Cerebral circulatory responses of near-term ovine fetuses during sustained fetal placental embolization

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Gagnon, Robert, Tasha Lamb, and Bryan Richardson. Cerebral circulatory responses of near-term ovine fetuses during sustained placental embolization. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2001–H2008, 1997.—To test the hypothesis that, in response to an increase in placental vascular resistance and progressive fetal asphyxia, the changes in external carotid blood flow waveforms are directly related to changes in external carotid vascular resistance, we embolized the fetal side of the placenta in pregnant sheep and measured cerebral and external carotid artery circulatory changes in relation to changes in external carotid blood flow waveforms. Chronically catheterized fetal sheep at 0.85 of gestation were embolized (n = 11) in the descending aorta for 6 h, until fetal arterial pH fell to ~6.90. Fetuses became rapidly hypoxemic (P < 0.0001) and developed a mixed respiratory and metabolic acidosis (P < 0.0001 for Pco2, pH, and base excess). There was a transient 40% increase in external carotid blood flow at pH ~7.25 and a parallel 32% increase in fetal arterial blood pressure (both P < 0.01), whereas the external vascular resistance remained unaltered. Cerebral blood flow increased by 130% (P < 0.0001) and developed a mixed respiratory and metabolic acidosis (P < 0.0001 for Pco2, pH, and base excess). There was a transient 40% increase in external carotid blood flow at pH ~7.25 and a parallel 32% increase in fetal arterial blood pressure (both P < 0.01), whereas the external vascular resistance remained unaltered. Cerebral blood flow increased by 130% (P < 0.0001), and cerebral vascular resistance decreased by 125% (P < 0.0001) throughout the study. The external carotid resistance index (RI) decreased by 32% (P < 0.0001) at the time external carotid vascular resistance remained unchanged. This fall in external carotid RI was due almost entirely to a 110% increase in external carotid fundamental impedance (P < 0.001). We conclude that the poor relationship between the changes in external carotid vascular resistance and RI indicated that other hemodynamic factors such as vascular impedance to pulsatile flow must be measured for correct interpretation of changes in flow waveform shape under hypoxic conditions. In addition, changes in external carotid blood flow were not proportional to changes in cerebral blood flow in this model.

fetal brain; fetal hypoxia; placental insufficiency; fetal cerebral circulation

IN RESPONSE TO acutely induced hypoxemia in fetal sheep, there is an increase in brain blood flow caused by a decrease in cerebral vascular resistance, thus maintaining oxygen delivery and consumption (12, 21). This increase in brain blood flow is maintained for at least 48 h with prolonged hypoxemia (5). In human pregnancies complicated with placental insufficiency, changes in Doppler-derived indexes of vascular resistance recorded in the cerebral vasculature suggest a decrease in cerebral vascular resistance in response to hypoxemia (3, 29). However, attempts to validate the relationship between changes in blood flow waveforms and vascular resistance in the cerebral vasculature have been relatively disappointing (19, 24). It is now established that other hemodynamic variables such as the pressure pulsatility index (PI) and the vascular impedance to pulsatile flow need to be taken into account to predict the changes in blood flow waveforms in different vascular beds under a wide range of hemodynamic conditions (1).

Fetal placental embolization in the ovine fetus causes fetal hypoxemia with an increase in the Doppler-derived or flow-derived umbilical artery resistance index (RI) which parallels changes in umbilical vascular resistance during both acute (1, 2) and chronic (7, 8) embolization. Because hypoxia produces vasodilation of the cerebral vasculature in the ovine fetus in isolated cerebral vessels (9, 18) and a decrease in cerebral vascular resistance in vivo (5, 12, 21), a decrease in the flow-derived RI in the cerebral arteries would be expected during fetal placental embolization. Transit-time ultrasound-monitored carotid blood flow has been suggested as a method to continuously measure changes in cerebral blood flow in fetal sheep (10, 25). Therefore, the purpose of this study was to test the hypothesis that, in response to sustained fetal placental embolization with a resulting increase in placental vascular resistance and progressive fetal metabolic acidosis, the changes in carotid blood flow waveforms are directly related to changes in calculated carotid vascular resistance and to investigate the relationship between external carotid artery and cerebral blood flows.

