Cerebral Metabolism in the Newborn Lamb with Polycythemia

TED S. ROSENKRANTZ, ANTHONY F. PHILIPPS, PETER S. SKRZYPCZAK, AND
JOHN R. RAYE

*University of Connecticut Health Center, Department of Pediatrics, Division of Neonatology,
Farmington, Connecticut 06032*

ABSTRACT. Infants with polycythemia and hyperviscosity are known to have a reduced cerebral blood flow. Eight newborn lambs were studied to determine what effect the reduction in cerebral blood flow might have on the cerebral delivery and uptake of oxygen, glucose, lactate, pyruvate, β -hydroxybutyrate, and acetoacetate. Measurements of cerebral blood flow, hematocrit, blood viscosity as well as delivery and uptake of the forementioned substrates were made during a control period and at 60, 180, and 300 min after an exchange transfusion with packed newborn red blood cells was performed to increase the hematocrit. Sixty min after the exchange transfusion, cerebral blood flow fell while cerebral oxygen delivery and uptake were stable. Although arterial glucose concentration remained unchanged, there was a significant fall in cerebral glucose delivery. At 180 min after the exchange transfusion, the arterial glucose concentration fell from 90 to 70 mg/100 ml causing the cerebral glucose delivery to further decrease. This resulted in a significant fall in the cerebral glucose uptake and glucose:oxygen quotient. At 300 min arterial glucose concentration remained low but a rise in cerebral blood flow resulted in a small increase in the cerebral glucose delivery and consequently the cerebral glucose uptake and glucose:oxygen quotient returned to normal. We conclude that polycythemia results in a decrease in cerebral glucose delivery and uptake during normoglycemia. (*Pediatr Res* 23: 329-333, 1988)

Abbreviations

CBF, cerebral blood flow
PRBC, packed red blood cells
G/O₂, glucose/oxygen quotient
cmp, counts/min

Polycythemia and hyperviscosity occur in 3-5% of all newborn infants and as many as 40% of affected infants have long-term neurologic and developmental sequelae (1-3). The etiology of the central nervous system damage is not known. It had been postulated that the cerebral blood flow of these infants was reduced secondary to an elevation in blood viscosity, resulting in cerebral ischemia and hypoxia (4, 5). We have previously shown in the newborn lamb with polycythemia that the reduction in cerebral blood flow is due to an associated elevation in arterial

oxygen content, not viscosity, and that oxygen delivery to the brain is normal (6).

In the study of Black *et al.* (3) infants with polycythemia and concurrent hypoglycemia were at the highest risk for poor outcome. This led to consideration of whether the delivery of cerebral metabolic fuels, particularly glucose, might be limited by the reduction of cerebral blood flow that occurs in the polycythemic state and might the reduced substrate delivery adversely affect substrate uptake by the brain.

Glucose, normally the primary cerebral fuel, is present in the water phase of blood and therefore exists primarily in the plasma portion of the blood as the red blood cell water content is relatively low due to the corpuscular hemoglobin content. In the infant with polycythemia, the red cell volume is increased whereas the plasma fraction of the blood is reduced. A reduction in the plasma fraction in combination with a reduction in cerebral blood flow would be expected to result in a lowered cerebral plasma flow. This would mean that at a similar plasma glucose concentration, cerebral glucose delivery would be greatly reduced in the infant with polycythemia as compared to an infant with a normal hematocrit. Additionally, the cerebral delivery of other metabolic substrates might also be similarly restricted. The following study was designed to test these hypotheses.

METHODS

Surgical. Eight newborn lambs were catheterized under ketamine (8 mg/kg intramuscularly) and pentobarbital (16 mg intravenously) anesthesia with local infiltration with 1% lidocaine solution. Tygon catheters (ID 1.02 mm, Norton Co., Akron, OH) were placed into the left ventricle of the heart via the right axillary artery, aortic root via the left axillary artery, abdominal aorta via the right femoral artery, and inferior vena cava via the right femoral vein. A polyvinyl catheter (ID 0.87 mm, Bolab, Inc., Lake Havasu, AZ) was inserted into the superior sagittal sinus and advanced 1 cm. Catheter placement was confirmed at autopsy.

