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The uterine and maternal placental blood flow during hyperoxia

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Clinical signs of fetal distress are usually met by giving extra oxygen to the mother. The question then arises whether maternal hyperoxia will increase the passage of oxygen to the fetus or whether any hemodynamic effects of the hyperoxia will curtail the effects of an increased transplacental diffusion gradient.

1 Introduction

Rorke et al. [10] in humans and several investigators using animals [5, 4, 1] have demonstrated that an increase of maternal oxygen tension causes only a disproportionately small increase of fetal oxygen tension. Such an effect might be explained by the fact that the placental venous P_{O_2} increases only moderately and thus that the pressure head for oxygen diffusion is not elevated in proportion to maternal arterial P_{O_2}. However, a contributary factor might be a constriction of the vessels in the maternal placenta during hyperoxia. Little information is available about the influence of hyperoxia on blood flow to the pregnant uterus. The distribution of the blood flow between the myometrium and the maternal part of the placenta in particular, does not appear to have been investigated.

Kirschbaum et al. [8] found that the uterine flow in anesthetized pregnant ewes was changed only minimally by acute inhalation of pure oxygen (Method: electromagnetic flowmeter), while Assali et al. [1] demonstrated a decrease of the uterine blood flow when the ewes were breathing hyperbaric oxygen, using the electromagnetic flow-meter method. Battaglia et al. [3] on the other hand found no significant effect of acute changes of the arterial oxygen pressure upon uterine blood flow (4-aminoantipyrine method). Another approach to the problem was adopted by Makowski et al. [9], who calculated "hemoglobin flow" to the uterus of pregnant ewes (electromagnetic flow-meter method) and found a small decrease of this parameter during hyperoxia.

However, the relevant organ for study with regard to fetal oxygenation is naturally, the placenta rather than the uterus in toto.

The present study was designed to give **a quantitative measure of both the maternal placental and the myometrial blood flow** and to answer the question **whether hyperoxia provokes vasoconstriction of the vascular bed of the maternal placenta.**

2 Material and methods

Experiments were carried out on 9 pregnant rabbits with dated gestation of 26—29 days (pregnant term 31 ± 2 days). The mean body weight was 4.46 kg $\pm$ 0.18 (SD).

Anesthesia was induced and maintained with pentothal (induction 25 mg/kg and a total dose of 75 mg/kg during the wohle experimental period of 3 hours). Blood pressure and heart

frequency were recorded through a catheter in the right brachial artery. The same catheter was used for arterial blood sampling.

Radioactive carbonized microspheres were injected via a PE 160 catheter placed in the left cardiac ventricle, the position of the tip controlled by pressure measurements. The microspheres were tagged with different nuclides, ^{46}Sc or ^{169}Yb, and had a diameter of 25 $\pm$ 5 micron (Minnesota Mining & Manufacturing Company). The withdrawal of the reference blood sample was started 15 seconds before injection of microspheres, and continued for a total time of 2 minutes. The microspheres were injected over a period of 15—20 seconds. The injection chamber was carefully agitated before and during the injection by a high frequency mechanical whirlmixer, and the chamber was afterwards flushed with 6—10 ml of 6 per cent Dextran. Further particulars about the methods used for counting are given in an accompanying paper [7]. This paper also contains results suggesting that the spheres were homogeneously mixed in the cardiac output and that the sampling time of two minutes for the reference blood sample was adequate.

Periods of normoxia and hyperoxia were randomly alternated by ventilating the animal with gas mixtures of 30 per cent or 100 per cent oxygen, so that normoxia preceded hyperoxia in 5 experiments, and the reverse sequence was used in 4 experiments. The steady state situation was usually established after ten minutes ventilation with the desired gas mixture, the blood sample for blood gas determination being taken at the end of this period.

Cardiac output was measured repeatedly during each experiment using a thermodilution method. A fine calibre thermistor placed in the aorta recorded the variations of temperature. The thermistor was connected to a WHEATSTONE bridge with maximal linearity around 37—38°C. The signals were recorded on a SERVOGOR writer and the calculations of cardiac output performed according to GANZ [6]. At each stage the mean of 3—4 separate determinations of cardiac output was calculated.

At the end of the experiment the rabbit was killed with an overdose of pentothal. The organs of interest were carefully dissected, cut in pieces and analyzed for gamma activity in a well crystal, using a two-channel PACKARD auto gamma spectrometer.