MATERIALS AND METHODS

Surgical procedures. Eleven singleton fetal lambs of the Western Cross breed were prepared surgically between 125 and 128 days of gestation (term, 147 days). Ewes were given 600 mg of thiopental sodium (Abbott, Montreal, Quebec, Canada) intravenously; the ewes were intubated and maintained on a closed-circuit anesthesia system with 0.5–1.5% halothane (Halocarbon, North Augusta, SC) and a 50:50 (vol/vol) mixture of oxygen and nitrous oxide, with a flow rate between 2 and 3 l/min. The uterus was exposed, and an incision was made over the left side of the fetal chest. An incision was then made at the third intercostal space, and, after retraction of the ribs, the pericardium was opened, the proximal portion of the main pulmonary artery was carefully dissected, and a transit-time flow probe (8–10 mm; S-series; Transonic Systems, Ithaca, NY) was placed on the main pulmonary artery trunk.

An additional surgical incision was made laterally over the fetal neck, exposing the right external jugular vein and, deeper in the incision, the external carotid artery as previously described (10, 20). It is not technically feasible to have access to the internal maxillary artery in fetal sheep for insertion of a flow probe because of its anatomical location deep into the base of the skull. A transit-time flow probe (3 mm; S-series; Transonic Systems) was placed on the right external carotid artery just proximal to the junction with the
internal maxillary artery, at its entrance into the base of the skull, for continuous measurement of both pulsatile and mean external carotid artery blood flow (QEC). Small arterial branches at the junction between the external carotid and internal maxillary artery were not ligated. Polyvinyl catheters (3 F; OD 0.33 mm; V4; Bolab, Lake Havasu City, AZ) were inserted into the fetal brachiocephalic artery via the right axillary artery, the inferior vena cava via a hindlimb vein, the trachea, the abdominal aorta with the tip 1–2 cm above the common umbilical artery via the femoral artery, and the amniotic cavity. A polyvinyl catheter (VIII; Bolab) was also placed into the maternal femoral vein. Teflon-coated stainless steel wire electrodes (Cooner, Chatsworth, CA) were sewn on the fetal chest for continuous recording of fetal heart rate (FHR). All catheters and flow probes were exteriorized through the flank of the ewe, and the abdomen was closed in layers. At surgery and for 3 days thereafter, intramuscular injections (4 ml) of Pen-dri-Strep (200,000 IU of sodium penicillin G and 250 mg/ml dihydrostreptomycin; Roger, London, Ontario, Canada) were given to the ewe. Crystaphen (1 ml; 1,000,000 IU penicillin G; Ayerst, Montreal, Canada) was injected daily for 3 days into the fetal femoral vein and into the amniotic sac.

After surgery, sheep were housed in individual metabolic cages with hay and water available ad libitum. Ewes were maintained on a 12:12-h light-dark cycle and allowed at least 5 days to recover from surgery before the experiments began. This study was approved by the Animal Care Committee of St. Joseph’s Health Centre and The University of Western Ontario in accordance with the guidelines of the Canadian Council on Animal Care.

Experimental protocol. On the fifth day postrecovery, after a 2-h control recording period, fetal placental embolization was performed over an ~6-h period as previously described (8). Briefly, fetuses were embolized by injecting 2 × 10³ 15-µm nonradiolabeled latex microspheres into the descending abdominal aorta every 15 min over a 6-h period until the fetus developed progressive metabolic acidosis. When a fetal femoral arterial pH of ~7.00 was reached, embolization was stopped. Fetal arterial blood samples (0.4 ml) for measurements of blood gases were taken every 30 min during embolization. Fetal femoral arterial blood lactate concentrations were measured (0.5 ml fetal blood) during the control period and at a predetermined fetal arterial pH of ~7.25, ~7.00, and ~6.90. Within 1 h after the last radioactive microsphere injection, the ewes were euthanized and the uterus and its content were removed, dissected, and weighed.