Postoperatively, the animals were returned to their mothers and allowed a 48-h recovery period before study. Postnatal age and weight at the time of surgery were 4.8 ± 0.8 days (mean $\pm$ SE) and 4.1 ± 0.2 kg, respectively.

Physiologic measurements. Blood pressure and heart rate were measured using a physiologic pressure transducer (Statham Laboratories, Hato Rey, PR) and recorded on a Hewlett Packard polygraph (Hewlett Packard, Waltham, MA). Arterial blood gases and pH were analyzed using the Corning Blood Gas Analyzer 178 (Corning Scientific Instruments, Medford, MA). Oxygen content in whole blood was measured with a Lex-O₂-Con (Lexington Instruments Corp., Waltham, MA) (7). Hematocrit was measured in duplicate using a microcentrifuge. Whole blood viscosity was determined using a Wells-Brookfield Cone/Plate

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Correspondence, Dr. T. S. Rosenkrantz, University of Connecticut Health Center, Department of Pediatrics, Farmington Avenue, Farmington, CT 06032.

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Viscometer at shear rates of 5.7, 11.50, 23.0, 46.0, and 115.0 s⁻¹. Similar changes were observed at all shear rates; therefore, only viscosity values at a shear rate of 46.0 s⁻¹ are presented herein. Whole blood glucose was measured using the glucose oxidase method (7). Lactate, pyruvate, β -hydroxybutyrate, and acetoacetate were measured enzymatically (8, 9). Insulin concentration was determined by a modification of the double antibody immunoassay technique (10). Ovine insulin standards were kindly supplied by Mary Root, Ph.D. (Eli Lilly and Co., Indianapolis, IN).

Blood flow determinations. CBF was measured using radio-nuclide-labeled microspheres (15 $\pm$ 5 μ m diameter, New England Nuclear, Boston, MA) as described by Heymann *et al.* (11). Microspheres were labeled with ⁵⁷Co, ¹¹³Sn, ⁹⁵Nb, or ⁴⁶Sc. For each flow determination, 8.5 $\times$ 10⁵ microspheres, suspended in a 1 ml solution of 10% dextran and 0.01% Tween 80, were injected into the left ventricle over a 30-s period. A reference sample of blood was withdrawn from the aortic root for a 2-min period at a constant rate of 1.94 ml/min, starting 25 s before the injection of microspheres. After fixation in 10% formalin, the brain was sectioned into 0.2–1.5 g pieces. Radioactivity of the brain sections and reference blood samples were measured with a gamma counter (Searle Analytic, Inc., Des Plaines, IL) and multi-channel analyzer (Nuclear Data, Inc., Schaumburg, IL). The following formula was used to calculate tissue blood flow.

$$\frac{\text{cmp of microspheres in tissue}}{\text{cmp of microspheres in reference sample}} \times \text{rate of withdrawal} = \text{tissue blood flow.}$$

Brain blood flow was expressed as ml/min/100 g wet weight.

Study design. Lambs were separated from their mothers on the morning of the study, brought to the laboratory and lightly restrained. The animals were then allowed to acclimate for a 60-min period. At the end of that period, measurements were made of heart rate and mean arterial blood pressure. Arterial blood was sampled for blood gases and pH, hematocrit and viscosity as well as for oxygen content and the concentrations of glucose, lactate, pyruvate, β -hydroxybutyrate, acetoacetate, and insulin. Sagittal sinus venous blood was also obtained for oxygen content and the concentrations of glucose, lactate, pyruvate, β -hydroxybutyrate, and acetoacetate. Lastly, an arterial sample of blood was drawn from the aortic root during the injection of radio-nuclide-labeled microspheres for determination of CBF. After these measurements, an exchange transfusion was performed over 60 min in each lamb to raise the hematocrit and viscosity. Age-matched newborn PRBC (60 ml/kg) were used. The cells had been previously stored in citrate-phosphate-dextrose blood bags, washed twice with 0.9% saline solution, and packed just before the study. The hematocrit of the PRBC was 90–95%. The previous physiologic and metabolic measurements were repeated 60, 180, and 300 min after the exchange transfusion. At the end of the study the lambs were killed and the brains removed. The brains were weighed and preserved in 10% formalin for later measurement of radioactivity and calculation of CBF.

