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cerebrum

Cerebral Reactions during Intrauterine Asphyxia in the Sheep. I. Circulation and Oxygen Consumption in the Fetal Brain

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Extract

Cerebral blood flow (CBF) with the ^{133}Xe clearance technique and cerebral oxygen consumption were measured in the fetal lamb using chloralose-anesthetized ewes and acutely exteriorized fetuses with intact umbilical circulation. To induce fetal hypoxia at different pH levels, three different procedures were used: (*1*) the ewe was ventilated with a hypoxic gas mixture, containing 8–15% O_2 in N_2; (*2*) 5–10% CO_2 was added to the hypoxia gas mixture; (*3*) during hypoxia a continuous rapid infusion of $NaHCO_3$ solution was given intravenously to the fetus. Blood gas tensions, pH, and oxygen saturation were measured repeatedly.

Multiple regression analysis was carried out on the data with the variables Sa_{O_2}, Pa_{O_2}, Pa_{CO_2}, and pH considered as independent variables and flow as the dependent variable. All complete sets of observations were used amounting to 74 observations in 11 animals. No significant correlation was found between CBF and pH. Sa_{O_2} showed the highest correlation to CBF. No further improvement of this correlation was obtained when Pa_{CO_2} was added as independent variable. Pa_{O_2} and Pa_{CO_2} described jointly the variations of CBF as well as Sa_{O_2} alone.

The oxygen consumption of the brain decreased during hypoxia when Sa_{O_2} was reduced below 40%. The decrease of the metabolic rate for oxygen was a function both of the degree of hypoxia and of pH. When an acidosis was added to the hypoxia a significant reduction of the oxygen consumption of the brain resulted compared with the same degree of hypoxia at normal or only moderately reduced pH levels.

Speculation

The cerebral blood flow of the fetal lamb is regulated mainly via the amount of oxygen available to the brain, and changes of CO_2 tension affect CBF via a displacement of the hemoglobin dissociation curve.

Cerebral oxygen consumption is reduced to dangerously low levels when a severe acidosis is combined with hypoxia because of a failure to extract the oxygen available in the arterial blood.

Introduction

The response of the cerebral vasculature to hypoxia and hypercarbia has been studied extensively in adult animals. The information available from fetuses or newborn animals is sparse. Studies using flow metering in one carotid artery on the fetal and newborn lamb have demonstrated that carotid artery blood flow increases during hypoxia and hypercarbia [7, 9, 10].

However, using a semichronic preparation Quilligan *et al.* [13], were unable to demonstrate any significant increase of carotid blood flow in the lamb fetus during hypercarbia. Using isotope wash-out techniques, Purves and James [12] demonstrated the occurrence of autoregulation and of vasodilatation due to hypoxia in the cerebral circuit. Their estimate of the oxygen consumption of the fetal brain was recently claimed to be an underestimate by Macowski *et al.* [8]. The latter authors based their calculations on results obtained with the microsphere injection method in a chronic lamb fetus preparation.

The present study was designed to establish the quantitative relation between cerebral blood flow and cerebral oxygen consumption, on the one hand, and the degree of hypoxia, on the other, in the fetal brain. A further goal was to investigate whether this relation is affected by simultaneous changes of pH, *i.e.*, whether an acidosis superimposed on the hypoxia modified the vascular response to the hypoxia or affected the oxygen consumption of the brain.

Methods

The experiments were conducted on 11 ewes of mixed breed with 12 fetuses. The estimated gestational age ranged from 94 to 145 days (term 145–150 days). The gestational age was estimated from the fetal weight and crown-rump length using standard curves [6].

Food was restricted for 24 hr before the experiment, water provided *ad libitum*. The anesthesia was induced with pentothal (5%, 0.1 ml/kg) and chloralose (1.4 ml/kg), given intravenously. The chloralose was 25 mg/ml in 5% borax solution.

To avoid hypoglycemia, a slow, continuous intravenous infusion of 10% glucose solution (50–100 ml/hr) was given to the ewe throughout the whole experiment. The ewes were tracheotomized and ventilated with known gas mixtures using an open-circuit ventilator, Starling's Ideal animal ventilator [15]. Maternal blood pressure and heart rate were recorded through a catheter placed in the medial plantar artery of one foreleg. This catheter was also used for arterial blood sampling from the mother.

