respirator, and rapidly split the sternum to excise the lungs. We clamped the hili of both lungs at end-inspiration, at an airway pressure of 25 cm H2O, with the heart still beating, and removed the lungs for measurement of blood content, extravascular water, and dry lung tissue weight. We did this with nine lambs immediately after a 4- to 6-hour period of steady state hypoxia, and compared the results to measurements made on lungs of control lambs killed during ventilation with air. Control and experimental lambs had undergone the same surgical procedures.

We rapidly froze in liquid nitrogen part of the inflated lung tissue of six lambs and prepared a section from each for microscopy by the method of Storey and Staub (1962).

**Analytic Methods**

We centrifuged samples of lymph and blood and measured the concentration of protein in the supernatant fluid by the biuret method (Henry et al., 1957), with protein fractionation by cellulose acetate electrophoresis (Microzone 110, Beckman instruments, Inc.). We measured the pH and partial pressure of gases in arterial blood with a blood gas analyzer (Acid-Base Analyzer PHM 71, Radiometer Co.), with calibration at 40°C, the normal body temperature of lambs.

We calculated the weight of extravascular lung water per gram of dry lung tissue, exclusive of blood, for all lambs by a modification (Erdmann et al., 1975) of the method described by Pearce et al. (1965). We expressed pulmonary blood flow (cardiac output), lung lymph flow, and lymph protein flow (lymph flow x lymph protein concentration) relative to the weight of dry, bloodless lung tissue. We also expressed protein flow in relation to the concentration of protein in the plasma of each animal.

**Statistical Analysis**

We used the paired t-test (Snedecor and Cochran, 1972) to compare measurements made during air breathing with those obtained during steady state hypoxia, accepting P < 0.05 as indicative of
LUNG FLUID BALANCE IN HYPOXIC NEWBORN LAMBS/Bressack and Bland

Figure 1 Effects of 6 hours of hypoxia on lung lymph flow, concentrations of protein in lymph and plasma, and average vascular pressures of an unanesthetized 2-week-old lamb.

Results

Figure 1 shows the results of a typical experiment in which a lamb breathed 11% oxygen in nitrogen for 6 hours after a 2-hour control period in air. Hypoxia produced an abrupt increase in the flow of lymph, with an associated decrease in the concentration of protein in lymph, as pressure in the pulmonary artery doubled. Vascular pressures, protein concentrations, and lymph flow returned to baseline with resumption of air breathing.

Because the effects of hypoxia for 3 hours were indistinguishable from those observed in the longer experiments, we pooled (in Tables 1 and 2) the data for the 17 experiments.

Effects of Hypoxia on Respiration and Circulation

Table 1 is a summary of the effects of hypoxia on respiration and systemic circulation in the 14 lambs. The decrease in the partial pressure of oxygen in arterial blood (Pao2) from 81 ± 3 torr to 32 ± 1 torr caused tachypnea and hyperpnea, as indicated by the changes in pleural pressure. These alterations in the pattern of breathing produced a decrease in the partial pressure of carbon dioxide in arterial blood (Paco2) and an increase in pH. Heart rate increased with hypoxia, but there was no change in aortic blood pressure.

Effects of Hypoxia on Lung Fluid and Protein Transport

Table 2 shows the data related to lung fluid and protein transport. Average pressure in the pulmonary artery (Ppa) almost doubled during hypoxia, while average pressure in the left atrium (Pla) did not change. Pulmonary blood flow increased, on average, by 14%, and calculated pulmonary vascular resistance increased by 69%. These circulatory effects were associated with an 80% increase in the flow of pulmonary lymph and a concomitant decrease in the concentration of protein in lymph from 3.8 ± 0.2 g/dl to 3.2 ± 0.1 g/dl. During hypoxia, average lymph protein flow increased by 45% above the control value. The concentration of protein in plasma was unaffected by hypoxia; the ratio of the concentration of protein in lymph to that in plasma decreased significantly from 0.65 to 0.54. Hypoxia did not significantly change the concentration of albumin relative to globulin in lymph or plasma.

Postmortem Findings

Table 3 shows the content of blood and extravascular water in the lungs of nine lambs killed after 4-6 hours breathing 10-12% oxygen, compared to measurements made on the lungs of 10 control lambs killed without preceding hypoxia. Lung blood per gram of dry lung tissue was significantly less in the hypoxic lambs, but there was no significant difference in lung water content. Consistent with these findings, we observed by light microscopy that the lungs of hypoxic lambs were more pallid than those of control lambs; as shown in Figure 2, there was no evidence of alveolar or interstitial edema or hemorrhage in the lungs of lambs made hypoxic for 4-6 hours.

