Cerebral Vascular Response to Hemorrhagic Hypotension in Newborn Lambs: The Influence of Developing Anemia (43688)

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Abstract. **The ability of newborn animals to autoregulate cerebral blood flow (CBF) has been documented. Most studies of the cerebral vascular response to hypotension utilize hemorrhage, generally confounded with anemia. We studied the cerebral blood flow and metabolic response of chloralose and urethane anesthetized newborn lambs to regulated hypotension. Lambs (≤7 days old) were catheterized for radioactive microsphere determinations of CBF. The dorsal sagittal sinus was catheterized to obtain cerebral blood samples for the calculation of oxygen uptake. Cerebral perfusion pressure was reduced in a step-wise fashion with hemorrhagic hypotension. Animals spontaneously became anemic with hypotension (AH; $n = 8$). In a group of animals (NH; $n = 6$), anemia was prevented by infusion of autologous red blood cells. Arterial pressure was reduced from control to 50, 40, and 30 mm Hg. In the AH group hematocrit fell 37% but was not different from control in the NH group. Total CBF was maintained in all groups. The lowest perfusion pressures studied were 25 ± 1 and 22 ± 1 mm Hg in AH and NH groups respectively. Oxygen delivery decreased (37%) only in the AH group, secondary to anemia. Calculated oxygen consumption was maintained in the AH group but increased (≈50%) in the NH group at 50 and 40 mm Hg. The ratio of oxygen uptake to oxygen delivery (fractional oxygen extraction) increased linearly in both groups as arterial pressure decreased. The major findings of these experiments are (i) The anesthetized newborn lamb can maintain CBF when perfusion pressure falls to 25 mm Hg and this autoregulatory capacity (classically defined) is not dependent on a change in hematocrit and, presumably, viscosity; (ii) Cerebral hypotension, anemic or not, appears to be accompanied by an increase in fractional extraction of oxygen.** [P.S.E.B.M. 1994, Vol 205]

Autoregulation of cerebral blood flow (CBF) is an important homeostatic mechanism in assuring cerebral perfusion during hypotension (1–6). Newborn animals seem to be capable of maintaining CBF at perfusion pressures near 30 mm Hg (2, 6), whereas, CBF begins to fall at perfusion pressures below 50 mm Hg in some newborn animal studies (4) and in adult animals (7).

Many studies of CBF autoregulation in newborn models have used hemorrhagic hypotension (4, 8, 9) to alter cerebral perfusion pressure (CPP). In studies where hematocrit was reported, hemorrhage was accompanied by development of anemia (4, 8, 9). Anemia decreased blood oxygen content which alters CBF (12–14) independent of perfusion pressure. Hudak *et al.* (10, 11) have demonstrated that changes in hematocrit also can change cerebral vascular resistance independent of O_2 content. Either of these stimuli of anemia may support CBF by enhancing the reduction of cerebrovascular resistance (CVR) associated hypotension. We hypothesize that, if hematocrit is maintained during hemorrhagic hypotension, the lower

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limit of autoregulation will occur at a higher CPP than when hematocrit is allowed to fall. In anemic hypotension, O_2 delivery decreases (4, 8, 9). If the hypothesis stated above is correct, the O_2 delivery in the nonanemic animals will also fall but due to a decrease in CBF. We compared the cerebrovascular and metabolic response to hypotension in newborn lambs which became anemic (AH) with those of lambs in which anemia was prevented (NH) during hypotension.

Materials and Methods

Surgery. Newborn lambs ≤7 days old (2–6 kg) were anesthetized with α-chloralose (50 mg/kg) and urethane (500 mg/kg) iv, intubated and ventilated with a Harvard positive pressure respirator. End-expired CO_2 (Beckman LB2 CO_2 meter) and fractional inspired oxygen (F_{IO2}; Applied Electrochemistry) were monitored continuously. Respiratory rate, pressures and inspired O_2 were adjusted to maintain arterial $PaCO_2$ constant between 35 and 45 mm Hg and arterial oxygen saturation greater than 95%. A 5 French pigtail catheter (Cordis) was placed into the left ventricle via the left femoral artery. Placement was confirmed by observing characteristic left ventricular pressure tracing and at necropsy. Each brachial artery was cannulated with a PE 190 catheter to continuously measure blood pressure (Statham Db-23) and to obtain arterial blood samples. A 22G catheter was placed in the dorsal sagittal sinus, via a small midline burr hole in the parietal bone with the catheter tip approximately 1 cm proximal to the confluence of the sinuses, to obtain cerebral venous pressure and blood samples. Arterial and cerebral venous blood samples were analyzed for PO_2, PCO_2, pH (Radiometer ABL-3, Copenhagen), O_2 content (Lex-O_2-Con, Lexington Instruments), and hematocrit (Hct). A large (PE-240 to PE-320) catheter was placed into the abdominal aorta via the right femoral artery and was connected to the blood pressure control reservoir. After surgery animals were paralyzed (succinylcholine chloride 50 mg/kg) and heparinized (500 units/kg). Acidosis was prevented with administration of sodium bicarbonate (1 mEq/kg/hr iv). Supplemental doses of all agents were given as needed. Data were continuously recorded on a Gould (2800 series) recorder.