The abdomen of the ewe was opened with a low paramedian incision, the uterus exposed, and its wall stitched to the abdominal wall. The uterus was opened, and the fetus delivered onto a thermoregulated board, heated to maintain a rectal temperature at 39° ± 0.5°.

The fetal trachea was cannulated immediately after delivery. To avoid fetal breathing this cannula was connected to a water-filled bag.

The fetus was heparinized with 1,000 IU of heparin. Fetal blood pressure and heart rate were recorded through a polyethylene catheter in the right bracheal artery with a Statham P23 AC-pressure transducer [16]. Arterial blood samples were taken from the same catheter. A polyethylene catheter, PE50, was placed in arteria lingualis or arteria thyreoidea superior in a retrograde direction with the tip of the catheter just inside the common carotid artery. Blood samples representative of cerebral venous blood were taken from the superior sagittal sinus through an indwelling scalp vein needle, cemented to the scalp with tissue adhesive.

Through the catheter in the common carotid artery 50–150 μCi ^{133}Xe in 0.5 ml saline was injected as a bolus for each determination of cerebral blood flow [17]. The exponential decay of the activity was measured for 20 min with a 2-inch thallium-activated scintillation detector through a collimator, 2 cm in diameter, placed over the side of the injection. The collimator was placed at the midpoint between the external auditory meatus and sagittal sinus of the fetal head. An additional lead shield reduced the radiation from other parts of the preparation. The counter was connected to a rate meter with a variable time constant, Philips PW4242 [18]. A time constant of 1 s was used for the first 4 min of the decay curve, and one of 4 s for the remainder. The rate meter output was recorded on a linear potentiometer ink recorder [19] with a maximal amplitude of 20 cm. The expired air from the ewe was led outside the laboratory to keep the background activity low. The decay curve was plotted semilogarithmically after background subtraction. This curve was analyzed graphically according to the method of Häggendal *et al.* [2] to give two straight lines, a fast and a slow component. The fast component has been taken to represent blood flow through gray matter [2, 12]. The slow component has been claimed to represent white matter blood flow, but because of the likelihood of recirculation this phase has been disregarded in the present analysis. Blood flow was calculated using the formula: blood flow $= \lambda \ln 2/T_{1/2}$ (milliliters/(100 g·min)).

The partition coefficient λ was read from the curves presented by Purves and James [12] using the hematocrit, measured at each xenon injection. The same authors tested the significance of the components of the washout curve and demonstrated the similarity between the fast component and the monoexponential decay curve obtained after a microinjection of tracer into the cortical layer. It should be realized, however, that our measurements of "cerebral blood flow" only

represent flow through an anatomically ill-defined portion of the cerebral cortex and do not represent overall cerebral blood flow.

In some experiments the blood flow through one common carotid artery was measured continuously with an electromagnetic flowmeter [16]. No attempts were made to ligate branches supplying the parts of the head other than the brain. Maternal and fetal arterial blood pressure, fetal heart rate and carotid blood flow were recorded using a Grass *model 7B* polygraph [20]. The ewes were ventilated with known gas mixtures with 30% O_2 to maintain fetal Pa_{O_2} and Pa_{CO_2} within normal limits [5]. To induce fetal hypoxia at different pH levels, three different procedures were used: the ewe was ventilated with a hypoxic gas mixture, containing 8–15% O_2 in N_2, to bring the Pa_{O_2} of the ewe from 80–120 to 25–40 mm Hg; 5–10% CO_2 was added to the hypoxic gas mixture; during hypoxia a continuous, rapid infusion of 1 M $NaHCO_3$ solution was given via the jugular vein to the fetus at a rate of 1.1–1.6 ml/(min·kg). Each period of hypoxia lasted 20 min. The ^{133}Xe was injected 10 min after starting the hypoxia and blood samples were taken 5 min later.