Hemodynamic measurements. Fetal aorta blood pressure, brachiocephalic arterial blood pressure, central venous blood pressure, tracheal pressure, and amniotic pressure were recorded continuously with pressure transducers (Statham model P-231D; Gould, Oxnard, CA) and a 16-channel chart recorder (model 7; Grass Instruments, Quincy, MA). Mean fetal brachiocephalic and aortic blood pressure referenced to amniotic pressure were calculated as diastolic pressure + (40% of systolic pressure – diastolic pressure). The frequency response of the catheter-transducer system used to measure pulse pressure was determined using the "pop-test" method as previously described (14). The fetal catheter and transducer were filled from a 1-liter reservoir of 0.9% NaCl that had been boiled to minimize air content and reduce bubble formation. Heparin was added to the saline reservoir at a concentration of 10 U/ml after boiling. The damped natural frequency of the catheter-manometer system was 6.1 Hz.

Electrical signals from the two chest electrodes were recorded with a Hewlett-Packard 8040A FHR monitor (Hewlett-Packard, Boeblingen, Germany) and were analyzed online using the Oxford Sonicaid (Oxford, UK) System 8000 (6). Both main pulmonary artery and external carotid artery pulsatile and integrated blood flows were recorded with a dual-channel model T208 Doppler ultrasonic transit-time flowmeter (Transonic Systems) interfaced with the Grass polygraph. The flow probes were calibrated by the manufacturer and recalibrated before insertion into the fetus. Pulsatile aorta and brachiocephalic arterial blood pressure, venous blood pressure, amniotic pressure, and pulsatile and integrated main pulmonary artery and external carotid arterial blood flows were digitized at a 250-Hz sampling rate using a computerized data acquisition program (CADA; Hartronix, Concord, Ontario, Canada).

Umbilical artery Doppler flow velocity waveforms were recorded with a real-time Duplex scanner (Ultramark 8; Advanced Technology Laboratories, Bothell, WA) with a 3.5-MHz sector scanner as previously described (7). We previously reported (7) that, under control conditions, there was a significant negative correlation between the instantaneous FHR value and the umbilical artery RI (slope = −0.00129 beats/min). Therefore, RI [RI = (S – D)/S, where S is peak-systolic flow velocity and D is end-diastolic flow velocity] corrected to an FHR value of 160 beats/min (RI160) was averaged for the 10 waveforms recorded before the onset of embolization and at a pH of ~7.25, ~7.00, and ~6.90.

Analytical measurements. Fetal arterial blood samples were drawn into heparinized syringes and placed on ice. Fetal arterial PO2, PCO2, base excess, and pH were measured with a blood gas analyzer (ABL-3; Radiometer, Copenhagen, Denmark) with measurements corrected to a fetal temperature of 39.5°C. Arterial oxygen saturation and hemoglobin were measured by 10 U/ml after boiling. The damped natural frequency of the catheter-manometer system was 6.1 Hz.

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Blood flow measurements. Regional blood flow was measured with 15-µm-diameter microspheres (DuPont NEN, Boston, MA) labeled with one of five different radioisotopes (141Ce, 51Cr, 85Sr, 95Nb, or 48Sc) according to methods previously described (5, 21). A well-dispersed suspension containing ~1.5 × 106 microspheres was injected into the fetal inferior vena cava over ~30 s. Reference samples were withdrawn from the brachiocephalic artery and the descending aorta at a rate of 2.40 ml/min with a Harvard Apparatus (South Natick, MA) infusion withdrawal pump for 2 min after the injection of microspheres into the inferior vena cava. All blood flow measurements were done in the absence of fetal breathing movement. Fetal breathing movements were defined as repeated negative deflections in tracheal pressure (corrected for amniotic pressure) of >2 mmHg lasting for >30 s. At postmortem, cotyledons and the brain were dissected free, weighed separately, and analyzed for radioactivity with a gamma counter (Compu gamma model 1281; LKB Wallace Oy, Torku, Finland). The fetal brain was dissected into the following regions: right and left cerebral cortex, subcortical structures (corpus striatum, thalamus, hippocampus, and superior and inferior colliculi), brain stem structures (midbrain and brain stem reticular formations, ventral pons, and ventral medulla) and cerebellum (hemispheres and vermis).
The fetal spinal cord was dissected separately and was not included in the calculation of total cerebral blood flow (Q_{\text{brain}}). The reference blood samples and all regional brain samples contained 400 microspheres.

Data analysis. During acute embolization, the mean fetal brachiocephalic and aorta blood pressures, mean central venous pressure, amniotic pressure, mean Q_{\text{car}} (in ml/min), and mean FHR were analyzed every 5 min between 0800 and 1600. The average of these variables were analyzed for 15 min before and after each of the four radioisotope microsphere injections.