Data analysis. Substrate delivery was calculated as the product of the arterial blood concentration and CBF. Substrate uptake

or production was calculated as the product of CBF and the arterial-venous (sagittal sinus) concentration difference of the substrate.

The cerebral G/O₂ was calculated by the following formula:

$$\text{cerebral G/O}_2 = \frac{6 \times \text{cerebral glucose uptake} (\mu\text{mol/min/100 g})}{\text{cerebral oxygen uptake} (\mu\text{mol/min/100 g})}$$

Substrate extraction (%) was calculated as follows:

$$\text{cerebral substrate extraction} = \frac{\text{cerebral substrate uptake}}{\text{cerebral substrate delivery}} \times 100.$$

Data were analyzed using one-way analyses of variance for repeated measures, Student's *t* tests and linear regression analyses.

RESULTS

Exchange transfusions were performed without difficulty in each of the eight newborn lambs. The heart rate decreased after the exchange transfusion from 241 $\pm$ 13 bpm (mean $\pm$ SE) to 189 $\pm$ 28 (p < 0.01) and then remained stable throughout the remainder of the study (Table 1). The mean arterial blood pressure was 79 $\pm$ 4 mm Hg during the control period and was stable throughout. The pO₂ was 83 $\pm$ 3 mm Hg, pCO₂ was 38 $\pm$ 1 mm Hg, and the pH was 7.46 $\pm$ 0.01 at the start of this study. The pO₂ was unchanged, whereas the pCO₂ and pH both decreased after the exchange transfusion to 33 $\pm$ 1 and 7.39 $\pm$ 0.1, respectively. The values were then stable at these levels for the remainder of the study. The hematocrit rose from 27 $\pm$ 2 to 51 $\pm$ 3%, 60 min after the exchange transfusion and was 46 $\pm$ 2%, 300 min after the transfusion (p < 0.001) (Fig. 1). There was a corresponding rise in viscosity from 3.1 $\pm$ 0.3 centipoise (shear rate = 46 s⁻¹) to 6.6 $\pm$ 1.1 (p < 0.001). This represents an increase of more than 3 SD from the control value. Arterial oxygen content rose from 14.3 $\pm$ 0.7 to 24.6 $\pm$ 1.1 vol% 60 min postexchange transfusion (p < 0.001) and remained at that level. There was a similar increase in the cerebral arteriovenous difference of the blood oxygen content (Table 2). Conversely, cerebral blood flow was initially 106.5 $\pm$ 2.7 ml/min/100 g and fell to 58.1 $\pm$ 4.8, 68.9 $\pm$ 4.9, and 78.6 $\pm$ 7.3 ml/min/100 g at 60, 180, and 300 min after the exchange transfusion, respectively. As a result of these changes in oxygen content and cerebral blood flow, the cerebral oxygen uptake did not change from a control value of 7.6 $\pm$ 0.1 ml/min/100 g tissue for the duration of the study.