Brain Blood Flow, Oxygen Consumption, and Oxygen Delivery. Brain blood flow was measured using the radioactive microsphere technique (15). Microspheres (15 ± 2 μm) used were labeled with ^{141}Ce, ^{85}Sr, ^{46}Sc, (3M Co.) and ^{113}Sn (New England Nuclear Co.). Approximately 1–1.5 × 10^6 microspheres were sonicated, agitated and injected into the left ventricle for each measurement. Withdrawal of the arterial reference sample was begun just prior to injection and was continued for at least 2 min after injection. Approximately 1600 microspheres or more were collected in the reference sample to ensure accuracy (16).

At the conclusion of the experiment, the animal was euthanized with an overdose of anesthesia. The brain was removed and placed in buffered formalin for 3 days. The brain was then sectioned into rostral spinal cord, brain stem, diencephalon, hippocampus, caudate nucleus, cerebellum, and cerebrum. Gray matter was shaved from the forebrain cortex and counted separately. All tissues, reference blood and standards were counted in a Serle 1185 γ-counter. Backscatter from higher energy isotopes into windows of lower energy isotopes was subtracted with the method described by Heymann *et al.* (15). Blood flow was determined using the equation: $Q_{tis} = cpm_{tis} * Q_{ref} * 100/cpm_{ref}$ where Q_{tis} is the flow to a tissue in ml/min/100 g, cpm_{tis} is the corrected counts in the tissue divided by weight in grams, Q_{ref} is the arterial reference flow rate, and cpm_{ref} is counts in the arterial reference.

Cerebral oxygen uptake (ml O_2/min/100 g) was calculated by multiplying the arterio-venous oxygen content difference by blood flow to the cerebrum (12–14). Oxygen delivery (ml O_2/min/100 g) to all brain tissue was calculated by multiplying blood flow by arterial oxygen content. Fractional O_2 extraction is the arterio-venous O_2 content difference divided by the arterial O_2 content. Cerebral perfusion pressure (CPP) was calculated by subtracting mean sagittal sinus blood pressure from mean arterial blood pressure (MABP). Vascular resistances were derived by dividing CPP by blood flows.

Experimental Protocol. Mean arterial blood pressure was controlled with a large reservoir (4 liter) connected to the large femoral artery catheter (17). The desired pressure was set in the reservoir and MABP equilibrated with it. After surgery was complete, the animals were allowed to stabilize for approximately 30 min. Control measurements of all parameters were taken. MABP was then reduced to 50, 40, and 30 mm Hg. All measurements were repeated only after on-line measured physiologic parameters had stabilized for at least 5 min. Eight animals spontaneously became anemic with hypotension (AH). In six lambs (NH) the drop in hematocrit was minimized by taking blood from the reservoir during each pressure reduction, centrifuging it, and reinfusing autologous packed red blood cells.

Data Analysis. To illustrate the influence of anemia on CBF in the absence of CPP changes, a theoretical flow was calculated. This theoretical flow is generated by an adjustment of each control flow in the AH group to account for subsequent changes in hematocrit only. Thus, at each subsequent measurement, we could compare the theoretical flow, independent of perfusion pressure, to the observed flow during

anemic hypotension and determine the relative difference between pure anemia and AH. The relationship between CBF and hematocrit has been determined in lambs (10): CBF = $1263/Ca_{O2} + 13$ where Ca_{O2} is arterial O_2 content expressed in Vols %. Using this relationship, each control CBF was adjusted to determine a theoretical perfectly autoregulated CBF (accounting for observed changes in hematocrit and oxygen content due to anemia). Within each animal, observed CBF was divided by the theoretical CBF and multiplied by 100 to express observed CBF as the percent of theoretical CBF.

Two-way analysis of variance (MABP × Hct) with replications was used to determine statistical significance. If the F-ratio indicated statistical significance was reached ($P < 0.05$), Duncan's new multiple range test was used to compare individual means (18). Linear regression was performed to examine the relationship between fractional O_2 extraction of the brain and CPP. All data are expressed as means ± SEM.

