Cerebral and Peripheral Circulatory Responses to Intracranial Hypertension in Fetal Sheep

Andrew P. Harris, Raymond C. Koehler, Christine A. Gleason, M. Douglas Jones Jr., and Richard J. Traystman

Fetal head compression during normal labor can increase intracranial pressure (ICP). We studied the cerebral and peripheral blood flow responses to ICP elevation in utero in chronically catheterized fetal sheep using the radiolabeled microsphere technique. ICP was elevated, stepwise, in increments of 6±1 mm Hg by infusion of artificial cerebrospinal fluid into a lateral ventricle. When ICP was raised to within 28 mm Hg of baseline mean arterial blood pressure (i.e., ICP above 22 mm Hg), arterial pressure began to increase. Above this ICP level, up to 41 mm Hg, mean cerebral perfusion pressure was maintained by equivalent increases in arterial pressure. Cerebral blood flow and O2 uptake at the highest ICP levels were not different from baseline values. Changes in peripheral organ blood flow were graded according to the level of ICP. At the highest level (ICP=41 mm Hg), renal, gastrointestinal, and skin blood flow decreased by 68%, 69%, and 65%, respectively. Myocardial and adrenal blood flow doubled, whereas heart rate and cardiac output were unchanged. Placental blood flow increased in proportion to arterial pressure. Arterial plasma epinephrine, norepinephrine and arginine vasopressin increased by nearly two orders of magnitude. Therefore, as ICP approaches baseline mean arterial pressure, fetal lambs are capable of sustaining cerebral perfusion by initiating profound visceral vasoconstriction without curtailing placental blood flow. Since cerebral O2 uptake was maintained, there is no evidence that stimulation of the peripheral response requires pronounced cerebral ischemia. This highly developed Cushing response may be important for ensuring cerebral viability when the fetal head is compressed during parturition. (Circulation Research 1989;64:991-1000)

Compression of the human fetal head during normal labor can produce transient changes in the fetal electroencephalogram.1 Some investigators have related these changes to transient cerebral ischemia resulting from increased intracranial pressure (ICP).2,3 Ordinarily, the entire fetal body is buoyed by amniotic fluid. However, as the human fetal head dilates the cervix, pressures 40-60 mm Hg greater than amniotic fluid pressure are exerted on the fetal head during uterine contractions,4 and this external pressure may be fully transmitted to the intracranial space.5 Thus, ICP may increase more than fetal arterial pressure and produce cerebral ischemia. Moreover, data from fetal lambs indicate limited cerebral blood flow autoregulation when cerebral perfusion pressure is reduced by lowering systemic arterial pressure.6 If cerebrovascular autoregulation is also limited when ICP increases, fetal cerebral metabolism may be transiently compromised even in normal labor.

Several studies suggest that fetal animals, like adults, are capable of increasing systemic arterial pressure to maintain cerebral perfusion pressure (Cushing response).6,8 Studies in adult animals indicate that either an increase in peripheral vascular resistance9 or cardiac output10,11 contributes to an increase in arterial pressure at high ICP. In either case, the Cushing response might be less effective in a fetus because the effectiveness of neurohumoral vascular control may be diminished by immaturity.12 Moreover, the ability of the fetus to generate large increases in arterial pressure may be limited by an inability to increase its already extremely high cardiac output.13 Finally, the ability to increase peripheral resistance would be limited.
by the fact that about 40% of fetal cardiac output supplies the placenta. Vasoconstriction of placental vessels would clearly be disadvantageous. Thus, the fetus would require disproportionately greater vasoconstriction in other regions to generate an increase in arterial pressure equivalent to postnatal animals.

We examined in utero the ability of fetal sheep to regulate cerebral blood flow when graded increases in ICP were produced by infusions of artificial cerebrospinal fluid (CSF) into the lateral cerebral ventricles. Peripheral organ blood flow, plasma catecholamine levels, and plasma arginine vasopressin (AVP) were measured concurrently. We hypothesized that when ICP was elevated sufficiently to exhaust cerebrovascular autoregulation and to impair cerebral blood flow and \( O_2 \) uptake, an increase in arterial blood pressure would help maintain cerebral perfusion pressure. However, we postulated that the effectiveness of this mechanism would be limited by the fetus’ inability to increase cardiac output and perhaps by an inability of the autonomic nervous system to regulate peripheral vascular tone.