The specific activity of each single microsphere of ^{46}Sc and ^{169}Yb was counted at each measurement. Based on the calculations, the number of spheres in each sample was determined, and no organ sample was accepted unless it contained at least 400 microspheres.

In the statistical analysis of the results the mean ($\bar{x}$), the standard deviation (SD), and the standard error of the mean (SEM) were calculated. Comparisons were carried out by means of Group Comparison Test. The level of significance were marked as follows:

$$* = 0.05 > p > 0.01 \quad ** = 0.01 > p > 0.001$$
$$*** = p < 0.001.$$

3 Results

No changes were observed in cardiac output, heart frequency or mean arterial pressure when changing randomly from normoxia to hyperoxia (Tab. I). The injection of microspheres caused only minor changes of the functions just mentioned.

Tab. I. Mean values $\pm$ SEM of cardiac output, heart frequency and arterial pressure during normoxia and hyperoxia.

	cardiac output		heart frequency		mean art. pressure	
	n	ml/min	n	beats/min	n	mmHg
normoxia	9	774±22.6	9	304±5.7	9	88±1.5
hyperoxia	9	778±27.0	9	310±6.6	9	86±2.0
significance		n. s.		n. s.		n. s.

The maternal P_{CO_2}, P_{O_2} and pH during control situation (inhalation of 30 per cent oxygen) were within the ranges previously observed [7]. The arterial P_{O_2} rose from an average of 96 mm Hg to an average of 471 mm Hg when the inspired oxygen was increased from 30 to 100 per cent. The slight decrease of maternal arterial P_{CO_2} was not statistically significant, the pH was not affected (Tab. II). Tab. III and Fig. 1 display the changes of blood flow to different organs. **The**

Tab. II. Mean arterial blood gases ± SEM during normoxia and hyperoxia.

	n	P_{O_2} mm Hg	n	P_{CO_2} mm Hg	n	pH
normoxia	9	95.6±3.6	9	41.5±1.2	9	7.35±0.02
hyperoxia	9	470.6±13.9	9	40.0±1.5	9	7.36±0.03

blood flow to the myometrium decreased when the animal breathed 100 per cent oxygen. This decrease was statistically significant. The placental blood flow also demonstrated a statistically significant decrease during hyperoxia. When the blood flows were expressed in absolute values myometrial flow decreased from 12.7 ± 1.5 ml/min to 9.6 ± 1.4 ml/min, and the placental blood flow was diminished from 25.2 ± 4.6 ml/min to 18.9 ± 3.7 ml/min.

The fraction of the cardiac output going to the myometrium was 1.64 per cent during normoxia and 1.23 per cent during hyperoxia. The corresponding values for the maternal placenta were 3.25 per cent and 2.43 per cent, respectively.

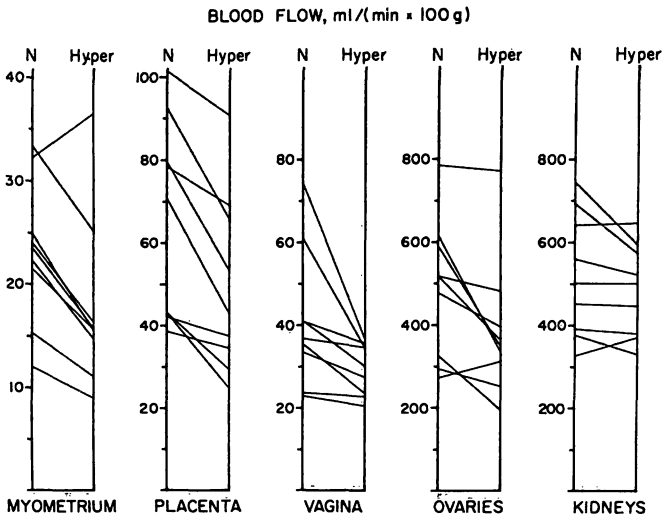

Fig. 1. Graphic demonstration of blood flow in different organs when changing from normoxia to hyperoxia. N = normoxia; Hyper = hyperoxia.