The ewes were randomly exposed to normoxia, hypoxia, or hypoxia plus pH changes. Between the different periods of hypoxia, control periods were inserted in which the ewes were ventilated with 30% O_2 in N_2 for 30–60 min. Blood gas tensions and pH were immediately measured at 38° with a Radiometer pHM27GM [21], using standard Po_2 and Pco_2 electrodes. Oxygen saturation (So_2) was measured, using a filter photometer, Radiometer OSM 1 [21]. The oxygen content was calculated from the saturation value and the hemoglobin concentration, on the assumption that 1 g hemoglobin maximally binds 1.34 ml O_2. The oxygen consumption of the brain was calculated from the blood flow measurement and the arteriovenous difference for O_2 content. This is not a measure of overall cerebral oxygen consumption but corresponds to the part of the brain represented by the fast components of the clearance curve, provided that this part of the brain drains its venous blood into the sagittal sinus.

Statistical Methods

Multiple regression analysis was carried out on the data with the variables So_2, Po_2, Pco_2, and pH considered as independent variables and flow as the dependent variable. All complete sets of observations were used, amounting to 74 observations from 11 animals. To decrease variance arising from different intra-individual levels of blood flow or blood gases the analysis was also performed after normalization of the variables. As the reference for each individual the value with Po_2, Pco_2, and pH values within the normal range given by Joelsson *et al.* [5] was used. In 9 of the 11 fetuses, this corresponded to the first observation performed. Confidence intervals and significances were determined using standard procedures, well described in Snedecor and Cochran [14].

Results

Blood gases, heart rate, and mean arterial blood pressure for the ewe and the fetus are tabulated in Table I. These are basal values obtained immediately before the first period of hypoxia. Table I also contains information about the cerebral blood flow and cerebral oxygen consumption obtained as basal values in the present series.

The reactions to hypoxia of cephalic blood flow, ^{133}Xe clearance, heart rate, and arterial blood pressure are exemplified in Figures 1 and 2. In a total of 35 periods of hypoxia in 12 different animals, the ^{133}Xe clearance increased on each occasion as compared with the control period. In 16 periods of hypoxia, the

Table I. Basal values for blood gases, hematocrit (Hct), cerebral blood flow (CBF), mean arterial blood pressure (BP), heart rate (FHR), and cerebral oxygen consumption ($\dot{V}o_2$) in fetal lamb[1]

Subject	pH	Pa_{O_2}, mm Hg	Pa_{CO_2}, mm Hg	Hct, %	CBF, ml/(min·100 g)	BP, mm Hg	FHR, beats/min	$\dot{V}o_2$, ml/(min·100 g)
Ewe (11)								
$\bar{x}$	7.45	115	35.3	28.6		93.6		
SD	0.06	22.5	5.2	4.62		19.2		
Range	7.35–7.55	80–152	29–48	23–38		75–140		
Fetus (12)								
$\bar{x}$	7.29	28.7	43	49	56.1	52	162	2.04
SD	0.08	3.0	4.9	5.1	13.1	10.4	29.4	0.78
Range	7.17–7.41	24–33	34–50	40–57	36–80	36–75	114–222	1.3–3.5

[1] Number of experimental animals is shown in parentheses.

cephalic blood flow (measured with the electromagnetic flow probe applied to one carotid artery) increased on 15 occasions and stayed unchanged on one occasion. The increase of the cephalic blood flow was not always proportional to the increase of the rate of ^{133}Xe clearance. The electromagnetic flow probe measurements were used to define the time when a steady state had been reached during hypoxia, usually after 5–10 min, and to observe when the hyperemia accompanying hypoxia had faded away, usually after 30–45 min.

The increase of the cerebral blood flow, as measured with the ^{133}Xe clearance rate, was related to the degree of hypoxia as well as to the degree of hypercarbia. Figure 3 demonstrates the relation between the arterial CO_2 tension and the cerebral blood flow when the whole material is divided into two groups according to either a normal or a low Po_2 in arterial blood. A linear relation between cerebral blood flow and Pco_2 at normal oxygen tensions appears to be distorted at low oxygen tensions, when the blood flow has already increased. To test whether such a nonlinear relation between cerebral blood flow and blood gases existed a statistical analysis was undertaken.

