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Cerebral reactions to intrauterine asphyxia in the sheep
III. Effects of alterations of hematocrit and viscosity

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The observation that the fetus and newborn has a greater ability to survive an asphyctic insult than the adult stems from old age. Likewise, the fact that an individual can withstand a period of asphyxia but survive with a permanent brain damage is thoroughly documented.

In an attempt to evaluate the role of a few specified factors in the causation of the insult to the brain a series of experiments were conducted on the fetal lamb [2, 6]. **In these experiments it was demonstrated that hypoxia altered the electrical activity of the brain, as measured by the somato-sensory evoked EEG responses** (SER). SER was affected both in shape and in amplitude when arterial P_{O_2} was reduced below 20 mm Hg and was completely abolished at very low P_{O_2} levels (10—12 mm Hg). **Hypoxia also induced a cerebral vasodilatation and a reduction of the cerebral oxygen consumption. The combination of hypoxia and acidosis elicited the same responses but at higher arterial oxygen tensions.** Although the cerebral blood flow rose to maximum values, the oxygen consumption of the brain was markedly reduced during the combination of acidosis and hypoxia. Thus, this combination resulted in a significant diminution of the extraction of the oxygen available in the blood. It was speculated that this effect on oxygen extraction was due either to an impaired microcirculation or to a primary effect on the brain cells.

The present series of experiments was undertaken to elucidate the **possible importance of rheological factors in the asphyctic situation.** The study was designed to see whether **an improvement of the rheological characteristics of the blood, by decreasing the viscosity and the hematocrit, would increase the ability of the brain to withstand hypoxia in general,** and in particular, would restore the capacity to extract oxygen from the blood during hypoxia at low pH levels.

This problem has both a theoretical and a practical-clinical interest since the demonstration of an impaired microcirculation in the brain during asphyxia would imply that treatment of rheological factors could be rewarding.

Curriculum vitae

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1 Methods

The experiments were conducted on 17 ewes of mixed breed with 25 fetuses. Their gestational age ranged from 105 to 145 days (term 145—150 days). The gestation was dated in 15 ewes and was estimated from fetal weight and crown-rump length in two ewes using standard curves [5]. Food was restricted 24 hours prior to the experiment, water ad libitum. The anesthesia was induced with pentothal (5%, 0.1 ml/kg) and was maintained with chloralose (25 mg/ml, 1.4 ml/kg) given intravenously. The ewes were tracheotomized and ventilated with known gas mixtures, using an open circuit respirator. Maternal blood pressure and maternal arterial blood gases were recorded through a catheter in the medial plantar artery of one foreleg.

The uterus was exposed through a paramedian abdominal incision and stitched to the abdominal wall. The uterus was opened and the fetus delivered onto a heated small table. Care was taken not to disturb the umbilical circulation. Fetal arterial blood pressure and heart rate were recorded from a catheter in the right brachial artery by a STATHAM P23 AC-pressure transducer. Arterial blood samples were taken from the same catheter. Blood samples representative of cerebral venous blood were taken through an indwelling catheter in the sagittal sinus. A catheter was placed in the superior thyroid artery with its tip just inside the common carotid artery. Through this catheter ^{133}Xe in saline was injected for the determination of cerebral blood flow. The decay of activity was measured with a scintillation detector placed over the fetal head on the same side as the injection with the collimator at the midpoint between the external auditory meatus and the sagittal sinus. The decay curve was recorded on a potentiometer writer. The curve was later analyzed graphically and separated into a slow and a fast component. The fast component was taken to represent gray matter blood flow [7].

Evoked EEG responses were recorded from the surface of the intact scalp. Cup electrodes were fixed over the part corresponding to the suprasylvian gyrus, with the indifferent electrode fixed at the posterior part of the fetal head. The EEG was monitored on a GRASS polygraph model 7B. The data were also stored on a tape recorder. A mechanical tap on the muzzle close to the nostril on one side was used as the tactile stimulus. The response obtained was thus a somato-sensory evoked EEG response — SER.

The basic components of SER are the primary positive deflection P_1 and the secondary response N_1. In more mature fetuses some later components followed. The changes of SER during the experiments were divided in six grades (Fig. 1). **Grade 0:** normal response. **Grade 1:** First distinct changes in form of amplitude reduction of at least 30% of one of the basic deflections (P_1—N_1) and/or distinct reduction of the late components. **Grade 2:** P_1 and N_1 as in 1, plus the complete loss of the late components. **Grade 3:** Decrease of P_1 or N_1 to less than 50% of the original amplitude. **Grade 4:** Beginning of the breakdown of the whole response. This period lasts usually only 1—3 minutes and is followed by **grade 5:** No response at all. Grade 2 depends on fetal maturity and the character of the response and is therefore not always demonstrable.

