Regional Cerebral Blood Flow: Studies in the Fetal Lamb during Hypoxia, Hypercapnia, Acidosis, and Hypotension

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ABSTRACT. In order to determine the relative roles of O₂ tension and content, CO₂ tension, hydrogen ion concentration, arterial blood pressure, and cardiac output in the regulation of fetal cerebral blood flow (CBF), we used radioactively labeled microspheres to measure flow to 20 major brain regions in 24 chronically catheterized fetal lambs. We continually monitored fetal heart rate and blood pressure, and periodically measured arterial PO₂, PCO₂, pH, and hematocrit. In addition to CBF measurements during control periods, we measured CBF during: 1) hypoxia (O₂ content < 6 ml·dl⁻¹; O₂ tension < 15 torr) induced by having the ewe breathe a gas mixture with low O₂ concentration, 2) hypercapnia (PCO₂ > 50 torr) induced by increasing the maternal inspired CO₂, 3) acidosis and alkalosis (7.60 > pH > 6.60) induced by infusing lactic acid or bicarbonate into the fetus, and 4) hypotension (blood pressure < 35 mm Hg) and hypertension (blood pressure > 55 mm Hg) induced by rapidly phlebotomizing or transfusing the fetus. We used multiple regression analysis and analysis of covariance to examine the dependence of total cerebral blood flow on arterial O₂ tension and content, CO₂ tension, pH, blood pressure, and cardiac output. The results demonstrated that 1) fetal CBF increased linearly as oxygen tension or content decreased and a hierarchy of responsivity occurred (brainstem > subcortex and cortex), 2) fetal CBF increased as carbon dioxide tension increased with a different hierarchy of responsivity (brainstem > subcortex > cortex), and 3) autoregulation of fetal CBF over a wide range of blood pressure or cardiac output was maintained for both total CBF and the various brain regions examined. (*Pediatr Res* 18:1309-1316, 1984)

Abbreviations

CBF, cerebral blood flow

During the past several years, numerous investigators have used the radioactive microsphere technique to measure newborn and fetal cerebral blood flow in different species (1, 19, 24, 25, 36, 40). In these studies, which have examined changes in flow as a function of changes in blood gas tensions, pH, and blood

pressure, it has frequently been difficult to separate clearly the effects of these variables because of their physiological interactions. A second problem is that of the significant variability associated with the microsphere method, so that a fairly large number of animals and blood flow determinations are required to distinguish physiological changes.

The purpose of this study was to examine the effects of each of several major variables on total cerebral flow as well as flow to 20 individual brain regions. These variables included arterial oxygen tension and content, carbon dioxide tension, hydrogen ion concentration, blood pressure, and cardiac output. We posed the following questions. 1) What is the chief determinant of fetal cerebral blood flow? 2) To what degree do other variables contribute to the regulation of cerebral flow? 3) What are the limits of autoregulation of fetal cerebral blood flow? 4) To what extent do changes in flow to various brain regions occur in response to changes in these major variables?

MATERIALS AND METHODS

Twenty-four ewes of 120 to 140 days gestation, and their fetuses which weighed 3.80 kg (±0.68SD), were chronically catheterized as previously described (1, 2).

Four to 6 days postoperatively, we carried out the experimental studies. During a control period, we recorded fetal and maternal blood pressures and heart rates and obtained anaerobic heparinized blood samples from the fetal ascending and descending aortae, superior and inferior vena cavae, and maternal artery. We measured the O₂ and CO₂ tensions and pH, using appropriate microelectrodes corrected to the appropriate temperature [39.5° C for the fetus (Radiometer BMS 3A; London Co., Westlake, OH)] and measured the hematocrit. We calculated O₂ content, using O₂ tension, hematocrit, and assumed fetal oxyhemoglobin dissociation curve corrected for pH and PCO₂.

To determine blood flows to the fetal brain and other organs we used microspheres 15 ± 1 μm in diameter labeled with ⁴⁶Sc, ⁵¹Cr, ⁹⁵Nb, ¹⁰³Ru, ¹¹³Sn, or ¹⁵³Gd (New England Nuclear Co., Boston, MA). Approximately 1 million spheres were suspended in a solution of 10% dextran and 0.05% polyoxyethylene sorbitan monooleate (Tween 80) to minimize aggregation and provide for even distribution. Over a 15-s period, we injected two-thirds of the microspheres into the inferior and one-third into the superior vena cava. During the period of injection and for 90 s thereafter, we withdrew reference blood samples at the rate of 4.8 ml·min⁻¹ simultaneously from the ascending and descending aortae, using an infusion withdrawal pump (Model 972; Harvard Apparatus Co. Inc., Millis, MA).

