Dopamine does not limit fetal cerebrovascular responses to hypoxia

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Mayock DE, Bennett R, Robinson RD, Gleason CA. Dopamine does not limit fetal cerebrovascular responses to hypoxia. J Appl Physiol 102: 130–134, 2007; doi:10.1152/japplphysiol.00399.2006.—Dopamine is used clinically to stabilize mean arterial blood pressure (MAP) in sick infants. One goal of this therapeutic intervention is to maintain adequate cerebral blood flow (CBF) and perfusion pressure. High-dose intravenous dopamine has been previously demonstrated to increase cerebrovascular resistance (CVR) in near-term fetal sheep. We hypothesized that this vascular response might limit cerebral vasodilation during acute isocapnic hypoxia. We studied nine near-term chronically catheterized unanesthetized fetal sheep. Using radio-labeled microspheres to measure fetal CBF, we calculated CVR at baseline, during fetal hypoxia, and then with the addition of an intravenous dopamine infusion at 2.5, 7.5, and 25 μg·kg⁻¹·min⁻¹ while hypoxia continued. During acute isocapnic hypoxia, CBF increased 73.0 ± 14.1% and CVR decreased 38.9 ± 4.9% from baseline. Dopamine infusion at 2.5 and 7.5 μg·kg⁻¹·min⁻¹, begun during hypoxia, did not alter CVR or MAP, but MAP increased when dopamine infusion was increased to 25 μg·kg⁻¹·min⁻¹. Dopamine did not alter CBF or affect the CBF response to hypoxia at any dose. However, CVR increased at a dopamine infusion rate of 25 μg·kg⁻¹·min⁻¹. This increase in CVR at the highest dopamine infusion rate is likely an autoregulatory response to the increase in MAP, similar to our previous findings. Therefore, in chronically catheterized unanesthetized near-term fetal sheep, dopamine does not alter the expected cerebrovascular responses to hypoxia.

HYPOTENSIVE NEWBORNS are often treated with intravenous vasopressor medications, most commonly dopamine. Maintenance of an adequate blood pressure is thought to be important since hypotension has been implicated as a risk factor for ischemic and hemorrhagic brain injuries. (1, 18, 19). One therapeutic goal of pressor therapy is the maintenance of, or improvement in, cerebral blood flow (CBF) and oxygen delivery. However, limited data are available to suggest that this therapeutic goal is achieved, and some investigators have raised concerns that this practice may be harmful to human infants (28). In newborn lambs, Feltes et al. (5) demonstrated that while dopamine increased mean systemic arterial pressure at infusion rates over 5 μg·kg⁻¹·min⁻¹, CBF did not increase until infusion rates greatly exceeded usual clinical use. Seri and colleagues demonstrated that low- to medium-dose dopamine infusions in sick preterm infants did not alter CBF velocity (26) although previous work by this group demonstrated increased cerebrospinal fluid dopamine levels during intravenous dopamine infusion (27).

Epiodes of hypoxemia occur during fetal distress and can also be clinically problematic in neonates having difficulties adapting to the extrauterine environment. Many of these infants will have hypotension necessitating volume expansion and treatment with vasopressor medications such as dopamine. During hypoxemia, CBF normally increases and cerebrovascular resistance (CVR) decreases. In near-term fetal, newborn, and adult sheep, this vasodilatory response is thought to occur in an effort to preserve cerebral oxygen delivery (15). These studies suggest that hypoxic cerebrovasodilation maintains oxygen delivery if the hypoxic stress is not overly severe (15). However, in the preterm fetal sheep, these compensatory mechanisms might not be sufficient to provide enough oxygen to maintain cerebral metabolism (6). In preterm and near-term fetal sheep, we previously demonstrated that high-dose dopamine infusion caused cerebral vasoconstriction that was likely an autoregulatory response to the increase in mean arterial pressure (8). This finding is in keeping with adult human studies where systemically administered catecholamines do not appear to affect CBF (4, 16, 20, 26, 30), partly because of the impermeability of the blood-brain barrier to catecholamines (29). However, some studies suggest that dopamine infusion may result in cerebral hyperemia in adult sheep (22) and in adult humans with severe head injuries (24). It is not known whether dopamine infusion might limit the cerebral vasodilatory response to hypoxia in the developing brain. We therefore undertook this study to determine the cerebral vascular and metabolic responses to acute isocapnic hypoxia in the near-term fetal sheep during dopamine infusion. We utilized this model to specifically address the interaction of hypoxia and dopamine while avoiding other complicating factors such as metabolic acidosis, hypotension, and infection.