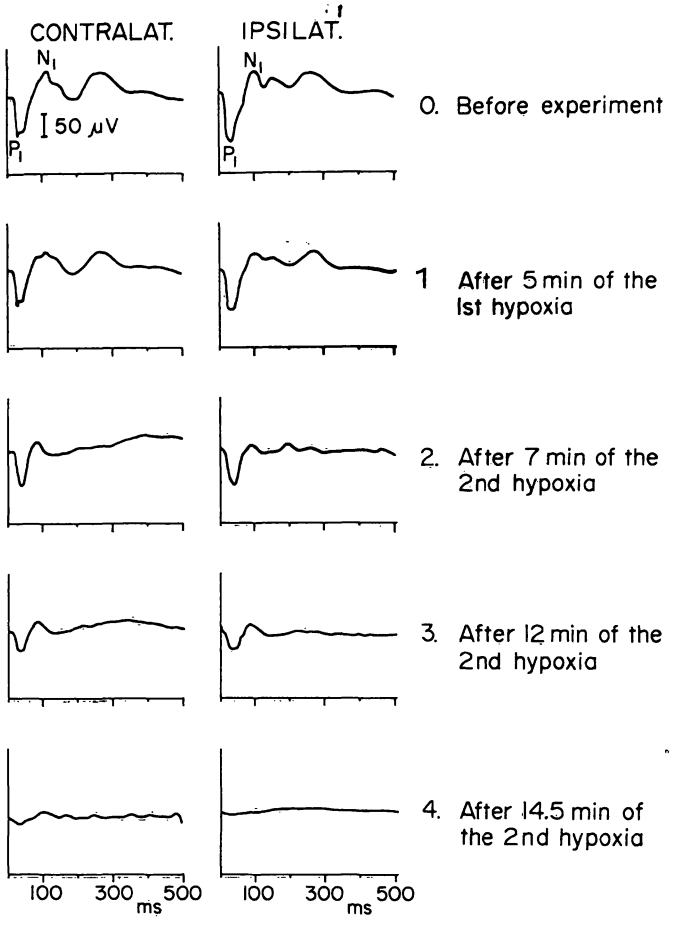

Fig. 1. From exp. No. 4/73. Mature lamb fetus, 129 days of gestation. Example of SER changes during hypoxia. For explanation of Grade 0 to 4, see text.

The ewes (and thereby the fetuses) were exposed to alternate periods of normoxia and hypoxia. Blood gas tensions and pH were immediately measured on a Radiometer pHM 27 using standard P_{O_2} and P_{CO_2} electrodes. Oxygen saturation (Sa_{O_2}) was measured on a filter photometer. The oxygen content was calculated from the saturation value and the hemoglobin concentration, assuming that 1 g Hb maximally binds 1.34 ml O_2. The oxygen consumption of the brain was calculated from the blood flow and the a-v O_2-difference.

The viscosity and the hematocrit values of the fetus were decreased by partly substituting the blood volume with three different fluids, performed as an isovolemic exchange transfusion with 10—40 ml/kg body weight. In six experiments the blood was substituted with 6% Dextran (Macrodex®, PHARMACIA Ltd., Sweden; molecular weight 70.000, viscosity: 2.81 cP), in five experiments with 4% Ficoll® (PHARMACIA Ltd., Sweden; molecular weight ~80.000, viscosity: 1.03 cP). Ficoll® is a polymer of sucrose and epichlorohydrin. In five experiments the viscosity was altered with Haemaccel®, a polymer of gelatine peptides (HOECHST Ltd, West Germany; molecular weight 35.000, viscosity: 1.29 cP). The hematocrit value was determined after each exchange transfusion.

In some experiments the viscosity and the hematocrit were increased during the experiments via an exchange transfusion with packed red cells collected from the fetus at an early stage of the experiment (seven cases) or from a twin fetus (one experiment).
The viscosity was determined with the OSWALD Viscometer. Only one type of plasma substitute was used in each experiment.
A more detailed account of the experimental procedures is given in [2, 6].

2 Results

Three different variables were used to assess the cerebral function, namely the cerebral blood flow (CBF), the cerebral oxygen consumption and the somato-sensory evoked EEG responses (SER). Each of these three variables was treated as the dependent variable and a multiple regression analysis was performed against the other two variables and blood gas values, hematocrit and viscosity as the independent variables. The correlation matrix for the complete set of 79 observations is given in Tab. I, where only those correlations are included which proved statistically significant ($P < 0.05$). In this table, viscosity is not included, since only 49 such observations were performed. However, when these 49 complete sets of observations were separately investigated **a very strong correlation was apparent between the hematocrit and the viscosity** ($r = 0.83$) and, moreover, the correlation matrix gave in every instance the same correlations as in Tab. I, although in some cases with somewhat lower correlation coefficients. Viscosity in itself apparently did not contribute any extra information not contained in the hematocrit value. Therefore the further analysis of the data is based on the 79 complete sets of observations and using hematocrit instead of viscosity as one independent variable.
No systematic differences were observed when the three different groups of experiments (exchange transfusion against the three different kinds of plasma expander) were compared in terms of the reactions of CBF, oxygen consumption of the brain or SER to hemodilution or to hypoxia.