The initial values for arterial whole blood glucose concentration and cerebral glucose delivery were 101.3 $\pm$ 7.5 mg/100 ml and 102.6 $\pm$ 10.5 mg/min/100 g, respectively (Fig. 2). At 60 min postexchange transfusion, arterial whole blood glucose concentration was unchanged but cerebral glucose delivery fell to 54.2

Table 1. Heart rate, mean arterial blood pressure, PO₂, pCO₂, and pH during control and study periods (mean $\pm$ SE)

	Time postexchange transfusion (min)			
	Control	60	180	300
Heart rate (beats/min)	241 $\pm$ 13	189 $\pm$ 10*	189 $\pm$ 6*	189 $\pm$ 10*
Mean arterial blood pressure (mm Hg)	79 $\pm$ 4	84 $\pm$ 5	79 $\pm$ 4	77 $\pm$ 5
pO ₂ (mm Hg)	83 $\pm$ 3	79 $\pm$ 4	84 $\pm$ 4	76 $\pm$ 3
pCO ₂ (mm Hg)	38 $\pm$ 1	33 $\pm$ 1†	32 $\pm$ 2†	34 $\pm$ 1†
pH	7.46 $\pm$ 0.01	7.39 $\pm$ 0.01*	7.38 $\pm$ 0.02†	7.37 $\pm$ 0.02*

* p < 0.01 versus control.

† p < 0.05 versus control.

± 8.0 mg/min/100 g (53% of the control value) ($p < 0.01$). Due to an increase in cerebral glucose extraction from 10.6 ± 1.5 to $19.5 \pm 3.0\%$ ($p < 0.02$), cerebral glucose uptake was unchanged. At 180 min postexchange transfusion, the glucose concentration in arterial blood fell to 70.1 ± 5.2 mg/100 ml ($p < 0.01$), decreasing the cerebral glucose delivery to its lowest value during the study, 47.4 ± 5.9 mg/100 g/min (46% of the control value) ($p < 0.001$). Cerebral glucose extraction did not increase any further ($18.2 \pm 2.6\%$) and cerebral glucose uptake decreased at this time ($p < 0.05$). At 300 min after the exchange transfusion, the arterial glucose concentration remained low but there was a small increase in the cerebral blood flow. As a result, the cerebral glucose delivery returned to the level observed at 60 min postexchange transfusion. Cerebral glucose extraction remained elevated, $19.2 \pm 4.0\%$. This was associated with a return of the cerebral glucose uptake to control levels.

To examine whether the measured cerebral uptake of glucose could totally provide for the aerobic metabolic demands of the brain and to control for variation in the cerebral metabolic rate, cerebral G/O_2 were calculated and are shown in Table 3. This illustrates that at 180 min postexchange transfusion, when cerebral glucose delivery was at its lowest point, there was a significant decrease in the G/O_2 .

Regression analysis was used to further analyze the relationship between arterial glucose concentration, cerebral glucose delivery, and uptake. Arterial glucose concentration, cerebral glucose delivery, and uptake data for the entire study were grouped for these analyses. Between cerebral glucose delivery rates of 40–150 mg/min/100 g, the cerebral glucose uptake was relatively con-

stant (Table 4). At cerebral glucose delivery rates below 40 mg/min/100 g, the cerebral glucose uptake fell to 7.3 ± 1.4 mg/min/100 g ($p < 0.05$).

Cerebral glucose uptake was also examined as a function of the arterial glucose concentration. The range of arterial glucose concentrations was 38 to 135 mg/100 ml. No relationship was found between the arterial glucose concentration and cerebral glucose uptake.

Table 5 shows the control and postexchange transfusion values for lactate, pyruvate, β -hydroxybutyrate, and acetoacetate uptake/production. As observed, there were no significant changes from baseline during the study. Regression analysis revealed that cerebral delivery of these substrates was linearly correlated to cerebral blood flow ($p < 0.001$). Therefore, as CBF fell at 60, 180, and 300 min, the delivery of these substrates was restricted. The control plasma insulin concentration was 84.4 ± 9.1 μ u/ml and was unchanged during the study.

DISCUSSION

It is well documented that infants with polycythemia and hyperviscosity are at significant risk for developmental and neurologic sequelae (3, 4, 12–14). Previous work has shown that while the cerebral blood flow of infants with polycythemia is reduced, the concomitant elevation in arterial oxygen content results in a normal delivery of oxygen at the capillary level (6). Herein we have further documented that due to an increase in the arteriovenous difference of the blood oxygen content, the uptake of oxygen by the brain during periods of polycythemia

Fig. 1. Values for hematocrit, arterial oxygen content, CBF, and cerebral oxygen uptake during control and study periods.