The cerebral perfusion pressure was calculated as the difference between mean brachiocephalic arterial blood pressure and mean central venous pressure. The external carotid vascular resistance (R_{\text{car}}) was calculated as the ratio between cerebral perfusion pressure and mean Q_{\text{car}} (in ml/min) or relative (in ml min^{-1} 100 g^{-1}) Q_{\text{brain}} as determined by the radioisotope microsphere technique. The following external carotid hemodynamic variables, which are known to affect the shape of the flow waveform, were estimated in addition to vascular resistance: brachiocephalic pressure PI (PI = (systolic arterial blood pressure – diastolic arterial blood pressure)/mean arterial blood pressure), brachiocephalic pulse pressure (systolic blood pressure – diastolic blood pressure), external carotid pulse flow (systolic blood flow – diastolic blood flow), and external carotid fundamental impedance (brachiocephalic pulse pressure/external carotid pulse flow). Brachiocephalic arterial blood pressure and external carotid artery flow waveforms were analyzed over a 40-s period (~100 waveforms) at the time of each radioactive microsphere injection to calculate the brachiocephalic pulse pressure and pressure PI, external carotid pulse flow, external carotid fundamental impedance, and external carotid artery RI_{160}. The mean coefficient of variation in the calculation of external carotid artery RI 160 was averaged for 10 waveforms during each of the radioisotope microsphere injections.

Table 1. Cardiovascular and brachiocephalic arterial blood measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>pH 7.25</th>
<th>pH 7.00</th>
<th>pH 6.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO2, mmHg</td>
<td>19.2 ± 0.7</td>
<td>11.6 ± 0.8*</td>
<td>12.9 ± 0.5*</td>
<td>12.9 ± 0.7*</td>
</tr>
<tr>
<td>PCO2, mmHg</td>
<td>52.1 ± 1.0</td>
<td>56.2 ± 1.2*</td>
<td>64.8 ± 1.0*</td>
<td>70.7 ± 1.8*</td>
</tr>
<tr>
<td>CaO2, mmol/l</td>
<td>3.0 ± 0.1</td>
<td>0.9 ± 0.1*</td>
<td>0.6 ± 0.0*</td>
<td>0.5 ± 0.0*</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.01</td>
<td>7.24 ± 0.01*</td>
<td>6.99 ± 0.01*</td>
<td>6.89 ± 0.01*</td>
</tr>
<tr>
<td>Pulse excess, mmol/l</td>
<td>2.9 ± 0.2</td>
<td>4.3 ± 0.5*</td>
<td>-17.9 ± 0.4*</td>
<td>-22.3 ± 0.4*</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.0 ± 0.1</td>
<td>4.5 ± 0.3*</td>
<td>11.3 ± 1.1*</td>
<td>13.7 ± 1.0*</td>
</tr>
<tr>
<td>FHR, beats/min</td>
<td>180 ± 4</td>
<td>161 ± 5*</td>
<td>168 ± 7</td>
<td>169 ± 6</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>39 ± 2</td>
<td>51 ± 3*</td>
<td>45 ± 3</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>19 ± 1</td>
<td>24 ± 2*</td>
<td>19 ± 2</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>Pressure pulsatility index</td>
<td>0.50 ± 0.03</td>
<td>0.46 ± 0.04</td>
<td>0.41 ± 0.03</td>
<td>0.43 ± 0.04</td>
</tr>
<tr>
<td>Right ventricular output, ml·min^{-1}·kg^{-1}</td>
<td>198 ± 13</td>
<td>175 ± 13</td>
<td>138 ± 8*</td>
<td>84 ± 9*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 11 fetal sheep. FHR, fetal heart rate; CaO2, fetal arterial oxygen content. *P < 0.05 vs. control.
progressive fall in fetal arterial pH, there was a progressive return of $Q_{\text{car}}$ to a mean value at pH 6.90 of 57 ± 5 ml/min, which was not significantly different from control (Fig. 2). In contrast, $Q_{\text{brain}}$ remained elevated throughout the embolization period (Fig. 2).