2.1 Cerebral blood flow

A statistically **significant correlation was observed between the CBF and the hematocrit** (Tab. I). The correlation is displayed in Fig. 2. It should be noted that this figure contains all CBF-values, both at normal blood gas tensions and during hypoxia, hypercapnia and acidosis. The figure thus gives the range of variation of CBF at different levels of hematocrit. The graph suggests a non-linear relationship with a moderate effect of hematocrit alterations above the 30—35 per cent level and a more pronounced increase of CBF when the hematocrit is reduced below this level.
CBF also demonstrated **a significant correlation to the degree of hypoxia,** whether expressed as Sa_{O_2} or Pa_{O_2}. A significant negative correlation was further found with the oxygen extraction

Tab. I. Correlation matrix for 79 observations. Correlation coefficients between the following variables: CBF — cerebral blood flow in ml/min × 100 g, pH, Hct — hematocrit in per cent, Sa_{O_2} — oxygen saturation in per cent, a-v O_2 difference — oxygen extraction in ml/100 ml, $\dot{V}_{O_2}$ — oyxgen consumption in ml/min × 100 g, Pa_{O_2} — partial pressure of oxygen in mm Hg, and SER — somato-sensory evoked responses in arbitrary units.

	CBF	pH	Hct	Sa_{O_2}	a-v O_2-difference	$\dot{V}_{O_2}$	Pa_{O_2}
CBF	1.00						
pH		1.00					
Hct	—0.41		1.00				
Sa_{O_2}	—0.38	0.44		1.00			
a-v O_2-difference	—0.50	0.35	0.31	0.74	1.00		
$\dot{V}_{O_2}$		0.29		0.61	0.79	1.00	
Pa_{O_2}	—0.42			0.81	0.54	0.36	1.00
SER	0.35	—0.37		—0.60	—0.38		—0.58

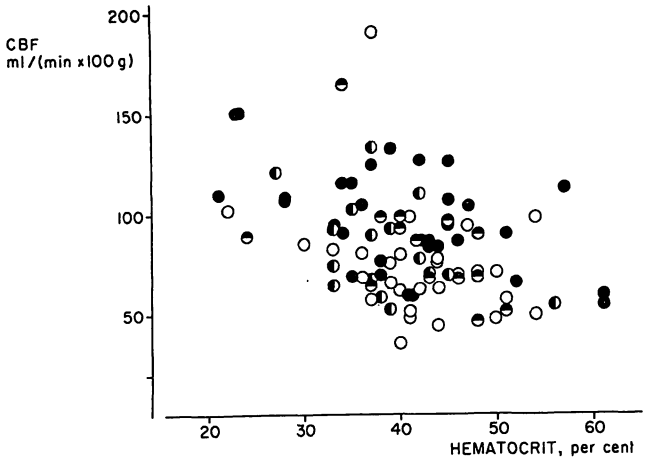

Fig. 2. Graphic correlation between cerebral blood flow and hematocrit at different blood gas tensions.

- ○ Normoxia ($Pa_{O_2} \geqq 20$ mm Hg), — Normocapnia ($Pa_{CO_2} \leqq 55$ mm Hg)
- ● Hypoxia ($Pa_{O_2} < 20$ mm Hg), — Normocapnia ($Pa_{CO_2} \leqq 55$ mm Hg)
- ◐ Normoxia ($Pa_{O_2} \geqq 20$ mm Hg), — Hypercapnia ($Pa_{CO_2} > 55$ mm Hg)
- ◉ Hypoxia ($Pa_{O_2} < 20$ mm Hg), — Hypercapnia ($Pa_{CO_2} > 55$ mm Hg).

(cerebral a-v O_2-difference). **No statistically significant correlation was found with either pH or cerebral oxygen consumption.**

To reveal a possible change of correlation between CBF and the other variables during hypoxia the material was split into two groups: "normoxia" ($Sa_{O_2} > 45$ per cent, 59 observations) and "hypoxia" ($Sa_{O_2} < 45$ per cent, 20 observations) (Tab. II).

In the "normoxic" group the CBF gave exactly the same relations with the independent variables as in the total material. In the "hypoxic" group, however, no significant correlation between CBF and the oxygen extraction was obtained, while, instead, CBF was significantly correlated to the cerebral oxygen consumption.

2.2 Cerebral oxygen consumption

Neither hematocrit nor viscosity showed any correlation to the cerebral oxygen consumption. The strongest correlations were found between cerebral oxygen consumption and Sa_{O_2}

Tab. II. Correlation matrix at "normoxia" ($Sa_{O_2} > 45$ per cent), and at "hypoxia" ($Sa_{O_2} < 45$ per cent). The same variables and abbreviations are used as in Tab. I.