Mean values, standard deviations, range, and correlations for the 74 observations on 11 fetuses are given in Tables II and III. The correlations presented are obtained from absolute as well as normalized values. Although high correlations exist between the connected pairs of variables So_2-Po_2 and Pco_2-pH, the correlation between either So_2 or Po_2 with one of Pco_2 or pH is only weak. This demonstrates that the oxygenation of the fetus could be altered independently with regard to acid-base parameters. Because there is no significant correlation between blood flow and pH, the latter variable is disregarded in the further analysis. So_2 shows the highest correlation to blood flow, both when absolute and normalized values are used (Table III). A regression analysis with flow *versus* So_2 explains more than 50% of the variance of flow, using normalized variables ($R^2 = 0.56$). No significant improvement is obtained when the other variables (Pco_2, Po_2) are added ($R^2 = 0.58$).

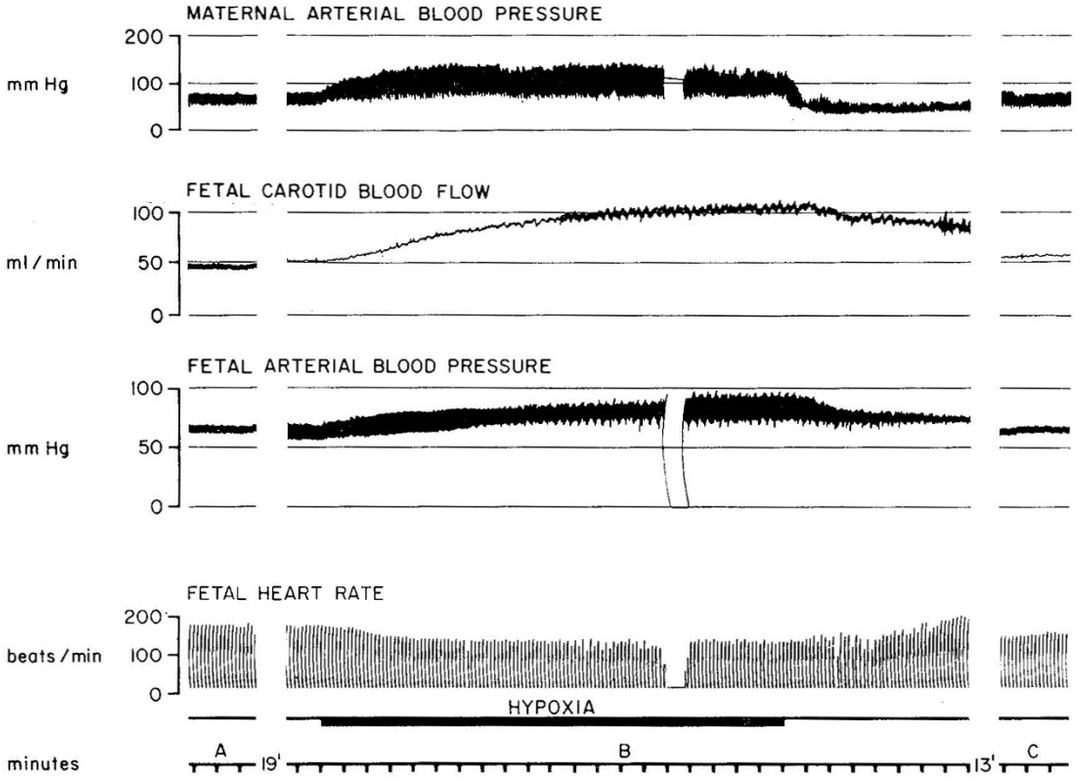

Fig. 1. Example of the reactions of carotid blood flow, arterial blood pressure, and heart rate in the fetus during hypoxia and CO_2 retention. Estimated gestational age 142 days. During control periods (*A* and *C*) the ewe was ventilated with 30% O_2, during hypoxia (*B*) 10% O_2, 10% CO_2, and 80% N_2. *A*, *B*, and *C* correspond to times when ^{133}Xe was injected intra-arterially. The recorded Xe clearance curves are displayed in Figure 2.