As a result of the transient increase in fetal brachiocephalic arterial blood pressure (Table 1) combined with a modest transient increase in $Q_{\text{car}}$ (Fig. 2), the calculated $R_{\text{car}}$ remained unaltered throughout the embolization period (effect of time: $P = 0.21$ by ANOVA) (Fig. 3). However, there was a 110% increase in external carotid fundamental impedance (effect of time: $P < 0.001$ by ANOVA) (Table 2) and a highly significant fall in the external carotid artery flow-derived RI 160 (effect of time: $P < 0.0001$ by ANOVA) (Fig. 1, top; Table 2).

The decrease in the external carotid artery RI 160 was due mostly to a progressive increase in end-diastolic blood flow and, to a lesser extent, a terminal fall in peak-systolic blood flow at pH 6.90 (effects of time: $P < 0.0001$ and $P < 0.001$, respectively, by ANOVA) (Table 2).

The external carotid artery RI (20), similar to the umbilical artery RI or PI (1, 8), is affected by the pressure PI and the vascular impedance to pulsatile flow, in addition to downstream vascular resistance in the following relationship as defined by Adamson and...
Table 2. Fetal external carotid artery hemodynamic measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>pH ~7.25</th>
<th>pH ~7.00</th>
<th>pH ~6.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak-systolic flow, ml/min</td>
<td>145 ± 16</td>
<td>153 ± 16</td>
<td>129 ± 12</td>
<td>100 ± 13*</td>
</tr>
<tr>
<td>End-diastolic flow, ml/min</td>
<td>23 ± 4</td>
<td>48 ± 5*</td>
<td>55 ± 4*</td>
<td>39 ± 4*</td>
</tr>
<tr>
<td>Pulseflow, ml/min</td>
<td>122 ± 15</td>
<td>105 ± 12</td>
<td>75 ± 10</td>
<td>61 ± 12*</td>
</tr>
<tr>
<td>Fundamental impedance, mmHg·ml⁻¹·min</td>
<td>0.18 ± 0.02</td>
<td>0.25 ± 0.03</td>
<td>0.30 ± 0.04*</td>
<td>0.38 ± 0.06*</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>40 ± 2</td>
<td>52 ± 3*</td>
<td>46 ± 3</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Vascular resistance, mmHg·ml⁻¹·min</td>
<td>0.74 ± 0.11</td>
<td>0.64 ± 0.06</td>
<td>0.63 ± 0.05</td>
<td>0.74 ± 0.06</td>
</tr>
<tr>
<td>RI 160</td>
<td>0.84 ± 0.03</td>
<td>0.68 ± 0.03*</td>
<td>0.57 ± 0.03*</td>
<td>0.59 ± 0.04*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9 fetal sheep. RI 160, resistance index corrected for a fetal heart rate of 160 beats/min. *P < 0.05 vs. control.

Langille (1): flow PI is proportional to (pressure PI × vascular resistance)/fundamental impedance. When the brachiocephalic pressure PI and the external carotid fundamental impedance were included with the calculated R Car in the above equation, with a resulting index related to changes in the external carotid artery RI 160, then the changes in the external carotid artery RI 160 during fetal placental embolization could be almost entirely explained (Fig. 4) by a strong relationship between these two variables for each of the nine fetuses studied (r = 0.94, range 0.89–0.98). Moreover, because the brachiocephalic pressure PI and the calculated R Car remained relatively unaltered (Table 1, Fig. 3), the fall in the external carotid artery RI 160 was due almost entirely to an increase (110%) in the external carotid fundamental impedance during progressive fetal hypoxia or asphyxia (Table 2).

Cerebral and placental hemodynamic measurements. During embolization, there was a decrease in calculated cerebral vascular resistance (R Brain) from 1.25 ± 0.21 mmHg·ml⁻¹·min during the control period to 0.61 ± 0.01 mmHg·ml⁻¹·min at pH ~ 7.25 (Fig. 3). The changes in R Brain (Fig. 3) and Q Brain (Fig. 2) remained constant throughout the study period (effects of time: P < 0.02 and P < 0.001, respectively). The sustained increase in Q Brain was not sufficient to maintain cerebral oxygen delivery, which fell significantly from 507 ± 58 µmol·min⁻¹·100 g⁻¹ during the control period to 386 µmol·min⁻¹·100 g⁻¹ at pH ~ 7.00 (P < 0.05 vs. control) and 262 ± 21 µmol·min⁻¹·100 g⁻¹ at pH ~ 6.90 (P < 0.05 vs. control; effect of time: P < 0.01 by ANOVA). In response to fetal placental embolization, there were regional differences in blood flow changes within the fetal central nervous system (Table 3). The highest percentage change in blood flow at pH ~ 6.90, compared with control, was observed in the spinal cord (+265%), followed by the brain stem, subcortex, cerebellum, and cerebral cortex.