Tab. III. Mean values of blood flow ml/(min × 100 g) ± SEM to different organs during normoxia and hyperoxia. The significance was calculated by means of Pairing Design Test.

	n	myometrium ml/(min × 100 g)	n	placenta ml/(min × 100 g)	n	ovaries ml/(min × 100 g)	n	vagina ml/(min × 100 g)	n	kidneys ml/(min × 100 g)
normoxia	9	23.5±2.3	9	66.4±8.4	9	492.4±56.8	9	41.4±5.7	9	523.1±49.8
hyperoxia	9	17.9±2.8	9	50.9±7.6	9	386.4±56.5	9	30.0±2.1	9	486.0±36.3
significance		**		**		*		*		n. s.
per cent change in blood flow from normoxia to hyperoxia		28.8±2.2		23.7±4.3		23.5±5.5		22.3±5.5		8.6±2.6

4 Discussion

When the arterial oxygen tension in maternal blood is increased above normal values, fetal values of arterial oxygen tension are usually increased. There is, however, a curvilinear relationship, so that the increment of fetal P_{O_2} values for any given change of maternal P_{O_2} will be less the higher the maternal P_{O_2}.

This type of relationship has been demonstrated in humans by Rorke et al. [10], and in sheep by Comline et al. [4]. Thus, the fetus appears to be protected from high levels of P_{O_2} [2]. This phenomenon has been attributed to vasoconstriction of the maternal placental bed, to vasoconstriction of the umbilical circulation of the fetus, to an uneven distribution of maternal versus fetal blood flow within the placenta, or to the oxygen consumption of the metabolically active placenta itself.

The possibility of a constriction of the maternal part of the placental circulation appears not to have been explored previously. Such a vasoconstriction might be of functional significance, since it would not only affect the transport of oxygen over the placenta but would also lead to a diminished nutritional supply to the fetus.

The present series of experiments show that **a moderate diminution of the blood flow through the maternal placenta takes place during hyperoxia,** with blood flow values of 25.2 ± 4.6 during the control situation and a reduction to 18.9 ± 3.7 ml/min at high oxygen tensions. This implies a **mean reduction of 24 per cent.** Such a reduction of the blood flow — although small — is large enough to be of consequence for the quantity of oxygen carried to the maternal part of the placenta. The small amount of physically dissolved oxygen at high P_{O_2} levels will in no way compensate for the reduced blood flow, provided the mother is fully oxygenated in the control situation. If this reduction of placental blood flow during hyperoxia also occurs in man it might at least partly explain the results of RORKE et al. [10], in which the change from 66 to 100 per cent of inspired oxygen to the mother actually caused a decrease of the P_{O_2} in the umbilical vein and artery.

In the present series of experiments hyperoxia was associated with a reduction of the blood flow to the placenta and to the myometrium (Fig. 1, Tab. III). This finding is in line with previous reports of reduction of total uterine blood flow under the same circumstances [1, 9].

The reduction of uterine blood flow occurred at an unchanged perfusion pressure (Tab. I). Therefore, a true **vasoconstriction** must have occurred in the myometrium and in the placenta. The mechanism behind this vasoconstriction is obscure. It may be speculated, however, that it occurs either as a local effect on the uterine vessels or as a part of a generalized sympatho-adrenal activation. Neither the cardiac output, the heart frequency, the arterial blood pressure nor the blood flow through the kidneys changed during hyperoxia (Fig. 1, Tab. I). This may be taken as indirect evidence of the lack of a generalized sympatho-adrenal discharge. One is then left with the suggestion of a local vascular effect of hyperoxia.

The results of the present experiments thus indicate that maternal hyperoxia will produce constriction of the total uterine vascular bed which will result in a diminished quantity of oxygen available on the maternal side of the feto-maternal membrane. This might explain at least part of the special features of the feto-maternal relationship. It is hypothesised that the observed vasoconstriction is mediated as a local vascular effect rather than as an increased sympatho-adrenal activity.

Summary

In the clinical situation of fetal distress extra oxygen is often supplied to the mother as a routine procedure. However, the effect of breathing pure oxygen on the utero-placental circulation is not known but indirect evidence suggests that a blood flow reduction might take place. Previous direct measurements are few and only the combined flow to the whole uterus has been estimated. Therefore, a study was designed to measure separately the blood flow to the maternal placenta and the myometrium during induced hyperoxia as compared with normoxic conditions.

Nine pregnant rabbits with dated gestations of 26—29 days were studied under barbiturate anesthesia. The animals were ventilated with 30 and 100 per cent oxygen alternatingly, which resulted in arterial P_{O_2} levels of 96 ± 4 (SEM) and 471 ± 14 (SEM) mm Hg, respectively **(Tab. II.).** To avoid a systematic effect from a deterioration of the preparation the sequence was altered so that normoxia preceded hyperoxia in five experiments while the reverse was true in four experiments.