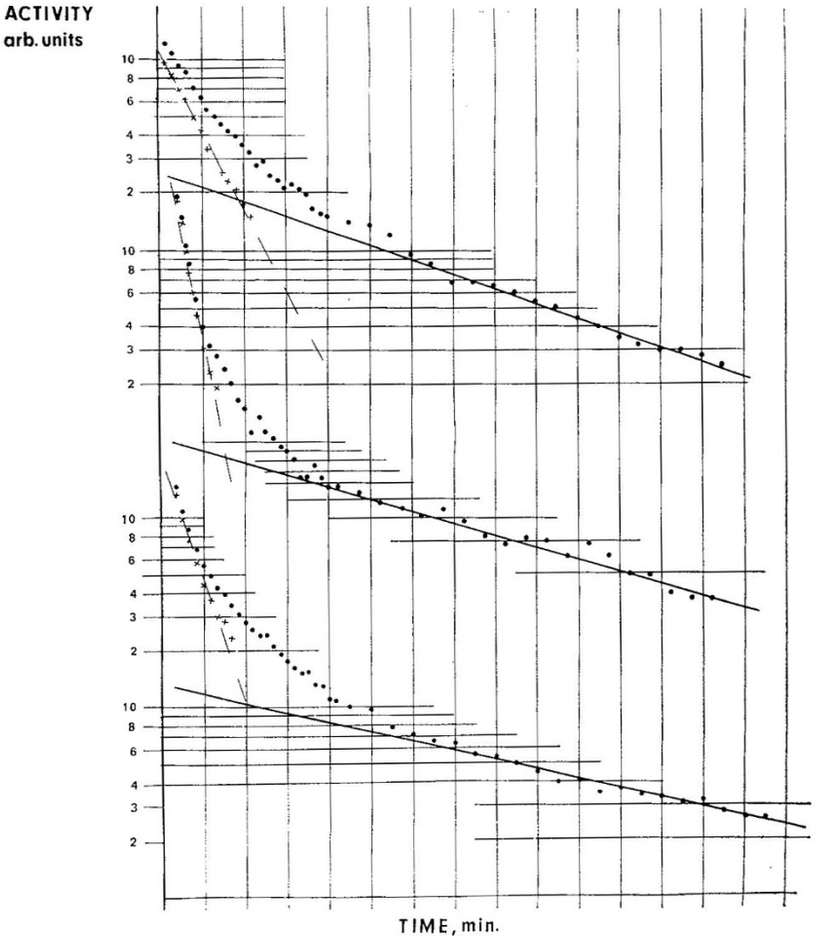

Fig. 2. Semilogarithmic plots of the ^{133}Xe clearance curves obtained from the same experiment as in Figure 1, with curves *A*, *B*, and *C* from top to bottom. Peak activity for each curve corresponds to about 300 cpm. ●: recorded values after background subtraction; ——: fitted visually to the last part of the curve; +: obtained after subtracting the —— from ●. – – –: fitted visually to + (the calculated cerebral blood flow values for the test component were 69 ml/(min·100 g) in *A*, 190 ml/(min·100 g) in *B*, 116 ml/(min·100 g) in *C*).

If So_2 is left out of the model, about 50% of the flow variance is again explained by Po_2 and Pco_2 jointly ($R^2 = 0.48$). Thus, the two models, flow = $a_1\ So_2 + a_0$ and flow = $b_1\ Po_2 + b_2\ Pco_2 + b_0$, describe the variation in cerebral blood flow equally well. The confidence limits for the variables obtained in these two models are given in Table IV.

The residual variances in the two models were tested against the magnitude of the flow. A significant correlation was found ($R = 0.66$ and 0.72, respectively, for *models a* and *b*). This indicates diminishing reliability of the model at high cerebral blood flows. A nonlinear model might thus be a better predictor.

The same type of statistical analysis was carried out using So_2, Po_2, Pco_2, and pH in the sagittal sinus blood as independent variables and CBF as the dependent variable. However, the relations found explained less of the variance of flow than when the corresponding blood gas values in the arterial blood were used.