Results

Table I shows arterial pressures, gases, pHs, and hematocrits during experimental hypotension. Mean arterial pressures were very similar in the two experimental groups. Arterial PO_2 did not change significantly during hypotension in either group. PCO_2 increased slightly but statistically significantly from 37 to 40 mm Hg in the AH group only. Arterial pH changed significantly only in the AH group at 30 mm Hg (decrease to 7.30 ± 0.04). We believe the above changes were of minimal physiological consequence. Hematocrit decreased significantly 37% in AH but did not change in the NH group. Paralleling Hct, oxygen content decreased 36% in AH but did not change in NH.

Table I also shows sagittal sinus pressures, gases, pHs, and hematocrits during experimental hypotension. Sagittal sinus hydrostatic pressure decreased 33% in AH and 34% in NH, reflecting hypovolemia.

Table I. Effect of Hypotension on Arterial and Cerebral Venous Blood Gases, pH, and Hematocrit[a]

		Control	50 mm Hg	40 mm Hg	30 mm Hg
Arterial					
Pressure	AH[b]	92 ± 5.2	49 ± 0.9[f]	40 ± 0.5[f]	30 ± 0.6[f]
(mm Hg)	NH[c]	98 ± 3.1	50 ± 1.1[f]	37 ± 0.7[f]	28 ± 0.7[f]
PO_2	AH	135 ± 10	116 ± 10	111 ± 10	115 ± 13
(mm Hg)	NH	105 ± 9	108 ± 15	104 ± 12	97 ± 11
PCO_2	AH	37 ± 1.5	36 ± 1.2	37 ± 1.1	40 ± 1.4[e]
(mm Hg)	NH	35 ± 1.7	38 ± 0.9	41 ± 2.5	41 ± 1.3
pH	AH	7.45 ± .02	7.41 ± .03	7.39 ± .03	7.30 ± .04[f]
	NH	7.40 ± .01	7.32 ± .05	7.33 ± .07	7.36 ± .04
O_2 content	AH	13.5 ± 0.8	11.2 ± 0.6[f]	9.7 ± 0.7[f]	8.6 ± 0.7[f]
(Vols %)	NH	13.9 ± 1.4	12.7 ± 1.3[h]	12.7 ± 1.1[h]	13.0 ± 1.6[h]
Hematocrit	AH	27 ± 1.5	22 ± 0.8[f]	19 ± 0.8[f]	17 ± 0.9[f]
(%)	NH	31 ± 2.7[h]	28 ± 3.0[h]	28 ± 2.3[h]	28 ± 3.2[h]
Venous					
Pressure	AH	7.9 ± 0.5	5.7 ± 0.6[f]	5.1 ± 0.6[f]	5.3 ± 0.7[f]
(mm Hg)	NH	8.8 ± 1.3	6.0 ± 0.9[f]	6.1 ± 0.8[f]	5.7 ± 0.8[f]
PO_2	AH	25 ± 1.5	22 ± 2.0	18 ± 1.3[f]	17 ± 1.2[f]
(mm Hg)	NH	27 ± 1.6	19 ± 1.1[f]	16 ± 2.1[f]	14 ± 2.9[f]
PCO_2	AH	47 ± 1.9	49 ± 1.3	53 ± 1.7[f]	60 ± 3.2[f]
(mm Hg)	NH	47 ± 1.3	53 ± 2.0	61 ± 2.3[f]	62 ± 2.8[f]
pH	AH	7.37 ± .02	7.31 ± .02	7.28 ± .03[f]	7.17 ± .04[f]
	NH	7.32 ± .01	7.23 ± .05[e]	7.22 ± .06[e,g]	7.24 ± .03
O_2 content	AH	5.6 ± .54	3.2 ± .35[f]	2.4 ± .42[f]	1.5 ± .28[f]
(Vols %)	NH	6.6 ± .84	3.3 ± .55[f]	2.6 ± .72[f]	2.6 ± 1.1[f]
Hematocrit	AH	27 ± 1.2	23 ± 1.0[f]	19 ± 0.9[f]	17 ± 0.9[f]
(%)	NH	31 ± 3.0[h]	23 ± 3.0[h]	28 ± 2.5[h]	28 ± 3.6[h]
$CMRO_2/O_2$ D[d]	AH	0.59 ± .02	0.72 ± .02[f]	0.76 ± .04[f]	0.83 ± .02[f]
	NH	0.53 ± .02	0.74 ± .03[f]	0.80 ± .05[f]	0.80 ± .09[f]
$CBF/CMRO_2$	AH	0.129 ± .007	0.128 ± .008	0.140 ± .09	0.147 ± .010
	NH	0.146 ± .017	0.111 ± .009	0.105 ± .011[h]	0.114 ± .022[g]

[a] Values are expressed as mean ± SEM. Vascular pressures are expressed as mean pressures.
[b] AH designates the hypotensive group of animals allowed to become anemic ($n = 8$).
[c] NH designates animals in which anemia was prevented by infusions of autologous red blood cells ($n = 6$).
[d] O_2 D represents oxygen delivery to the cerebrum.
[e] $P < 0.05$ different from control.
[f] $P < 0.01$ different from control.
[g] $P < 0.05$ different from AH.
[h] $P < 0.01$ different from AH.