Blood pressure and heart rate were continuously recorded and blood gases were determined at intervals. Cardiac output was measured repeatedly with a thermodilution technique.

To measure the placental and the myometrial blood flows the microsphere technique was used. Radioactive microspheres, tagged with ^{46}Sc and ^{691}Yb, of 25 ± 5 micron diameter, were injected in the left cardiac ventricle through a catheter passed in a retrograde direction from one carotid artery. Blood flows were calculated from the number of spheres trapped in each organ related to the number of spheres in a reference sample, drawn from one femoral artery at a constant, known rate during and after the injection.

No changes were observed in cardiac output, heart frequency or mean arterial pressure when changing from normoxia to hyperoxia **(Tab. I).**

The blood flow in the myometrium decreased from 23.5 ± 2.3 to 17.9 ± 2.8 ml/(min × 100 g) (= 29 per cent) from normoxia to hyperoxia and in the placenta the corresponding change was from 66.4 ± 8.4 to 50.9 ± 7.6 ml/(min × 100 g) (= 24 per cent) (Fig. 1, Tab. III). This decrease in blood flow was **statistically significant** and was parallelled by a significant increase in

vascular resistance indicating a true vasoconstriction during hyperoxia.
It is concluded that **breathing pure oxygen induced a moderate constriction of the placental and myometrial vascular beds.** The accompanying reduction of blood flow may be of consequence for the amount of oxygen carried to the maternal part of the placenta and made available for fetal oxygenation.

Keywords: Blood flow (myometrial, placental), hyperoxia, normoxia, rabbits.

Zusammenfassung

Untersuchungen über die uterine und plazentare Durchblutung während Hyperoxie

Häufig wird der Mutter bei fetaler Asphyxie routinemäßig Sauerstoff zusätzlich verabreicht. Obwohl über die Wirkung des Atmens von reinem Sauerstoff auf die uteroplazentare Durchblutung nichts bekannt ist, gibt es indirekte Hinweise, die vermuten lassen, daß eine Durchblutungsdrosselung stattfinden kann. Bis heute gibt es wenige Direktmessungen, und bisher wurde nur die Gesamt-Durchblutung der Gebärmutter bestimmt. Aus diesem Grunde sollten in dieser Studie der Blutstrom zur mütterlichen Seite der Plazenta und zum Myometrium getrennt während induzierter Hyperoxie gemessen und mit jenem unter normoxischen Bedingungen verglichen werden.
Für die Studie wurden neun schwangere Kaninchen vom 26.—29. Schwangerschaftstag, die unter Barbiturat-Narkose waren, verwendet. Die Tiere wurden abwechselnd **mit 30 und 100% Sauerstoff beatmet,** was zu einem **arteriellen P_{O_2}-Gehalt von 96 ± 4 bzw. 471 ± 14 mmHg** führte **(Tab.II).**
Um eine systematische, negative, durch die Versuchsanordnung bedingte Wirkung zu vermeiden, wurde die Reihenfolge der Experimente so gewählt, daß in fünf Versuchen die Normoxie der Hyperoxie voranging, während in vier Versuchen das Gegenteil der Fall war.
Blutdruck und Herzschlag-Frequenz wurden kontinuierlich, die aktuellen Blutgase intermittierend bestimmt. Das Herzschlag-Volumen wurde wiederholt mit einer Thermodilutions-Technik gemessen.
Für die getrennte Bestimmung der plazentaren und der myometrialen Durchblutung kam die Mikroperlen-Technik zur Anwendung. Radioaktive mit ^{46}Sc und ^{169}Yb markierte Mikroperlen, die einen Durchmesser von 25 ± 5 Micron aufweisen, wurden retrograd mit einem Katheter, der in der Arteria carotis lag, in den linken Ventrikel injiziert.
Die Durchblutung wurde aus dem Verhältnis der in jedem Organ registrierten Anzahl an Perlen und der Menge an Perlen in einer Vergleichsprobe berechnet, die aus einer der Femoral-Arterien zu konstanten und bekannten Zeitpunkten während und nach der Injektion entnommen worden war.
Beim Übergang von Normoxie auf Hyperoxie wurden keinerlei Veränderungen des Herzschlag-Volumens, der Herzfrequenz und des mittleren arteriellen Blutdrucks beobachtet **(Tab. I).**
Beim Wechsel von Normoxie auf Hyperoxie sank jedoch die Durchblutung des Myometriums von 23,5 ± 2,3 auf 17,9 ± 2,8 ml/(min × 100 g) (entspricht 29%) und in der Plazenta von 66,4 ± 8,4 auf 50,9 ± 7,6 ml/(min × 100 g) (= 24%) (Fig. 1, Tab. III).
Dieser Rückgang der Durchströmung war **statistisch signifikant** und war von einem ebenfalls **signifikanten Anstieg des Gefäßwiderstandes** begleitet, was für eine echte Vasokonstriktion während der hyperoxämischen Phase spricht.
Aus den Befunden wird der Schluß gezogen, daß das **Atmen von reinem Sauerstoff zu einer mäßigen Einengung des plazentaren und myometrialen Gefäßbettes** führt.
Die daraus resultierende Durchströmungs-Verminderung kann Folgen haben für die Menge des zur mütterlichen Seite der Plazenta transportierten und dem Feten zur Verfügung stehenden Sauerstoffes.