The oxygen consumption of the brain during basal conditions amounted to 2.0 ml/(min·100 g) (Table I). During hypoxia the oxygen consumption diminished to a variable extent. This decrease occurred when the arterial oxygen saturation was lowered below 40%. However, the decrease of the metabolic rate was a function both of the degree of hypoxia and of pH (Fig. 4). From this figure two extreme groups were selected for comparison. Only values of oxygen saturation below 40% were considered. One group of values, in which the oxygen consumption was only moderately reduced (oxygen consumption above 1.0

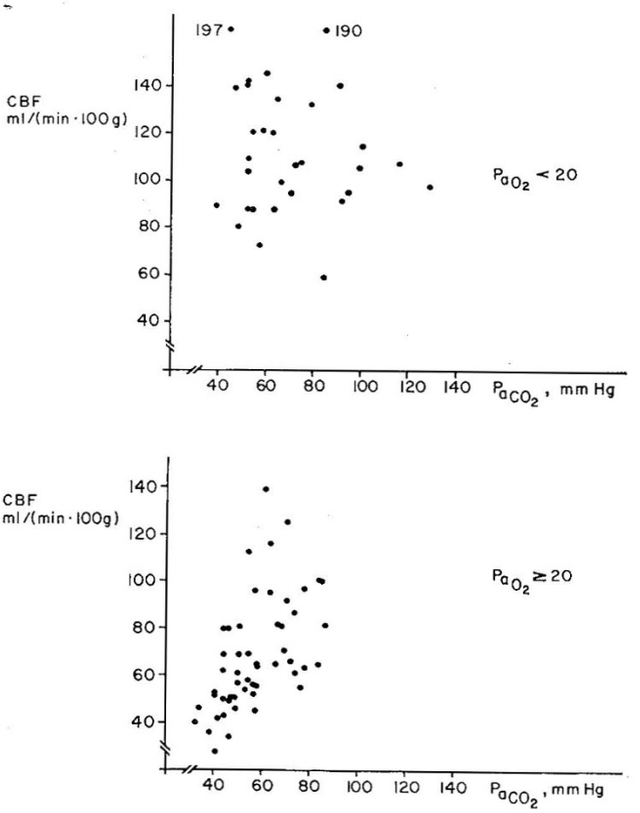

Fig. 3. Graphic correlation between P_{CO_2} and cerebral blood flow (CBF). The upper part of the figure gives values collected during hypoxia ($Pa_{O_2} < 20$). The lower part of the figure demonstrates the correlation at a normal Pa_{O_2} ($Pa_{O_2} \geq 20$).

Table II. Description of variables used for multiple regression analysis

Variable	Mean	SD	Range
Flow, ml/(min·100 g)	84	35	28–197
S_{O_2}, %	49	27	28–88
P_{O_2}, mm Hg	22	7.7	9–39
P_{CO_2}, mm Hg	62	19	32–128
pH	7.24	0.18	6.81–7.71

Table III. Correlation matrix between absolute (above) and normalized values (below)

Variable	Flow	S_{O_2}	P_{O_2}	P_{CO_2}	pH
Flow	1.00				
S_{O_2}	−0.58	1.00			
	−0.75				
P_{O_2}	−0.55	0.78	1.00		
	−0.60	0.84			
P_{CO_2}	0.37	−0.52	−0.26	1.00	
	0.48	−0.52	−0.23		
pH	0.10	0.16	−0.14	−0.53	1.00
	−0.12	0.15	−0.20	−0.56	

ml/(min·100 g)), was contrasted with the group of values with the most severe reduction (oxygen consumption below 0.5 ml/(min·100 g)). Table V compares the two groups with respect to oxygen consumption, arterial oxygen saturation, cerebral blood flow, and arterial pH. The difference of pH between the groups is statistically significant, using the Wilcoxon rank test.

