Two principal mechanisms have been proposed to explain closure of the ductus arteriosus. Barcroft et al.\textsuperscript{1,2} thought that functional closure of this vessel occurred shortly after clamping the umbilical cord and that the stimulus for closure was neurogenic. Kennedy and Clark\textsuperscript{3,4} failed to find a neurogenic mechanism and suggested that closure was related to increased oxygenation of the blood following the onset of breathing. Barron\textsuperscript{5} tested this hypothesis by injecting 100 ml of oxygenated blood in the jugular vein of a lamb but noted no effect on the ductus. Dawes and his co-workers,\textsuperscript{6,7} however, in a series of systematic studies carried out in the fetal lamb observed that inflation of the lungs with oxygen led to constriction of the ductus and to production of a murmur over it. This murmur was attributed to passage of blood through the narrowed lumen of the ductus. Ventilation of the lungs with nitrogen had no such effect. They concluded that these changes were due to a specific vasoconstrictive effect of oxygen upon the ductus. Yet these same investigators reported similar constriction of the ductus in fetal lambs with hypoxia and asphyxia.\textsuperscript{7} They suggested that, in these circumstances, the constriction might have been due to excessive secretion of catechol amines stimulated by the hypoxia and the asphyxia.

Although the studies of Dawes and his associates provided valuable information regarding the effects of blood oxygen on the ductus, they were unsupported by direct measurements of pressure and flow in the ductus and in the pulmonary artery.

In a previous paper,\textsuperscript{8} we showed that in the fetal lamb, clamping of the umbilical cord and initiation of breathing is followed by a reversal in the direction and a significant decrease in the magnitude of blood flow in the ductus arteriosus.

In the present studies, the effects of changing blood pO\textsubscript{2} on circulation in the ductus arteriosus were investigated. Experiments were performed in vitro and in vivo and were designed to permit assessment of mechanical effects of ventilating the lungs, of the pressure gradient across the ductus, of clamping the umbilical cord, and of neurogenic or humoral stimuli.

**Part I. Effects of Oxygen and Nitrogen on the Isolated Ductus In Vitro**

**Methods**

Experiments were carried out on eight specimens obtained from full term lambs delivered by Cesarean section and sacrificed by clamping the cord prior to lung expansion. The ductus arteriosus with adjacent segments of the pulmonary artery and aorta was removed en bloc. The proximal aorta, the brachiocephalic trunk and the two branches of the pulmonary artery were ligated. The pulmonary artery and descending aorta were cannulated and the specimen suspended without tension in a constant temperature (37°C) bath containing phosphate buffered Ringer's solution (pH 7.33 to 7.35). The cannula in the descending aorta was attached to an electromagnetic flowmeter. The ductus was perfused through the pulmonary artery with fresh heparinized maternal blood. The outflow was collected in an open reservoir through a cannula attached to the downstream side of the flowmeter. The blood was then pumped from this reservoir through a heat exchanger and into a plastic gas exchanger\textsuperscript{*} (fig. 1).

\textsuperscript{*}Travenol Laboratories, Incorporated.
The pO\textsubscript{2} of the blood was altered by bubbling oxygen, air or nitrogen through the gas exchanger. Blood from the gas exchanger was collected in an open perfusion reservoir. Perfusion pressure was maintained close to 50 mm Hg by keeping the level of blood in the reservoir relatively constant. This perfusion pressure was selected because it approximates that in the pulmonary artery of the fetal lamb in vivo. The perfusion pressure was measured continuously proximal to the pulmonary artery by a Statham strain gauge. A gated sine-wave electromagnetic flowmeter was used to measure flow, and a Beckman polarographic needle electrode measured the pO\textsubscript{2} of perfusing blood. The pH and pCO\textsubscript{2} of the blood were measured with the Astrup microequipment. Pressure, flow and pO\textsubscript{2} were recorded simultaneously on an Offner Dynograph.

