When fetal asphyxia or hypoxia is induced by reduction of uterine and umbilical circulations or by administration of a gas mixture of low oxygen content to the mother, there is an increase in the fetal arterial pressure. The effects on the fetal heart rate appear to be variable. Bradycardia has been observed by several investigators. Born et al. noted that the changes in heart rate depended on the degree of hypoxia; when hypoxia was "moderate," tachycardia occurred. Only when the oxygen lack became severe was there bradycardia. Reynolds and Paul found that the changes in the fetal heart rate during hypoxia were variable, slow rates usually being associated with more severe hypoxic states.

Despite this wealth of study of the effects of asphyxia and hypoxia on arterial pressure and heart rate, little is known of the effects of these procedures on the regional circulation of the fetus. Born et al. measured the umbilical blood flow with a venous occlusion plethysmograph and observed an increase in flow during hypoxia. This method of measuring the umbilical flow, however, entails occlusion of the umbilical veins which reduces the venous return to the heart and the cardiac output.

In the present report, the circulatory responses of the pregnant uterus and of the fetus to hypoxia and hypercapnia were investigated simultaneously using electromagnetic flowmeters. The studies include the changes in the regional circulation of the fetus induced by transitory constriction of the umbilical vessels and by severance of the umbilical cord and onset of breathing.

Methods

Fifteen ewes with a total of 22 fetuses were studied between 140 and 150 days of gestation. Regional blood flows were measured with gated sine-wave electromagnetic flowmeters described by Westersten, Herrold, and Assali. The physical characteristics and calibration curves of this instrument have been published elsewhere. The flow transducers were specially designed for each vessel under study so that a perfect fit could be obtained between the vessel wall and the transducer. The procedure was as follows: The ewes were starved for 24 hours. Spinal anesthesia was induced to a level of T9 to T10 with 5 to 9 ml Xylocaine 1 per cent. The ewe was placed on the surgical table in right lateral recumbency. Maternal arterial pressure was recorded with a Statham strain gauge from a polyethylene tube inserted into the carotid or femoral artery. The abdomen was incised from the umbilicus to the inguinal area. The uterine horn containing the fetus was marsupialized to the abdominal wall. The main trunk of the uterine artery was visualized in the broad ligament and an infiltration of Cyclaine was made around it so that spasm of the artery would not occur during manipulation. A 2- to 3-cm. segment of the artery was freed from surrounding structures and slipped into the channel of a flowmeter transducer, which was then fixed to the uterine wall with two sutures in order to prevent kinking of the vessel.

The uterus was then opened and a loop of umbilical cord was exteriorized. A 2- to 3-cm. segment of an umbilical artery was freed and attached to a flow transducer. The umbilical cord was replaced inside the uterus and the hind legs of the fetus were brought out and the femoral arteries exposed. One artery was connected to a flow transducer and the other to a Statham strain gauge by means of a polyethylene tube. The legs were replaced inside the uterus and the head and neck of the fetus were exteriorized. A condom filled with saline solution was placed immediately around the mouth of the lamb to
In the animals subjected to hypoxia, oxygen saturation of maternal and fetal arterial blood was determined at frequent intervals before and during the induction of hypoxia using the Van Slyke-Neill apparatus. Control recordings of maternal and fetal pressures and flows were obtained for 30 to 45 minutes before experiments were performed. Recordings continued for the duration of the procedure and for some time thereafter.

The following procedures were tested for their effects on mother and/or fetus:

(a) Administration of 10 per cent O₂ in nitrogen or 8 per cent CO₂ in air to the mother. The gas mixtures were given at a constant flow and pressure through a mask connected to a Douglas bag.

(b) Graded constriction of both uterine arteries. In these experiments, the main trunk of the uterine artery on both sides of the midline was exposed in the broad ligament and was attached to a flow transducer. A loop of polyethylene tubing was anchored around each artery proximal or distal to the probe and its ends were threaded through a small piece of a larger tube. By tightening the loop gradually, a progressive constriction of the artery could be accomplished. The magnitude of reduction in uterine blood flow in each horn of the uterus was monitored with the flowmeters.