$Sa_{O_2} > 45$ per cent (59 observations)

	CBF	pH	Hct	Sa_{O_2}	a-v O_2-difference	$\dot{V}_{O_2}$	Pa_{O_2}
CBF	1.00						
pH		1.00					
Hct	—0.40		1.00				
Sa_{O_2}	—0.28			1.00			
a-v O_2-difference	—0.52	0.35	0.37	0.65	1.00		
$\dot{V}_{O_2}$		0.31		0.48	0.72	1.00	
Pa_{O_2}	—0.31			0.73	0.39		1.00
SER	0.37			—0.48			—0.46

$Sa_{O_2} < 45$ per cent (20 observations)

	CBF	pH	Hct	Sa_{O_2}	a-v O_2-difference	$\dot{V}_{O_2}$	Pa_{O_2}
CBF	1.00						
pH		1.00					
Hct	—0.48		1.00				
Sa_{O_2}			0.34	1.00			
-av O_2-difference				0.56	1.00		
$\dot{V}_{O_2}$	0.30			0.53	0.89	1.00	
Pa_{O_2}	—0.38			0.52			1.00
SER		—0.39					—0.36

and oxygen extraction. When the material was subdivided into a "normoxic" and a "hypoxic" group no alterations occurred in these relations. As mentioned above, a statistically significant correlation between oxygen consumption and CBF became apparent in the "hypoxic" group, but was not seen in the whole material.

The oxygen extraction (a-v O_2 difference) was significantly correlated both to pH and to oxygen saturation (Tab. I). When the material was subdivided, multiple regression analysis showed no improvement of the residual variance when pH was added to the regression of oxygen extraction on Sa_{O_2} in the normoxic group. In contrast, such an improvement was seen in the hypoxic group.

2.3 Somato-sensory evoked EEG-responses

The correlation matrix and the multiple regression analysis **failed to demonstrate any influences on the SER by a change in hematocrit or viscosity either at normal oxygenation or during hypoxia.** However, in **some experiments where a marked reduction of the hematocrit was induced the SER demonstrated the same type of response as during hypoxia** (see Fig. 3).

The SER deteriorated both with falling Sa_{O_2} or Pa_{O_2} values and low pH levels (Tab. I). When the material was subdivided it became apparent that **the SER was strongly correlated to the degree of hypoxia both in the "normoxic" and the "hypoxic" group,** while the correlation between **a deterioration of the SER and a low pH value was obvious only in the "hypoxic" group.**

Thus the SER became more seriously affected by the combination of hypoxia and acidosis than by hypoxia itself. An example of this type of relation is given in Fig. 4.

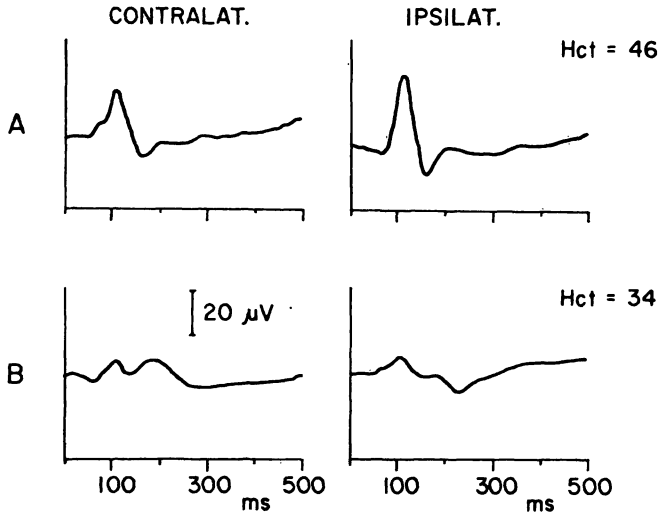

Fig. 3. From exp. No. 9/73. Immature lamb fetus, 107 days of gestation. Example of SER changes when the normal hematocrit of 46% is diluted to 34% with Ficoll®. Both recordings during normoxia.

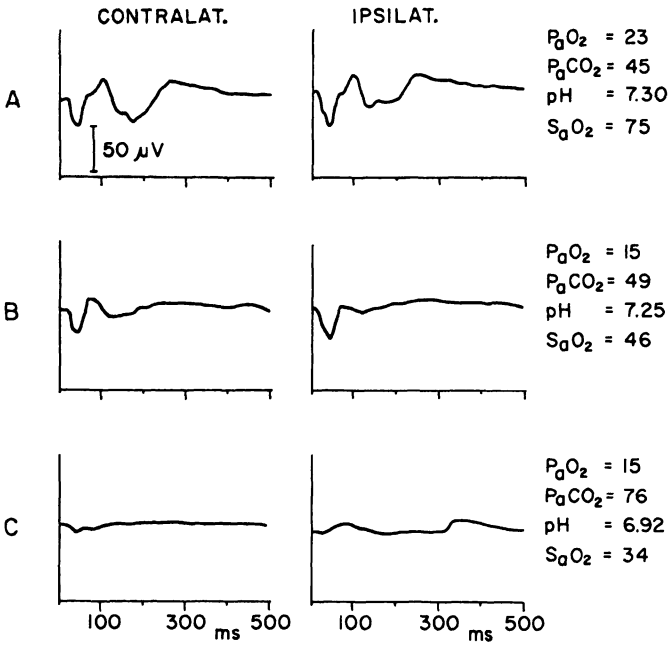

Fig. 4. From exp. No. 10/73. Mature lamb fetus, 131 days of gestation. Example of the effect of hypoxia in combination with acidosis on SER. A: Normoxia, B: Hypoxia, C: Hypoxia and acidosis.