**Materials and Methods**

**Preparation**

We studied four groups of fetal lambs at 128–132 days of gestation (with term at 145 days). All animals were of mixed breed. With the ewes under halothane anesthesia, the uterus was exposed by a midline abdominal incision. The scalp and extremities of the fetuses were exposed through uterine incisions. Polyvinyl chloride catheters were placed into the fetal inferior vena cava (via a pedal vein), the abdominal aorta (via a pedal artery), the brachiocephalic artery (via an axillary artery), and the sagittal sinus (proximal to the confluence of sinuses) as previously described. The catheter in the brachiocephalic artery was positioned near the junction of the axillary artery and the carotid artery by first advancing the catheter into the left ventricle, and then withdrawing it to a point 2.5 cm beyond the aortic valve. Through a burr hole in the skull, a flexible Silastic, straight ventricular catheter with multiple side ports (model 901302, Cordis, Miami, Florida) was placed directly into a cerebral lateral ventricle. The catheter was filled with artificial CSF. The composition of the artificial CSF in meq/1 was Na⁺ 151, K⁺ 3, Ca²⁺ 2.5, Mg²⁺ 1.2, Cl⁻ 134, HCO₃⁻ 25, and urea 6. An additional catheter was sewn to the ear to measure amniotic fluid pressure at the level of the external auditory meatus. All catheters were sewn into place, and the uterine and abdominal incisions were closed. The catheters were exteriorized through the ewe’s flank. Procaine penicillin (1,200,000 units) was administered to the ewe and ampicillin (500 mg) was infused directly into the amniotic fluid daily until the day of study. The ewes recovered a minimum of 48 hours prior to study. At the conclusion of the study, animals were killed with T-61 euthanasia solution (American Hoechst, Summerville, New Jersey), and all catheter positions were verified at autopsy. All experimental procedures were approved by the institutional animal care and use committee.

**Measurements**

Organ blood flows were measured using the radio-labeled microsphere technique. Approximately 1.5 million microspheres (15±1 µm diameter) labeled with \(^{153}\text{Gd}, ^{51}\text{Cr}, ^{113}\text{Sn}, ^{103}\text{Ru}, ^{52}\text{Nb}, \) and \(^{48}\text{Sc} \) (Dupont-New England Nuclear Products, Boston, Massachusetts) were injected over 1 minute into the inferior vena cava. Reference blood samples were withdrawn from the brachiocephalic artery and the abdominal aorta at a rate of 2.54 ml/min with a syringe pump (Harvard Apparatus, Dover, Massachusetts). Withdrawals were begun 0.5 minutes before the microsphere injection and continued for 1 minute after the injection was completed. The microsphere injections were not associated with changes in heart rate or blood pressure. Multiple representative samples of heart, kidneys, liver, gastrointestinal tract, adrenal glands, upper and lower body skin, and upper and lower body carcass were taken at autopsy. The carcass and skin were divided at the T4 interspace for separate calculation of blood flow. The brain was divided into cerebellum, medulla, pons, midbrain, diencephalon, caudate nucleus, and cerebrum. Samples were also taken from primary supply regions of the middle and posterior cerebral arteries and from the anterior-middle and posterior-middle cerebral arterial border regions. Radioactivity in each sample was determined using a multichannel autogamma scintillation spectrometer (model 9042, Packard, Downers Grove, Illinois). All reference blood samples contained greater than 2,000 microspheres, and all tissue samples contained greater than 400 microspheres. Blood flows were calculated by the surrogate organ technique, which requires that the concentration of micropheres in the blood at the withdrawal site of the reference sample equals the concentration in the blood going to the organ of interest. Thus, the brachiocephalic and abdominal aortic reference samples were used to calculate blood flow to tissues supplied by preductal blood and postductal blood, respectively. Cardiac output was determined by summing flow to the placenta and all organs, except lungs, and dividing by total fetal weight (without placenta).

Brachiocephalic arterial (\( \text{CaO}_2 \)) and sagittal sinus (\( \text{CvO}_2 \)) oxygen contents were measured using the Lex-O₂-Con-TL. (Lexington Instruments, Waltham, Massachusetts). Blood pH and partial pressure of \( \text{O}_2 \) (\( \text{P}_\text{O}_2 \)) and \( \text{CO}_2 \) (\( \text{P}_\text{CO}_2 \)) were measured at 39.5°C using a Radiometer BMS3 Mk2 (Radiometer, Copenhagen). The \( \text{P}_\text{O}_2 \) at 50% oxyhemoglobin saturation (\( \text{P}_{50} \)) was determined from blood samples in the 30–70% \( \text{O}_2 \) saturation range assuming a Hill coefficient of 2.58. Abdominal aortic blood pressure, lateral
ventricular pressure (ICP), and amniotic fluid pressure were continuously recorded with Statham pressure transducers. Heart rate was continuously recorded from the abdominal aortic pressure trace. Blood pressure and ICP were referenced to amniotic fluid pressure measured at the level of the fetal auditory meatus. Cerebral perfusion pressure was defined as the difference between mean arterial pressure and ICP. Cerebral blood flow refers to cerebrum only. Cerebral vascular resistance was calculated as cerebral perfusion pressure divided by cerebral blood flow. Cerebral O₂ uptake was calculated as the product of cerebral blood flow and Cao₂. Cerebral fractional O₂ extraction is the ratio of cerebral O₂ uptake to O₂ transport.