(c) Constriction of both umbilical arteries alone, both umbilical veins alone, and of the whole umbilical cord. Transitory constriction of the umbilical veins and arteries separately and of the whole cord was accomplished by placing individual loops of polyethylene tubing around these structures. These loops could be manipulated from outside the uterine cavity in such a way as to permit constriction of any two umbilical vessels or of the whole cord at any given time.

(d) Cutting of the umbilical cord and onset of breathing by the newborn lamb.

Frequently, several of these tests were performed on the same animal with adequate control intervals between subsequent tests.
FETAL CIRCULATION

EFFECTS OF HYPOXIA

FIGURE 1

Effects of administration of 10 per cent O2 in N2 to the ewe on the maternal heart rate, arterial pressure, and uterine blood flow and on the fetal heart rate, arterial pressure, and regional blood flow. In this, and in subsequent figures, the integrated records for flows and pressures were plotted in a condensed form.

Results

EFFECTS OF HYPOXIA AND HYPERCAPNIA

Table 1 presents the average data on the effects of hypoxia (10 experiments) and hypercapnia (8 experiments) on mother and fetus. Figures 1 and 2 illustrate typical examples of each of these procedures.

Administration of 10 per cent O2 in N2 to the ewe for a period of 15 to 20 minutes evoked a moderate elevation in the maternal arterial pressure and heart rate. Uterine blood flow increased slowly five to eight minutes after the onset of inhalation and reached significantly high values at the end of hypoxia. When the ewe was allowed to breathe air, maternal blood pressure, heart rate, and uterine flow returned to control values. Maternal arterial blood O2 saturation decreased from an average of 94 per cent to 65 per cent at the end of hypoxia and returned to near control values upon the breathing of air.

The effects of hypoxia on the fetus consisted of a progressive and significant decrease in the heart rate which began five to seven minutes after the onset of inhalation of the low O2 mixture. Fetal arterial pressure and carotid and umbilical blood flows increased significantly and remained elevated until the end of hypoxia, while femoral blood flow decreased slightly. These changes subsided when the ewe breathed air. Fetal arterial O2 saturation decreased from an average of 60 per cent in the control period to an average of 40 per cent at the end of the inhalation.

Administration of 8 per cent CO2 in air to the mother for a period of 15 to 20 minutes also induced increases in maternal heart rate, arterial pressure, and uterine blood flow of a magnitude and pattern closely similar to those induced by the low O2 mixture (table 1 and fig. 2). The fetal changes consisted of a progressive and significant decrease in heart rate, and an increase in arterial pressure and in blood flows in the umbilical, carotid, and femoral arteries.

Circulation Research, Volume XI, September 1968
EFFECTS OF UTERINE ISCHEMIA

Effects of transitory reduction in uterine blood flow on the fetal heart rate, arterial pressure, and on the carotid and umbilical flows.

EFFECTS OF BILATERAL CONSTRICTION OF UTERINE ARTERIES

Table 2 presents the data on the fetal response to this procedure. Figure 3 illustrates a single experiment.

Reduction in uterine blood flow of less than 50 per cent of the control values for three to four minutes had no effect on the ewe and evoked only a slight bradycardia in the fetus. The blood pressure and blood flows of the fetus were not altered significantly. A decrease in uterine blood flow greater than 50 per cent and for the same time likewise had no effect on the mother. In the fetus, however, the heart rate decreased markedly one-half to one minute after the onset of constriction, while the arterial pressure and the umbilical and carotid flows increased. These changes subsided rapidly when the constriction was released.

TABLE 2

Effects of Graded Constriction of Uterine Arteries on Arterial Pressure, Heart Rate, and Regional Blood Flows of the Fetus in Utero*