3 Discussion

The present study was prompted by findings in the exteriorized fetal lamb that the combination of hypoxia and acidosis impaired the cerebral functions in terms of electrical activity and oxygen consumption more seriously than hypoxia alone [2, 6]. Since these findings could be explained by a reduction of the oxygen extraction from the blood it was considered relevant to evaluate the possibility that microcirculatory and rheological factors contributed to the deleterious effect of combined hypoxia and acidosis.

In vitro studies have established that the viscosity increases out of proportion in comparison with

the hematocrit when the blood is severely acidotic [1]. Thus, reduction of blood viscosity might increase the resistance towards asphyxia.

The use of a macromolecular electrolyte solution for the prevention of brain damage during ischemia has been suggested previously by VALLI [8] and subjected to experimental trial.

However, **the present results fail to demonstrate any beneficial effect on the cerebral tolerance to asphyxia of the reduction of viscosity or hematocrit.** The series of experiments was started by using a 6% Dextran solution to dilute the blood. Two other types of plasma expanders were later added to the study for two reasons. Firstly, the Dextran solution has a comparatively high intrinsic viscosity (2.81 cP compared to 1.60 cP for plasma) and plasma expanders with an intrinsic viscosity close to that of plasma should be tested. Secondly, we wanted to exclude possible species specific sensitivity reactions to the plasma substitute by testing different substances.

Hemodilution is associated with a gradual increase of the cerebral blood flow in adult dogs [3, 4]. The same relationship was now obtained also in the fetal lamb both at ordinary levels of arterial oxygenation and during hypoxia (Tab. I, Fig. 2). However, **the blood flow augmentation was not large enough to compensate for the loss of oxygen capacity implying that the oxygen extraction was not facilitated.** Instead, a marked hemodilution at times caused the same effect on the SER as a moderate hypoxia (Fig. 3). It is evident that both the cerebral oxygen consumption and the SER must be affected at extreme degrees of hemodilution. Most of the observations in the present series, however, fall in the hematocrit intervall of 30—50 per cent, which may explain why no statistically significant correlation was obtained.

A multiple regression analysis failed to demonstrate any further correlations than those apparent from Tab. I. When, however, the "normoxic" and "hypoxic" groups were separately investigated some items of interest became apparent.

During normoxia the CBF showed a significant negative correlation with the a-v oxygen extraction over the brain but was uncorrelated to the cerebral oxygen consumption. In contrast to these findings no statistically significant correlation was found between CBF and oxygen extraction during hypoxia while a relation instead existed between the oxygen consumption and the blood flow.

Thus, at normal levels of oxygenation the cerebral oxygen consumption is maintained during low blood flows by an increased extraction of oxygen. During hypoxia no such reciprocity between CBF and oxygen extraction exists and the oxygen consumption falls at lower blood flows.

The influence of pH on cerebral function was modified by the degree of oxygenation. In the total group statistically significant covariation was found between arterial pH and oxygen extraction, oxygen consumption of the brain as well as SER changes (Tab. I). In the normoxic group, however, no statistically significant correlation was found between pH and SER. Moreover in the **hypoxic group, multiple regression analysis demonstrated a significant reduction of the residual variance when oxygen extraction was correlated to arterial pH and oxygen saturation in combination compared to when correlated to saturation alone.** Thus, the same impairment of oxygen extraction by the brain during the combination of hypoxia and acidosis is demonstrated as in the previous studies [2, 6], and this impairment was not relieved by decreasing the blood viscosity.

Summary

In previous experiments performed on fetal lambs it was demonstrated that hypoxia affects the somato-sensory evoked EEG responses (SER) of the brain, reduces the cerebral oxygen consumption and induces a cerebral vasodilatation. The combination of hypoxia and acidosis results in the same type of alterations but at higher arterial oxygen tensions. The common denominator for the serious effects of hypoxia in combination with acidosis appeared to be a significantly diminished oxygen extraction.

Both from a theoretical and a practical viewpoint it seemed relevant to evaluate **the importance of rheological factors** in this connection. The purpose of this investigation was thus to study whether **a decrease of the viscosity and hematocrit of the blood would increase the ability of**

the fetal brain to withstand a period of hypoxia, and, in particular, **to restore the capacity of the brain to extract oxygen during hypoxia at low pH levels.**

The material consisted of 17 ewes with 25 fetuses. The ewes were anesthetized and ventilated with known gas mixtures. Periods of normoxia and hypoxia were alternated by changing the concentrations of oxygen from 30 to 10—15 per cent. Each period of hypoxia had a duration of 20 minutes. The fetus was delivered through an abdominal incision, leaving the circulation through the umbilical cord intact, as far as possible. Blood samples representative of cerebral venous blood were taken from a catheter in the superior sagittal sinus. Arterial blood samples were drawn from the right brachial artery.

