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Effect of continuous infusion of norepinephrine on maternal pelvic and fetal umbilical blood flow in pregnant sheep

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1 Introduction

The uterine vascular bed contains alpha-adrenergic receptors [7] and reacts with a strong vasoconstriction upon alpha-adrenergic receptor stimulation. The vasoconstrictive effects of catecholamines on uterine blood flow have been studied in pregnant and non-pregnant sheep [1, 3, 5, 6, 8, 9, 11].

Bolus injections or continuous infusions with catecholamines either intravenously or directly intraarterially in the pelvic vessel cause vasoconstriction and a decrease in blood flow in various vessels of the maternal pelvic arterial bed as the common internal iliac artery, the internal iliac artery and the median uterine artery with a probably more marked effect on median uterine artery blood flow [1, 5, 6, 11].

In the present study we measured maternal pelvic blood flow at two locations, namely in the internal iliac artery and the median uterine artery. The objective of the study was to assess whether any difference in flow reactions between the vascular beds of the two vessels existed during continuous norepinephrine infusion to the ewe. Furthermore the effects of maternal norepinephrine administration on fetal umbilical blood flow, blood pressure, heart rate and acid-base balance were studied.

2 Materials and methods

The experiments were carried out in ten pregnant sheep of the Dutch Texel breed. Surgical instrumentation was performed under aseptic conditions and under general anesthesia, induced with pentobarbitone and continued with 5% halothane in a 2 : 1 mixture of nitrous oxide and oxygen. In the last third of pregnancy (term 146 days) the uterus was exposed through a paramedian abdominal incision.

A precalibrated electromagnetic flow transducer was placed around the median uterine artery on the ventrolateral side of the pregnant uterine horn. A small polyvinyl wing was attached to the cable of the flow transducer and this wing was secured to the uterine wall preventing movements of the flow transducer around the vessel and guaranteeing a perpendicular position to the vessel. Another electromagnetic flow transducer was placed around the maternal internal iliac artery after its origin from the common internal iliac artery. An inflatable balloon occluder was placed distal to both flow transducers for the assessment of zero blood flow.

The fetal lambs were approached by hysterotomy in the uterine wall lying over the fetal pelvis. They were provided with an inflatable balloon

occluder around the total umbilical cord, an electromagnetic flow transducer around the intraabdominal common part of the umbilical veins and with catheters and electrodes for registration of arterial blood pressure (FBP), amniotic fluid pressure (IUP) and fetal heart rate (FHR). Fetal blood pressure was measured in the descending aorta. All catheters and electrodes were exteriorized through a stab incision in the ewe's flank and protected in a pouch attached to the ewe's skin. Blood flow in the maternal internal iliac artery (QIIA) and median uterine artery (QMUA) and in the fetal common umbilical vein (QUV) was measured with a Skalar Transflow 601 flowmeter system (Skalar, Delft, Holland). Fetal arterial blood pressure and amniotic fluid pressure were determined with pressure transducers with the zero point at the level of the ewe's spine.

All signals were led to amplifiers (Hewlett Packard 8800 series), displayed on a monitor and an eight-channel strip chart recorder and stored on magnetic tape.

Antibiotics (ampicillin 1000 mg) were administered intravenously to the ewe before operation and also infused (ampicillin 500 mg) into the amniotic cavity during surgery. For the first three days postoperatively the mother received procaine penicillin (2,000,000 IU) and dihydrostreptomycin (2000 mg) intramuscularly.

The animals were allowed to recover for at least three days after surgery. Gestational age at the time of the experiments was between 104 and 142 days. Mean maternal body weight $\pm$ SD was 43.3 ± 3.4 kg (range 36–47 kg). Some animals were also subjected to infusion protocols with acetylcholine and fenoterol. The interval between two subsequent infusion experiments was at least 24 hours.

Norepinephrine was administered intravenously to the ewe via an indwelling catheter in either a jugular vein, a mammary vein, or a hindleg vein. The insertion place of the catheter varied, because reinsertion at another location was sometimes necessary, when the catheter was blocked or was lost by the ewe's manoeuvres. The drug solutions were continuously

infused by means of a perfusion pump. The extension catheter and the stopcock which connected the syringe containing the drug solution and the maternal venous catheter were filled with the drug solution prior to the start of the infusion to avoid any lag time between the start of the infusion and the arrival of the drug in the ewe's venous circulation. The dose of the drug was increased during the infusion period by increasing the infusion rate.

The experimental protocol for these tests comprised the following periods:

1. A control period of 30 minutes was observed during which the blood flows in the internal iliac artery and/or the median uterine artery as well as the available fetal parameters were recorded continuously. At the end of the control period a fetal arterial blood sample was withdrawn for analysis of fetal acid base balance.
2. A testing period of 60 minutes then followed, during which the drug was infused intravenously in increasing dose of respectively 4, 8, 20 and 40 micrograms of norepinephrine per minute, each infusion period lasting 15 minutes. During this period blood flow in the internal iliac artery and/or median uterine artery was recorded continuously together with fetal parameters. Fetal acid base balance was determined at the end of the drug infusion period.
3. A post infusion period of 30 minutes then followed. A third fetal arterial blood sample was withdrawn for fetal acid base balance determination at the end of the post infusion period of 30 minutes.