<table>
<thead>
<tr>
<th>Degree of reduction in uterine blood flow</th>
<th>Arterial pressure mm. Hg</th>
<th>Heart rate beats/min.</th>
<th>Carotid flow ml/min.</th>
<th>Umbilical flow ml/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>(before) 55</td>
<td>228</td>
<td>28</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>(during) 59</td>
<td></td>
<td>30</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>(after) 55</td>
<td>230</td>
<td>28</td>
<td>152</td>
</tr>
<tr>
<td>50%</td>
<td>(before) 56</td>
<td>230</td>
<td>29</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>(during) 58</td>
<td>210</td>
<td>30</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>(after) 57</td>
<td>240</td>
<td>28</td>
<td>150</td>
</tr>
<tr>
<td>90%</td>
<td>(before) 55 ± 5</td>
<td>228</td>
<td>25 ± 6</td>
<td>116 ± 20</td>
</tr>
<tr>
<td></td>
<td>(during) 68 ± 4</td>
<td>160</td>
<td>32 ± 3</td>
<td>130 ± 23</td>
</tr>
<tr>
<td></td>
<td>(after) 50 ± 4</td>
<td>230</td>
<td>22 ± 3</td>
<td>110 ± 15</td>
</tr>
</tbody>
</table>

*See footnote * to table 1.
flow changed in a pattern similar to that of the arterial pressure, while the change in femoral flow was inconsistent. When the constriction was released, arterial pressure, heart rate, and blood flows returned to control values. In the majority of the lambs, constriction of the umbilical arteries was accompanied by gasps and attempts to breathe; respiratory efforts were not observed during constriction of the umbilical veins. Transitory constriction of the whole cord evoked responses similar to those observed after constriction of the umbilical arteries.

**EFFECTS OF SEVERING THE UMBILICAL CORD AND ONSET OF BREATHING**

The events which followed the cutting of the umbilical cord were in general comparable to those observed after constriction of the umbilical arteries. In all experiments, the arterial pressure and carotid flow increased immediately after the cutting of the cord and the fetal heart rate decreased (table 4 and fig. 5). When the lamb breathed regularly, the arterial pressure and carotid flow remained higher than control readings despite occasional fluctuations. The heart rate, which had been slow and irregular, began to accelerate toward control values.

If the lamb experienced respiratory difficulties, the arterial pressure, carotid flow, and heart rate would begin to decrease, the latter becoming irregular.

In eight lambs, the circulatory dynamics were tested when the animal was in the head-down position. In each instance, the carotid flow increased markedly when the head was down and returned to control values when the lamb was placed in the horizontal position. No consistent pattern of change in the arterial pressure and heart rate was observed (table 4 and fig. 5).

### TABLE 3

<table>
<thead>
<tr>
<th>Vessels constricted</th>
<th>Arterial pressure mm. Hg</th>
<th>Heart rate beats/min.</th>
<th>Carotid flow ml./min.</th>
<th>Femoral flow ml./min.</th>
<th>Umbilical arterial flow ml./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical veins</td>
<td>(before) 58 ± 4</td>
<td>212</td>
<td>24 ± 2</td>
<td>11 ± 1</td>
<td>135 ± 20</td>
</tr>
<tr>
<td></td>
<td>(during) 44 ± 6</td>
<td>106</td>
<td>17 ± 4</td>
<td>6 ± 0.5</td>
<td>96 ± 28</td>
</tr>
<tr>
<td></td>
<td>(after) 60 ± 4</td>
<td>221</td>
<td>25 ± 4</td>
<td>12 ± 2</td>
<td>148 ± 18</td>
</tr>
<tr>
<td>Umbilical arteries</td>
<td>(before) 63 ± 6</td>
<td>243</td>
<td>28 ± 3</td>
<td>10 ± 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(during) 64 ± 4</td>
<td>118</td>
<td>34 ± 4</td>
<td>11 ± 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(after) 50 ± 7</td>
<td>L126 ± 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(during) 54 ± 5</td>
<td>239</td>
<td>27 ± 8</td>
<td>9 ± 1</td>
<td></td>
</tr>
<tr>
<td>Whole cord</td>
<td>(before) 64 ± 4</td>
<td>174</td>
<td>23 ± 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(during) 76 ± 7</td>
<td>80</td>
<td>36 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(after) 63 ± 6</td>
<td>160</td>
<td>22 ± 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See footnote * to table 1.

**T** = immediate effects.

**TL** = delayed effects (see text).
EFFECTS OF CUTTING THE CORD

FIGURE 5
Changes which followed cutting of the umbilical cord in a lamb which breathed spontaneously and survived.