Blood gas tensions and pH were measured anaerobically and oxygen saturation, viscosity and hematocrit were determined separately. Cerebral blood flow (CBF) was estimated using the clearance curves from ^{133}Xe injected intra-arterially. SER were recorded from the intact fetal scalp using a mechanical tap on the nostril region as a tactile stimulus. SER were obtained after averaging 15—20 responses with computer technique. The oxygen consumption of the brain was calculated from the CBF value and the a-v difference for oxygen content.

The viscosity and the hematocrit of the fetus were altered by exchanging fetal blood with 6% Dextran® (viscosity 2.81 cP), 4% Ficoll® (viscosity 1.03 cP), 3.5% Haemaccel® (viscosity 1.29 cP) or packed fetal red cells.

Alternate periods of normoxia and hypoxia were performed at different degrees of hemodilution.

A strong correlation was found between hematocrit and viscosity. When these two variables were tested separately against the other variables (CBF, SER, cerebral oxygen consumption, and the different blood gases) the same correlations were found. Since more determinations of the hematocrit were available, viscosity was left out of the further analysis. In **Tab. I** a correlation matrix is given for the variables studied.

A significant correlation was obtained between CBF and hematocrit so that the CBF increased at low hematocrit values **(Fig. 2).** In the range of hematocrit studied no statistically significant correlation was obtained either between hematocrit and cerebral oxygen consumption or hematocrit and SER either at high or low levels of oxygenation. Thus the augmentation of CBF during hemodilution was not large enough to compensate for the loss of oxygen capacity. **The facilitation of oxygen extraction during asphyxia aimed at by reducing hematocrit and viscosity was thus not achieved.**

Multiple regression analysis demonstrated a **correlation between SER and pH during hypoxia** but not at normal levels of oxygenation. It was further demonstrated that an **inverse relationship existed between CBF and the oxygen extraction at normal levels of oxygenation** but not during hypoxia.

It is concluded that the oxygen consumption of the brain is maintained at a stable level during normoxia because of a reciprocity between CBF and oxygen extraction but that hypoxia makes the oxygen consumption directly dependent on the CBF. **When acidosis is superimposed on hypoxia the cerebral function further deteriorates as demonstrated by impairment of SER and the oxygen extraction (Figs. 3—4).** This impairment cannot be restored by affecting rheological factors such as hematocrit or viscosity.

Keywords: Acidosis, blood flow, brain (fetal), electroencephalogram, hematocrit, oxygen (consumption), viscosity.

Zusammenfassung

Reaktionen des Zentralnervensystems auf intrauterine Asphyxie beim Schaf — III. Über den Einfluß von Veränderungen des Hämatokrits und der Blutviskosität

Frühere Experimente am Schafs-Feten haben gezeigt, daß eine Hypoxie die somato-sensorisch auslösbaren EEG-Veränderungen (SER) des Gehirns beeinflußt, den zerebralen Sauerstoffverbrauch verringert und eine Gefäßerweiterung im ZNS hervorruft. Die Kombination von Hypoxie und Azidose führt zu gleichartigen Veränderungen, jedoch bereits bei höheren arteriellen Sauerstoffspannungen. Der gemeinsame Nenner für den deletären Effekt von Hypoxie in Verbindung mit Azidose scheint eine signifikant erniedrigte Sauerstoff-Aufnahme zu sein. In diesem Zusammenhang mag es sowohl aus theoretischer wie aus praktischer Sicht wichtig sein, die **Bedeutung strömungsmechanischer Faktoren** zu untersuchen.

Das Ziel dieser Studie war es daher zu untersuchen, ob eine **Reduktion von Blutviskosität und Hämatokrit die Fähigkeit des fetalen Gehirns, eine Hypoxieperiode zu überstehen, erhöht** und insbesondere, ob die **Kapazität des Gehirns, Sauerstoff während Hypoxie und bei tiefen pH-Werten aufzunehmen, wiederhergestellt wird.** Das Versuchsmaterial bestand aus 17 schwangeren Schafen mit insgesamt 25 Feten. Die Schafe wurden narkotisiert und mit bekannten Gasgemischen beatmet. Durch Veränderung der Sauerstoffkonzentration von 30 auf 10 bis 15% wurden normoxische bzw. hypoxische Perioden im Wechsel erzeugt. Jede Hypoxiephase dauerte 20 Minuten. Der Fet wurde durch einen Bauchschnitt geboren, wobei die Nabelschnur-Zirkulation soweit wie möglich intakt blieb. Die für das venöse zerebrale Blut repräsentativen Proben wurden dem Sinus saggitalis superior entnommen. Die arteriellen Blutproben entstammten der rechten Arteria brachialis.

