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14. Supported by NIH grant NS 13976.

20 October 1981

Oxygen Delivery to the Brain Before and After Birth

Abstract. *We studied the relationship between cerebral oxygen consumption and cerebral oxygen delivery (cerebral blood flow × arterial oxygen content) in fetal, newborn, and adult sheep. Relative to the amount of oxygen consumed, cerebral oxygen delivery in the fetus exceeds that in the lamb and adult by 70 percent. This may represent a protective advantage for the fetus or simply a necessary adaptation to the low arterial oxygen pressure in the intrauterine environment.*

A number of physiologic differences distinguish intrauterine from postnatal life. At birth, arterial PO_2 and blood pressure rise, while arterial PCO_2 falls (*1*). Blood pressure continues to rise to adult values. Each of these variables can affect cerebral blood flow (CBF) (*2*), and thus the supply of oxygen and metabolic substrates to the brain. Meanwhile, cerebral O_2 consumption (per gram of brain) rises after birth, then falls with maturation (*2, 3*). As development proceeds, the net result for the quantitative relationship between the brain's requirement for metabolic substrates, on the one hand, and their delivery by arterial blood, on the other, is unknown. In this report we examine only one aspect of this issue: developmental changes in the relationship between cerebral O_2 consumption and cerebral O_2 delivery.

We studied eight fetal sheep in utero at 125 to 135 days of gestation (0.86 to 0.93 of term), nine newborn lambs at 4 to 8 days of age, and five adult sheep. We placed catheters in the brachiocephalic artery and superior sagittal sinus while subjects were anesthetized (*4, 5*). Between 1 and 4 days after surgery, we made four to ten paired measurements of O_2 content in arterial and sagittal sinus blood. In order to compare subjects over a range of arterial O_2 content, the inspired O_2 concentration was varied from 6 to 25 percent by established techniques (*4, 5*). Changes in arterial CO_2 tension were prevented by appropriate modifications of the inspired gas mixture. We measured CBF twice in each animal with the radioactive microsphere technique (*4, 5*). The CBF (milliliters per 100 g per minute) represents flow to all cerebral tissue anterior to the cephalic border of the pons. Cerebral oxygen consumption was calculated according to the Fick principle, by multiplying CBF by the cerebral arteriovenous O_2 difference.

The relationship between cerebral metabolic rate for O_2 ($CMRO_2$) and the total amount of O_2 available to the brain is given by the ratio of $CMRO_2$ (CBF × cerebral arteriovenous O_2 difference) to cerebral O_2 delivery (CBF × arterial O_2 content). This represents the fraction of available O_2 that the