In each fetus, we measured blood flow during a control period and during one to four experimental conditions. The duration of these interventions varied between 10 and 60 min, until a new

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steady state was reached, before the blood flow determinations were made. Arterial blood gas determinations performed both before and after microsphere injections were not statistically different. The conditions studied included 1) hypoxia induced by reducing the ewe's inspired oxygen from room air to 8–10% O₂ (with 5% CO₂ and balance N₂), 2) hypercapnia induced by increasing the maternal inspired CO₂ concentration to 10–15%, 3) acidosis or alkalosis induced by infusing either lactic acid or sodium bicarbonate (1 mEq·ml⁻¹ at a rate from 0.375 to 1.5 mEq·min⁻¹), and 4) hypotension or hypertension induced by rapidly bleeding or transfusing the fetus with 25 to 60 ml·kg⁻¹ blood.

Following a specific intervention and determination of cerebral blood flow, we altered either the inspired gas concentrations, lactic acid or bicarbonate infusion rate, or the vascular volume to further alter that specific variable until a new steady state was reached, and at that time we repeated the flow determinations. In about one-third of the measurements, two stresses were applied simultaneously. When PCO₂ or pH was not varied experimentally, we changed inspired gas concentrations or infused a sodium bicarbonate solution to prevent variations.

At the conclusion of the study, the ewe and fetus were sacrificed with 30 ml of T-61 euthanasia solution (Hoechst, Somerville, NJ). The fetus was removed, towel dried, and weighed. The major fetal organs (heart, lungs, liver, gastrointestinal tract, kidneys, adrenals, and spleen) as well as the carcass, skin, placental cotyledons, and amniotic membranes were removed, weighed, ashed, and reweighed. We dissected the fetal brain, which weighed 51.0 ± 5.3 g, into 20 discrete regions, including the following: cortical structures (the gray and deep white matter of the frontal, parietal, temporal, and occipital lobes); subcortical structures (thalamus, hypothalamus, caudate nucleus, and hippocampus); brainstem structures (midbrain, pons, and medulla); cerebellum; spinal cord; and the combined watershed areas between the anterior-middle and middle-posterior cerebral arteries. These samples as well as the remaining brain tissue were weighed separately and placed into plastic covered vials. All samples were counted for radioactivity (Auto-Gamma scintillation spectrometer, Model 5912; Packard Instrument Co. Inc., Downers Grove, IL). Specimens from the brain weighed 2 to 10 g and contained 500 to 10,000 microspheres/g. Using a digital computer, we calculated the quantity of microspheres per organ and then converted the counts to absolute blood flows expressed either as ml·min⁻¹·100 g organ weight⁻¹ or as ml·min⁻¹·kg of fetus⁻¹.

We computed the mean and standard deviation of each variable under control conditions. Multiple analysis of covariance was used to compute the regression of total or regional cerebral flow on arterial oxygen tension and content, PCO₂, pH, blood pressure, and cardiac output. This method allowed the elimination of variability among animals and the comparison of slopes among brain regions using an extension of Duncan's multiple range test. Logarithmic and reciprocal transformations of the independent variables were examined for possible improvement of fit.

In order to depict graphically the dependence of total or regional cerebral flow on a single independent variable, each flow value was adjusted for differences of the other independent variables from their mean control values, using the coefficients obtained by the analysis of covariance. Each value was also adjusted for the difference of that animal's mean flow (when adjusted for all independent variables) from the overall mean. This adjustment procedure resulted in data sets for which standard single-variable regression analysis would give the same coefficients as the original multivariate analysis of covariance.

RESULTS

Table 1 presents the mean control values and the ranges of experimental values obtained during the entire course of the study for fetal heart rate, arterial blood pressure, arterial PO₂,

Table 1. Control mean values and experimental ranges

	Control (± SD)	Experimental range
Heart rate (beats/min)	158 ± 15	54–250
Mean arterial pressure (mm Hg)	45.5 ± 5.3	11–88
Arterial PO ₂ (torr)	26.0 ± 5.4	10.8–58.5
O ₂ content (ml·dl ⁻¹)	8.7 ± 2.3	0.8–14.4
Arterial PCO ₂	51.0 ± 3.9	39.6–112.6
Arterial pH	7.343 ± 0.023	6.503–7.590
Hematocrit (%)	33.0 ± 5.8	21–52
Hemoglobin (g/100 ml)	10.6 ± 1.9	6.7–16.7
Cardiac output (ml/min/kg)	482 ± 109	29–719
Cerebral blood flow (ml/min/100 g)	170 ± 63	17–458
Cortex	149 ± 59	15–358
Gray	157 ± 66	17–350
Frontal	137 ± 88	15–481
Parietal	160 ± 72	17–387
Temporal	116 ± 67	19–337
Occipital	166 ± 76	16–488
Watershed	184 ± 81	20–503
MCA/ACA*	236 ± 125	19–767
MCA/PCA	149 ± 82	9–415
White	131 ± 52	11–391
Frontal	136 ± 62	8–417
Parietal	124 ± 50	8–301
Temporal	127 ± 63	17–415
Occipital	134 ± 70	6–428
Subcortex	181 ± 75	183–467
Hypothalamus	156 ± 72	20–498
Thalamus	215 ± 103	22–722
Caudate nucleus	211 ± 98	8–543
Hippocampus	130 ± 44	16–382
Cerebellum	199 ± 85	18–451
Brainstem	227 ± 85	34–712
Midbrain	232 ± 91	34–722
Pons	202 ± 82	24–677
Medulla	234 ± 89	32–712
Cervical cord	119 ± 36	22–432

* MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

PCO₂, pH, and O₂ content, hemoglobin and hematocrit, cardiac output, and total and regional cerebral blood flow. A multiple regression equation of the form $\bar{Q} = a + b_1 [O_2] + b_2 \ln PCO_2 + b_3/\bar{Q}_{co}$, where $\bar{Q}$ = flow to a given brain region, $\bar{Q}_{co}$ = cardiac output, and a , b_1 , b_2 and b_3 are coefficients, was found to fit the blood flow measurements with a high degree of significance. This fit could not be improved at the $p < 0.05$ level by adding additional terms involving PO₂, blood pressure, or pH, while elimination of any of the included terms resulted in a significant decrease in the significance of the regression. The analysis of covariance for total cerebral blood flow resulted in the following regression coefficients: $a = -230$ (ml·min⁻¹·100 g⁻¹); $b_1 = -10.0 \pm 2.8$ ([O₂] in ml·dl⁻¹); $b_2 = 128 \pm 34$ (PCO₂ in torr); $b_3 = -7900 \pm 1300$ ($\bar{Q}_{co}$ in ml·min⁻¹·kg⁻¹). The standard deviation about the regression was 44.2 ml·min⁻¹·100 g⁻¹; the significance of the regression was $p < 10^{-6}$. When the measurements were adjusted for interanimal variability, a multiple correlation coefficient of $r = 0.78$ was obtained.

Oxygen content and total and regional cerebral blood flow. When we varied fetal ascending aortic oxygen content between 0.8 and 14.4 ml·dl⁻¹, total cerebral blood flow (corrected for PCO₂ and cardiac output) decreased linearly as O₂ content increased (Fig. 1). The mean blood flows to the cortical, subcortical, and brainstem regions as a function of O₂ content were computed

Fig. 1. Relation of fetal total cerebral flow to ascending aortic O_2 content corrected to control values of PCO_2 , cardiac output, and for interanimal variability. The dashed lines represent the 95% confidence limits of the mean based on the adjusted data. $CBF (ml \cdot min^{-1} \cdot 100 g^{-1}) = 275 - 10.0 [O_2](ml \cdot dl^{-1})$.

by use of multiple analysis of covariance (Fig. 2). We noted a definite increase in flow in response to a decrease in O_2 content. The variation among the 20 brain regions of the response of blood flow to changes in O_2 content was statistically significant ($p < 0.05$). The average response of cortical ($-9.3 \pm 2.4 ml \cdot min^{-1} \cdot 100 g^{-1} \cdot ml [O_2]^{-1} \cdot dl$) and subcortical ($-12.1 \pm 3.4 ml \cdot min^{-1} \cdot 100 g^{-1} \cdot ml [O_2]^{-1} \cdot dl$) regions was not significantly different ($p > 0.05$), in contrast to the brainstem response ($-21.1 \pm 4.6 ml \cdot min^{-1} \cdot 100 g^{-1} \cdot ml [O_2]^{-1} \cdot dl$) which was significantly higher.

This is further summarized in Figure 3 showing the per cent change in flow/per cent change in O_2 content for 20 separate brain regions. These responses were normalized to the mean control flows so that any differences present would be attributable to a redistribution of flow from one region to another. There was no difference in per cent change in flow between the watershed regions of the anterior-middle and middle-posterior cerebral arteries and of either the cortical gray or the white matter flow. The mean response of the brainstem regions was about 40% greater than that of the cortical and subcortical regions, but this difference and the differences among the various subregions studied were not statistically significant.