MATERIAL AND METHODS

All experimental protocols were approved by the relevant institutions’ Animal Care and Use Committees (University of Washington and Johns Hopkins University). Mixed-breed fetal sheep were obtained from time-dated pregnancies. We studied nine fetuses at 132 ± 1 days gestation (full-term gestation is 150 days). Surgical preparation. For 24 h before fetal surgery, food was withheld from the ewe, but it was allowed free access to water. Fetal surgery was performed under sterile conditions. The ewe was premedicated with atropine (0.2 mg/kg im) and xylazine (0.1 mg/kg im), then anesthetized with inhaled isoflurane (0.5–3%). The trachea was intubated, and the ewe was mechanically ventilated. A 16-gauge venous catheter was placed percutaneously in a maternal jugular vein for fluid administration during surgery. After the abdominal skin was prepared, the uterus was exposed through a midline incision. The fetal head and limbs were exposed one at a time through small uterine
incisions for placement of catheters into the superior sagittal sinus, the brachiocephalic trunk (via axillary arteries), the brachial/axillary vein, and the inferior vena cava (IVC) via pedal veins. A catheter (Tygon tubing) was sewn to a fetal hoof to measure amniotic fluid pressure. The fetal weight was estimated by visual inspection (8, 17). Vascular catheters were prefilled with heparinized saline (10 units/ml). All incisions were sutured closed. The catheters were exteriorized to the ewe’s flank and secured there in a pouch. The ewe received bicillin (1,200,000 units im) on completion of surgery. Ampicillin (500 mg) was administered into the amniotic fluid via the amniotic fluid catheter, and the estimated volume of lost amniotic fluid was replaced with warmed saline. Fetuses were studied 24–48 h after surgery (11). Maternal analgesia was maintained with buprenorphine, a medication with very limited placental transfer (0.005 mg/kg im every 12 h), as needed (23).

Physiological measurements. Fetal arterial blood pressure, heart rate, amniotic fluid pressure, and superior sagittal sinus pressure (SSP) were continuously monitored. Arterial and sagittal sinus pressures were referenced to amniotic pressure, and 1-min averages were compared during the different time periods. We utilized SSP as an estimate of intracranial pressure (ICP). Cerebral perfusion pressure (CPP) was calculated as the difference between MAP and SSP. Fetal CBF was determined using the radiolabeled microsphere technique (13). Approximately 1,000,000 (0.4 ml) microspheres labeled with $^{57}$Co, $^{51}$Cr, $^{153}$Gd, $^{103}$Ru, $^{95}$Nb, $^{113}$Sn, or $^{46}$Sc (DuPont NEN, Boston, MA) were injected into the fetal IVC. Reference samples were withdrawn from a brachiocephalic artery (1.5 ml/min) beginning 30 s before the microsphere injection and continuing for 1 min after the injection was completed. After the study protocols were completed, the ewe and fetus were killed with an overdose of pentobarbital injection was completed. After the study protocols were completed, the ewe and fetus were killed with an overdose of pentobarbital and the brain was removed for blood flow determination. All supratentorial brain tissue was counted to determine CBF. Blood flow to the cerebellum and brain stem was also determined. Radioactivity in tissue and blood samples was determined using a multichannel gamma counter (Minaxi gamma counting system, model 5550, Packard, Downers Grove, IL). Each sample was corrected for decay time, background counts, and spillover by use of a matrix inversion method (25).

Blood samples for pH, blood gases, hemoglobin concentration, and oxygen saturation were drawn anaerobically into heparinized Natelson glass pipettes. Blood gases and pH were measured at ewe core body temperature using a Radiometer ABL 5 (Radiometer, Copenhagen, Denmark). Oxygen saturation and hemoglobin concentration were measured using a Radiometer OSM-3 Hemoximeter (Radiometer).

Acute fetal hypoxemia was induced by having the ewe breathe lowered inspired oxygen concentration from a plastic bag placed around its head. Carbon dioxide gas was blended into this hypoxic gas mixture to maintain stable fetal arterial PCO$_2$ levels. Stable fetal hypoxemia and eucapnia were maintained by adjusting the inspired oxygen and carbon dioxide concentration administered to the ewe as dictated by results of frequent fetal arterial sampling.

Dopamine infusion doses were calculated on the basis of fetal weight at the time of surgery. Actual weights determined at necropsy were then used to determine actual infusion doses administered. Dopamine infusion concentration was calculated to give a similar volume of infusion at each concentration as previously described (8). Each level of dopamine infusion was continued for 10 min to ensure stable blood pressure responses and catecholamine levels.

Measurements. For each measurement, simultaneous blood samples were obtained from the brachiocephalic artery and superior sagittal sinus for determination of pH, blood gases, hemoglobin concentration, and oxygen saturation. After blood sampling and replacement, radiolabeled microspheres were injected into the fetal IVC while a reference blood sample was withdrawn from the brachiocephalic artery.