Table IV. Variables for two models[1]

$CBF = 162 - 1.37\ (\pm 0.28)\ S_{O_2}\ (R^2 = 0.56)$
$CBF = 104 - 2.46\ (\pm 0.84)\ P_{O_2} + 0.61\ (\pm 0.19)\ P_{CO_2}\ (R^2 = 0.48)$

[1] Based on normalized data and transformed to standard variables for convenience by using the mean initial values S_{O_2} = 75%, P_{O_2} = 29 mm Hg, and P_{CO_2} = 43 mm Hg. Confidence intervals given are at 5% level. Cerebral blood flows (CBF) are in milliliters/minute·100 g, S_{O_2} in per cent, and P_{O_2} and P_{CO_2} in mm Hg.

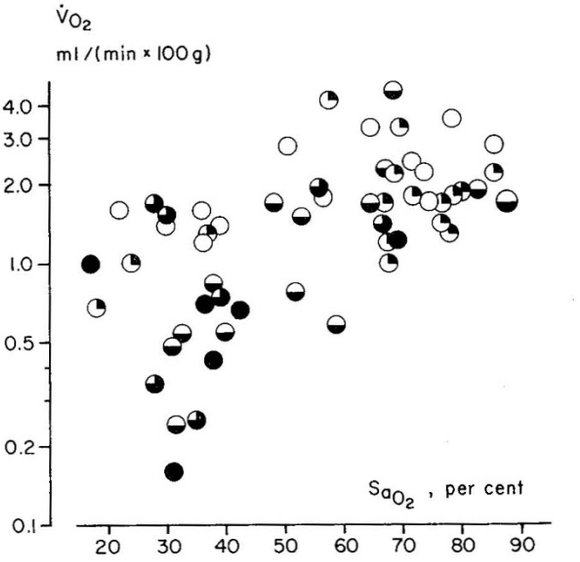

Fig. 4. Graphic correlation between Sa_{O_2} and the brain oxygen consumption ($\dot{V}_{O_2}$). The open circles are at a pH ≥ 7.30; the three-quarter open circles at pH 7.20–7.29; the semifilled circles at pH 7.10–7.19; the three-quarter filled circles at pH 7.00–7.09; and the filled circles at pH ≤ 7.00.

Table V. Comparison between all values in Figure 4 with high group and low group

Group	$\dot{V}_{O_2}$	Sa_{O_2}	pH	CBF[1]	*n*
High group[2]	1.50	32.3	7.39	107	9
Low group[3]	0.32	32.5	7.02	105	6

[1] CBF: cerebral blood flow.
[2] $Sa_{O_2} < 40\%$ and $\dot{V}_{O_2} > 1.0$ ml/(min·100 g).
[3] $Sa_{O_2} < 40\%$ and $\dot{V}_{O_2} < 0.5$ ml/(min·100 g).

Discussion

To compensate for the slight depression of arterial oxygen tensions following anesthesia the ewes were ventilated with 30% oxygen in air. In this way it was possible to match the blood gas values of the fetuses with those obtained from the chronic lamb fetus preparation [5], although our fetuses had slightly lower pH levels. This demonstrates that the acute, exteriorized preparation can be maintained at normal conditions in this respect. Our basal values for cerebral blood flow and for cerebral oxygen consumption are about half of those reported by Makowski *et al.* [8] using the microsphere distribution technique in the intrauterine fetus, but are closely similar to the values given by Purves and James [12], who used the ^{133}Xe clearance method in the acutely exteriorized fetus. Although the blood gas values from the series of Purves and James [12] are virtually the same as our results, Makowski *et al.* [8] found both a lower mean Pa_{O_2} value and a higher Pa_{CO_2} value. Both deviations tend to increase the CBF. The two techniques are, however, not strictly comparable because the microsphere method gives a measure of blood flow representing overall cerebral blood flow including the various parts of the brain while the xenon clearance method measures blood flow in some part of the cortical gray matter.

The significant correlations between CBF and S_{O_2}, P_{O_2}, and P_{CO_2} demonstrated in Table III have been repeatedly found in adult animals and man previously. The lack of correlation between CBF and changes of pH when P_{CO_2} effects are excluded (Table III) was suggested also by Harper and Bell [1] using adult dogs. However, this is a much disputed question and the present results contribute little to this discussion, inasmuch as the pH and P_{CO_2} factors are not well separated in this study (Table III).