Carbon dioxide tension, pH, and total regional cerebral flow. Cerebral blood flow increased as a function of CO_2 tension between 39.6 and 112.6 torr when corrected for O_2 content and cardiac output (Fig. 4). However, a diminishing response (*i.e.*, $ml \cdot min^{-1} \cdot 100 g^{-1} \cdot torr PCO_2^{-1}$) was noted between change in CBF at control PCO_2 of 51 torr ($\Delta CBF/\Delta PCO_2 = 2.51 \pm 0.67 ml \cdot min^{-1} \cdot 100 g^{-1} \cdot torr PCO_2^{-1}$) and CBF at higher PCO_2 values of 70 torr ($\Delta CBF/\Delta PCO_2 = 1.83 \pm 0.49 ml \cdot min^{-1} \cdot 100 g^{-1} \cdot torr PCO_2^{-1}$). When we varied arterial pH by lactic acid or sodium bicarbonate infusion, we observed no significant relation between total CBF and changes in arterial pH from 6.56 to 7.59 when corrected to control values of PCO_2 , cardiac output, and for interanimal variability. Using multiple analysis of covariance (Fig. 5), we observed a significantly ($p < 0.05$) increasing response of mean regional flows between the cortex ($1.89 \pm 0.58 ml \cdot min^{-1} \cdot 100 g \cdot torr PCO_2^{-1}$), subcortex ($3.73 \pm 0.82 ml \cdot min^{-1} \cdot 100 g \cdot torr PCO_2^{-1}$), and brainstem ($6.65 \pm 1.10 ml \cdot min^{-1} \cdot 100 g \cdot torr PCO_2^{-1}$) as the PCO_2 was elevated.

This is further summarized in Figure 6, showing the per cent change in flow/per cent change in CO_2 tension for 20 separate brain regions. These responses were normalized to the mean control flows as previously noted. In contrast to the findings for O_2 content, significant ($p < 0.05$) variability was seen among the CO_2 responses of the various brain regions. The average subcortical response was 62% greater than the average cortical response, while the response of the brainstem was 84% greater than that of the cortex. Of particular interest was the caudate nucleus, in which the CO_2 response was 66% less than the average for the subcortex.

Cardiac output, blood pressure, and total and regional cerebral blood flow. We varied mean arterial blood pressure from 11 to 88 mm Hg, and cardiac output from 29 to 719 $ml \cdot min^{-1} \cdot kg^{-1}$ (Table 1). Cerebral blood flow corrected for O_2 content and PCO_2 remained constant over a cardiac output range of 200 to 719 $ml \cdot min^{-1} \cdot kg^{-1}$ (Fig. 7) and over a mean arterial pressure range of 30 to 78 mm Hg. The multiple regression analysis was able to explain a larger proportion of the experimental variability of cerebral flow by including cardiac output than by including blood pressure. No further variability could be explained by adding a blood pressure term to the regression analysis. Figure 8 shows curves based on the multiple analysis of covariance computed for mean cortical, subcortical, and brainstem flows as a function of cardiac output. There did not appear to be any significant difference in the autoregulation of flow in these regions or in any of the 20 subregions studied.

DISCUSSION

It has been assumed that arterial CO_2 tension and, to a lesser extent, O_2 content primarily regulate cerebral blood flow in the fetus as in the adult. Although early studies in acutely anesthetized, exteriorized fetal lambs supported this concept (7, 32), subsequent studies in the chronically catheterized lamb not only failed to support these findings, but showed that O_2 content or tension was the major determinant and that fetal responsivity to

Fig. 2. Relation of fetal regional cerebral flow to ascending aortic O_2 content corrected to control values of PCO_2 , cardiac output, and for interanimal variability. $CBF (cortex) (ml \cdot min^{-1} \cdot 100 g^{-1}) = 229 - 9.3 [O_2](ml \cdot dl^{-1})$; $CBF (subcortex) (ml \cdot min^{-1} \cdot 100 g^{-1}) = 286 - 12.1 [O_2] (ml \cdot dl^{-1})$; $CBF (brainstem) (ml \cdot min^{-1} \cdot 100 g^{-1}) = 422 - 21.1 [O_2](ml \cdot dl^{-1})$.

Fig. 3. Per cent change in regional flow/per cent change in O_2 content for 20 brain regions. The error bars represent the standard deviation of the individual slopes.

Fig. 4. Relation of fetal total cerebral blood flow to ascending aortic CO_2 tension corrected to control values of O_2 content, cardiac output, and for interanimal variability. The dashed lines represent the 95% confidence limits based on the adjusted data. $CBF (ml \cdot min^{-1} \cdot 100 g^{-1}) = -333 + 128 \ln PCO_2 (torr)$.