Venous pH, PO_2, and O_2 content decreased in both experimental groups as perfusion pressure was lowered. Venous PCO_2 and the fractional extraction of oxygen increased in both groups. Venous PCO_2 increased 28% in both groups.

The CBF response to hypotension in the newborn lamb is shown in Figure 1a. Total brain blood flow did not change when perfusion pressures were dropped. CBF was maintained at a mean perfusion pressure of 25 ± 1 in the AH group and 22 ± 1 mm Hg in the NH group. Theoretical CBFs are also shown in Figure 1a. These calculated values indicate the CBFs corrected for anemia, independent of CPP. As expected, these values rise as hematocrit falls. Theoretical flows and observed AH flows were virtually identical until a MABP of 30 mm Hg was reached at which point the theoretical flows continued to rise and the observed flows remained at control level. Vascular resistances are shown in Figure 1b. CVR decreased in similar fashion in both experimental groups. Theoretical CVRs decreased to a greater extent than those observed. At 30 mm Hg CVR was 0.67 ± 0.06 in the AH group whereas the predicted value was 0.44 ± 0.04 mm Hg/ml/min/100 g. Regional CBFs are shown in Table II. Blood flows to the eight brain regions studied did not decrease during hypotension. In the AH group, there was a significant increase in blood flow to the hindbrain (rostral spinal cord, brain stem, diencephalon, and hippocampus) at 40 mm Hg. Figure 2 expresses regional blood flows of the AH group as a percent of the flow predicted from the Hudak algorithm. All regions were below the theoretical flows at a CPP of 22 mm Hg. Hindbrain structures were about 80% of the theoretical values whereas the forebrain CBFs were only about 65% of the theoretical values.

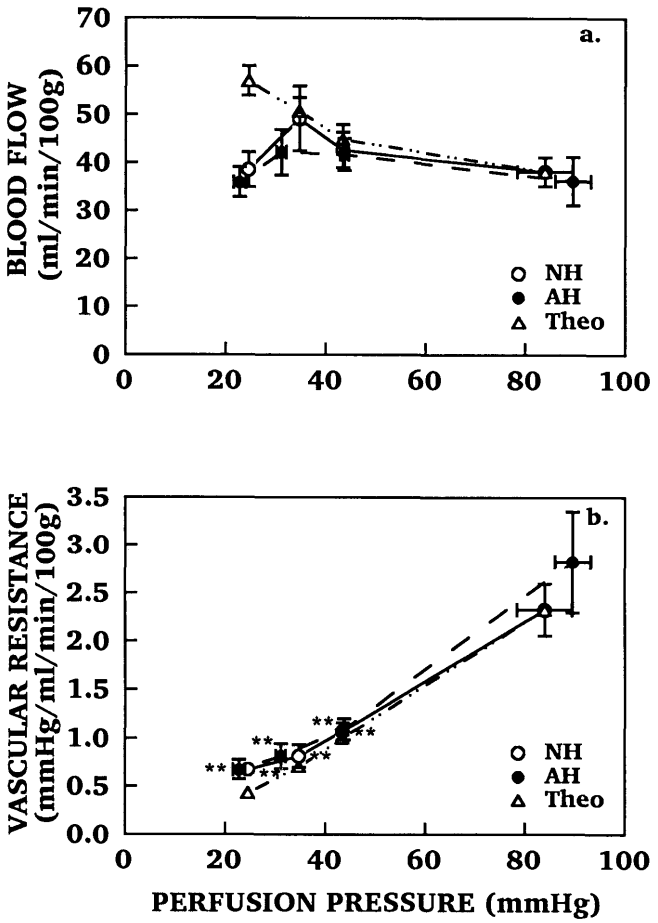

Figure 1. Cerebral blood flow (a) and vascular resistance (b) versus perfusion pressure. Animals that became anemic (AH; n = 8) as arterial pressure was reduced are represented by open circles connected with solid line. The corrected hematocrit group (NH; n = 6), animals received autologous red blood cell infusions to maintain hematocrit, are represented by filled circles connected with a dashed line. Open triangles represent blood flows and vascular resistances of the AH group corrected for changes in hematocrit (Theo) with Hudak (10) algorithm. Points are means ± SEM. **Different from control $P < 0.01$.