Fetal placental embolization was associated with a 360% increase in the calculated umbilical-placental vascular resistance (effect of time: P < 0.001 by ANOVA) (Fig. 5). The changes in Doppler-derived umbilical artery RI 160 paralleled the changes observed in umbilical-placental vascular resistance (effect of time: P < 0.0001 by ANOVA) (Fig. 5). The mean umbilical blood flow decreased from 180 ± 19 ml·min⁻¹·kg⁻¹ before embolization to 128 ± 13 ml·min⁻¹·kg⁻¹ at pH ~ 7.25, 70 ± 14 ml·min⁻¹·kg⁻¹ at pH ~ 7.00, and 61 ± 14 ml·min⁻¹·kg⁻¹ at pH ~ 6.90 (effect of time: P < 0.0001 by ANOVA). ANOVA indicated a progressive fall in the mean right ventricular output from 198 ml·min⁻¹·kg⁻¹ during the control period to 84 ml·min⁻¹·kg⁻¹ at pH ~ 6.90 (P < 0.005) (Table 1).

DISCUSSION

The results of the current study demonstrate that, in the near-term fetal sheep, in response to sustained hypoxic stress associated with progressive mixed respiratory and metabolic acidosis, there was a modest and transient 40% increase in Q Car and a parallel 32% increase in fetal arterial blood pressure, whereas R Car remained unaltered. In contrast, Q Brain increased by 130% and R Brain decreased by 125% throughout the study. The external carotid artery RI 160 decreased by 32% at the time R Car remained unchanged. This fall in the external carotid artery RI 160 was due almost entirely to an increase (110%) in the external carotid fundamental impedance to pulsatile flow and not to a change in R Car.

In response to a sustained (7 h) isocapnic hypoxic stress induced by lowering maternal inspired oxygen concentration and resulting in progressive metabolic acidosis, we previously reported an ~110% increase in Q Brain, followed by a progressive fall in Q Brain at pH < 7.15. The cerebral arterial resistance index RI160 decreased by 125% throughout the study period to 7.25 ± 0.11 mmHg·ml⁻¹·min during the control period to 6.90 ± 0.25 mmHg·ml⁻¹·min at pH ~ 7.00 (P < 0.05 vs. control).
Regional blood flow changes within the fetal central nervous system

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>pH ~7.25</th>
<th>pH ~7.00</th>
<th>pH ~6.90</th>
<th>%Change From Control at pH ~6.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>198±31</td>
<td>590±57*</td>
<td>726±50*</td>
<td>722±75*</td>
<td>+265</td>
</tr>
<tr>
<td>Brain stem</td>
<td>317±47</td>
<td>891±80*</td>
<td>986±53*</td>
<td>955±112*</td>
<td>+201</td>
</tr>
<tr>
<td>Subcortex</td>
<td>285±40</td>
<td>681±61*</td>
<td>744±48*</td>
<td>744±66*</td>
<td>+161</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>235±34</td>
<td>540±51*</td>
<td>546±40*</td>
<td>582±49*</td>
<td>+179</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>159±24</td>
<td>333±33*</td>
<td>351±27*</td>
<td>367±31*</td>
<td>+131</td>
</tr>
<tr>
<td>Brain</td>
<td>177±24</td>
<td>409±36*</td>
<td>412±28*</td>
<td>439±35*</td>
<td>+148</td>
</tr>
</tbody>
</table>

Values are means ± SE for 11 fetal sheep. *P < 0.05 vs. control.

associated with a fall in fetal arterial blood pressure. In the current study, the expected increase in \( Q_{\text{brain}} \) was well maintained until at least \( \text{pH} \sim 6.90 \). During fetal placental embolization, there was a progressive deterioration in transplacental gas exchange as demonstrated by a progressive increase in fetal arterial \( PCO_2 \). It is therefore likely that the combined vasodilatory effects of both fetal hypoxemia and hypercapnia (11) resulted in the sustained increase in \( Q_{\text{brain}} \) observed in the current study.