Discussion

The present data, obtained from ewes subjected to regional anesthesia, indicate that transitory fetal hypoxia induced by administering a low O₂ mixture to the mother or by impairing O₂ transfer from mother to fetus produces a progressive decrease in fetal heart rate and an increase in fetal arterial pressure. Hypercapnia, reduction of blood flow in the umbilical arteries, and cutting of the umbilical cord evoked similar responses. Although these findings are in agreement with those observed by Barcroft, Paul, Jacobson and Windle, Hon, and Martin and Young, they are not in accord with those of Born et al., who noted fetal tachycardia during "moderate" hypoxia and partial occlusion of the umbilical vein. The difference in the results cannot be due to the degree of hypoxia, since the reduction in maternal and fetal O₂ saturation in our series was closely comparable to that of Born. Furthermore, the recording of the various parameters in our experiments was continuous throughout the various phases of hypoxia, so that any tachycardia should have been detected. We believe that the discrepancy is primarily due to the difference in the experimental techniques and particularly in the type of anesthetic used. Born et al. utilized pentobarbital as a general anesthetic and studied the fetus outside the uterus; Reynolds and Paul also used pentobarbital, although the fetus was studied in utero. In our experiments, regional block was used and the fetus remained in utero. The effect of anesthesia on the fetus is of considerable importance, since Born and his co-workers stated clearly that in their experiments the heart rate was influenced considerably by the depth of anesthesia.

The cause of the increase in the fetal arterial pressure and of the bradycardia observed during hypoxia or after occlusion of the umbilical cord evoked similar responses. Although these findings are in agreement with those observed by Barcroft, Paul, Jacobson and Windle, Hon, and Martin and Young, they are not in accord with those of Born et al., who noted fetal tachycardia during "moderate" hypoxia and partial occlusion of the umbilical vein. The difference in the results cannot be due to the degree of hypoxia, since the reduction in maternal and fetal O₂ saturation in our series was closely comparable to that of Born. Furthermore, the recording of the various parameters in our experiments was continuous throughout the various phases of hypoxia, so that any tachycardia should have been detected. We believe that the discrepancy is primarily due to the difference in the experimental techniques and particularly in the type of anesthetic used. Born et al. utilized pentobarbital as a general anesthetic and studied the fetus outside the uterus; Reynolds and Paul also used pentobarbital, although the fetus was studied in utero. In our experiments, regional block was used and the fetus remained in utero. The effect of anesthesia on the fetus is of considerable importance, since Born and his co-workers stated clearly that in their experiments the heart rate was influenced considerably by the depth of anesthesia.

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TABLE 4

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Arterial pressure mm Hg</th>
<th>Heart rate beats/min</th>
<th>Carotid flow mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutting the cord</td>
<td>(before) 65 ± 6</td>
<td>240</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>(10)</td>
<td>(immed) 80 ± 8</td>
<td>333</td>
<td>32 ± 4</td>
</tr>
<tr>
<td>(later) 70 ± 5</td>
<td></td>
<td>500</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Regular breathing</td>
<td>(before) 70 ± 4</td>
<td>186</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>(6)</td>
<td>(after) 75 ± 3</td>
<td>196</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Head-down position</td>
<td>(before) 78 ± 5</td>
<td>158</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>(8)</td>
<td>(during) 80 ± 4</td>
<td>155</td>
<td>48 ± 5</td>
</tr>
<tr>
<td></td>
<td>(after) 70 ± 3</td>
<td>165</td>
<td>33 ± 4</td>
</tr>
</tbody>
</table>

*See footnote * to table 1.
umbilical cord is controversial. Barcroft and Reynolds and Paul have suggested an initial vagal stimulation followed by direct effects of hypoxia on the heart. Born et al. believe that catecholamine secretion might play a significant role. While some of these factors may enter into play during hypoxia, we believe that the primary factor which evokes the rise in arterial pressure after severing the umbilical cord or occluding the umbilical arteries is the elimination of the low vascular resistance of the placenta from the fetal vascular bed. Experiments to be reported have shown that the rise in pressure after cord clamping is still striking even if the fetus had been well oxygenated prior to the clamping. The pressure rise can also be faithfully reproduced by analogue computer. The bradycardia is probably initiated by baroreceptor reflexes, although later it may become dependent on a direct effect of hypoxia on the heart.