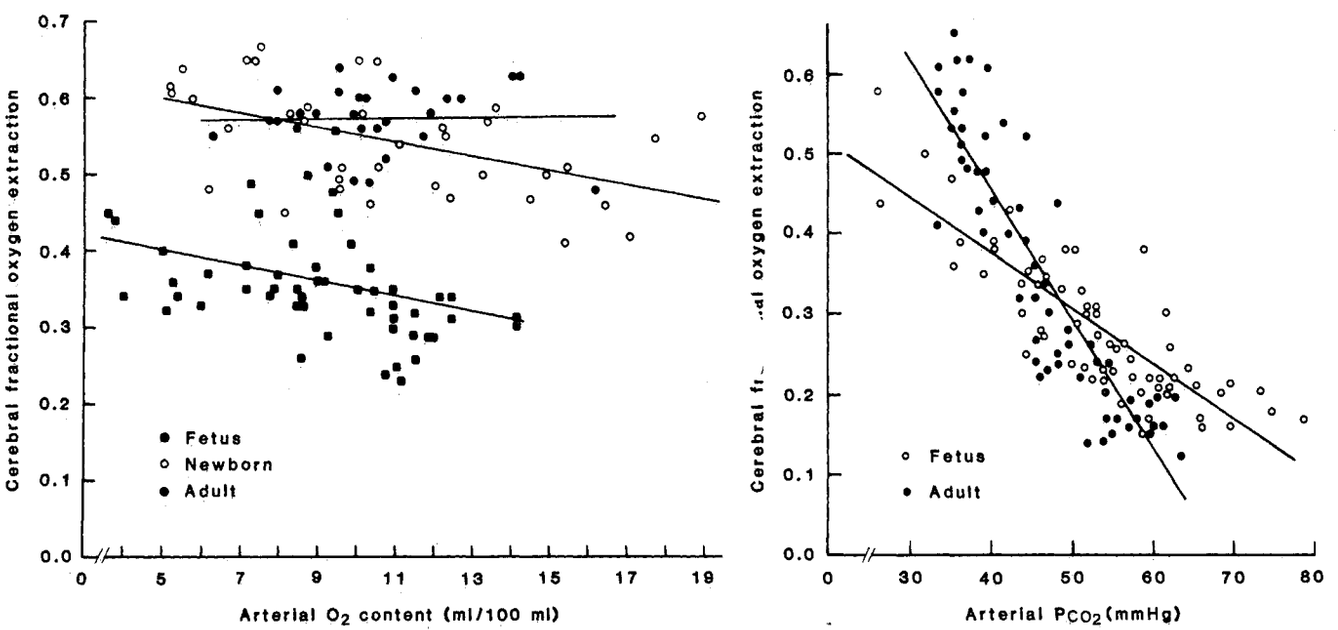

Fig. 1 (left). Relation of cerebral fractional oxygen extraction to arterial O_2 content (milliliters per 100 ml) in fetuses, lambs, and adults as the inspired O_2 concentration was changed. Fetus: $y = -0.01x + 0.45$, $r = -.40$, $P < .01$; lamb: $y = -0.009x + 0.65$, $r = -.49$, $P < .01$; adult: $y = 0.0004x + 0.57$, $r = .02$. Fig. 2 (right). Relation of cerebral fractional oxygen extraction to arterial PCO_2 (mmHg) in fetuses and adults as the inspired CO_2 concentration was changed. Fetus: $y = -0.0068x + .64$, $r = -.84$, $P < .01$; adult: $y = -.0164x + 1.11$, $r = .90$, $P < .01$. The regression coefficients differed significantly ($P < .05$) when compared by a two-tailed t-test for independent means [$t(118) = 8.1$, $P < .05$].

0036-8075/82/0416-0324$01.00/0

brain extracts from arterial blood. Since CBF appears in the numerator and denominator the ratio reduces to the ratio of the cerebral arteriovenous O_2 difference [($CaO_2 - CvO_2$)] to the arterial O_2 content [CaO_2] (*5*). This simplifies even further to $1 - (CvO_2/CaO_2)$. Thus a complex relationship reduces to the ratio of two easily measured variables.

Over a fourfold range of arterial O_2 content, cerebral fractional O_2 extraction was consistently lowest in the fetus (Fig. 1). The fetal fractional extraction increased as we reduced arterial O_2 content, but even at low O_2 content fetal values rarely reached postnatal levels.

A low fetal fractional O_2 extraction could be due to low fetal $CMRO_2$, increased cerebral O_2 delivery, or both. We calculated $CMRO_2$ (in milliliters per 100 g of brain weight per minute) for each group: fetus, 4.1 ± 0.2 (mean ± standard error of the mean); lamb, 6.1 ± 0.4; adult, 4.7 ± 0.3. Fetal $CMRO_2$ was not different from the adult, although both fetus and adult differed significantly [$F(2, 41) = 12.54$; $P < .05$. Newman-Keuls test, $P < .05$] from the lamb. In contrast, fetal O_2 delivery is higher than that of the adult. Fetal cerebral blood flow is twice that in the adult (121.8 ± 10.1 versus 63.8 ± 3.9 ml per 100 g/min) despite similar arterial O_2 content (10.7 ± 0.9 versus 12.8 ± 1.1 ml per 100 ml).