The pO\textsubscript{2} of maternal blood used for perfusion was first reduced to about 14 mm Hg by bubbling 100% nitrogen through the gas exchanger. Following a 15-minute control period during which pressure, flow and pO\textsubscript{2} were recorded, the pO\textsubscript{2} of the perfusing blood was gradually increased by bubbling 100% oxygen (five experiments) or compressed air (three experiments) through the gas exchanger. After the maximal effects of oxygen or compressed air had been obtained, the pO\textsubscript{2} of the blood was gradually reduced by bubbling 100% nitrogen through the gas exchanger.

**Results**

A typical example of the effects on ductus flow of gradually increasing the pO\textsubscript{2} of the perfusing blood with 100% oxygen is shown in the upper part of figure 2. Blood flow fell progressively as the pO\textsubscript{2} increased. The lower part of figure 2 shows the effect on ductus flow of lowering the pO\textsubscript{2} of the perfusing blood by bubbling 100% nitrogen through it. Blood flow rose slowly as the pO\textsubscript{2} fell.

Concomitant with the decrease in flow during perfusion with highly oxygenated blood, there was a visible diminution in the diameter of the ductus arteriosus. The external diameter of the ductus appeared to be restored during perfusion with oxygen-poor blood.

When oxygen was bubbled into the perfusion system, the pH of the perfusing blood rose from 7.38 to 7.78 and the pCO\textsubscript{2} fell from 42 to 8.7 mm Hg. When nitrogen was used, the pH varied between 7.78 and 7.83 and the pCO\textsubscript{2} between 8.0 and 8.4.

In the three experiments in which compressed air was used to raise the pO\textsubscript{2} the perfusing blood, the changes in flow were similar to those induced by 100% oxygen except that the rate of decrease in flow was more gradual.

Figure 3 presents the results obtained in five consecutive perfusion experiments with 100% oxygen. Each datum represents the mean values of flow plotted against the pO\textsubscript{2} of the perfusing blood. The correlation coefficient of the regression line is -0.986. It is clear from these results that flow through
the isolated ductus decreases progressively with increasing oxygen pressure in the perfusing blood, thus indicating vasoconstriction.

**Part II. Experiments In Vivo: Effects of Ventilating Lungs with Oxygen or Nitrogen**

**Methods**

Experiments were carried out on 22 ewes and their 25 lambs. The uterus and fetus were exposed under spinal anesthesia as described previously. The lamb was delivered and breathing prevented with a saline-filled condom fitted over the head. The fetus was placed on a table adjacent to the mother and kept warm with a thermostatically controlled recirculating water pad supplemented by warm towels. The cord was protected and kept inside the uterus by clamping the edges of the uterine incision to the skin of the fetal abdomen. A thoracotomy was performed on the unanesthetized fetus and gated sine-wave electromagnetic flow transducers were placed around the pulmonary artery and the ductus arteriosus as described previously. The flowmeters were repeatedly calibrated in vivo and in vitro with blood and the linear calibrations did not vary by more than 5%. Zero flow was obtained by momentarily occluding the blood vessel; the electrical zero was adjusted to the mechanical zero. This procedure was repeated several times during the experiment in order to correct base line drift. The polarity of the transducer used to measure ductus flow was adjusted so that flow above the base line indicated flow from right to left, i.e., from pulmonary artery to aorta. Pressures in the pulmonary artery and aorta were measured through 16-gauge Rochester plastic needles anchored to the vessel walls and connected to matched Statham P23 transducers by equal lengths of identical polyethylene tubing.

Pulmonary artery pressure was measured at the root of the ductus arteriosus and the aortic pressure at the isthmus, just above the junction of the ductus and the aorta. Each pressure transducer was connected to a separate channel of an Offner Dynograph. In some experiments, the differential pressure between the pulmonary artery and aorta was also recorded by connecting the output of each pressure channel to a Sanborn 268B differential pressure transducer. The matched Statham transducers were interconnected and calibrated simultaneously in relation to the same zero level. The Sanborn differential pressure transducer was calibrated so that its zero (pulmonary artery pressure = aortic pressure) was stable within ± 3% throughout the −40 to +40 range. Oxygen pressures in maternal arterial and fetal aortic bloods were measured on anaerobically collected samples at 38°C with a Beckman polarographic macroelectrode contained in a glass-lucite cuvette.11 The pH and pCO₂ of the same blood were analyzed by the Astrup method.10 Flows and pressures were recorded on the Offner Dynograph and the means were obtained by electronic integrators.