Under normoxic conditions, our observed mean \( Q_{\text{car}} \) of \( \sim 58 \text{ ml/min} \) was similar to a previous observation by Richardson et al. (20) of \( \sim 59 \text{ ml/min} \) obtained at similar gestational age and with the use of a similar recording technique. The finding that \( Q_{\text{car}} \) is relatively higher than \( Q_{\text{brain}} \) is also in agreement with previous reports (10, 25) and can be accounted for by extracerebral blood flow. During sustained hypoxemia, both \( Q_{\text{car}} \) and \( Q_{\text{brain}} \) initially increased at \( \text{pH} \sim 7.25 \), although the relative increase in \( Q_{\text{car}} \) (40%) was only one-third that of \( Q_{\text{brain}} \) (130%). The smaller degree of increase in \( Q_{\text{car}} \) in response to sustained hypoxemia may be the result of vasoconstriction of the extracerebral vasculature in response to hypoxemia, which would decrease extracerebral blood flow and limit the degree of increase in \( Q_{\text{car}} \), which is a measure of both cerebral and extracerebral blood flow, as demonstrated with our results under control normoxic conditions.

Under normal conditions, blood supply to the brain in both the ovine and human fetus is predominantly provided by the carotid arteries (4). However, in the ovine species the internal carotid artery is virtually absent. The internal maxillary artery, which is just proximal to the external carotid artery in relation to the brain, is the primary source of blood flow into the circle of Willis via the carotid rete, whereas the vertebral-spinal-basilar vascular system does not contribute to \( Q_{\text{brain}} \) under normoxic conditions (4). Therefore, if the same arterial pathway would persist during hypoxemia, absolute \( Q_{\text{brain}} \) should be less than or, at the most, equal to \( Q_{\text{car}} \), even if extracerebral blood flow was reduced to near 0 ml/min. At \( \text{pH} \sim 7.25 \), \( Q_{\text{car}} \) was almost equal to \( Q_{\text{brain}} \), which would support this possibility. However, as the arterial pH fell at \( \sim 7.00 \), \( Q_{\text{brain}} \) became progressively higher than \( Q_{\text{car}} \). This observation indicated that an artery other than the external carotid artery had to be recruited to carry flow to the brain to sustain an increase in absolute \( Q_{\text{brain}} \) higher than that in \( Q_{\text{car}} \). A possible explanation is that collaterals between the vertebral and ventral spinal arteries may have been recruited. We observed the highest percentage increase in blood flow in the spinal cord (+265%) at \( \text{pH} \sim 6.90 \). These observations strongly support the concept that the vertebral-spinal-basilar arterial system markedly dilates and becomes an alternate and essential shunt in addition to the carotid arterial system to maintain \( Q_{\text{brain}} \) during progressive mixed metabolic and respiratory acidosis. In addition, Williams et al. (27) reported that the occipitovertebral anastomosis needed to be ligated to produce ischemic brain damage in the ovine fetus with inflatable occluder cuffs placed around both carotid arteries.

It was of interest that the changes in external carotid artery RI were not directly related to changes in calculated \( \text{R}_{\text{car}} \). The fall in external carotid artery RI \( \sim 160 \) was sustained to \( \sim 6.90 \) without any change in \( \text{R}_{\text{car}} \) and at a time \( Q_{\text{car}} \) had returned to control values. The large increase (110%) in external carotid vascular impedance could explain almost entirely the changes observed in flow waveforms because vascular resistance and pressure PI remained relatively unchanged. Impedance to pulsatile flow depends primarily on the attributes of the artery, including its radius, wall thickness, and wall stiffness. Impedance is only affected by the attributes of the microcirculation to the extent that they modify the wave reflections of the pressure and flow pulse waves (16). In the adult rabbit, short-term (20 min) acute hypoxia causes relaxation in the basilar and internal carotid arteries and vasoconstriction in the common carotid artery (17, 18). Isolated
endothelium-denuded cerebral arteries of near-term fetal lambs respond to short-term (15 min) hypoxia with relaxation much more pronounced (45–65%) and faster in the middle cerebral and basilar arteries than in the common carotid artery (10–18%) (9). It is not known whether the response of the intact cerebral circulation to severe hypoxemia would be different from that of endothelium-denuded isolated vessels. However, high-altitude hypoxemia in fetal sheep is associated with a depression of both vascular smooth muscle and endothelium-dependent vasodilation of the cerebral arteries (13). Pearce et al. (17) also reported in isolated endothelium-intact rabbit arteries that hypoxia promotes the simultaneous release of both endothelium-derived contracting factor (EDCF) and endothelium-derived relaxing factor (EDRF). The ratio of EDCF to EDRF released during hypoxia was highest in the common carotid and lowest in the basilar arteries, suggesting that simultaneous vasoconstriction of the carotid vessels and vasodilation of the basilar arteries could occur in vivo in response to severe hypoxia.