Figure 3a shows oxygen delivery to the brain during hypotension. Oxygen delivery was maintained at all pressures studied in the NH group. In contrast, due to the development of anemia in the AH group, the oxygen delivery to the brain decreased when a perfusion pressure of 25 mm Hg was reached. Oxygen uptake of the cerebrum was not reduced by the decrease in O_2 delivery as shown in Figure 3b. Oxygen uptake did not decrease in either group. Oxygen uptake of the cerebrum in the NH group increased significantly from 2.20 ± 0.29 to 3.20 ± 0.25 and 3.51 ± 0.48 at 50 and 40 mm Hg respectively but was not different from control at 30 mm Hg.

The relationship between oxygen supply (O_2 delivery) and oxygen demand (O_2 uptake) was examined by evaluating the ratio of O_2 uptake to O_2 delivery (fractional O_2 extraction) of the cerebrum. The average values show a tendency for fractional extraction to increase as CPP decreases (Table I). This is illustrated better in Figure 4. Neither the slopes nor the y-intercepts from the regression analysis were significantly different between groups. The relationship between CBF and $CMRO_2$ was examined by calculating their ratio ($CBF/CMRO_2$). This ratio was generally stable as MABP decreased (Table I). These values did diverge significantly at 40 and 30 mm Hg reflecting the increase in $CMRO_2$ without an increase in CBF in the NH group.

Discussion

Several precautions must be observed when using the microsphere technique (16, 19). One of the concerns that must be addressed is: are there adequate numbers of microspheres in counted samples? We injected approximately 1–1.5 × 10^6 into each animal to assure 1600 microspheres in each reference sample and more than 400 in each tissue sample. Care was

Table II. Effect of Hypotension on Regional CBFs[a]

		Control	50 mm Hg	40 mm Hg	30 mm Hg
Cord	AH	37 ± 3.3	46 ± 6.0	55 ± 8.0[b]	41 ± 4.6
	NH	43 ± 5.6	52 ± 7.0	52 ± 7.5	43 ± 4.5
Brain stem	AH	50 ± 4.1	62 ± 6.7	73 ± 10.6[c]	61 ± 5.0
	NH	55 ± 7.2	71 ± 7.0	74 ± 12.7	60 ± 5.8
Diencephalon	AH	40 ± 3.4	47 ± 5.0	56 ± 7.7[b]	48 ± 4.2
	NH	40 ± 5.1	51 ± 4.2	53 ± 8.0	46 ± 4.2
Hippocampus	AH	30 ± 2.7	38 ± 3.8	43 ± 5.4[b]	36 ± 3.6
	NH	31 ± 4.6	37 ± 3.7	37 ± 5.1	34 ± 3.6
Caudate	AH	49 ± 4.5	50 ± 4.9	57 ± 6.9	45 ± 3.9
	NH	40 ± 4.4	50 ± 4.4	45 ± 4.9	41 ± 4.0
Cortical gray	AH	36 ± 3.3	39 ± 4.2	47 ± 6.6	36 ± 3.8
	NH	33 ± 5.7	38 ± 3.5	37 ± 4.5	32 ± 2.9
Cerebrum	AH	35 ± 2.9	37 ± 3.1	43 ± 5.8	33 ± 3.1
	NH	31 ± 4.8	35 ± 2.9	36 ± 4.3	30 ± 2.5
Cerebellum	AH	55 ± 3.8	64 ± 7.3	73 ± 12.3	56 ± 6.6
	NH	53 ± 6.9	60 ± 5.9	63 ± 8.4	49 ± 6.5
Total brain	AH	38 ± 3.0	43 ± 3.7	49 ± 6.7	38 ± 3.6
	NH	36 ± 5.1	42 ± 3.3	42 ± 4.7	36 ± 3.1

[a] Blood flows were measured with radioactive microspheres. Values are expressed as means ± SEM. AH designates the hypotensive group of animals allowed to become anemic (n = 8); NH designates animals in which anemia was prevented by infusions of autologous packed red blood cells (n = 6).
[b] $P < 0.05$ different from control.
[c] $P < 0.01$ different from control.

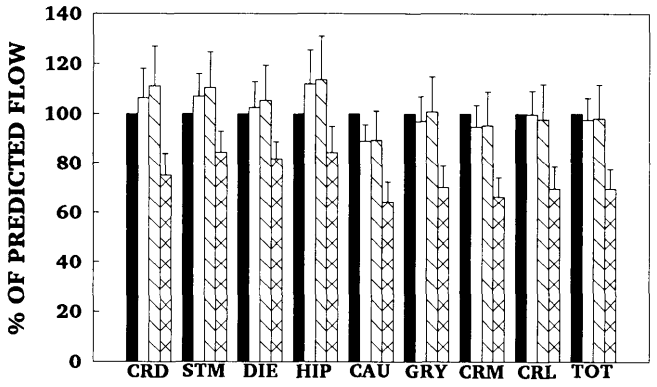

Figure 2. Regional cerebral blood flows of the AH group expressed as a percent of that predicted by mathematical model of Hudak *et al.* (10). Solid bars are control values; open bars represent CBFs measured at MABP = 50 mm Hg; hashed bars are CBFs at 40 mm Hg; cross hashed bars are CBFs at 30 mm Hg. CRD = rostral spinal cord; STM = brain stem; DIE = diencephalon; HIP = hippocampus; CAU = caudate nucleus; GRY = cortical gray; CRM = cerebrum; CRL = cerebellum; TOT = total brain.