Schlüsselwörter: Durchblutung (myometrial, plazentar), Hyperoxie, Normoxie, Kaninchen.

Résumé

A propos de l'influence de l'hyperoxie sur le débit utérin et placentaire

Il arrive souvent, qu'en pratique obstétricale, on soit amené à donner de l'oxygène à la mère, en cas de souffrance foetale. Toutefois, les effets de l'administration d'oxygène pur à la mère, sur la circulation utéro-placentaire sont inconnus, cependant, il semble logique de penser qu'une diminution de débit peut survenir. C'est la raison pour laquelle nous avons réalisé des mesures séparées de débits utérins et placentaires, au cours d'épisodes alternant de normoxie et d'hyperoxie.
Neuf lapines, entre 26 et 29 jours de gestation, furent étudiées sous anesthésie barbiturique, ventilation artificielle utilisant des mélanges de 30 et 100% d'oxygène en alternance, ce qui aboutit à des chiffres de P_{O_2} respectifs de 96 ± 4 (SEM) et de 471 ± 14 (SEM) mmHg **(Tab. II).**
Afin d'éviter un effet systématique dû à une détérioration de la préparation, dans 5 cas, nous avons fait précéder

l'hyperoxie par un épisode de normoxie, dans le reste des cas, nous avons pratiqué l'inverse.
Nous avons enregistré en permanence la pression sanguine et le rythme cardiaque, les gaz du sang étaient déterminés à intervalles réguliers et le débit cardiaque mesuré de façon répétée par thermodilution.
Nous avons utilisé la technique des microsphères pour mesurer les débits utérin et placentaire: des microsphères marquées au ^{46}Sc et à l'^{169}Yb, de 25 $\pm$ 5 microns de diamètre, furent injectées dans le ventricule gauche à l'aide d'un cathéter monté à contre courant à partir d'une carotide. Les débits furent calculés par évaluation du nombre de sphères dans chaque organe, par rapport au nombre de sphères contenues dans un échantillon de référence prélevé au niveau d'une artère fémorale, présentant un taux de radioactivité connu et constant, pendant et après l'injection.
On n'a observé aucune variation de débit ni de fréquence cardiaques, ni de pression artérielle en passant d'un état de normoxie à un état d'hyperoxie **(Tab. I).**

Le débit sanguin myométrial a chuté de 23,5 $\pm$ 2,3 à 17,9 $\pm$ 2,8 ml/min $\times$ 100 g (= 29 pour cent), en passant de la normoxie à l'hyperoxie. Le débit placentaire est passé de 66,4 $\pm$ 8,4 à 50,9 $\pm$ 7,6 ml/min $\times$ 100 g (= 24 pour cent) (Fig. 1, Tab. III).
Cette diminution du débit sanguin est **statistiquement significative** et est associée à une augmentation significative de la résistance vasculaire, signant une réelle vasoconstriction au cours de l'hyperoxie.
Nous pouvons en conclure **que l'administration d'oxygène pur à la mère induit une vasoconstriction modérée des lits vasculaires myométriaux et placentaires.** Cette réduction de débit peut avoir des conséquences sur la quantité d'oxygené amenée dans la chambre intervilleuse et par voie de conséquence, sur l'apport d'oxygène au foetus.

Mots-clés: Débit sanguin (myométrial, placentaire), hyperoxie, lapines, normoxie.

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