Using a computerized electrical analog model of the umbilical-placental circulation based on in vivo hemodynamic measurements in fetal sheep, Surat and Adamson (23) demonstrated that a decrease in vessel radius of only 20% in response to vasoconstrictors would decrease the umbilical artery RI by ~50%. Large changes in wall thickness or elastic modulus (wall stiffness), both artery attributes that, in addition to vessel radius, could affect vascular impedance, had minimal impact on the shape of the flow waveforms. We observed an ~35% decrease in external carotid R_I160 at pH ~7.00. With the assumption that the external carotid artery flow waveform shape would respond in a fashion similar to that of the umbilical artery waveform to a change in radius, a decrease of only 15% in external carotid artery radius due to vasoconstriction would be sufficient to explain a 35% decrease in R_I160 (23) in the absence of change in calculated R_car as observed in the current study at pH ~6.90.

Although we speculate that the changes in the external carotid artery flow waveform shape might be due to changes in vessel radius, we cannot exclude the possibility that the attributes of the cerebral microcirculation under severe hypoxic conditions may have changed to the extent that they modified the wave reflections of the pressure and flow pulse waves in a fashion similar to that of the umbilical microcirculation (2). It is currently unknown whether the cerebral microvasculature is a major contributor to the external carotid artery flow waveform shape under hypoxic conditions. However, our data suggest that, under severe hypoxic conditions with a 3.6-fold increase in placental vascular resistance, a large proportion (50–60%) of the increase in Q_brain could be derived from the vertebral–spinal–basilar arterial system and may not contribute to the changes we observed in carotid artery flow waveform shape.

It has long been recognized that, during pregnancies complicated with placental insufficiency and abnormal umbilical artery Doppler flow velocity waveforms, there is usually a decrease in Doppler-derived cerebral artery RI or PI (3, 15, 26, 28–30) due to an increase in end-diastolic flow velocity, similar to the current study. Attempts to correlate the changes in cerebral Doppler blood flow velocity waveforms with changes in the time-averaged velocity, an indirect measure of blood flow, have failed for the internal carotid and anterior cerebral arteries (15). Moreover, Vyas et al. (26) found no correlation between time-averaged velocity and Doppler-derived PI in the middle cerebral artery of the hypoxemic human fetus. However, the end-diastolic flow velocity was consistently increased in all cerebral vessels with an increase in umbilical artery Doppler-derived RI (26). Our results also clearly demonstrated that, during fetal placental embolization, it was mostly the end-diastolic carotid blood flow that was affected, with a terminal fall in peak-systolic carotid blood flow only at pH ~6.90 at the time cardiac output was reduced by more than 50%. These observations confirm that the possible influence of large vessel caliber on vascular impedance needs to be considered in future work on cerebral blood flow waveforms during hypoxia. Blood pressure pulsatility also needs to be considered but was not a factor in the current study.

In summary, in the current study, the external carotid artery flow waveform shape was altered without changing R_car or Q_car during sustained fetal placental embolization in the near-term fetal sheep. The mechanisms by which blood flow waveform shape in large cerebral arteries is altered during hypoxia or asphyxia remain to be further elucidated, in particular the large increase (110%) in fundamental impedance to pulsatile flow, which was the major determinant affecting the carotid artery blood flow waveform shape. We speculate that under conditions of exaggerated demand, alternate sources of blood flow such as the basilar arterial system may contribute to the maintenance of cerebral perfusion in the near-term fetal sheep.

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