Fig. 2. Values for CBF, arterial whole blood glucose concentration, cerebral glucose delivery, and cerebral glucose uptake during control and study periods.

Table 2. Arterial oxygen content (CaO_2) and cerebral arterial venous (sagittal sinus) difference in oxygen content during control and study periods (mean $\pm$ SE)

	Time postexchange transfusion (min)			
	Control	60	180	300
CaO_2 (vol%)	14.3 ± 0.7	$24.6 \pm 1.1^*$	$23.4 \pm 0.9^*$	22.1 ± 0.7
Cerebral $Ca-vO_2$ (vol%)	7.2 ± 0.2	$13.1 \pm 1.0^*$	$11.9 \pm 0.8^*$	$10.0 \pm 0.4^*$

* $p < 0.001$ versus control.

and hyperviscosity is similar to that found when the hematocrit is normal. Therefore, it is unlikely that neurologic damage seen in infants with polycythemia is related to brain ischemia/hypoxia due to the increased hematocrit and viscosity and the associated reduction in cerebral blood flow.

Glucose appears to be an essential substrate for normal cerebral function. The neurologic abnormalities and cerebral metabolic dysfunction that accompany hypoglycemia and cerebral glucopenia are well documented (15–17). In studies of newborn and adult animals as well as adult humans, cerebral blood flow has been shown to be unaffected by changes in blood glucose concentration. That is, there is no compensatory increase in cerebral blood flow when the blood concentration of glucose is low (15, 18, 19). Therefore, when the arterial blood glucose concentration decreases, glucose delivery decreases proportionally. Under normal conditions, the newborn and adult brain is able to extract the necessary amount of glucose for normal cerebral function as long as the plasma glucose concentration is >30 mg/100 ml (15, 18, 20). As the glucose concentration and, therefore, cerebral glucose delivery decreases below this point, there is an acute reduction in cerebral uptake of glucose (15).

If the cerebral uptake of glucose is a function of the plasma or blood glucose concentration, independent of changes in cerebral blood flow, then infants with polycythemia should have adequate uptake of glucose to meet the oxidative metabolic demands of the brain as long as the glucose concentration is normal. If, on the other hand, cerebral glucose uptake is dependent on total

cerebral glucose delivery ($\text{CBF} \times \text{arterial glucose concentration}$), it would be expected that in the polycythemic model, uptake might be diminished during periods of normal plasma glucose concentration due to the reduction in cerebral glucose delivery. The diminution in delivery would be the result of a reduction in the total amount of circulating glucose due to the decrease in plasma space and a reduction in CBF. In fact, this appeared to be the case 180 min after the exchange transfusion. At this time, despite a normal arterial whole blood glucose concentration, cerebral glucose delivery was at its minimum and there was an acute reduction in cerebral glucose uptake. The G/O_2 at that time would suggest that at a minimum, 29% of the cerebral oxidative requirements was unmet by the measured rate of cerebral glucose uptake. At 300 min, the arterial glucose concentration was unchanged but due to a minor increase in CBF, there was an increase in cerebral glucose delivery and the cerebral glucose uptake returned to normal. The above data may be interpreted to indicate that cerebral glucose delivery rather than blood glucose concentration is the determining factor in cerebral glucose uptake. It also suggests that the brains of infants with polycythemia may become glucopenic during periods when the blood glucose concentration is significantly above values traditionally considered to be low.

Analysis of the relationship of arterial glucose concentration, cerebral glucose delivery, and cerebral glucose uptake values for the entire study confirms the above conclusion. That is, the cerebral glucose uptake did not vary with changes in arterial glucose concentration but was strongly correlated to changes in cerebral glucose delivery.