taken to assure reference sample was accurate during hypotension and anemia. Also, the duration of reference withdrawal was extended during hypotension to compensate for slower washout of the spheres from the heart. The consistency of the reference sample during hypotension was checked to guard against potential errors observed by Rosenberg *et al.* (19).

The major findings of these experiments are (i) that the anesthetized newborn lamb is capable of maintaining CBF when perfusion pressure falls to 25 mm Hg and this autoregulatory capacity (classically defined) is not dependent on a change in hematocrit or, presumably, viscosity; and (ii) that cerebral hypotension appears to be accompanied by an increase in fractional extraction of oxygen.

Although earlier reports suggest that CBF autoregulation (defined as constant blood flow with changes in perfusion pressure) may not be effective at or near birth (20), this study as well as others indicate that CBF autoregulation is effective early in life (2, 6, 8, 9) or before birth (1, 5). This study demonstrates that the anesthetized-newborn lamb maintains brain blood flow to a CPP as low as 25 mm Hg during hemorrhagic hypotension. Our results are in close agreement with studies of brain pressure-flow relationships in newborn lambs whether unanesthetized (9), sedated (8), or comatose (8). These studies observed that CBF was maintained to a MAP of 24 mm Hg (9) and a CPP of 28 mm Hg (8). Hernandez *et al.* (6) observed that in puppies CBF was preserved to perfusion pressures as low as 27 mm Hg. They hypothesized that ability to maintain CBF at low pressures was due to a lower normotensive MABP (57 mm Hg). Their hypothesis can not explain our observations since normotensive controls were observed to be 92 ± 5 and 98 ± 3 mm Hg and CBF was still maintained at a CPP of 25 mm Hg.

In contrast to our data, Laptook *et al.* (4) found that blood flow to the cerebrum falls substantially (30%–50%) once an arterial pressure of 40 mm Hg is reached in N_2O anesthetized piglets. The reason for this discrepancy is not known. The fall in hematocrit was similar to that found in the present study; there-

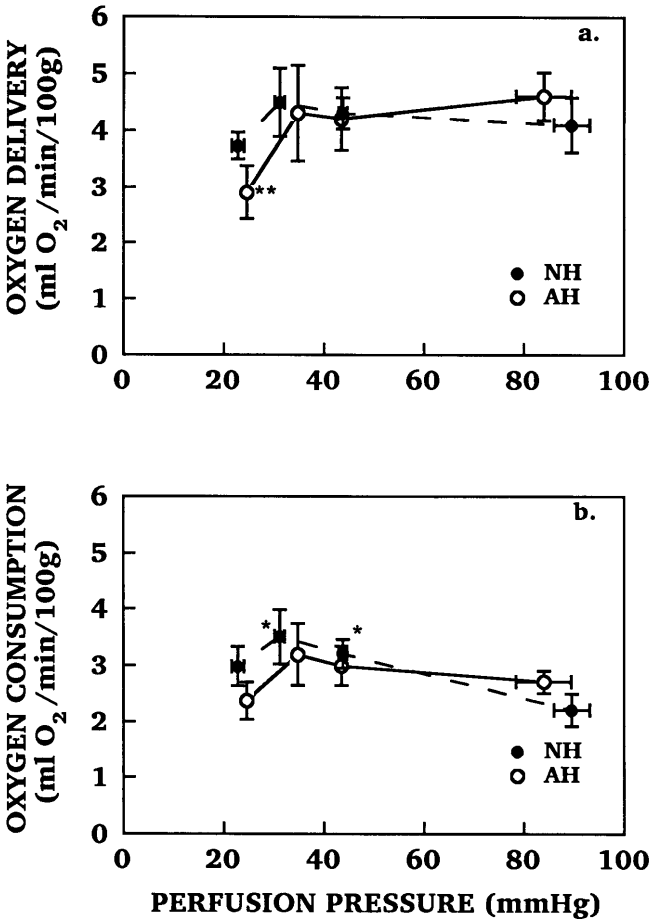

Figure 3. Cerebral oxygen delivery (a) and uptake (b) versus perfusion pressure. Animals that became anemic (AH; n = 8) as arterial pressure was reduced are represented by open circles connected with solid line. The corrected hematocrit group (NH; n = 6), animals received autologous red blood cell infusions to maintain hematocrit, are represented by filled circles connected with a dashed line. Points are means ± SEM. *Different from control $P < 0.05$. **Different from control $P < 0.01$.