The internal iliac artery and median uterine artery blood flow at the side of the pregnant horn were not simultaneously measured in all experiments due to the fact that one of the flowmeters had lost its grip on the vessel during the experimental period or due to unstable flow signals.

Internal iliac artery blood flow (QIIA) could be measured during 7 experiments in 5 animals, median uterine artery blood (QMUA) flow during 13 experiments in 8 animals and finally

umbilical venous blood flow (QUV) during 13 experiments in 9 animals.

Mean values of maternal internal iliac and median uterine artery blood flow and fetal umbilical venous blood flow, heart rate and arterial blood pressure were calculated over intervals of five minutes. These intervals comprised a five minute period during the control period (= C) preceding the start of the drug infusion and the last five minutes of each sequential infusion period of fifteen minutes duration.

The fetal and maternal parameters were therefore calculated over the intervals 10 to 15 (= 15), 25 to 30 (= 30), 40 to 45 (= 45) and 55 to 60 (= 60) minutes after the start of the infusion. During the thirty minute recovery period they were calculated over the intervals 70 to 75 (= 75) and 85 to 90 (= 90) minutes after the beginning of the infusion.

Fetal heart rate and arterial blood pressure were recorded in every single experiment, but arterial blood pressure could not be analyzed in all experiments due to interference by blood sampling procedures or technical problems.

This explains the difference in the number of fetal heart rate and arterial blood pressure analyses in the various experiments, mentioned in the tables. Fetal pH and blood gas values were determined during control period (= C), and at the end of the infusion (= 60) and recovery period (= 90). Statistical analysis was performed by comparing the control values with the data of the test and recovery period by means of Wilcoxon's matched-pairs signed-ranks test. The fetal biochemical data were analyzed by a paired Student's t-test.

3 Results

Large differences in absolute blood flow in the internal iliac and median uterine artery existed between different animals at the same period of gestation. Internal iliac artery blood flow varied at 120 days gestation between 380 and 675 ml/min in different animals, and median uterine artery blood flow ranged at the same time of gestation from 150 to 420 ml/min in different animals. Short term variations of

Figure 1. Decreases in internal iliac (QIIA) and median uterine (QMUA) artery blood flow when the ewe was startled (↑).

Figure 2. The influence of micturition (↑) on median uterine artery blood flow (QMUA).

often considerable magnitude occurred in the maternal pelvic blood flow. Apart from the influences of changes in cardiac output, arterial blood pressure and heart rate, which were not recorded, the effect of autonomic tone changes on maternal internal iliac and median uterine artery blood flow is impressive. This is illustrated by the abrupt and often prolonged decreases in blood flow occurring during micturition and defecation and also during moments when the ewe became frightened by sudden unexpected movements of the investigator (figure 1). Figure 2 shows an example of the decreases in maternal blood flow during micturition.

Minor variations in blood flow were observed during postural changes of the ewe. There was a small increase in mean blood flow after a postural change from the standing to a lying position. Blood flow in different maternal positions was not further analyzed in this study. Small short lasting decreases in median uterine artery blood flow were also found during increase in uterine tone, as reflected in the amniotic pressure. The experiments with decreases in maternal blood flow associated with micturition, defecation, fright and uterine contractions or contractures were excluded from the study.

3.1 Effect of norepinephrine on the maternal and fetal parameters

The blood flow in the maternal vessels substantially decreased immediately following the onset of the infusion period as is shown in figure 3, together with a fall in maternal heart rate. Blood flow gradually returned towards the pre-infusion level despite the continued norepinephrine administration.

In five of the seven experiments internal iliac artery blood flow was still decreased at the end of each sequential infusion period, but in two experiments blood flow had returned to or above the control value.

The blood flow was further reduced with each following infusion period of fifteen minutes during which a higher dose of norepinephrine was administered. Again a slow return of blood flow occurred during the rest of the infusion period. The mean values of each interval are shown in table I. Only the blood flow in the internal iliac artery at the end of the first infusion period was significantly reduced to 91.5% of the control value ($p < 0.05$).

The blood flow in the median uterine artery showed the same response pattern as the changes in the internal iliac artery flow, al-

Figure 3. Initial decreases in internal iliac (QIIA) and median uterine (QMUA) artery blood flow followed by a slow recovery during continuous intra-venous administration of 4 γ norepinephrine per minute to the ewe. ($\downarrow$ start of the infusion).

