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

ROBERT GAGNON, TASHA LAMB, AND BRYAN RICHARDSON
Department of Obstetrics and Gynaecology and Department of Physiology, Medical Research Council Group in Fetal and Neonatal Health and Development, The Lawson Research Institute, The University of Western Ontario, London, Ontario, Canada N6A 4V2

Gagnon, Robert, Tasha Lamb, and Bryan Richardson. Cerebral circulatory responses of near-term ovine fetuses during sustained fetal 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 artery 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 hypoxic (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.

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 must 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. Transient 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 base of the skull and the transonic probe was used to collect carotid blood flow data.
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 (Q_{car}). 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. Fetal femoral arterial blood flow was measured using 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 flow signals were digitized at a 250-Hz sampling rate using a computerized data acquisition program (CADA; Hartronix, Concord, Ontario, Canada).

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 in duplicate with an OSM-3 hemoximeter device (Radiometer). Fetal arterial oxygen content (CaO2; mmol/l) was then calculated with a capacity of 1.34 ml of oxygen per gram of hemoglobin. Whole blood lactate dehydrogenase (LDH; 10,000 U/l) and glucose-6-phosphate dehydrogenase (G6PDH; 2300 STAT+, Yellow Springs Instruments, Yellow Springs, OH).

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 46Sc) 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 (Compugamma 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脑). The reference blood samples and all regional brain samples contained >400 microspheres.

Data analysis. During acute embolization, the mean fetal brachiocephalic and aorta blood pressure, mean central venous pressure, amniotic pressure, mean Q脑 (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 radioactive 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脑) was calculated as the ratio between cerebral perfusion pressure and mean Q脑 as measured by the transit-time flow probe (in mmHg·ml⁻¹·min⁻¹). The cerebral vascular resistance (R脑) was calculated as the ratio between cerebral perfusion pressure and mean Q脑, respectively, by ANOVA. As a result, the calculated cerebral vascular resistance (R脑) remained unaltered throughout the study. Mean FHR decreased significantly at pH 7.25, followed by a progressive return to control values as the fetal arterial pH fell below 7.00 (effects of time: P < 0.01 and P < 0.05, respectively, by ANOVA). As a result, the calculated brachiocephalic pressure PI  remained unaltered throughout the study. Mean FHR decreased significantly at pH 7.25, followed by a progressive return to control values as the fetal arterial pH fell below 7.00 (effect of time: P < 0.01 by ANOVA).

RESULTS

Fetal cardiovascular and brachiocephalic arterial blood measurements. The fetal arterial blood gases and cardiovascular measurements from the control period and pH values of ~7.25, ~7.00, and ~6.90 are shown in Table 1. The mean number of hours of embolization required to reach the predetermined fetal arterial pH of 7.25, 7.00, and 6.90 were 2.0 ± 0.2, 4.6 ± 0.2, and 5.6 ± 0.2 h, respectively. During embolization, fetuses became progressively hypoxemic and developed a mixed respiratory and metabolic acidosis (effect of time: P < 0.0001 for PO₂, PCO₂, CaO₂, pH, lactate, and base excess by ANOVA). Both mean brachiocephalic arterial blood pressure and arterial pulse pressure increased significantly at pH ~7.25, followed by a progressive return to control values as the fetal arterial pH fell below 7.00 (effects of time: P < 0.01 and P < 0.05, respectively, by ANOVA). As a result, the calculated brachiocephalic pressure PI remained unaltered throughout the study. Mean FHR decreased significantly at pH ~7.25, followed by a progressive return to control values as the fetal arterial pH fell below 7.00 (effect of time: P < 0.01 by ANOVA).

Fetal external carotid artery hemodynamic measurements. Figure 1 illustrates a typical example of the changes in the external carotid artery flow-derived waveforms and the umbilical artery Doppler-derived flow velocity waveforms during embolization. In Fig. 2, microsphere-determined absolute Q脑, was expressed in milliliters per minute and represented as unilateral cerebral blood flow for comparison with Q脑. Before embolization, mean Q脑 was 59 ± 6 ml/min, which was significantly higher (P < 0.01) than the mean Q脑 of 38 ± 4 ml/min, indicating that at least 35% of the measured cerebral blood flow was extracerebral. In response to embolization, there was a 130% increase in Q脑 at pH ~7.25 compared with only a 40% increase in Q脑. During

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>0.6 ± 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>6.69 ± 0.01*</td>
</tr>
<tr>
<td>Pulse excess, mmol/l</td>
<td>2.9 ± 0.2</td>
<td>4.3 ± 0.5*</td>
<td>4.6 ± 0.4*</td>
<td>-22 ± 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 ± 1.1*</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⁻¹</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⁻¹</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>RI₁₆₀</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. RI₁₆₀, 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 RI₁₆₀, then the changes in the external carotid artery RI₁₆₀ 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 RI₁₆₀ 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 RI₁₆₀ 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 RI₁₆₀ decreased by 32% at the time R_car remained unchanged. This fall in the external carotid artery RI₁₆₀ 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...

![Embolization](image-url)
associated with a fall in fetal arterial blood pressure. In the current study, the expected increase in Q˙brain was well maintained until at least pH ~6.90. During fetal placental embolization, there was a progressive deterioration in transplacental gas exchange as demonstrated by a progressive increase in fetal arterial PCO₂. It is therefore likely that the combined vasodilatory effects of both fetal hypoxemia and hypercapnia resulted in the sustained increase in Q˙brain observed in the current study.

Under normoxemic conditions, our observed mean Q˙car of ~58 ml/min was similar to a previous observation by Richardson et al. (20) of ~59 ml/min obtained at similar gestational age and with the use of a similar recording technique. The finding that Q˙car is relatively higher than Q˙brain is also in agreement with previous reports (10, 25) and can be accounted for by extracerebral blood flow. During sustained hypoxemia, both Q˙car and Q˙brain initially increased at pH ~7.25, although the relative increase in Q˙car (40%) was only one-third that of Q˙brain (130%). The smaller degree of increase in Q˙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˙car, which is a measure of both cerebral and extracerebral blood flow, as demonstrated with our results under control normoxemic 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˙brain under normoxemic conditions (4). Therefore, if the same arterial pathway would persist during hypoxemia, absolute Q˙brain should be less than or, at the most, equal to Q˙car, even if extracerebral blood flow was reduced to near 0 ml/min. At pH ~7.25, Q˙car was almost equal to Q˙brain, which would support this possibility. However, as the arterial pH fell at ~7.00, Q˙brain became progressively higher than Q˙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˙brain higher than that in Q˙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 pH ~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˙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 Rcar. The fall in external carotid artery RI160 was sustained to pH ~6.90 without any change in Rcar and at a time Q˙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 hemo-dynamic measurements in fetal sheep, Surat and Adam son (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 RI in fetal sheep. 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 RI in fetal sheep (23) in the absence of change in calculated R_car as observed in the current study at pH ~7.00.

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 hypoxic 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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