Protocol. After baseline measurements were obtained, severe fetal hypoxemia was induced. Acute fetal hypoxemia was defined as a 50% decrease from baseline in fetal arterial oxygen saturation. This has been previously shown to result in an approximate doubling of CBF in fetal sheep (6). After initiation of hypoxia, frequent fetal arterial blood samples were analyzed for hemoglobin oxygen saturation, and the oxygen concentration administered to the ewe was carefully adjusted to maintain the goal of 50% decrease in fetal arterial oxygen saturation from baseline. Once two fetal arterial samples separated by 2 min were at the desired saturation level, samples were obtained from fetal arterial and sagittal sinus venous for blood gas analysis and for blood flow calculations. CBF was then assessed with microspheres. Dopamine infusion was then started at 2.5 $\mu$g·kg$^{-1}$·min$^{-1}$ (estimated fetal weight), and repeat measurements were obtained after 10 min. Dopamine infusion was then increased to 7.5 $\mu$g·kg$^{-1}$·min$^{-1}$, and measurements were repeated after 10 min. Dopamine infusion was then increased to 25 $\mu$g·kg$^{-1}$·min$^{-1}$ with repeat measurements after 10 min (Fig. 1).

Data analysis/calculations. CBF was calculated as CBF = $\frac{\text{CPM}_{\text{brain}}}{\text{CPM}_{\text{ref}}} \times \text{CPM}_{\text{ref}}$, where $\text{CPM}_{\text{brain}}$ and $\text{CPM}_{\text{ref}}$ represent radioactivity (counts/min) in brain and reference samples, respectively. Cerebral O$_2$ consumption (CMRO$_2$) was calculated as CMRO$_2$ = ($C_aO_2 - C_vO_2$) × CBF, where $C_aO_2$ and $C_vO_2$ represent cerebral arterial and venous oxygen content, respectively. Cerebral oxygen delivery (OD) was calculated as OD = $C_aO_2$ × CBF, and cerebral oxygen extraction (E) was calculated as E = CMRO$_2$/OD. Cerebral vascular resistance (CVR) was calculated as $\text{CVR} = (\text{MAP} - \text{SSP})$/CBF.

Measurements were calculated, and data were reported as means ± SE for all study fetuses. Differences within the group were analyzed by one-way repeated-measures ANOVA. If the F test was significant, specific differences were sought with the Student-Newman-Keuls test. Significance was considered at $P < 0.05$.

RESULTS

Nine near-term fetal sheep (5 male) were studied. Predicted fetal weight by inspection at the time of fetal surgery was 3.7 ± 0.2 kg, and actual fetal weight determined at necropsy was 3.6 ± 0.3 kg.

Baseline measurements. Baseline measurement of blood gases, pH, heart rate, arterial blood pressure, hematocrit, hemoglobin, and CBF are presented in Table 1. These measures are similar to those previously published for fetal sheep at this gestation (8, 17).

Response to hypoxia. Fetal heart rate and MAP did not change during severe hypoxia (Table 1).

During hypoxia, fetal CBF increased by 73.0 ± 14.1% and CVR decreased by 38.9 ± 4.9% from baseline (Fig. 2, top and
and CMRO₂ did not change (Table 2).

Baseline physiological data and responses to hypoxia and added dopamine

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Hypoxia</th>
<th>Hypoxia + 2.5 DA</th>
<th>Hypoxia + 7.5 DA</th>
<th>Hypoxia + 25 DA</th>
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<td>Heart rate, beats/min</td>
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</table>

Values are means ± SE. Dopamine (DA) infusions were at 2.5, 7.5, and 25 μg·kg⁻¹·min⁻¹. MAP, mean arterial blood pressure; PaO₂ and PaCO₂, arterial PO₂ and PCO₂, respectively; SaO₂, arterial oxygen saturation; CaO₂, arterial oxygen content; Hb, hemoglobin concentration. *Significantly different (P < 0.05) from baseline value.

middle, respectively). Despite the severity of hypoxia, the increase in CBF was adequate to maintain cerebral oxygen delivery (Fig. 2, bottom). Cerebral oxygen delivery and extraction and CMRO₂ did not change (Table 2). Blood flow changes to the cerebellum and brain stem were similar to CBF (Fig. 3).

Response to dopamine during hypoxia. Dopamine infusion at 2.5 and 7.5 μg·kg⁻¹·min⁻¹ during hypoxia did not result in changes in heart rate or MAP (Table 1). Both heart rate and MAP increased at dopamine infusion of 25 μg·kg⁻¹·min⁻¹ (Table 1).

During hypoxia, no change in CVR was noted at dopamine infusion at 2.5 and 7.5 μg·kg⁻¹·min⁻¹ (Fig. 2, middle). Dopamine had no effect on CBF during hypoxia at any dose studied (Fig. 2, top). Blood flow to the cerebellum and brain stem mirrored that of the cerebral hemispheres during combined hypoxia and dopamine infusion (Fig. 3). However, CVR increased at a dopamine infusion rate of 25 μg·kg⁻¹·min⁻¹ (Fig. 2, middle) while cerebral oxygen delivery and extraction and CMRO₂ did not change (Table 2).