The studies comprised the following steps:

**(A) CONTROL PERIOD**

Pulmonary artery flow and pressure, and ductus flow and aortic pressure were recorded continuously for 15 to 30 minutes while the fetus was lying next to its mother. Two or three samples of maternal and fetal blood were collected simultaneously for pO₂, pH, and pCO₂ determinations.

**(B) PERIOD OF LUNG EXPANSION AND VENTILATION**

In 21 lambs, the lungs were expanded and ventilated after the control period and while the umbilical circulation was still intact. In the remaining four lambs, the cord was clamped first and lung expansion followed. In either case, the trachea was cannulated, cleared of fluid, and connected to a Bird positive-negative pressure respirator. Pressure and flow in the respirator were regulated to achieve complete lung expansion. In 12 experiments, the lungs were inflated first with 100% oxygen and respiration was maintained with this gas for 20 to 30 minutes. This was followed by nitrogen ventilation given over a 10- to 15-minute period. In nine lambs, the lungs were expanded and ventilated first with nitrogen and oxygen inhalation followed. In both groups, flows and pressures were recorded during three to four alternating periods of oxygen and nitrogen inhalations. Fetal blood pO₂, pH, and pCO₂ were measured at frequent intervals.

**(C) CLAMPING OF THE UMBILICAL CORD**

In the 21 lambs studied with intact umbilical
### Table 1

Effects of Lung Ventilation with Oxygen on Pulmonary and Aortic Pressures, and Pulmonary and Ductus Flows

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mlHg</td>
<td>mlHg</td>
<td>ml/min/Kg</td>
<td>ml/min/lCq</td>
<td>ml/min/lCq</td>
</tr>
<tr>
<td>C</td>
<td>Early</td>
<td>Late</td>
<td>C</td>
<td>Early*</td>
<td>Late*</td>
</tr>
<tr>
<td>C</td>
<td>Early</td>
<td>Late</td>
<td>C</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>45</td>
<td>32</td>
<td>260</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>35</td>
<td>30</td>
<td>207</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>58</td>
<td>45</td>
<td>198</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>50</td>
<td>40</td>
<td>200</td>
<td>137</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>34</td>
<td>30</td>
<td>161</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>55</td>
<td>45</td>
<td>215</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>66</td>
<td>50</td>
<td>226</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>44</td>
<td>40</td>
<td>219</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>42</td>
<td>33</td>
<td>166</td>
<td>77</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>38</td>
<td>30</td>
<td>188</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>186</td>
<td>92</td>
</tr>
<tr>
<td>12</td>
<td>66</td>
<td>35</td>
<td>28</td>
<td>235</td>
<td>105</td>
</tr>
</tbody>
</table>

Average: 64; 46; 37; 58; 66; 205; 219; 257

*Flow from left to right

*Figures under C represent the average of several two to three-minute readings recorded during control period. Figures under Early represent peak response observed during the first three to five minutes of O2 ventilation, and those under Late represent peak response observed during remaining period of O2 ventilation.
TABLE 2
Effects of Lung Ventilation with Nitrogen on Pulmonary and Aortic Pressures, and Pulmonary and Ductus Flows

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Pulm. Art. Press. mmHg Early</th>
<th>Aortic Press. mmHg Early</th>
<th>Pulm. Art. Flow ml/min/kg Early</th>
<th>Pulm. Art. Flow ml/min/kg Late</th>
<th>Ductus Flow ml/min/kg Early</th>
<th>Ductus Flow ml/min/kg Late</th>
<th>Blood PO2 Early</th>
<th>Blood PO2 Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>32</td>
<td>45</td>
<td>53</td>
<td>52</td>
<td>50</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>30</td>
<td>46</td>
<td>48</td>
<td>43</td>
<td>40</td>
<td>238</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>50</td>
<td>66</td>
<td>73</td>
<td>64</td>
<td>62</td>
<td>166</td>
<td>155</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>40</td>
<td>58</td>
<td>60</td>
<td>60</td>
<td>50</td>
<td>230</td>
<td>200</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>40</td>
<td>56</td>
<td>60</td>
<td>40</td>
<td>42</td>
<td>241</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>50</td>
<td>63</td>
<td>60</td>
<td>72</td>
<td>60</td>
<td>205</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>48</td>
<td>68</td>
<td>71</td>
<td>68</td>
<td>66</td>
<td>220</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>40</td>
<td>56</td>
<td>57</td>
<td>50</td>
<td>47</td>
<td>230</td>
<td>210</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>30</td>
<td>47</td>
<td>56</td>
<td>45</td>
<td>43</td>
<td>196</td>
<td>194</td>
</tr>
<tr>
<td>Average</td>
<td>69</td>
<td>40</td>
<td>56</td>
<td>63</td>
<td>55</td>
<td>51</td>
<td>214</td>
<td>196</td>
</tr>
</tbody>
</table>