Fig. 5. Relation of fetal regional cerebral blood flow to ascending aortic CO_2 tension corrected to control values of O_2 content, cardiac output, and for interanimal variability. $CBF (cortex) (ml \cdot min^{-1} \cdot 100 g^{-1}) = -229 + 96.2 \ln PCO_2 (torr)$; $CBF (subcortex) (ml \cdot min^{-1} \cdot 100 g^{-1}) = -566 + 190 \ln PCO_2 (torr)$; $CBF (brainstem) (ml \cdot min^{-1} \cdot 100 g^{-1}) = -1106 + 339 \ln PCO_2 (torr)$.

PCO_2 changes was less than in the newborn or adult animal (1, 18, 19, 33, 34, 40).

A major problem of such studies has been the difficulty of evaluating the effects of changes in isolated independent variables such as O_2 content, CO_2 tension, pH, or blood pressure, because of their interactive nature. For example, fetal hypoxia results in hypocapnia, acidosis, and hypertension, whereas hypercapnia results in an increase in arterial PO_2 , a decrease in O_2 content

(because of the shift to the right of the oxyhemoglobin dissociation curve), respiratory acidosis, and a rise in mean arterial blood pressure (24, 26).

Most fetal cerebral blood flow measurements have been of either the entire brain or several of its major regions. Investigation of smaller regions has been difficult, because techniques which use flow probes or xenon clearance fail to discriminate between

Fig. 6. Per cent change in regional flow/per cent change in CO_2 tension for 20 brain regions. The error bars represent the standard deviation of the individual slopes.

Fig. 7. Relation to fetal total cerebral flow to fetal cardiac output corrected to control values of O_2 content, CO_2 tension, and for interanimal variability. The dashed lines represent the 95% confidence limits of the means based on the adjusted data. $\text{CBF (ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}) = 186 - 7920 \cdot \dot{Q}_{\text{co}}^{-1}$ where $\dot{Q}_{\text{co}}$ is cardiac output in $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ body weight.

the various regions and autoradiographic studies allow only one determination per experiment. Radioactive microspheres allow four or five serial determinations but have considerable inherent variability, and require tissue samples of adequate mass to contain sufficient numbers of trapped spheres. To reduce errors below 10% requires a sample of tissue weighing 1–2 g with about 500 spheres. Thus, although flow measurements to areas such as the caudate nucleus and watershed regions are feasible, smaller structures such as the germinal matrix, or specific brainstem nuclei cannot be studied without using such large numbers of spheres as to potentially alter the microcirculation.

Fig. 8. Relation of fetal regional cerebral flow to fetal cardiac output corrected to control values of O_2 content, CO_2 tension, and for interanimal variability. $\text{CBF (cortex) (ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}) = 162 - 6320 \cdot \dot{Q}_{\text{co}}^{-1}$; $\text{CBF (subcortex) (ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}) = 197 - 7660 \cdot \dot{Q}_{\text{co}}^{-1}$; $\text{CBF (brainstem) (ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}) = 254 - 12,800 \cdot \dot{Q}_{\text{co}}^{-1}$.

Thus, because of both the conflicting results of previous investigations, as well as the above-noted limitations, we thought it appropriate to vary the four major variables: O_2 tension and content, CO_2 tension, pH, and blood pressure individually and in combinations, using statistical techniques to determine the relative importance of these regulators of both total and regional cerebral flow. As an aside, we should note that the multiple analysis of covariance used to characterize the dependence of flow on the various determinant variables is based on a linear model which assumes no interactions among these variables (*e.g.*, an arterial O_2 content change from 9.0 to 7.0 $\text{ml} \cdot \text{dl}^{-1}$ is assumed to produce the same change in blood flow whether arterial PCO_2 remains constant at 50 or at 70 torr). Although this assumption is not precisely true, because interactions generally contribute to an increase in residual variance about regression, the fact that the linear model was successful in accounting for enough of the experimental variability to be highly statistically significant

makes it likely that interactions are much less important than the overall relations found.

Oxygen content and total and regional cerebral blood flow. The finding that oxygen content is the major determinant of fetal cerebral flow is supported by several previous studies (2, 7, 17, 19, 32), although this is the first investigation in which a normalized dose-response curve could be determined from data, including wide ranges of PCO_2 , pH, blood pressure, and cardiac output (Fig. 1). In a similar preparation, Jones and coworkers (17) demonstrated a hyperbolic relationship between O_2 content and CBF. Our previous studies showed similar results, with an increase in total and regional flows of 80 to 120% as fetal O_2 content decreased from control values of 11 to 5 $\text{ml} \cdot \text{dl}^{-1}$ (1). In addition, cerebral flow remained elevated throughout 90 min of hypoxic stress, despite progressive acidosis and hypertension (1). Peeters and coworkers (31) showed that fetal cerebral flow was primarily related to changes in O_2 content rather than to tension. This was also observed in these studies (Fig. 1) in which total cerebral flow increased linearly as O_2 content decreased from 15 to 0.8 $\text{ml} \cdot \text{dl}^{-1}$. Jones *et al.* (16, 17) have also shown that cerebral oxygen delivery ($\text{CBF} \times \text{O}_2$ content) is 70% greater in the fetus than in the newborn lamb or adult sheep, despite similar cerebral oxygen consumption rates in these animals. This appears to be unrelated to the higher O_2 affinity of fetal hemoglobin than that of the newborn or adult or to the progressive increase of the cerebral microvasculature during perinatal brain growth.