Plasma epinephrine and norepinephrine concentrations were measured using high-pressure liquid chromatography (HPLC) with electrochemical detection. Five milliliters of blood from the descending aorta was collected in a tube containing 100 μl of 67 mM EDTA and 175 mM Na₂S₂O₅, and the plasma was separated and frozen at −70°C. Before HPLC analysis, sample purification for amines was obtained by an alumina absorption procedure. The sensitivity of the assay is 40 pg/ml. Plasma AVP concentration was measured by a commercially available radioimmunoassay (Immuno Nuclear Corp, Stillwater, Minnesota). Five milliliters of blood from the descending aorta was collected in an EDTA tube, and the plasma was separated and frozen. The sensitivity of the assay is 2.5 pg/ml. The antibody shows less than 0.01% cross reactivity with oxytocin and 0.14% cross reactivity with vasotocin. Recovery studies show 84% to 88% recovery over the range 3 to 90 pg/ml.

Glucose and lactate concentrations were measured in duplicate samples of whole blood. Blood (1.0 ml) was withdrawn into heparinized syringes and immediately deproteinized with barium hydroxide and zinc sulfate (glucose) or ice-cold perchloric acid (lactate). Glucose and lactate concentrations were then determined enzymatically (Sigma Chemical Co, St. Louis, Missouri). Blood for 2,3-diphosphoglycerate (2,3-DPG) analysis was precipitated with trichloracetic acid and analyzed enzymatically (Sigma). Results were expressed in micromoles per gram of hemoglobin. Hemoglobin was measured spectrophotometrically (OSM2, Radiometer, Copenhagen).

Experimental Protocol

The ewes were placed standing in a wooden pen with food and water ad libitum at least 1 hour before baseline measurements were obtained. ICP was increased to approximately 15 mm Hg (Step 1) and thereafter in four additional stepwise increments of 6±1 mm Hg (Steps 2, 3, 4, and 5) by raising the level of a reservoir containing artificial CSF. ICP was always gradually elevated over a 1-minute period and was maintained at each level for 12 minutes.

Group I. In 10 animals, physiological measurements were made at baseline, and then repeated at 8–10 minutes after achieving each incremental level of ICP. These measurements included microsphere injections and arterial and sagittal sinus PO₂, PCO₂, pH, and O₂ content. After each microsphere injection, ICP was increased to the next level, and this measurement sequence was repeated for all five ICP increments.

Group II. In five animals, ICP was elevated in the same manner as in Group I, but microspheres were not injected. Instead, arterial blood was withdrawn at baseline and ICP steps 2, 3, 4, and 5 for determination of epinephrine, norepinephrine, AVP, 2,3-DPG, glucose, and lactate concentrations. These measurements were made in a separate group from those in which microspheres were injected to limit blood loss. Arterial and sagittal sinus PO₂, PCO₂, pH and O₂ content were measured and P50 was calculated.

Group III. In both Groups I and II, about 65 ml blood was withdrawn before the last incremental elevation of ICP. This blood loss may have potentiated the response to elevated ICP. To test this, five animals were subjected to the same time sequence of five incremental elevations of ICP. At baseline and at the fifth step elevation of ICP, microsphere-determined blood flow and plasma epinephrine, norepinephrine, and AVP concentrations were measured. This required only 18 ml of blood withdrawal before ICP was elevated. No blood was withdrawn at the intermediate ICP steps.

Group IV. To test for possible effects of six sequential microsphere injections and associated blood loss on organ blood flow, five fully catheterized animals were studied without ICP elevation. Microspheres were injected at 13-minute intervals in this time-control group.

Statistical Analysis

Effects of ICP elevation in each group were determined by one-way analysis of variance with repeated measures. Differences between baseline values and those measured during the five incremental ICP steps were tested with Dunnett’s post hoc test at p=0.05. Data are expressed as mean±SEM except where noted. Because the variance of epinephrine, norepinephrine and AVP values increased with the mean value, analysis was performed on the logarithmic transformation.

Results

Group I

Initial elevations of ICP from 6±1 to 15±1 and 22±1 mm Hg were not accompanied by changes in mean arterial blood pressure. Therefore, cerebral perfusion pressure declined to 30±2 mm Hg (Figure 1). Further increases in ICP produced nearly equiv-
alent step increases in arterial pressure. As a result, only small additional decrements in cerebral perfusion pressure occurred. At the highest ICP of 41 ± 1 mm Hg, which was within 9 mm Hg of the original baseline mean arterial pressure, cerebral perfusion pressure was sustained at 26±2 mm Hg. Cerebral blood flow was not significantly different from baseline at any step elevation of ICP (Figure 2). Cerebral vascular resistance fell significantly at the three highest levels of ICP, at which points arterial pressure had increased.