*Flow from left to right.
†Figures under C represent the average of several two to three-minute readings recorded during control period. Figures under Early represent peak response observed during first three to five minutes of N₂ ventilation, and those under Late represent peak response observed during remaining period of N₂ ventilation.
circulation, the cord was clamped while respiration was maintained with air or oxygen. The changes in flows and pressures which followed this procedure as well as those induced by short periods of nitrogen inhalation were recorded. In the four lambs in which the umbilical cords were cut prior to lung expansion, the effects of this procedure on flows and pressures were recorded for three to four minutes. Thereafter, the animal began to gasp and exhibit signs of distress and the recordings became unreliable. Therefore, artificial respiration with air or oxygen was instituted.

**Results**

**EFFECTS OF EXPERIMENTAL PROCEDURE ON THE EWE AND ITS LAMB**

Most ewes were hyperventilating when brought to the laboratory and continued to do so during the experiment. Effects of the spinal anesthesia were tested in a few animals in which the femoral artery was cannulated under local anesthesia and maternal arterial pressure and blood \( pO_2 \) recorded while the ewe was lying on her left side. Injection of the spinal anesthetic produced a 10% to 15% decrease in the arterial pressure and blood \( pO_2 \). No corrective measures were employed.

The lamb appeared to withstand the experimental procedure well. A variable decrease in blood pressure and blood \( pO_2 \) occurred during the procedure involved in placing the flow transducers around the ductus and pulmonary artery. Both pressure and \( pO_2 \), however, stabilized prior to lung expansion.

**PULMONARY ARTERY AND DUCTUS CIRCULATION BEFORE LUNG EXPANSION**

Control values for pulmonary artery pressure and flow, and ductus flow and aortic pressure for the 25 lambs are listed in tables 1, 2, and 3. Prior to expanding the lungs, the mean pulmonary artery pressure averaged 67 mm Hg and the aortic pressure 60 mm Hg. In five lambs (1, 6, 7 in table 1 and 1, 8 in table 2), the difference in the mean pressures was 1 mm Hg or less.

Blood flow in the pulmonary artery during the control period varied between 166 and 310 ml/kg/min. The flow in the ductus arteriosus was from the pulmonary artery → aorta (r to l) in every instance. Quantitatively, it varied more than the pulmonary flow and depended to a certain extent on the magnitude of the pressure difference between the pulmonary artery and aorta. In the five lambs which had an unusually small differential pressure, the mean ductus flow was relatively low (tables 1 and 2). If these cases were excluded, the ductus flow would range from 68 to 137 ml/kg/min. These figures are consistent with values previously reported.\(^8\)

**EFFECTS OF LUNG EXPANSION AND VENTILATION WITH OXYGEN**

Table 1 presents the data on the effects of expanding and ventilating the lungs with 100% oxygen in lambs with intact umbilical circulation. Figure 4 illustrates the pattern of changes. The oxygen effects were arbitrarily divided into an early phase which encompassed the first three to five minutes after lung expansion and a late phase which spanned the remaining period of oxygen ventilation.