We also examined changes in cerebral flow to several brain regions as oxygen content was varied (Fig. 2). Control flow values in these regions progressively increased from cortex to subcortex to brainstem (Table 1); however, as O_2 content decreased, the increase in flow was much greater to the brainstem than to the cortex and subcortex. The brain shows regional differences in cerebral O_2 consumption with the brainstem having the highest rate (11, 13, 22). This may explain the higher control flow values to this area, and the flow increase during hypoxia. Because mild and moderate hypoxia do not decrease O_2 consumption (13, 14, 40, 41), the brainstem should require higher levels of oxygen delivery and blood flow than the cortex and subcortex. However, we know of no studies of the regional differences in oxygen consumption during hypoxia in the fetus, newborn, or adult (11).

We also examined the normalized per cent change in flow/per cent change in O_2 content to 20 brain regions (Fig. 3). When perfusion pressure remained normal during hypoxia, we observed no difference in flow changes between the watershed regions of the anterior-middle and middle-posterior cerebral arteries. This probably resulted from the similarity of rates of brain tissue O_2 consumption and utilization in these areas, although data are not available for the fetal lamb. In monkeys, the O_2 consumption rates in the watershed area are similar to those rates in adjacent brain regions, although the rates differ between gray and white matter (40). We also observed no significant difference in change in flow/per cent change in O_2 content between gray and white matter, although control flow was higher in the gray than white matter. In fact, the mean increase of flow to white matter was proportionately greater than that to the gray matter (Fig. 3). This contrasts with results of previous studies which showed no increase in white matter flow during hypoxia, in either the exteriorized fetal lamb or in the newborn puppy (6, 30, 32). These latter findings have been used to support the neuropathological observation of periventricular leukomalacia in infants who have suffered asphyxial brain injury. However, it is unclear whether this insult is caused by the failure of flow to increase in the white matter, or to hypotension and disturbed autoregulation with subsequent decrease in flow.

The mean per cent increase in brainstem flow was greater than that in either the cortical or subcortical regions (Fig. 3). Proportionally greater flow appeared to occur in the medulla as contrasted with the pons or midbrain. Although not statistically significant, these results are qualitatively similar to those we previously reported (1, 2) and require confirmation. Such a flow

redistribution to medullary centers suggests that protective mechanisms exist to maintain appropriate neural control of vegetative autonomic functions.

Carbon dioxide tension, pH, and total and regional cerebral blood flow. As depicted in Figures 4 and 5, fetal CBF increased 2.5 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g} \cdot \text{torr} \text{PCO}_2^{-1}$ as CO_2 tension increased between 39.6 and 115 torr. This agrees with studies using ^{133}Xe in the exteriorized fetal lamb (flow increased 4.7 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g} \cdot \text{torr} \text{PCO}_2^{-1}$) and the microsphere technique in both the acutely anesthetized and chronically catheterized lamb (flow increased 1.7 and 3.53 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g} \cdot \text{torr} \text{PCO}_2^{-1}$), respectively (7, 34). In the present study, the response was diminished at higher PCO_2 values.

Response to PCO_2 changes appears less in both the fetus and newborn animal than in the adult. This has also been observed in the dog and monkey, but not in the human (23, 33, 40). In fetal, newborn, and adult sheep, Rosenberg *et al.* (34) showed total CBF increases of 3.53, 5.16, and 6.20 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \cdot \text{torr} \text{PCO}_2^{-1}$, respectively. The reason for the blunted fetal response is unknown but cannot be explained by changes in vascular conductance, relative hypotension, or differences in metabolic rate (34). Chronic hypercapnia can diminish the CBF CO_2 response (29), and perhaps the fetal response is inhibited by either its relatively higher PCO_2 or the associated decrease extracellular pH.

Regional blood flow increased incrementally from cortex to subcortex to brainstem as CO_2 tension increased (Fig. 5). The CO_2 responsivity in the caudate nucleus was much lower than that in other subcortical tissues. Neuropathological studies of the asphyxiated infant have shown damage to the basal ganglia (10), presumably associated with hypoxia (28) or kernicterus (37), but perhaps altered flow responsivity to changes in CO_2 tension might better explain the pathogenesis of these lesions.