The cerebral oxygen uptake was unchanged throughout the study including periods of time when cerebral glucose uptake was reduced as reflected by a G_2/O of less than 1.00. This finding would suggest cerebral utilization of alternate substrates. While there were not significant changes in the cerebral uptake of pyruvate, β -hydroxybutyrate, or acetoacetate, there was a trend toward increased cerebral uptake of lactate when cerebral glucose uptake was at its lowest point. Additionally, the brains may have increased the uptake and catabolism of substrates from the blood or cerebral stores that were not measured herein, such as amino acids. This phenomenon has been demonstrated by other investigators (16, 21–24).

Black *et al.* (3) found that concurrent hypoglycemia placed infants with polycythemia at the highest risk for poor neurologic outcome. The finding of decreased cerebral glucose delivery and use during a period of normoglycemia in the lamb model might lead to speculation that some of the neurologic sequelae observed in human infants with polycythemia may be due to cerebral glucopenia associated with a normal plasma or blood glucose concentration. At the same time, the finding of an unchanging

Table 3. G/O_2 during control and study periods (mean $\pm$ SE)

	Time postexchange transfusion (min)			
	Control	60	180	300
G/O_2	1.08 ± 0.15	1.10 ± 0.17	$0.73 \pm 0.10^*$	0.91 ± 0.14

* $p < 0.05$ compared to all other periods.

Table 4. Relationships between cerebral glucose delivery and cerebral glucose uptake (mean $\pm$ SE)

	Cerebral glucose delivery (mg/min/100 g)		
	80–150	40–79	0–39
Cerebral glucose uptake (mg/min/100 g)	10.7 ± 1.3 ($n = 6$)†	9.7 ± 1.2 ($n = 16$)	$7.3 \pm 1.4^*$ ($n = 7$)

* $p < 0.05$.

† No. of individual sets of measurements.

Table 5. Arterial concentration and cerebral uptake/production of lactate, pyruvate, β -hydroxybutyrate, and acetoacetate during control and study periods (mean $\pm$ SE)

		Time postexchange transfusion (min)			
		Control	60	180	300
Lactate	Conc*	1.73 ± 0.27	1.37 ± 0.17	1.34 ± 0.13	1.31 ± 0.22
	CM†	-0.006 ± 0.008	-0.010 ± 0.009	$+0.002 \pm 0.003$	-0.003 ± 0.004
Pyruvate	Conc	0.113 ± 0.022	0.107 ± 0.019	0.098 ± 0.010	0.068 ± 0.013
	CM	0	0	0	0
β -hydroxybutyrate	Conc	0.304 ± 0.045	0.205 ± 0.016	$0.139 \pm 0.026\ddagger$	$0.160 \pm 0.037§$
	CM	0.002 ± 0.002	0	-0.002 ± 0.002	-0.002 ± 0.002
Acetoacetate	Conc	0.037 ± 0.006	$0.019 \pm 0.005§$	0.023 ± 0.004	0.031 ± 0.006
	CM	0	0	0	0

* Blood substrate concentration in mM/liter.

† Cerebral substrate uptake (+) or production (–) in mM/min/100 g.

‡ $p < 0.01$ compared to control.

§ $p < 0.05$ compared to control.

cerebral oxygen uptake suggests that the brain of the infant with polycythemia may be able to use alternate substrates and maintain normal function despite a deficiency in cerebral glucose availability. Further investigation of cerebral metabolism and function in neonatal polycythemia will be necessary to clarify the role of cerebral glucopenia in the poor neurologic outcome of affected infants.

In summary, polycythemia did not alter cerebral oxygen delivery or uptake in the chronically catheterized newborn lamb. However, significant reductions in cerebral glucose uptake did occur in lambs with polycythemia while normoglycemic. This finding may be interpreted to indicate that cerebral glucose use in the newborn lamb is not dependent solely on the arterial blood glucose concentration but rather is dependent on cerebral glucose delivery, a function of plasma glucose concentration, plasma volume, and CBF.

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