In the early phase, pulmonary artery pressure fell significantly while the aortic pressure fell only slightly (table 1 and fig. 4). As a consequence, the pressure gradient favored the aorta. As this gradient widened,
FIGURE 4

Segments of a record illustrating pattern of changes in systemic and pulmonary artery pressures, and in the pulmonary artery and ductus flows during control, oxygen and nitrogen ventilation periods. Integrated parts are presented along with the phasic flows and pressures to facilitate reading. In this experiment, the two pressures were very similar. Although the phasic ductus flow presented a large negative component, the mean flow was above the zero base line indicating a flow from right to left. Oxygen ventilation reduced pulmonary pressure thereby making the pressure gradient in favor of the aorta. The negative component of the ductus flow became larger and this brought the mean flow to below the zero base line indicating a flow from left to right. During the peak of oxygen effect which was reached 15 minutes later, ductus flow decreased strikingly and its phasic pattern was altered. Nitrogen ventilation slowly increased ductus flow and restored its phasic pattern.
the direction of the flow in the ductus reversed and became from left to right. Quantitatively, ductus flow changed inconsistently in the majority of instances. In the lambs that had a small control pressure gradient, however, ductus flow increased markedly, and the increase coincided with the widening of the pressure difference between the pulmonary artery and aorta (table 1). Pulmonary artery flow increased markedly, and the increase coincided with the widening of the pressure difference between the aorta and the pulmonary artery (table 1). The late phase of oxygen effect was characterized by a further fall in the pulmonary artery pressure and by a progressive rise in the aortic pressure (table 1 and fig. 4). Pulmonary artery flow increased slowly and progressively. Ductus flow fell dramatically in every instance. The phasic flow pattern frequently became irregular and contact between the vessel wall and the transducer was lost. Concomitant with the fall in flow, there was a visible decrease in the external diameter and in the length of the ductus. In those instances, a smaller flow transducer than the one previously used but with the same calibration characteristics was refitted over the ductus.

The pO2 of the fetal aortic blood increased from an average of 26 mm Hg in the control period to an average of 47 in the early phase of oxygen ventilation; it reached an average of 160 mm Hg during the late phase of oxygen breathing (table 1). The wide individual variation in the pO2 values was probably related to differences in the degree of lung expansion and of vascular shunts among the various lambs. The pH of the fetal blood rose from an average of 7.31 to an average of 7.36; the pCO2 fell from an average of 33 to an average of 20 mm Hg; standard bicarbonate rose from an average of 15 mEq/liters to an average of 17 mEq/liters, and base excess fell from an average of -11 to an average of -8.

EFFECTS OF LUNG EXPANSION AND VENTILATION WITH NITROGEN

Table 2 lists the data on the effects of expanding and ventilating the lungs with 100% nitrogen in lambs with intact umbilical circulation. The effects of nitrogen were also arbitrarily divided into two phases. In the early phase (first three to four minutes), the pulmonary artery pressure fell markedly. Aortic pressure and pulmonary artery flow decreased moderately (table 2). Ductus flow changed direction and increased significantly in every instance (table 2). The rise coincided with the widening of the pressure difference between the aorta and the pulmonary artery (table 2).

During the late phase of nitrogen ventilation, the pulmonary artery pressure which had fallen began to rise progressively and consistently. The pulmonary artery flow and the aortic pressure decreased steadily throughout the period of nitrogen ventilation. Ductus flow which had risen in the early phase decreased progressively during the late phase of nitrogen administration (table 2).

In this group of lambs, the pO2 of the aortic blood decreased from an average of 28 mm Hg to an average of 18 mm Hg at the end of nitrogen inhalation. The pH rose from an average of 7.30 to 7.36, and the pCO2 fell from an average of 34 to 20 mm Hg. Values of standard bicarbonate and base excess were closely similar to those observed during oxygen ventilation.

EFFECTS OF OXYGEN AND OF NITROGEN AFTER THE LUNGS HAD BEEN EXPANDED

Figure 5 illustrates the pattern of changes of repeated ventilations with oxygen and nitrogen after the cord had been clamped. When oxygen was administered after nitrogen, the pulmonary artery pressure which had risen during nitrogen ventilation fell, and the aortic pressure and the pulmonary artery flow which had fallen, rose slowly. The flow in the ductus which had declined at the end of the period of nitrogen ventilation decreased further with oxygen and its phasic pattern became irregular (fig. 5).