Arterial pH decreased and arterial PCO2 increased at the highest ICP, but arterial PO2 remained unchanged throughout the experiment (Table 1). Cerebral venous PCO2 increased and pH decreased after the fourth step elevation of ICP, but cerebral venous PO2 was not significantly changed. Arterial hematocrit was unchanged over the course of the experiment (from 38±2% to 36±2%). The PO2 of hemoglobin at the in vivo pH increased from 21±1 to 30±1 mm Hg.

As a result of the increase in PO2 (decrease in oxyhemoglobin affinity) without a change in arterial PO2, CaO2 fell significantly when ICP was greater than 28 mm Hg (Figure 3). Since the decrease in CaO2 was not accompanied by an increase in CBF, cerebral O2 transport declined. Nevertheless, the arteriovenous O2 content difference increased, the fraction of supplied O2 that was extracted increased and cerebral O2 uptake was well maintained (Figure 3).

Blood flow to medulla, pons, and midbrain increased with increasing ICP (Figure 4). Blood flow to the diencephalon was not significantly different (p<0.06). Blood flow to the cerebellum and caudate nucleus were unchanged. The lack of a rise in blood flow to cerebellum indicates that the rise seen in brainstem was probably not due to incomplete transmission of pressure into the infratentorial compartment. Within cerebrum, there were no changes in blood flow to either the primary arterial supply regions of the posterior and middle cerebral artery, or to the border regions between the posterior and middle cerebral arteries and between the anterior and middle cerebral arteries. Oxygen transport to medulla, pons, midbrain, and diencephalon remained unchanged from baseline. In cerebellum and all regions within the cerebrum where blood flow failed to increase at the reduced level of CaO2, oxygen transport declined.

No bradycardia (either transient or persistent) occurred during the experiments, and heart rate at the highest ICP (172±7 beats/min) was not different from baseline (171±6 beats/min). Cardiac output was also unchanged with elevated ICP. However,

### Table 1. Blood Analysis in Group I

<table>
<thead>
<tr>
<th>ICP (mm Hg)</th>
<th>Baseline</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachiocephalic artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35±0.01</td>
<td>7.36±0.01</td>
<td>7.36±0.01</td>
<td>7.36±0.01</td>
<td>7.31±0.02*</td>
<td>7.23±0.04*</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>46±1</td>
<td>44±1</td>
<td>44±1</td>
<td>44±1</td>
<td>47±1</td>
<td>51±2*</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>18±1</td>
<td>19±1</td>
<td>20±1</td>
<td>21±1</td>
<td>19±1</td>
<td>21±2</td>
</tr>
<tr>
<td>Sagittal sinus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.33±0.01</td>
<td>7.33±0.01</td>
<td>7.34±0.01</td>
<td>7.32±0.01</td>
<td>7.26±0.02*</td>
<td>7.20±0.03*</td>
</tr>
<tr>
<td>PvcO2 (mm Hg)</td>
<td>48±1</td>
<td>48±1</td>
<td>46±1</td>
<td>48±1</td>
<td>51±1*</td>
<td>56±3*</td>
</tr>
<tr>
<td>PvcO2 (mm Hg)</td>
<td>15±1</td>
<td>14±1</td>
<td>13±1</td>
<td>12±1</td>
<td>13±1</td>
<td>13±1</td>
</tr>
</tbody>
</table>

ICP, intracranial pressure; PO2 and Pco2, partial pressure of O2 and CO2, respectively. Values are mean±SEM (n=10).

* p<0.05 versus baseline ICP.
there were pronounced decreases in blood flow to kidney and skin after the third step increase in ICP and to the gastrointestinal tract by the fourth step (Figure 5). At the highest ICP, renal blood flow decreased 68±8%, gastrointestinal blood flow decreased 69±7%, and skin blood flow decreased 65±9%. Blood flow to heart, adrenal glands, and placenta increased after the third ICP increment (Figure 5). Least squares analyses was performed on individual data points of the percent increase in placenta blood flow versus the percent increase in mean arterial pressure. The regression coefficient of 0.95 (r=0.66) was not different from unity, which indicates a pressure-passive response. Carcass blood flow and hepatic arterial blood flow (total liver microsphere concentration) were unaltered.