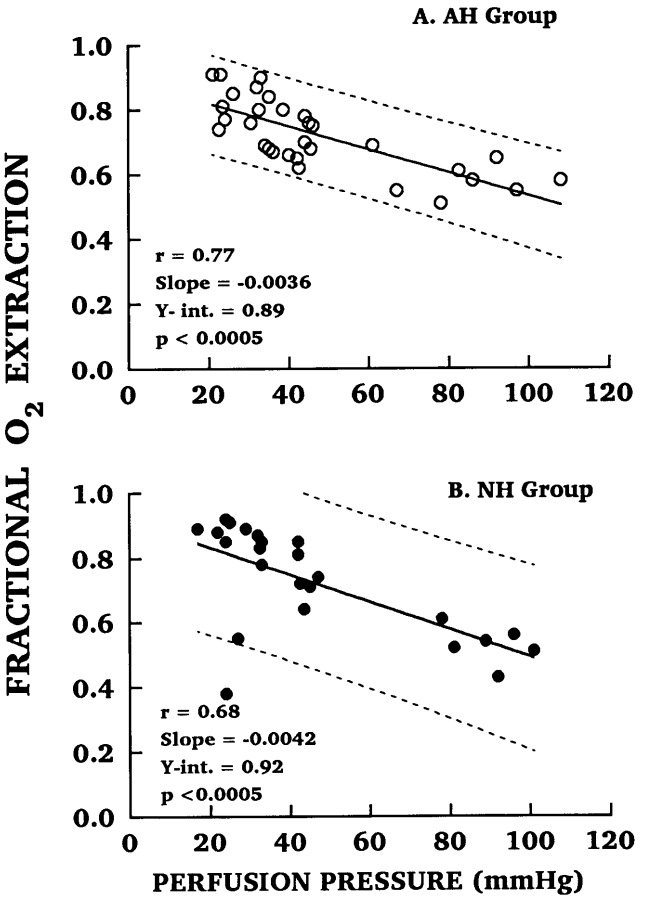

Figure 4. Effect of reducing arterial pressure on fractional extraction of oxygen by the brain. The fraction of oxygen removed by the area of the brain which drains into the dorsal sagittal sinus is shown for each observation. P-values in the lower left corner of each panel indicate that the slopes are different than 0.

fore, anemia cannot explain the differences in our results. One possible explanation may be that there are species differences in response to hypotension in the newborn period. However, Leffler *et al.* (21) observed maintenance of CBF when arterial pressure decreased to 38 mm Hg in unanesthetized piglets. The anesthetic used in the Laptook study is a vasodilator and may have directly interfered with the cerebral vascular response to hypotension. An alternative explanation is that baseline CBF was much higher in the Laptook studies. In other studies, including ours, in which baseline blood flows were lower (6, 8, 21–23), CBF was maintained to perfusion pressures of 30 mm Hg and lower. We hypothesize there may be a limit to the vasodilation that hypovolemic hypotension can induce (a minimum vascular resistance). Thus, when baseline blood flows are high, the break point of autoregulation must occur at a higher perfusion pressure. Vascular resistances calculated from other reports (2, 4, 6, 8, 9) indicate that the point of minimal cerebral vascular resistance with hypotension in newborn animals is near 0.5 mm Hg/ml/min/100 g and this appears to be independent of the study design or experimental model. Given that baseline blood flow to the cerebrum in Laptook studies was 109 ml/min/100 g, blood flow would be expected to fall as perfusion pressure falls below 50 mm Hg. With the same rationale, the lower limit of autoregulation in the present study would be approximately 20 mm Hg. The lowest resistance observed in this study was 0.67 ± 0.06 mm Hg/ml/min/100 g. However, this may not represent the absolute minimum achievable cerebral vascular resistance under other pathologic conditions such as hypoxia, hypercapnia, or asphyxia.

Our data indicate that a decrease in hematocrit and presumably the decrease in viscosity which accompanies it (10, 24) is not critical to the maintenance of CBF or cerebral O_2 consumption in newborn animals in the pressure range studied. Therefore, with the rigid definition, constant CBF over a range of CPPs, CBF autoregulation was unaltered by the concomitant development of anemia. However, other factors may be in-

fluencing CBF. Two of the more important factors are oxygen content and viscosity.