Discussion

Previous studies have demonstrated that measurement of pulmonary lymph flow and the concentration of protein in lymph is a sensitive index of the net transvascular movement of fluid and protein in the lung (Staub, 1971, 1974; Brigham et al., 1974;
TABLE 2 Data Pertaining to Lung Water and Protein Transport in 14 Lambs

<table>
<thead>
<tr>
<th>Lamb</th>
<th>Ppa (torr)</th>
<th>Ppa (torr)</th>
<th>Lymph</th>
<th>Plasma</th>
<th>Lymph:Plasma</th>
<th>Pulmonary blood flow (ml/min)</th>
<th>Lymph flow (ml/hr)</th>
<th>[Albumin]-[globulin]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18—34</td>
<td>2—3</td>
<td>3.0—2.4</td>
<td>4.7—4.6</td>
<td>0.64—0.53</td>
<td>98—127</td>
<td>0.06—0.08</td>
<td>0.80—0.86</td>
</tr>
<tr>
<td>2</td>
<td>16—33</td>
<td>2—2</td>
<td>3.7—2.9</td>
<td>6.5—6.7</td>
<td>0.57—0.44</td>
<td>147—197</td>
<td>0.05—0.05</td>
<td>0.84—0.88</td>
</tr>
<tr>
<td>3</td>
<td>16—28</td>
<td>3—2</td>
<td>4.3—3.6</td>
<td>6.8—6.7</td>
<td>0.62—0.54</td>
<td>101—114</td>
<td>0.09—0.18</td>
<td>0.88—1.21</td>
</tr>
<tr>
<td>4</td>
<td>17—37</td>
<td>3—3</td>
<td>3.8—3.1</td>
<td>5.9—5.7</td>
<td>0.65—0.54</td>
<td>99—138</td>
<td>0.10—0.15</td>
<td>0.85—1.01</td>
</tr>
<tr>
<td>5</td>
<td>17—27</td>
<td>1—0</td>
<td>3.0—2.9</td>
<td>5.7—5.7</td>
<td>0.53—0.51</td>
<td>112—180</td>
<td>0.17—0.22</td>
<td>1.07—1.12</td>
</tr>
<tr>
<td>6</td>
<td>20—31</td>
<td>2—1</td>
<td>3.4—2.8</td>
<td>5.3—5.5</td>
<td>0.64—0.50</td>
<td>77—90</td>
<td>0.08—0.17</td>
<td>0.87—0.98</td>
</tr>
<tr>
<td>7</td>
<td>18—31</td>
<td>3—2</td>
<td>3.3—2.4</td>
<td>6.2—6.0</td>
<td>0.54—0.40</td>
<td>89—91</td>
<td>0.11—0.25</td>
<td>0.89—0.93</td>
</tr>
<tr>
<td>8</td>
<td>16—32</td>
<td>1—1</td>
<td>3.6—2.8</td>
<td>5.2—5.1</td>
<td>0.70—0.55</td>
<td>176—185</td>
<td>0.11—0.23</td>
<td>0.96—1.06</td>
</tr>
<tr>
<td>9</td>
<td>15—29</td>
<td>2—2</td>
<td>4.0—3.3</td>
<td>5.9—5.9</td>
<td>0.68—0.56</td>
<td>68—92</td>
<td>0.06—0.12</td>
<td>0.94—1.06</td>
</tr>
<tr>
<td>10</td>
<td>17—35</td>
<td>1—1</td>
<td>3.9—3.4</td>
<td>5.8—6.2</td>
<td>0.67—0.55</td>
<td>102—113</td>
<td>0.14—0.29</td>
<td>0.94—0.97</td>
</tr>
<tr>
<td>11</td>
<td>13—23</td>
<td>1—1</td>
<td>4.2—3.8</td>
<td>5.9—6.2</td>
<td>0.71—0.61</td>
<td>84—108</td>
<td>0.13—0.18</td>
<td>1.12—1.19</td>
</tr>
<tr>
<td>12</td>
<td>15—33</td>
<td>3—4</td>
<td>4.3—3.3</td>
<td>5.9—5.9</td>
<td>0.73—0.56</td>
<td>118—147</td>
<td>0.06—0.10</td>
<td>0.76—0.75</td>
</tr>
<tr>
<td>13</td>
<td>16—30</td>
<td>4—5</td>
<td>3.7—3.2</td>
<td>5.8—5.8</td>
<td>0.63—0.55</td>
<td>153—183</td>
<td>0.21—0.40</td>
<td>1.18—1.54</td>
</tr>
<tr>
<td>14</td>
<td>16—32</td>
<td>1—4</td>
<td>5.2—4.3</td>
<td>6.9—6.9</td>
<td>0.76—0.69</td>
<td>82—93</td>
<td>0.07—0.10</td>
<td>1.22—1.14</td>
</tr>
<tr>
<td>Mean</td>
<td>16—31‡</td>
<td>2—2</td>
<td>3.8—3.2‡</td>
<td>5.9—5.9</td>
<td>0.65—0.54‡</td>
<td>108—123‡</td>
<td>0.10—0.18‡</td>
<td>0.95—1.03</td>
</tr>
</tbody>
</table>