DISCUSSION

The results of this study demonstrate that dopamine infusion does not attenuate the cerebral vasodilatory blood flow response to acute isocapnic hypoxia in near-term fetal sheep. Additionally, cerebral autoregulation during hypoxia appears to be preserved.

The cerebrovascular and metabolic responses to dopamine that we observed were not unexpected. Previous studies in fetal sheep in our laboratory demonstrated similar changes in CVR during dopamine infusion (8). However, we had anticipated that dopamine infusion might alter the cerebrovascular response to hypoxia. Systemic hypoxemia results in cerebrovascular dilatation and an increase in CBF presumably in an attempt to maintain cerebral oxygen delivery. This phenomenon has been described in most animal species (including humans) at developmental stages from fetus to adult (15). Hunter and colleagues (14), utilizing a direct tissue analytic method based on heat production, found that moderate hypoxia in fetal sheep resulted in regional tissue hypometabolism and question whether previous studies provide an adequate assessment of the cerebral metabolic changes induced by hypoxia. These results suggest that determination of global cerebral oxygen consumption by measurement of the arteriovenous oxygen content change per change in CBF may not be adequate to assess the brain’s full response.
It has been postulated that hypoxic cerebral vasodilatation is mediated by adenosine, both in adult (21) and fetal brain (2, 9, 14), in direct proportion to the severity of hypoxia. However, not all investigators have demonstrated such an effect (10). Adenosine also appears to have a direct suppressive effect of cerebral metabolism (2). The increase in CBF noted in our study maintained cerebral oxygen delivery as assessed by the arteriovenous oxygen content change per change in CBF and is similar to previously published data in near-term fetal sheep (15). More importantly, the cerebrovascular response to hypoxia was not altered by dopamine, even at doses high enough to cause systemic hypertension. At a dopamine infusion rate of 25 μg·kg⁻¹·min⁻¹, the increase in CVR was likely an autoregulatory response to the increase in systemic arterial pressure and not a direct vasoconstrictive action of dopamine on cerebral vessels although we did not directly assess the latter (8).

In human studies, systemically administered catecholamines do not affect CBF (4, 16, 20, 26, 30), partly because of the impermeability of the blood-brain barrier to catecholamines (29). Seri et al. (26) and Zhang et al. (30) both found no change in CBF during dopamine infusion in preterm human infants. In contrast, however, Seri and colleagues (27) demonstrated that low-dose dopamine infusion in preterm human infants resulted in an increase in cerebrospinal fluid catecholamine levels. This study did not present data regarding the effect of dopamine infusion on blood pressure and blood flow to organs although infants evaluated were similar gestationally to those in a subsequent publication (26). Fetal sheep appear to have a robust blood-brain barrier by 0.6 of gestation (93 days), and dopamine-induced arterial hypertension does not affect tracer amino acid permeability across the barrier (12). No direct study of dopamine infusion during hypoxia has been completed previously.

On the basis of the results of our study and other investigations noted above, it appears that dopamine has no direct cerebral vasoconstrictive effect in fetal sheep. Moreover, the fetuses in this study are otherwise stable with an intact placental circulation, are isocapnic, have stable hemoglobin levels,

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<td>E</td>
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Fig. 3. Changes in blood flow to the cerebellum (top) and brain stem (bottom) during hypoxia and dopamine infusion. *Significant difference (P < 0.05) from baseline measurements.
and appear to demonstrate intact cerebral autoregulatory activity. Indeed, the degree of hypoxia used in this study was not severe enough to overwhelm compensatory mechanisms.

In summary, our study results demonstrate that in stable, near-term fetal sheep, intravenous dopamine infusion does not limit the cerebral vasodilatory and metabolic responses to severe hypoxia. These results are consistent with data derived in studies of human infants in which no direct effect of dopamine on the cerebral vasculature was noted (11, 20). However, extreme caution is advised in extrapolating these results to sick, hypotensive infants (particularly those that are preterm), where loss of cerebral autoregulatory function might lead to pressure-passive brain blood flow. The blood-brain barrier may be compromised in such infants, and, possibly, dopamine may then have direct cerebrovascular constrictive effects. Our study fetuses were healthy, unanesthetized, and likely had intact cerebral autoregulation. Second, they were essentially on cardiopulmonary bypass (via the placenta). Last, the near-term fetal sheep is neurologically a precocial animal, may therefore be less likely to have developed the cerebral vasodilatory and metabolic responses to hypoxia seen in studies of human infants in which no direct effect of dopamine on the cerebral vasculature was noted (11, 20).

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