**Group II**

In five fetal sheep, ICP was elevated stepwise from 3 to 13, 19, 26, 31, and 39 mm Hg with the same time sequence as Group I to determine the mechanism of the change in P50 and to determine the plasma catecholamine and AVP responses. The arterial pressure response was similar in Groups I and II. At the highest ICP in Group II, mean arterial pressure had risen from 47±2 to 67±2 mm Hg and cerebral perfusion pressure had declined from 44±2 to 29±2 mm Hg. As in Group I, Cao decreased, and this was associated with both an increase in arterial PCO2 and lactate levels. The calculated P50 with the in vivo pH increased, as it did in Group I animals, from 18.1±0.6 to 24.0±1.9 mm Hg. Using a Bohr factor of -0.44 log PO2 per pH unit, an in vitro P50 at a standardized pH of 7.4 was calculated. There was no significant change of in vitro P50 of or 2,3-DPG. Electrophoresis of lysed red blood cells was also performed and no change in hemoglobin type was detected. Thus, in Group II animals, the Bohr shift appeared to account for the increased P50.

Remarkable increases in arterial blood glucose occurred during this stress (Table 2). This was associated with increases in plasma epinephrine of two orders of magnitude and increases in plasma norepinephrine of one and a half orders of magnitude at the highest ICP (Figure 6). Increases in catecholamines and glucose achieved statistical significance at an ICP of 26 mm Hg, at which point there was a significant increase in arterial pressure. Plasma AVP increased from a baseline level of 2 pg/
ml to 9 pg/ml at an ICP of 19 mm Hg and continued to rise to 390 pg/ml (range of 69 to 800 pg/ml) at an ICP of 39 mm Hg. Both the AVP and catecholamine responses were graded to the level of ICP and correlated with the pressor response (Figure 6).

Group III

In five animals, ICP was elevated stepwise from 7 to 16, 24, 28, 35, and 42 mm Hg with the same time sequence as in Groups I and II. However, blood flow and hormone measurements were made only at baseline and at the highest ICP. Mean arterial blood pressure increased from 53 ± 4 to 69 ± 5 mm Hg. Renal, gastrointestinal, and skin blood flow decreased by 54 ± 9%, 62 ± 8%, and 64 ± 9%, respectively, and were not different than the responses in Group I. Plasma epinephrine increased from 0.28 ± 0.13 to 4.90 ± 1.92 ng/ml, and plasma norepinephrine increased from 0.95 ± 0.11 to 7.56 ± 3.56 ng/ml. Plasma AVP increased from 2.9 ± 0.5 to 55 ± 25 pg/ml (range of 10 to 144 pg/ml). The increase in AVP in Group III was significantly less than the increase in Group II (Figure 6), whereas the catecholamine response was not significantly different.

Group IV

In five time-control animals, the average coefficient of variation in each animal for six determinations of renal, gastrointestinal and skin blood flow was 6.3 ± 1.6% (±SD), 13.6 ± 5.9%, and 8.7 ± 3.3%, respectively. Gastrointestinal and skin blood flow remained unchanged, but renal blood flow decreased 11 ± 2.5% (±SEM) on the sixth determination (Table 3).

Discussion

The major finding of this study is that near-term fetal lambs rely on a potent systemic pressor response to maintain cerebral perfusion and O₂ uptake when ICP increases. The mechanism of the

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**TABLE 2. Arterial Blood Analysis in Group II**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP (mm Hg)</td>
<td>7.37±0.02</td>
<td>7.39±0.02</td>
<td>7.36±0.01</td>
<td>7.32±0.01*</td>
<td>7.22±0.03*</td>
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<tr>
<td>pH</td>
<td>42±2</td>
<td>42±2</td>
<td>44±2</td>
<td>47±2</td>
<td>53±3*</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>21±2</td>
<td>24±2</td>
<td>20±1</td>
<td>20±2</td>
<td>22±2</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.8±0.6</td>
<td>14.3±0.5</td>
<td>14.4±0.4</td>
<td>14.3±0.5</td>
<td>14.2±0.4</td>
</tr>
<tr>
<td>O₂ content (ml/dl)</td>
<td>9.8±0.8</td>
<td>9.8±1.1</td>
<td>7.3±0.7*</td>
<td>6.9±0.8*</td>
<td>7.1±0.5*</td>
</tr>
<tr>
<td>2,3-DPG (μmol/g)</td>
<td>2.27±0.48</td>
<td>2.32±0.51</td>
<td>2.35±0.57</td>
<td>2.16±0.54</td>
<td>2.24±0.74</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
<td>1.8±0.2*</td>
<td>3.1±0.5*</td>
<td>7.5±1.7*</td>
</tr>
</tbody>
</table>

*ICP, intracranial pressure; PaO₂ and PaCO₂, arterial partial pressure of O₂ and CO₂, respectively; in vivo P₅₀, PO₂ at 50% oxyhemoglobin saturation at in vivo pH; in vitro P₅₀, PO₂ at 50% oxyhemoglobin saturation at a standard pH of 7.4; 2,3-DPG, 2,3-diphosphoglycerate (μmol/g of hemoglobin). Values are mean±SEM (n=5).