±SE ±1 ±3 ±5 ±2 ±1 ±2 ±2 ±02 ±02 ±8 ±10 ±01 ±02 ±04 ±06 ±04 ±05

* Per g of dry lung tissue, exclusive of blood, measured postmortem.
† Numbers to the left of the arrow are measurements made before hypoxia, those to the right are measurements during hypoxia.
‡ Significant difference, P < 0.05.

Staub et al., 1975; Erdmann et al., 1975; Bland et al., 1977), assuming that the concentration of protein in lymph approximates that in the pulmonary interstitium (Nicolaysen et al., 1975; Vreim et al., 1976). In newborn lambs, about two-thirds of the pulmonary lymph flows through the caudal mediastinal lymph node into the thoracic duct (Humphreys et al., 1967).

The 80% increase of pulmonary lymph flow that we observed in lambs breathing 10–12% oxygen in nitrogen for 4–6 hours and for control lambs without preceding hypoxia; results are expressed per unit of dry lung tissue, exclusive of blood, measured postmortem.† Significant difference, P < 0.05.

TABLE 3 Blood and Extravascular Water in the Lungs

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>No. of lambs</th>
<th>Weight of dry lung tissue (g)</th>
<th>Lung blood/dry lung tissue</th>
<th>Extravascular lung water/dry lung tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia for 4–6 hr</td>
<td>9</td>
<td>20.5 ± 1.7</td>
<td>1.50 ± 0.18</td>
<td>4.54 ± 0.13</td>
</tr>
<tr>
<td>Breathing air</td>
<td>10</td>
<td>20.5 ± 1.4</td>
<td>2.22 ± 0.25</td>
<td>4.72 ± 0.14</td>
</tr>
</tbody>
</table>

* For lambs killed after breathing 10–12% oxygen in nitrogen for 4–6 hours and for control lambs without preceding hypoxia; results are expressed per unit of dry lung tissue, exclusive of blood, measured postmortem.
† Significant difference, P < 0.05.

Figure 2 Photomicrograph of a section of frozen lung, taken at an inflation pressure of 25 cm H₂O, from a lamb killed after breathing 11% oxygen for 6 hours. Lung architecture is normal, and there is no visible fluid within the air spaces or surrounding blood vessels. Magnification is 8.5X.
Hypoxia did not increase pulmonary microvascular permeability to protein, in that the concentration of protein in lymph decreased during hypoxia. Had vascular permeability been affected, we would have expected the concentration of protein in lymph to remain stable or increase (Brigham et al., 1979; Bressack et al., 1979) as the flow of lymph increased. The fact that [albumin] : [globulin] in lymph did not decrease with hypoxia is further evidence that the sieving characteristics of the pulmonary endothelium did not change appreciably in these animals (Brigham et al., 1979; Bressack et al., 1979).

It is not likely that hypoxia increased lung fluid filtration solely by recruiting new vessels, thereby increasing vascular surface area for exchange of fluid in the lung. Had this been the major source of the increased flow of lymph, the concentration of protein in lymph would have been unchanged, and the content of blood in the lungs of hypoxic lambs should have been greater than that of control animals. Our finding of decreased blood in the lungs of lambs that were killed during hypoxia is consistent with the observation of Stahlan et al. (1967) who from indicator dilution curves estimated pulmonary blood volume in lambs before and during hypoxia. The reduced pulmonary blood volume in hypoxia probably reflects a constricted lung vascular bed.

Is it possible that hypoxia decreased intracellular fluid within the lung, diluting the concentration of protein within the pulmonary interstitium, and enhancing the flow of lymph? This is unlikely, in that lung water content was not significantly different after 6 hours of hypoxia than it was in control lambs; neither was there any difference in lung architecture microscopically between the two groups of lambs. Furthermore, the sustained nature of the increased lymph flow is more consistent with altered filtration of fluid from the bloodstream, rather than cellular dehydration.

The outcome of these experiments, and similar ones performed on adult sheep (Bland et al., 1977), indicate that the pulmonary microcirculation of newborn and mature sheep respond differently to alveolar hypoxia. In sheep, a decrease in the partial pressure of oxygen in arterial blood from 97 ± 2 torr to 38 ± 1 torr caused pulmonary vascular resistance to increase by 54%, with no change in the rate of flow or the concentration of protein of lung lymph. In lambs, hypoxia of a similar degree induced a 69% increase in pulmonary vascular resistance, with a substantial increase in the transvascular flow of fluid into the lungs. Pulmonary edema did not occur, presumably because lymph flow kept pace with transvascular filtration of fluid.