Why is cerebral O_2 delivery higher in the fetus? A rise in $PaCO_2$ increases CBF without changing arterial O_2 content or $CMRO_2$ (*2*); as a result, fractional O_2 extraction falls. Fetal $PaCO_2$ is higher than postnatal values (*1*); in our study fetal $PaCO_2$ was 48 ± 2 mmHg, in contrast to 35 ± 3 mmHg in the adult. If the relationship between fractional extraction and $PaCO_2$ could be described by a single function common to fetus and adult, one might attribute the differences between fetus and adult to $PaCO_2$.

We therefore sought evidence in a separate group of seven fetuses and seven adults that the difference in fractional O_2 extraction was simply the result of differences in $PaCO_2$. Experimental preparations and procedures were the same as in the first study except that we changed inspired CO_2 concentration rather than O_2. Figure 2 shows that $PaCO_2$ has a profound effect on fractional extraction in both groups, but the relationships are described by two distinct functions. Although adult and fetal fractional extraction happen to be equivalent at the fetal $PaCO_2$ of 48 mmHg, there is no reason to believe this is more than coincidental. The same is not true at the adult $PaCO_2$ of 35 mmHg.

These data do not eliminate the possibility that $PaCO_2$ contributes to differences in fractional extraction between fetus and adult. The $PaCO_2$ differences between adults and fetuses represent chronic situations that may not be mimicked by the acute changes in $PaCO_2$ in our experiments. Insofar as they are applicable, however, our data do not support the hypothesis that the only fundamental difference between fetus and adult is the $PaCO_2$.

The combination of a low fetal PaO_2 and the increased affinity of fetal hemoglobin for oxygen might contribute to the increase in fetal cerebral O_2 delivery. Because the affinity of fetal hemoglobin for oxygen is high (*6*), the fetus has a much lower PaO_2 than lambs or adults at the same oxygen content. In this study, PaO_2 values of 28, 91, and 110 mmHg in fetus, lamb, and adult, respectively, were associated with arterial O_2 contents of 10.7, 14.2, and 12.8 ml per 100 ml.

In theory, the quantity of O_2 within a tissue is a function of the total amount of O_2 in blood (that is, O_2 content), the PO_2 in the blood, the resistance to O_2 diffusion within the tissue, and the rate of oxygen consumption by the tissue (*7*). If hemoglobin affinity for oxygen increases, there will eventually be a noticeable decrease in tissue O_2 availability. Under such circumstances, CBF will rise (*8*), and fractional extraction will decrease. Recent measurements of CBF individuals with high-affinity hemoglobin bin variant (*9*) support this hypothetical sequence.

Our previous work in lambs (*5*) does not. We altered hemoglobin levels and PaO_2 in opposite directions so that arterial O_2 content remained constant. This resulted in combinations of arterial O_2 and PO_2 analogous to those produced by changing hemoglobin affinity. On theoretical grounds, one would expect blood flow to fall as PaO_2 rises. However, we found that blood flow and fractional extraction were the same with the "low" PaO_2 (40 mmHg)–high hemoglobin combination as with "high" PaO_2 (90 mmHg) and low hemoglobin. There are several possible explanations for the contradiction. (i) The low PaO_2 was not particularly low and may not have constituted sufficient stimulus to increase blood flow. (ii) For the same arterial O_2 content the high PaO_2 group had a lower hemoglobin level than the low. The correlation between hemoglobin concentration and blood viscosity (*10*) might have increased flow in the high group while depressing it in the low, masking an opposite tendency based on PaO_2. (iii) The major reason for increased flow in individuals with high-affinity hemoglobin may be that the chronically lower tissue PO_2 promotes an increase in the density of the cerebrovascular bed. This would not be reproduced by acutely changing the PO_2–O_2 content relationship.

In any case, relative to $CMRO_2$, fetal cerebral O_2 delivery exceeds that in the adult by 70 percent. As yet, the reason cannot be specified, nor is it clear whether this offers the fetus a relative advantage, anticipating the stresses of labor and delivery, or is simply a physiologic adaptation to the low fetal PO_2.

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14 August 1981; revised 22 October 1982