Several investigations have demonstrated the dependency of CBF on Ca_{O2} (12–14) and viscosity (10, 24). Thus, we attempted to examine the effect of anemia on the hypotensive pressure flow relationship. Hudak *et al.* (10) derived a mathematical relationship between Ca_{O2} and CBF when hematocrit was altered in newborn lambs. This relationship incorporates the effects both of changes in Ca_{O2} and changes in red blood cell concentration on CBF. We used this relationship to predict changes in CBF and CVR if only hematocrit, and not CPP, was changed in AH animals. The observed flows were remarkably similar to the predicted flows until a MABP of 30 mm Hg was reached. At this pressure, flows to all brain regions were less than predicted. Higher theoretical flows are due to lower calculated vascular resistances. Observed CVRs were approximately 50% greater than the theoretical values. We believe the theoretical vascular resistance is not beyond the minimal CVR achievable in this model since we have observed CVRs, induced by hypoxia (0.43 ± 0.09 mm Hg/ml/min/100 g; unpublished data), close to the theoretical values. However, the hypoxic effect of anemia did not induce greater vasodilation during severe hypotension. Independent of vasodilation, viscosity changes due to anemia should reduce vascular resistance (11, 24), provided Poiseuille's relationship is applicable. However this physical effect was not realized in these studies. We conclude that the contributions of anemia (both hypoxic and physical effects) and hypotension reducing vascular resistance are not additive at severe hypotension as they appear to be during mild hypotension (MABP = 40 mm Hg) with mild anemia.

A possible explanation for this limited reduction of CVR with AH is that anemia can induce isolated cerebral vasoconstriction. Hudak *et al.* (11) have observed constriction of small pial arteries with anemia. Brain blood flow in Hudak's study was elevated in spite of vasoconstriction of the vessels observed. Changes in viscosity did not account for the entire increase in CBF. Therefore, dilation of other cerebral vessels, in series with the pial vessels, must have occurred. An anemia-induced small vessel constriction may have prevented greater reduction of CVR to increase blood flow at 30 mm Hg.

It is interesting that the maintenance of metabolism was not dependent on maintenance of hematocrit. It is possible that anesthesia influenced this response. CBF responses could have been blunted by anesthesia, presumably due to lower $CMRO_2$, as barbiturate coma alters responses to hypoxia (8). However, examination of the ratios of CBF to $CMRO_2$ and $CMRO_2$ to oxygen delivery has been shown to normalize cerebral vascular responses at different states of $CMRO_2$ (8). The ratio of CBF to $CMRO_2$ (the reciprocal of the arteriovenous difference for oxygen) was constant over the course of the experiment in both groups (Table I). The results of this study indicate that the newborn brain is capable of protecting itself from a decrease in hematocrit during hemorrhagic hypotension through maintaining the extraction of oxygen resulting in an increase in the fractional extraction of oxygen.

Fractional extraction of oxygen increased in both hypotensive groups (Fig. 4). Fractional extraction of oxygen is the ratio of oxygen uptake (O_2 consumption during steady state) to oxygen delivery. An increase in this ratio indicates that the normal relationship has been altered such that oxygen delivery is low with respect to the oxygen demand of the brain. An increase in fractional extraction is not surprising in animals that became anemic (AH) since oxygen delivery decreased (Fig. 3) due to lower O_2 carrying capacity. Fractional extraction had to increase to maintain oxygen consumption. However, O_2 delivery did not decrease in the NH group, the increase in fractional O_2 extraction must then be a result of an increase in oxygen demand. This is validated by examining the ratio of CBF to $CMRO_2$ (Table I). $CBF/CMRO_2$ was significantly less in the NH group at the lower pressures, indicating a relatively increased O_2 demand. Calculated O_2 uptake did increase in the NH group (Fig. 3b). This has been reported by others studying hemorrhagic hypotension in adult animals (25, 26). Chen *et al.* (26) reported an increase in cerebral O_2 consumption when animals were hemorrhaged to near the lower limit of cerebral autoregulation. They also reported that this increase could not be sustained as blood flow began to fall with more severe hemorrhage in spite of continued increase in O_2 extraction. It is conceivable that O_2 consumption may be limited by O_2 delivery in this situation necessitating a switch to anaerobic metabolism. Confirmation of this hypothesis would necessitate the measurement of glucose consumption (not evaluated in the present study). In the study of Laptook *et al.* (27) in which blood flow and oxygen consumption fell with hypotension, glucose uptake increased 4-fold. Oxidative metabolism, limited in this case by low O_2 delivery, did not supply the brain's metabolic needs. We speculate that glucose uptake may have been elevated in the present study. Further studies are needed to determine whether the brain's metabolic demand is sufficiently met as blood pressure nears or exceeds the lower limit of blood flow autoregulation.

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