Our observations do not define the mechanism by which hypoxia increased the pulmonary transvascular gradient of hydraulic pressure in lambs without doing so in sheep, but certain possibilities are noteworthy. Pulmonary arterial pressure and cardiac output under baseline conditions were greater in lambs than in sheep, and it is possible that the pulmonary microcirculation of the lambs had a smaller reserve capacity to accommodate the increased flow of blood caused by hypoxia.

Hypoxia could have caused pulmonary venous constriction in the lambs without doing so in mature sheep. Work by Naeye (1965) suggested that hypoxia produces such an effect in calves, but does not do so in mature dogs. Rivera-Estrada et al. (1958) and Morgan et al. (1968) presented evidence that, even in adult dogs, most of the increase in pulmonary vascular resistance that occurs during hypoxia is the result of increased venous tone. Most investigators, however, have found that hypoxia produces predominantly arteriolar constriction (Kato and Staub, 1966; Bergofsky et al., 1968; Glazer and Murray, 1971; Malik and Kidd, 1976). In studies of lambs that were beyond the newborn period and weighed 25–38 kg, Hyman and Kadwotz (1975) showed that lobar ventilation with 5% oxygen in nitrogen increased pulmonary arterial pressure, without a comparable increase in pulmonary venous pressure, suggesting that the constrictive response was predominantly pre-venous. The apparent inconsistency of this observation and our results could stem from differences in the degree of hypoxia or in the age and maturity of the animals that were studied. We cannot exclude the possibility that water may leave the pulmonary vascular bed through small arterioles in hypoxic lambs, as Whyane and Severinghaus (1968) suggested, but if this is the case, it would appear to be an age-related phenomenon, in that lymph flow did not increase in adult sheep (Bland et al., 1977).

An alternative explanation for the increased flow of lymph in hypoxic lambs is that intense constriction of pulmonary arteries during hypoxia diverts the increased flow of blood to fewer vessels in the lung, thereby increasing the transvascular pressure gradient within those vessels. That is, redistribution of blood flow may transmit a greater percentage of pressure in the pulmonary artery to vessels that participate in fluid exchange. Hultgren and Grover (1968) invoked this theory to account for the development of pulmonary edema in humans who ascend to high altitude. Such an explanation is consistent with our findings of reduced lung blood in lambs with hypoxia.

In previous experiments with sheep, hypoxia led to hyperpnea, but did not cause an increase in respiratory frequency (Bland et al., 1977); in lambs hypoxia was associated with tachypnea, as well as hyperpnea and a decrease in mean pleural pressure.

Another consideration, therefore, is that the breathing pattern elicited by hypoxia enhanced pulmonary transvascular filtration of fluid in lambs by decreasing lung tissue pressure. Although this explanation for our findings is possible, recently Haberkern and Bland (unpublished observations) re-
produced the respiratory pattern observed in the hypoxia experiments by allowing eight lambs to breathe 10% carbon dioxide in air for several hours, inducing both tachypnea and hyperpnea, without an appreciable change in the steady state flow of pulmonary lymph.

In sheep, hypoxia caused an increase in the concentration of protein in plasma (Bland et al., 1977), thereby increasing the transvascular gradient of protein osmotic pressure, a change that tends to inhibit filtration of fluid into the lungs. This change did not occur in lambs during hypoxia, presumably because they did not have an associated diuresis. It is possible that this difference in the response to hypoxia may account partly for the failure of lymph flow to increase in hypoxic sheep as it did in hypoxic lambs.

We conclude from these experiments that sustained alveolar hypoxia does not increase pulmonary microvascular permeability to protein in lambs, but does increase the pulmonary transvascular pressure gradient, thereby enhancing filtration of fluid into the lungs. In normal lambs, the flow of lymph keeps pace with filtration, such that pulmonary edema does not occur.

Speculation. It is possible that by imposing an additional stress, such as exercise (Whayne and Severinghaus, 1968; Viswanathan et al., 1969), an intravascular infusion of fluid (Courtice and Korner, 1952), or raised pulmonary venous pressure (Haddy et al., 1950) in the presence of hypoxia, we could have induced pulmonary edema in the lambs. Likewise, during absorption of liquid from the lungs at birth, with concurrent hypoxia it is possible that the combination of increased transvascular and transepithelial filtration of fluid might exceed the reserve capacity of the microcirculation and lymphatic system in the lungs. In this way, perinatal hypoxia might produce pulmonary edema and respiratory distress.

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Alveolar hypoxia increases lung fluid filtration in unanesthetized newborn lambs.

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