Higher brainstem CO_2 responsivity could possibly be under neural control in order to maintain brain oxygenation, as suggested by recent studies in the newborn lamb (36). As compared to controls, survival, blood flow, and O_2 delivery to the brain and myocardium were greater in newborn lambs given 4.5% CO_2 when stressed by 50% blood volume depletion (36). Also, CO_2 responsivity could possibly be modulated and enhanced by opiate receptors in the brainstem, as the CO_2 sensitivity of fetal breathing movements is affected by opiate receptor blockade with naloxone (27). We observed no changes in CBF as arterial pH varied between 6.56 and 7.59 when corrected to control values of PCO_2 , cardiac output, and for interanimal variability. Similar findings have been observed in several other fetal studies, and would be expected since CBF appears to correlate with pH changes in cerebrospinal fluid rather than in arterial blood (3, 15, 19).

Cardiac output, blood pressure, and total and regional cerebral blood flow. Fetal cerebral autoregulation was present over a wide range of blood pressure and cardiac output (Fig. 7). In the adult brain, autoregulation is maintained between 70 and 150 mm Hg, but its relation to cardiac output has not been studied (3, 20). In the newborn puppy, autoregulation is maintained between 27 and 97 mm Hg, and in the newborn piglet between 40 to 150 mm Hg (12, 21). In newborn lambs subjected to 50% blood volume reduction, CBF was maintained at 77.5 to 79.6 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ as blood pressure decreased from 76 to 24 mm Hg (36). In fetal lambs, a 20% reduction in blood volume was accompanied with decreases in blood pressure of 21%, in cardiac output of 40%, and in CBF of 18% when corrected for the 4-torr increase in PCO_2 which occurred (39). In other studies, autoregulation was observed in normoxic fetal lambs as blood pressure ranged from 42 to 61 mm Hg (38). A 26% mean decrease in arterial blood pressure resulted in no significant change in total or regional brain blood flow (38).

In the present study, we varied arterial blood pressure from 11 to 88 mm Hg, and cardiac output from 29 to 719 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (Table 1). The mean cardiac output was 482 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$.

kg^{-1} , and autoregulation of flow was present between the range of 200 to $719 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (Fig. 7). This corresponded to a range in mean arterial blood pressure from 30 to 78 mm Hg. Cerebral blood flow was more clearly related to cardiac output than to blood pressure. This may be related to the relatively high cardiac output in the fetus, which is one of the most important adaptive mechanisms for maintaining O_2 delivery in the presence of relatively low arterial O_2 tension (35, 39). However, the fetal myocardium is functioning at the upper limits of the cardiac function curve, and during hypoxia cardiac output does not increase, but is redistributed (9, 27). During fetal volume depletion, cardiac output decreases substantially while blood pressure is maintained. For example, a 20% reduction in blood volume resulted in a 21% decrease in blood pressure, but a 40 to 45% decrease in cardiac output (33). In this same study, blood flow to the brain decreased 18%. However, the decrease in oxygen delivery associated with the fall in hematocrit due to blood volume reduction is associated with a compensatory 15–20% increase in cerebral flow. The actual decrease in cerebral flow would then not be 18%, but when corrected for the drop in hematocrit could approach 30 to 35%, a value much closer to the decrease in cardiac output.

With fetal hypotension due to acute hemorrhage, vascular volume was rapidly restored by shifts of interstitial and transplacental fluid to the vascular compartment, with only a mild reduction of blood pressure and hemodilution (4). To compensate for the decreased potential for brain O_2 delivery, cerebrovascular resistance must decrease with redistribution of blood flow, as cardiac output cannot increase sufficiently. However, with progressive hemorrhage, cerebrovascular resistance may not be able to decrease further. Thus, cerebral flow changes may reflect the cardiac output, despite the fact that blood pressure is maintained. This suggests that the relation between blood flow, vascular resistance, and perfusion pressure in the fetus may differ from that in the newborn and adult, and that maintenance of flow may be more closely related to cardiac output and cerebrovascular resistance than to perfusion pressure.

One must also consider that the higher correlation between cerebral flow and cardiac output, rather than blood pressure, was related to the fact that we did not measure actual cerebral perfusion pressure. However, in this entire series, venous pressure only varied between 3 and 8 mm Hg, and in other studies of fetal hemorrhage a mean decrease in venous pressure of 2 mm Hg was noted (4). It is unlikely that these venous pressure changes would significantly alter cerebral perfusion pressure to account for our results.