Contrary to what happened when the umbilical arteries or the whole cord was constricted or severed, occlusion of the umbilical veins evoked a prompt fall in arterial pressure and heart rate. The fall in pressure in this case was most likely due to a fall in the cardiac output caused by trapping of blood in the placenta, diminished venous return, and impaired right-heart filling. The bradycardia which ensued might have been due to stimulation of the Bainbridge reflex by inadequate filling of the right heart.

As to the effects of hypoxia and hypercapnia on the regional circulation in the mother and fetus, the present data show that these stimuli produce a marked increase in uterine and umbilical blood flows. It cannot be stated at present whether this increase was secondary to the rise in maternal and fetal arterial pressures or was due to active vasodilatation. At any rate, the increase in blood flow on both sides of the uteroplacental circulation during hypoxia would tend to compensate for the fall in $O_2$ transfer across the placenta and may assist the fetus in initially withstanding the effects of $O_2$ deprivation. The increase in blood flow in the fetal carotid artery is probably secondary to the rise in arterial pressure because these two parameters changed in the same direction in nearly all experiments. This increase may contribute to the protection of the fetal brain against the deleterious effects of $O_2$ lack. The decrease in femoral flow during hypoxia and the increase during hypercapnia were undoubtedly due to active alterations in the femoral resistance independent of the pressure changes.

The effects of obstruction of the umbilical blood flow on the fetal regional flow depend on the site of obstruction. As stated before, constriction of the umbilical veins leads to a decrease in the cardiac output and to a fall in the flow of the umbilical, carotid, and femoral arteries. Apparently these vessels accommodate their caliber to the reduced circulating blood volume. On the other hand, constriction of the umbilical arteries initially increases the carotid flow through its effects on the arterial pressure. If the constriction is prolonged, however, the inflow to the placenta and the flow in the umbilical vein are decreased and the fetus begins to deteriorate.

It is of interest to note the degree of constriction of the uterine arteries needed to reduce significantly the uterine blood flow and consequently produce fetal distress. The present data show that at least a 50 per cent reduction in flow for two to three minutes is necessary to affect the fetus to any significant degree. This is not too surprising in view of the many compensatory mechanisms which assist the fetus in withstanding a transitory reduction in oxygen supply. This does not imply that a minor but prolonged decrease in the caliber of the uterine arteries and a sustained fall in oxygen transfer from mother to fetus would not have deleterious effects.

The approximate 50 per cent increase in carotid blood flow of the fetus when it is in the head-down position undoubtedly provides additional perfusion of blood to the brain. Such classical positioning of newborn animals is thus placed on a reasonable scientific basis.
Summary

The effects of hypoxia (administration of 10 per cent O₂ in N₂ and constriction of the uterine arteries), of hypercapnia (administration of 8 per cent CO₂ in air), and of asphyxia (obstruction of the umbilical circulation) were studied on the fetus in utero in near-term pregnant ewes under spinal anesthesia.

Hypoxia and hypercapnia produced increases in the maternal arterial pressure, maternal heart rate, and uterine blood flow. Fetal arterial pressure and carotid and umbilical blood flows increased, while the fetal heart rate decreased. Fetal femoral flow decreased during hypoxia and increased during hypercapnia. There was a delay of five to six minutes between the initiation of hypoxia or hypercapnia and the appearance of fetal circulatory changes.

Transient reduction of uterine blood flow evoked insignificant hemodynamic alterations in the mother and fetus. A reduction of flow greater than 50 per cent of control values produced a fetal bradycardia along with increases in fetal arterial pressure, carotid and umbilical flows.

Constriction of the umbilical veins with the umbilical arteries intact produced a prompt bradycardia together with a decrease in fetal arterial pressure and regional blood flows. Constriction of the umbilical arteries alone also produced a bradycardia with an initial rise in arterial pressure and carotid flow. Similar changes were observed after cutting the umbilical cord. Elimination of the low resistance of the placenta played a major role in these changes.

Placing the lamb in the head-down position caused a marked increase in carotid blood flow without greatly modifying arterial pressure.

References

Hemodynamic Changes in Fetal Lamb in Utero in Response to Asphyxia, Hypoxia, and Hypercapnia

N. S. Assali, L. W. Holm and N. Sehgal

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