Die Blutgase und pH-Werte wurden unter anaeroben Bedingungen gemessen; Sauerstoffsättigung, Viskosität und Hämatokrit wurden separat bestimmt. Die zerebrale Durchblutung (CBF) wurde mit Hilfe von intra-arteriell appliziertem ^{133}Xe und dessen Claerance-Kurven gemessen. Die durch somato-sensorische Reize ausgelösten EEG-Veränderungen (SER) wurden von der intakten fetalen Kopfhaut abgeleitet; im Bereich der Nüstern der Tieres wurde ein mechanischer Reizgeber aufgebracht. Die enzephalographischen Signale wurden durch Mittelung

von 15—20 Antwortmustern mit Hilfe eines Computers quantifiziert. Der Sauerstoffverbrauch des Gehirns wurde aus der zerebralen Durchblutungsgröße (CBF) und der arterio-venösen Differenz des Sauerstoffgehaltes berechnet. Durch Austausch fetalen Blutes mit 6% Dextran (Viskosität 2,81 cP), 4% Ficoll® (Viskosität 1,03 cP), 3,5% Haemaccel® (Viskosität 1,29 cP) oder fetalem Erythrocyten-Konzentrat wurden Viskosität und Hämatokrit des fetalen Blutes verändert. Bei verschiedenen Hämodilutionsgraden wurden Perioden von Normoxie und Hypoxie erzeugt.

Zwischen Hämatokrit und Viskosität des Blutes fand sich eine enge Korrelation. Gleich gute Korrelationen fanden sich bei der isolierten Testung dieser beiden Parameter jeweils mit den anderen Variablen (CBF, SER, zerebraler Sauerstoffverbrauch und den verschiedenen Blutgasen). Da mehr Hämatokrit-Bestimmungen verfügbar waren, wurde der Parameter Blut-Viskosität bei der weiteren Analyse nicht mehr berücksichtigt. **Tab. I** gibt eine Korrelationsmatrix für die untersuchten Variablen.

Zwischen CBF und Hämatokrit konnte eine signifikante Korrelation in dem Sinne nachgewiesen werden, daß die zerebrale Durchblutung bei tiefen Hämatokritwerten zunimmt **(Fig. 2).** Innerhalb des untersuchten Hämatokrit-Bereiches fand sich weder eine signifikante Korrelation zwischen Hämatokrit und zerebralem Sauerstoff-Verbrauch noch zwischen Hämatokrit und EEG-Signalen (SER), und zwar sowohl bei hoher als auch bei tiefer Oxygenation; d. h. die Zunahme des CBF während der Blut-Verdünnungsphase war nicht groß genug, um den Verlust an Sauerstoffgehalt wettzumachen. **Die durch Herabsetzen von Hämatokrit und Blut-Viskosität angestrebte Erleichterung der Sauerstoff-Aufnahme während der Asphyxie wurde also nicht erreicht.**

Die multiple Regressionsanalyse ergab eine **Korrelation zwischen SER und pH während Hypoxie,** nicht jedoch bei normalen Oxygenationsverhältnissen. Ferner konnte gezeigt werden, daß eine **umgekehrte Beziehung zwischen CBF und der Sauerstoff-Aufnahme unter Normoxie** besteht, nicht jedoch bei Hypoxie. Die Autoren kommen zu dem Schluß, daß der Sauerstoff-Verbrauch des Gehirns während Normoxie stabil gehalten wird aufgrund der Reziprozität von CBF und Sauerstoff-Aufnahme, daß jedoch eine Hypoxie den Sauerstoff-Verbrauch des Gehirns direkt vom CBF abhängig werden läßt. Die Beeinträchtigung der SER und der Sauerstoff-Aufnahme zeigen klar, daß **die zerebralen Funktionen sich dann weiter verschlechtern, wenn eine Hypoxie von einer Azidose überlagert wird (Figs. 3—4).** Diese Beeinträchtigung der zerebralen Funktionen kann durch Beeinflussung strömungsmechanischer Faktoren wie Hämatokrit und Viskosität nicht ausgeglichen werden.

Schlüsselwörter: Azidose, Durchblutung, Enzephalographie, Gehirn (fetales), Hämatokrit, Sauerstoff (Verbrauch), Viskosität.

Résumé

Réactions cérébrales du foetus de mouton à l'asphyxie intra-utérine — III. Effets des altérations de l'hématocrite et de la viscosité sanguine

Des expérimentations antérieures réalisées sur des foetus de mouton, ont démontré que l'hypoxie modifie les potentiels cérébraux évoqués par des stimuli somato-sensoriels, réduit la consommation cérébrale en oxygène et engendre une vasodilatation cérébrale. L'association d'une acidose à l'hypoxie induit les mêmes altérations, mais à une P_{O_2} artérielle plus élevée. Le dénominateur commun de ces altérations apparaissant en présence d'hypoxie associée à une acidose semble être une diminution significative de la captation d'oxygène par le cerveau.