Administration of nitrogen after oxygen produced an initial rise in the mean ductus flow. The pattern of the phasic flow which had been altered by oxygen was restored (fig.
Segments of a record illustrating effects of repeated lung ventilations with oxygen and nitrogen on ductus flow in a lamb with interrupted umbilical circulation. Differential pressure was positive when the gradient favored the pulmonary artery and negative when it favored the aorta. Aortic pressure rose temporarily after clamping the cord but pulmonary pressure did not change significantly. Pulmonary and ductus flows decreased promptly but the latter remained from right to left. Oxygen ventilation reduced markedly the pulmonary artery pressure and the differential pressure became in favor of the aorta. Note the striking decrease in ductus flow and the marked alterations in its phasic pattern each time oxygen was given. Nitrogen inhalation restored partially the flow and its phasic pattern.
5). As nitrogen ventilation continued, however, ductus flow began to decrease together with the pulmonary flow. Pulmonary pressure rose when nitrogen followed oxygen while aortic pressure fell (fig. 5).

EFFECTS OF INTERRUPTION OF THE UMBILICAL CIRCULATION

In the 21 lambs whose lungs had been ventilated, clamping of the cord resulted in a prompt rise in the aortic pressure and a slight fall in the pulmonary artery pressure. Pulmonary artery flow decreased temporarily while ductus flow which had been reduced by oxygen or air ventilation decreased further after clamping the cord.

In the four lambs whose lungs had not been expanded, cutting the cord was also followed by an immediate rise in the arterial pressure and a slight fall in the pulmonary artery pressure (table 3). The flows in the pulmonary artery and ductus decreased significantly but the direction of ductus flow remained from right to left (fig. 5). Ventilation of the lungs with oxygen or air decreased the pulmonary pressure and restored the pulmonary flow. Ductus flow changed direction and slowly decreased.

Discussion

The present data obtained from studies performed in vitro on the isolated ductus arteriosus and in vivo on the unanesthetized fetal lamb indicate that at least three factors contribute to the control of blood flow in the ductus arteriosus. These factors are: (1) the PO$_2$ of the blood, (2) the pulmonary artery flow, and (3) the pressure difference between the pulmonary artery and aorta. It is not possible as yet to assess precisely the contribution of each of these factors to the maintenance of ductus flow in the steady state. Nevertheless, in a given experimental condition, the action of one factor may predominate in such a manner as to overshadow the others almost completely.

BLOOD OXYGEN

Of the three factors, the PO$_2$ of blood passing through the ductus appears to be the most important stimulus for functional closure of the ductus in neonatal life. The action of oxygen seems to be independent of the mechanical effects of lung inflation, of circulatory alterations incident to clamping the cord, of the acid-base status of the blood, and of neural or humoral mediators. It is, however, dependent on a certain blood PO$_2$ which has to be reached before any alteration in the ductus flow becomes evident. This fact probably explains the delay of five to eight minutes in the onset of oxygen effect noted by Born and his associates. It may also explain Barron's failure to observe any action on the ductus following the injection of 100 ml of oxygenated blood in a fetal lamb. Once this PO$_2$ is reached, the action of oxygen overwhelms any other hemodynamic factor which might contribute to the control of ductus circulation. This finding is corroborated by the fact that during lung ventilation with oxygen, the flow in the ductus was diminishing rapidly at a time when the pulmonary artery flow was increasing and the pressure difference between the systemic and pulmonary circuits was widening. These circulatory changes would tend to increase ductus flow rather than decrease it. The fact that the flow fell steadily emphasizes the sensitivity of the ductus walls to oxygen.

Our finding of a sustained rise preceded by a transitory fall in the arterial pressure during lung ventilation with oxygen is contrary to that of Born et al. who observed a consistent blood pressure fall. We believe that the divergency is due to technical differences related mainly to the use, by Born, of barbiturate anesthesia and of a positive pressure pump. Barbiturates are known to cross the placenta and affect the fetus. In our hands as well as in those of others, positive pressure pump reduces arterial pressure through a reduction in the cardiac output. The initial fall in blood pressure during oxygen ventilation can be explained by the initial increase in the magnitude of blood shunted from the aorta through the ductus. The subsequent rise in systemic pressure is probably related to the reduction in the magnitude of ductus
flow and to an increase in peripheral resistance.