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**TABLE 3. Blood Flow in Time-Control Fetal Sheep**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Renal</th>
<th>Gastrointestinal</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>172±34</td>
<td>93±10</td>
<td>18.1±1.7</td>
</tr>
<tr>
<td>13</td>
<td>160±30</td>
<td>87±17</td>
<td>17.3±1.9</td>
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<tr>
<td>26</td>
<td>173±36</td>
<td>90±6</td>
<td>19.5±3.5</td>
</tr>
<tr>
<td>39</td>
<td>166±26</td>
<td>97±17</td>
<td>17.6±1.3</td>
</tr>
<tr>
<td>52</td>
<td>165±34</td>
<td>103±10</td>
<td>18.9±2.5</td>
</tr>
<tr>
<td>65</td>
<td>153±26*</td>
<td>87±24</td>
<td>17.2±0.7</td>
</tr>
</tbody>
</table>

*Values are mean±SD (n=5).

*ICP, intracranial pressure; PaO₂ and PaCO₂, arterial partial pressure of O₂ and CO₂, respectively; in vivo P₅₀, PO₂ at 50% oxyhemoglobin saturation at in vivo pH; in vitro P₅₀, PO₂ at 50% oxyhemoglobin saturation at a standard pH of 7.4; 2,3-DPG, 2,3-diphosphoglycerate (μmol/g of hemoglobin). Values are mean±SEM (n=5).

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*ICP, intracranial pressure; PaO₂ and PaCO₂, arterial partial pressure of O₂ and CO₂, respectively; in vivo P₅₀, PO₂ at 50% oxyhemoglobin saturation at in vivo pH; in vitro P₅₀, PO₂ at 50% oxyhemoglobin saturation at a standard pH of 7.4; 2,3-DPG, 2,3-diphosphoglycerate (μmol/g of hemoglobin). Values are mean±SEM (n=5).

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maintenance of cerebral perfusion is a marked redistribution of systemic blood flow with no change in cardiac output. Blood flow to kidneys, gastrointestinal tract, and skin was curtailed, while placental, myocardial, and adrenal blood flow increased. The magnitude of the pressor response was associated with graded increases of plasma epinephrine, norepinephrine, and AVP.

**Comparison With Adult Cushing Response**

The pattern of cardiac output redistribution in fetal sheep is directionally similar to that reported in adult dogs during the Cushing response. The doubling of coronary blood flow in both fetal lambs and adult dogs is presumably related to increased myocardial work. The magnitude of the vasoconstrictor response in abdominal viscera, however, was considerably larger in the fetus. Renal and splanchic blood flow decreased by only 20% in dogs with ICP significantly above baseline arterial pressure, whereas they decreased by 60–70% in fetuses even though ICP never exceeded baseline arterial pressure. This difference is not explained by species difference, because elevation of ICP to within 20–25 mm Hg of baseline arterial pressure in newborn and 3-month-old lambs produces little change in renal and gastrointestinal blood flow.

There are several possible explanations for especially intense visceral vasoconstriction in fetuses in our study. First, it is possible that peripheral vasoconstriction in the adult was blunted by anesthesia and surgery. We studied unanesthetized fetuses in a chronic preparation. Anesthetized animals may have already had reduced baseline visceral blood flow and further reductions with elevated ICP may have been attenuated.

Second, the ability of the fetus to increase its cardiac output appears to be limited. Indeed, it has been suggested that fetal cardiac output is normally near maximal, and that the fetus may be unable to further increase its cardiac output. An increase in arterial pressure in the setting of fixed cardiac output can be achieved only by increasing vascular resistance.

Third, the efficiency of visceral vasoconstriction as a mechanism of fetal blood pressure elevation is impaired because the visceral circulation is in parallel with a large, low-resistance placental circulation that is relatively unresponsive to catecholamines and AVP. Because placental blood flow increased passively with arterial pressure, the increase in arterial pressure required relatively greater vasoconstriction in those organs that are responsive.

The precise mechanisms by which the fetus achieves this pronounced vasoconstriction are unknown, but two factors might contribute. First, pronounced vasoconstriction in fetuses may reflect relative underdevelopment of β-adrenergic receptors. At high ICP β-adrenergic blockade in dogs unmasks a large α-adrenergic vasoconstriction, the pattern of which closely resembles that in fetal lambs. However, a recent study showing that β-adrenergic vasodilation in the kidney is well-developed in near-term fetal sheep makes underdevelopment of β-adrenoceptors an unlikely explanation.