Tant au point de vue pratique que théorique, il semble intéressant d'évaluer **l'importance des facteurs hydrauliques** susceptibles de modifier ce processus. Le but de ce travail est donc de savoir si, **une diminution de la viscosité du sang et de l'hématocrite peut augmenter la capacité du cerveau foetal à subir une période d'hypoxie** et en particulier, pouvait **restaurer le pouvoir de captation de l'oxygène par le cerveau foetal au cours de l'hypoxie et de l'acidose.**

Nous avons étudié 17 brebis et 25 foetus, sous anesthésie et ventilation artificielle à des mélanges gazeux connus. Nous avons fait alterner des périodes de normoxie et d'hypoxie, en faisant varier la concentration en oxygène de 30 à 10 ou 15 pour cent. Chaque période d'hypoxie dura 20 minutes. Le foetus était délivré par césarienne abdominale en conservant la circulation funiculaire auss longtemps que possible. Des échantillons de sang, témoins de la circulation cérébrale, étaient prélevés à l'aide d'un cathéter inséré dans le sinus longitudinal supérieur. Le sang artériel était prélevé dans l'artère humérale droite.

Les gaz du sang et le pH étaient mesurés en anaérobie stricte, tandis que la saturation en oxygène, la viscosité et l'hématocrite étaient déterminés séparément. Le débit sanguin cérébral (CBF) était évalué en mesurant la clearance locale du Xénon 133, administré par voie intraartérielle. Les réponses cérébrales aux potentiels évoqués somato-sensoriels (SER) étaient enregistrées au niveau du scalp foetal après stimulation mécanique de la région nostrile. La valeur de SER était déterminée automatiquement par le calcul de la moyenne de 15 à 20 valeurs. La consommation en O_2 du cerveau était calculée à partir de la valeur du flux cérébral (CBF) et de la différence artério-veineuse du contenu en O_2.

La viscosité du sang et l'hématocrite du foetus étaient modifiés en remplaçant du sang foetal par du Dextran à 6% (viscosité: 2,81 cP) du Ficoll® à 4% (viscosité: 1,03 cP), de l'Haemaccel® à 3,5% (viscosité: 1,29 cP) ou des culots globulaires de sang foetal.

On faisait alors alterner des périodes de normoxie et d'hypoxie à différentes valeurs d'hémodilution.

Nous avons trouvé une forte corrélation entre l'hématocrite et la viscosité sanguine. Lorsque nous avons testé séparément ces deux variables vis à vis des autres (débit

sanguin cérébral, potentiel évoqué, consommation cérébrale en oxygène, et les gaz du sang), nous avons trouvé les mêmes corrélations. Etant donné qu'il était plus facile d'effectuer des déterminations de l'hématocrite plutôt que de la viscosité sanguine, nous avons éliminer cet examen des observations ultérieures. Le **Tab. I** représente la matrice des corrélations entre les différentes variables.

Nous avons trouvé une corrélation significative entre le flux cérébral et l'hématocrite: le débit cérébral augmente lorsque l'hématocrite diminue **(Fig. 2).** Dans l'ordre des valeurs d'hématocrite étudiés nous n'avons pas trouvé de corrélation significative entre l'hématocrite et la consommation du cerveau en oxygène, ni entre l'hématocrite et la valeur des potentiels évoqués quelque soit la concentration en oxygène du mélange respiré. Il semble donc que l'augmentation du débit cérébral en cas d'hémodilution ne soit pas suffisante pour compenser la diminution de l' apport en oxygène engendrée par cette hémodilution. **L'amélioration de l'extraction de l'oxygène, pendant l'asphyxie, obtenue en diminuant l'hématocrite et la viscosité du sang n'est donc pas efficace.**

L'anlyse des corrélations multiples a mis en évidence **une liaison entre la valeur des potentiels évoqués et le pH au cours de l'hypoxie** mais pas au cours de l'oxygénation normale. Nous avons également mis en évidence une **corrélation inverse entre la valeur du débit sanguin cérébral et l'extraction de l'oxygène lorsque la p_{O_2} était normale** mais pas en cas d'hypoxie.

En conclusion, nous pouvons dire que la consommation en oxygène du cerveau reste stable, en cas d'oxygénation normale, sous l'effet d'un mécanisme régulateur antagoniste, entre le débit cérébral et l'extraction dè l'oxygène du sang (quand le débit diminue, l'extraction d'O_2 augmente et vice versa). Par contre, l'hypoxie place la consommation en oxygène du cerveau en dépendance directe du débit sanguin cérébral. Lorsqu'une acidose s'ajoute à l'hypoxie, **les fonctions cérébrales se détériorent, fait que l'on peut mettre en évidence par la modification des valeurs de potentiels évoqués et la diminution de l'extraction d'oxygène (Figs. 3—4).** Ces altérations ne peuvent être améliorées en modifiant les facteurs hydrauliques tels que hématocrite ou viscosité du sang.

Mots-clés: Acidose, débit sanguin, cerveau (foetal), hématocrite, oxygène (consommation), potentiels évoqués, viscosité.

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