**Pulmonary Artery Flow**

The data obtained from the experiments on nitrogen ventilation of the lungs and those derived from the circulatory effects of clamping the umbilical cord indicate that alterations in pulmonary artery circulation may affect ductus flow and may obscure the effects of oxygen. Administration of nitrogen, whether it was before or after the lungs had been expanded with oxygen, caused an initial increase of blood flow in the ductus. Under these circumstances, the rise was most likely related to the increased pressure difference between the aorta and pulmonary artery and to the reduction in blood pO₂. After prolonged nitrogen ventilation, however, ductus flow decreased despite an extremely low blood pO₂. Such a decrease in ductus flow occurred at a time when the pulmonary artery flow was falling together with the systemic arterial pressure while the pulmonary artery pressure was increasing. These circulatory changes are similar to those observed in adult animals during nitrogen induced hypoxia. They have been attributed to a direct action of nitrogen and of hypoxia on the heart and on the pulmonary vascular resistance. The fall in ductus flow which follows clamping of the umbilical cord may also be related to the fall in pulmonary artery flow, because the two flows changed in the same direction. Such a decrease in pulmonary and ductus flows is probably related to sequestration and redistribution of blood caused by the abrupt elimination of the placental circulation.

**Pressure Gradient Across the Ductus**

Another factor which plays a role in the control of blood flow through the ductus is the pressure difference between the systemic and pulmonary circuits. This factor appeared to determine the magnitude of ductus flow before and during the early part of lung ventilation. The contribution of this factor to ductus circulation could possibly be better assessed by considering the flow-pressure relationship as a function of the changes in resistance across this vessel. However, the relationship between flow and pressure in this pulsatile system of three connecting large vessels is complex and not easily analyzed in terms of our present data. The problem is further complicated by the existence in the fetal heart of a certain degree of asynchrony in ventricular ejection similar to that described by Braunwald in adults. The ejection pulse in the pulmonary artery appears to precede its counterpart in the aorta by a time which varies from one animal to another and in the same animal as the experimental condition is altered. Under these circumstances, the quotient of instantaneous pressure differential and flow has no physical significance in terms of resistance.

**Summary of Part I**

Isolated ductus arteriosus vessels obtained from fetal lambs prior to lung expansion were perfused with blood of varying pO₂ at a constant temperature and pressure. Flow decreased progressively as the pO₂ of the perfusing blood increased. The changes were more striking at oxygen pressures greater than 50 mm Hg.

**Summary of Part II**

The effects of ventilating the lungs with oxygen and nitrogen on the pulmonary artery and ductus arteriosus circulation were investigated in near term fetal lambs with and without intact umbilical circulation. Oxygen ventilation increased transitorily the ductus flow through widening of the pressure difference between the pulmonary artery and aorta. Ductus flow was strikingly reduced as oxygen ventilation progressed. Pulmonary artery pressure fell while aortic
pressure rose. These changes could be reversed with nitrogen.

Nitrogen ventilation also produced an initial increase in ductus flow through an increase in the differential pressure between the pulmonary artery and aorta. Prolonged administration of nitrogen depressed ductus flow together with pulmonary flow and systemic arterial pressure. These changes were probably related to the direct effects of nitrogen and hypoxia on the heart and pulmonary circulation.

 Interruption of the umbilical circulation reduced temporarily ductus and pulmonary artery flows. This fall was related to circulatory readjustments caused by abrupt elimination of the placental circulation.

From the in vivo and in vitro studies, it appears that at least three factors contribute to the control of blood flow in the ductus: the pO₂ of the blood; the pulmonary artery flow; and the differential pressure between the pulmonary artery and aorta.

References
Studies on Ductus Arteriosus Circulation
N. S. Assali, John A. Morris, Major, Ronald W. Smith, William A. Manson, R. Bock and M. Rass

Circ Res. 1963;13:478-489
doi: 10.1161/01.RES.13.5.478
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/13/5/478

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/