Second, the vasoconstrictive component of the Cushing response may be potentiated by the hypoxic and moderately hypercapnic arterial blood gases of the normal fetus. Because cerebral hypoxia and acidosis have been implicated in the cardiovascular response to cerebral ischemia, low baseline tissue PO2 in the fetal brain may augment the cardiovascular response to further lowering of tissue PO2 by elevated ICP.

It should be noted that the ventricular fluid infusion technique that we used to raise ICP is not completely analogous to what occurs during labor. Fluid infusion at a rate slow enough to allow equilibration in all CSF compartments produces a generalized increase in brain interstitial fluid pressure and acts to decrease cerebral blood flow by compressing cerebral veins. During labor, when the head is engaged in the cervix, the stress exerted periodically on the skull is considerably higher than amniotic fluid pressure. The force exerted by the bone plates with unfused sutures onto the dura and cerebrum is spread over a large surface area; nevertheless, it may cause some deformation of underlying cerebrum in addition to increasing CSF pressure. Moreover, if caudal displacement of cerebrum is prominent, axial distortion of the brain stem may evoke the Cushing response. Pressure-stretch sensitive regions have been reported in dorsal medulla, which may be responsible for mediating the pressor response to axial brain stem distortion. Thus, external compression of the fetal head might lead to greater visceral vasoconstriction than fluid infusion at equivalent levels of ICP.

**Hormonal Response**

Plasma epinephrine and norepinephrine levels in human fetuses during labor and immediately after vaginal delivery are of the magnitude measured when ICP was elevated in fetal lambs in Groups II and III. Therefore, our data suggest that elevated catecholamines during normal labor may represent sympathoadrenal activation by cerebral compression. The other major stress associated with labor is fetal hypoxia. By way of comparison, increases in plasma epinephrine and norepinephrine to 10 ng/ml during hypoxia in fetal lambs requires lowering descending aorta PaO2 to about 6–8 mm Hg. Thus, using the criterion of the catecholamine response, an ICP of 39 mm Hg is equivalent to extreme arterial hypoxia.

We also found that plasma AVP increased with graded increases in ICP. Baseline AVP level is similar to other measurements in unstressed fetal lambs. With increases in ICP to 26, 31, and 39 mm Hg, where peripheral vasoconstriction was sig-
significant, AVP increased 15, 80, and 390 pg/ml, respectively, in Group II. By comparison with studies of AVP infusion in fetal lambs, increases in arterial pressure occurred when plasma AVP levels increased by 13 pg/ml\textsuperscript{33} and decreases in blood flow to gut occurred at 64 pg/ml\textsuperscript{20}. Thus, AVP levels in the present study were in a vasoactive range and may have contributed to the pressor response. Elevated levels of AVP have been measured at the time of delivery in human newborns and were especially high in those judged to have a difficult labor with fetal distress.\textsuperscript{34} Of particular interest is the remarkable correlation between AVP levels and cervical dilation before cesarean section.\textsuperscript{35} With greater cervical dilation, the head has progressed further into the birth canal and pressure on the skull is presumably greater.

One concern was that the sequential blood sampling in Group II resulted in significant fetal blood loss. Preceding the last set of measurements, 65 ml blood had been withdrawn. Because blood volume loss of as little as 10–15\% can double plasma AVP concentration,\textsuperscript{36} we studied an additional group (III) with blood loss limited to 18 ml, which represented approximately 5\% of fetoplacental blood volume.\textsuperscript{36} Although AVP concentrations at the highest ICP level were lower in Group III, they were nonetheless still greatly increased over baseline, and within the range known to produce vasoconstriction. Moreover, elevated plasma catecholamine levels and renal, gastrointestinal and skin vasoconstriction remained prominent in this group. In contrast, there was only a minor decrease in renal blood flow and no change in gastrointestinal and skin blood flow in Group IV subjected to similar blood loss over a similar time period, but without elevated ICP. Thus, the hormonal and vasoconstrictive responses were primarily the result of elevated ICP and not hemorrhage.

Weight-Specific Organ Flow and Total Organ Conductance

A rise in arterial blood pressure in the absence of a change in cardiac output means a reduction in whole body conductance, that is, total cardiac output divided by mean arterial blood pressure. In considering the mechanism of the increase in arterial pressure, it is important to keep in mind that large organs receiving a substantial portion of cardiac output, such as carcass, may make a larger contribution to the overall decrease in conductance than a smaller organ, such as kidney, despite a much larger weight-specific decrease in flow in the smaller organ. For example, when we compared control measurements with measurements at the next to last step elevation of ICP, the median contribution of kidney, gastrointestinal tract, skin, and carcass to the reduction in whole body conductance was 6\%, 16\%, 24\%, and 28\%, respectively. At the highest ICP, the corresponding contributions were 6\%, 24\%, 19\%, and 21\%. Although the weight specific decrease in kidney, gastrointestinal and skin blood flow is dramatic (Figure 5), the mechanism of the increase in systemic pressure involves a prominent contribution from increased vessel tone in carcass.