The findings presented in Figure 3 suggested to us that the correlation between CBF and P_{CO_2} might be valid only at normal P_{O_2} levels and vice versa. The question arose whether cerebral blood vessels that were already dilated by hypoxia could also respond to hypercarbia. Multiple regression analysis demonstrates that the residual variance increases at high CBF values when investigating the correlation between CBF, P_{O_2}, and P_{CO_2}. This indicates that the linear model explains a smaller proportion of the CBF changes at high blood flows than at low blood flows.

The mechanism by which Pco_2 of the arterial blood exerts its regulating influence on cerebral blood flow is not known, but has been extensively discussed. The most attractive hypothesis at present appears to be an action via a change of the extracellular pH of the brain. The evidence for this hypothesis was recently reviewed by Purves [11]. The present series of experiments raises another possibility, namely that changes of Pco_2 affect CBF via the displacement of the hemoglobin dissociation curve. From Table IV it is apparent that the changes of CBF can be as well described by So_2 alone as by the combination of Po_2 and Pco_2. Further, the addition of Pco_2 to the So_2 model does not increase the predictive power of this model.

These results suggest the possibility that fetal CBF is regulated by the oxygen saturation of the arterial blood. In the dog a relation between diminished oxygen capacity and raised CBF has already been documented [3].

With either model only little more than half of the CBF variations found are explained by the blood gases (Table IV). A number of other variables might be discussed. Among them are the maturity of the fetus and the neurogenic reflex activity. In experiments using the carotid blood flow method Mann [9] produced evidence to show that cephalic blood flow under basal conditions is unaffected by fetal maturity when expressed per gram of brain tissue. It is conceivable that autonomic nervous tone and reflex activity contribute markedly to the residual variance, as it is well documented, both in the baboon [4] and the fetal lamb [12], that the vascular response of the brain to alterations of blood gases is greatly modified by such circumstances.

A decrease of cephalic oxygen consumption during severe hypoxia in the fetus was described by Mann [10]. Using more moderate degrees of hypoxia, Purves and James [12] obtained no change of the metabolic rate of oxygen in four fetuses. The present results (Fig. 4) indicate a decrease of the oxygen consumption when the oxygen saturation of arterial blood is lowered below 40%. The magnitude of the reduction of oxygen consumption is a function of pH, so that the combination of hypoxia and acidosis produces a more marked inhibition of oxidative metabolism in the brain than hypoxia alone (Fig. 4, Table V). Because acidosis does not affect the total blood flow to the brain (Table V), the drastic reduction of oxygen consumption when hypoxia is combined with acidosis could be caused by two mechanisms: a reduced oxygen extraction from the blood because of a primary effect on the brain cells, or a reduced oxygen extraction because of an unequal distribution of blood flow within the tissue, *i.e.*, a disturbed microcirculation during the combination of hypoxia and acidosis.

Summary

Cerebral blood flow (CBF) and cerebral oxygen consumption were measured with the ^{133}Xe clearance method and blood gas analyses in 12 fetal lambs, of 94–145 days of gestational age. Periods of hypoxia were created by ventilating the ewe with appropriate gas mixtures. The pH of fetal blood was altered via addition of CO_2 gas to the ewe, or infusions of alkali to the fetus. Multiple regression analysis of CBF on blood gases demonstrated no correlation between CBF and pH, but a significant correlation between CBF and Pa_{O_2}, Pa_{CO_2}, and Sa_{O_2}. The parameter Sa_{O_2} alone gave the same correlation to CBF as Pa_{O_2} and Pa_{CO_2} in combination. It is suggested that Pa_{CO_2} influences the CBF of the fetus via a shift of the hemoglobin dissociation curve.

The oxygen consumption of the brain decreased during hypoxia. The decrease was significantly more profound when the hypoxia was combined with acidosis. Because cerebral blood flow in hypoxia was not, however, diminished in the presence of acidosis, it is suggested that acidosis reinforces the principal ill effects of hypoxia, reduced oxygen consumption in the brain, by a mechanism which curtails the ability of the brain to extract the oxygen made available to it.

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