In the cortex, subcortex, brainstem, and other regions of the brain, autoregulation was maintained, while reflecting the basal difference in blood flows between these regions (Fig. 8; Table 1). This pattern was also noted in other brain subregions, including the watershed distribution between the anterior-middle and middle-posterior cerebral arteries, as well as several of the subcortical regions. This finding agrees with studies by Tweed *et al.* (38) in the normoxic fetus, and has been noted by other investigators in the adult rhesus monkey (5, 8) and newborn dog (12), and in earlier studies in the fetal lamb (32). In contrast, in the newborn piglet, during normoxic hypovolemic hypotension, blood flow was decreased in the cerebellum and cerebral hemispheres but preserved to the brainstem (21). We could not examine the interaction of hypoxia and autoregulation because of an inability to study sufficient animals in each of the different subgroups to determine whether hypoxia or hypercapnia affected autoregulatory control. In another study in the fetal lamb in which asphyxia was induced for 1 to 1.5 h by umbilical cord compression, autoregulation was lost during periods of hypotension, but not hypertension, but a dose-response curve could not be generated (25). In a more recent study autoregulation was impaired over a blood pressure range of 46–73 mm Hg in hypoxic fetuses having an oxygen saturation less than 57%. However, factors other than hypoxia may have been responsible for the loss of autoregulation.

Further studies are needed to examine changes in autoregulatory control of cerebral flow in the normoxic fetus which is then made hypoxic with several measurements of cerebral flow while PCO_2 and pH are maintained within their normal ranges.

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Splanchnic Uptake and Release of Energy Substrates in the Fasting Baboon Infant

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ABSTRACT. Estimates of splanchnic energy substrate exchange in the primate infant have been obtained using a baboon model. The splanchnic bed of the fasting baboon newborn released glucose at an estimated rate of $14.5 \pm 5.0 \mu\text{mol}/\text{min} \cdot \text{kg}$ body weight. Splanchnic glucose release in the fasting 5–7-wk old baboon infant proceeded similarly at an estimated rate of $15.5 \pm 4.5 \mu\text{mol}/\text{min} \cdot \text{kg}$ body weight. The principal precursors taken up by the splanchnic bed were lactate, glycerol, and alanine. Uptake of alanine correlated in a linear fashion with glucose release. Lactate was the most important precursor in both age groups. Glucose recycling through lactate is an active mechanism in the primate fetus as well as in the young of other species. (*Pediatr Res* 18:1316–1320, 1984)

Abbreviations

HV, estimated hepatic vein concentration

A, arterial concentration

V₁, inferior vena cava concentration below the hepatic veinV₂, inferior vena cava above the hepatic veinF_{LC}, inferior vena cava flow below the hepatic veinF_{SP}, splanchnic flow

Quantitative data concerning splanchnic energy metabolism are readily available in adult man (5, 9, 23, 25, 31). In contrast, information regarding splanchnic substrate exchange in the neonate and infant is derived entirely from studies in subprimate species (3, 11, 24, 29, 30), isolated fetal organ studies (1, 2, 10),

or inferential data derived from infusion studies, tolerance tests (6, 14), and stable isotope methodology (15). Previous investigations using the newly born baboon as a model for the study of neonatal energy metabolism suggest that this animal resembles the small-for-gestational-age human infant in terms of response to fasting and diminished body fat (19, 20). Fasting plasma arterial levels of energy substrates in the newborn of this species are similar to those found in the stressed small-for-gestational-age human neonate. Further, cerebral uptake of energy substrates is similar to that observed in human infants (19). Therefore, in the present study, we have utilized the infant baboon in order to derive estimations of comparative splanchnic energy substrate exchange in a clinically relevant model.

MATERIALS AND METHODS

Experimental animals and procedure. Baboon neonates obtained from the University of Illinois Primate Colony (Chicago IL) were the products of timed matings. Six were delivered by cesarean section at term after a 175–180-day gestation and studied at 6 to 8 h of life. Two of these animals were then maintained in infant incubators and fed commercial infant formula (Similac, Ross Laboratories) until studied again at 5 to 7 wk of life. Three other baboon neonates, products of spontaneous deliveries, were studied for the first time at 5 to 7 wk of life.

Under local xylocaine anesthesia, catheters (PV3, Biolabs) were placed in the aorta, the left ventricular outflow tract, and in the inferior vena cava above and below the level of the hepatic vein (Fig. 1). Catheters were kept patent with heparinized saline (1 unit heparin/ml). Animals were maintained under a radiant warmer during procedures and restrained, but not sedated. The stability of the animals was assessed by the stability of arterial pH, oxygen content, lactate, hematocrit, cardiac output, and organ blood flows. Newborns were fasted from birth; animals studied at 5 to 7 wk of life were similarly fasted for 6 to 8 hr.

Studies were carried out 2 to 4 hr following catheter placement. Six to eight sets of three 1-ml samples obtained from the aorta, the inferior vena cava above and below the hepatic vein were

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