Cerebral Hemodynamics

Because the Cushing response is postulated to be elicited by cerebral ischemia,\textsuperscript{9} we were surprised that the peripheral cardiovascular response occurred in the absence of either reduced cerebral blood flow or O\textsubscript{2} uptake. It is possible that a more subtle decrease in cerebral oxygenation was responsible. Elevation of ICP in our model reduced cerebral O\textsubscript{2} transport, and although O\textsubscript{2} uptake was maintained, this required doubling fractional O\textsubscript{2} extraction. The decrease in O\textsubscript{2} transport to the forebrain with elevated ICP contrasts with brainstem areas where O\textsubscript{2} transport was maintained. This regional difference raises the possibility that forebrain hypoxia (a fall in tissue P\textsubscript{O\textsubscript{2}} that accompanies a rise in fractional O\textsubscript{2} extraction) alone may be sufficient for eliciting the peripheral vascular response in the fetus.

The reason for decreased cerebral O\textsubscript{2} transport with increased ICP is that cerebral blood flow did not compensate for the concurrent reduction of C\textsubscript{aO\textsubscript{2}}. Generally, a reduction of C\textsubscript{aO\textsubscript{2}} leads to increased cerebral blood flow and maintenance of cerebral O\textsubscript{2} transport.\textsuperscript{14} Assessment of the implications of the fall in O\textsubscript{2} transport is complicated by our finding that there was a simultaneous decrease in oxyhemoglobin affinity (increased P\textsubscript{50}). However, when we extrapolate from our previous work at normal perfusion pressures,\textsuperscript{14} the change in P\textsubscript{50} would only partially account for the observed fall in cerebral O\textsubscript{2} transport. Thus, the level of cerebral perfusion provided by the Cushing response appears inadequate in the sense that cerebral blood flow did not increase when C\textsubscript{aO\textsubscript{2}} fell, even when the shift in P\textsubscript{50} is considered, and O\textsubscript{2} transport was not appropriately maintained.

The principal reason for the aforementioned decrease in C\textsubscript{aO\textsubscript{2}} was the increase in P\textsubscript{50}. We found no acute change in 2,3-DPG or gross alteration in hemoglobin types that could account for the observed changes of P\textsubscript{50} in vivo. In Group II, the increase in P\textsubscript{50} was entirely explained by the fall in systemic pH (Bohr effect). However, the Bohr effect accounts for only a portion of the change in Group I, and we are unable to account for the rest. Estimates of the in vitro P\textsubscript{50} are based on single point measurements and are subject to some error. Thus, they may not be sufficiently precise to detect small changes in P\textsubscript{50} that could arise from some other factor.

The decrease in pH was related to increased arterial lactate levels associated with peripheral vasoconstriction. Incomplete placental elimination of CO\textsubscript{2} liberated by the lactic acid load also contributed to the drop in pH at the highest ICP. With more prolonged elevation of ICP, we anticipate that sustained lactic acid production would result in a continued drop in pH and, because of decreased...
oxyhemoglobin affinity (Bohr effect), a continued drop in $C_{a\text{O}_2}$. In this case, further peripheral vasoconstriction may maintain cerebral blood flow, but it might not fully restore cerebral $O_2$ transport. Thus, if this cerebral defense mechanism is important during parturition, its effectiveness may eventually become limited during prolonged, intense labor because of progressive metabolic acidosis.

We initially postulated that the pressor response would occur when cerebral perfusion pressure was lowered below the limit for cerebral blood flow autoregulation. However, we were unable to achieve a sufficiently wide range of perfusion pressure to examine the relation of pressure to cerebral blood flow or vascular resistance. The decline in cerebrovascular resistance at high ICP may have been due to the concurrent fall in $C_{a\text{O}_2}$ rather than the reduced perfusion pressure. Thus, our data neither confirm nor deny the hypothesis that fetal sheep are capable of cerebral blood flow autoregulation.

In conclusion, graded increases in ICP approaching baseline arterial pressure in near-term fetal lambs produces marked vasoconstriction in kidney, gastrointestinal tract, and skin. This vasoconstriction is accompanied by increased plasma catecholamines and AVP. The resulting pressor response is highly effective in sustaining cerebral blood flow and $O_2$ uptake. The Cushing response may represent a physiologically important mechanism for sustaining the fetus during parturition, particularly the human fetus with its relatively large, compliant skull.

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References


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