Table I. Effect of continuous intravenous administration of norepinephrine to the ewe on fetal heart rate (FHR), fetal arterial blood pressure (FBP), umbilical venous blood flow (QUV) and maternal internal iliac (QIIA) and median uterine artery blood flow (QMUA). Data are expressed as mean $\pm$ SEM ($\downarrow$ start of the infusion).

	-30'	0'	15'	30'	45'	60'	75'	90'
Norepinephrine	Control	$\downarrow$ 4 γ /Min.	8 γ /Min.	20 γ /Min.	40 γ /Min.	Recovery		
FHR (BPM) N = 17	160 $\pm$ 5.0	157 $\pm$ 5.3	162 $\pm$ 9.7	164 $\pm$ 4.6	167 $\pm$ 4.9	166 $\pm$ 4.6	170 $\pm$ 5.7	
FBP (MM.HG.) N = 15	37.7 $\pm$ 3.1	37.3 $\pm$ 3.0	37.7 $\pm$ 3.6	42.2 $\pm$ 3.1	39.9 $\pm$ 3.6	41.1 $\pm$ 3.6	41.4 $\pm$ 3.7	
QUV (ML./Min.) N = 13	351 $\pm$ 57	354 $\pm$ 60	440 $\pm$ 131	458 $\pm$ 112	472 $\pm$ 133	461 $\pm$ 131	472 $\pm$ 132	
QIIA (ML./Min.) N = 7	356 $\pm$ 46	326 $\pm$ 45	311 $\pm$ 22	282 $\pm$ 38	284 $\pm$ 29	336 $\pm$ 38	291 $\pm$ 41	
QMUA (ML./Min.) N = 13	260 $\pm$ 39	249 $\pm$ 41	261 $\pm$ 38	244 $\pm$ 36	225 $\pm$ 27	285 $\pm$ 35	274 $\pm$ 34	

$\Delta p < 0.05$

though none of the values significantly differed from control. In eight experiments blood flow was still decreased at the end of each infusion period, while in the remaining five experiments blood flow was either decreased or had already returned to or above the control value at the end of each infusion period. The mean values showed a small and insignificant decrease in flow at the end of each infusion period, with a return to control value in the recovery period.

Table II. Fetal pH and blood gas values before, during and after the administration of norepinephrine to the ewe (mean $\pm$ SD; N = 17). pH is expressed in units, Po₂ and Pco₂ are expressed in kPa.

Norepinephrine	C	60 min.	90 min.
pH	7.32 $\pm$ 0.06	7.30 $\pm$ 0.06	7.29 $\pm$ 0.05
Pco ₂	5.11 $\pm$ 0.64	5.72 $\pm$ 1.84	6.33 $\pm$ 2.31
Po ₂	3.55 $\pm$ 0.59	4.26 $\pm$ 2.41	5.13 $\pm$ 3.09

Fetal heart rate did not change during the infusion period but showed a small and significant ($p < 0.05$) increase in the recovery period. Fetal arterial blood pressure and umbilical venous blood flow did not significantly change. No significant changes occurred in fetal pH and blood gas values (table II), which latter values showed a great standard deviation.

4 Discussion

The observations on maternal pelvic blood flow in these experiments demonstrate not only that a great variation in uterine blood flow exists between different animals in the same period of gestation, but more importantly they demonstrate the relatively great short term variations occurring in uterine blood flow. The same phenomenon has been described by CLAPP [4]. No signs of fetal distress in the fetal heart rate pattern were observed during the spontaneous blood flow decreases.

These variations in blood flow indicate on the one hand the great safety margin of the uterine blood flow rate for the fetus, but they also imply on the other hand a certain restriction in regard to the interpretation of the effects of administered drugs on uterine blood flow. This is especially the case if not immediate short term effects of vasoactive substances are the subject of study but if the influences on blood flow during a longer experimental period are concerned.

Only few authors [1, 4] mention some of the problems associated with maternal pelvic blood flow measurements by means of chronically implanted electromagnetic flow transducers. The fact that these problems are possibly more often encountered than mentioned probably finds reflection in the design of many studies, in which only the immediate effects after bolus administrations or short lasting infusions are measured.

4.1 Effect of norepinephrine on the maternal and fetal parameters

The magnitude of the decreases in internal iliac and median uterine artery blood flow were ex-

cept during one interval not significantly different from control and were much smaller than those reported by others [1, 2, 3, 5, 11].

In each of these studies the maximum response upon norepinephrine administration either in a bolus injection intraarterially or intravenously [1, 3, 5] or in a continuous systemic intravenous or local intraarterially infusion [2, 9, 11] were assessed. As can be seen in figure 3 the maximum response occurred in the first few minutes after the start of the infusion and the blood flow decrease at that moment is impressive, but is not substained throughout the total infusion period. In fact after an initial substantial decrease blood flow had already returned towards the control level at the end of the 15 minute infusion period in several experiments. These observations not only explain the differences in magnitude of the flow decreases between the results of others and the present data but also lead to the tentative conclusion that systemic infusion of norepinephrine leads to a substantial decrease in internal iliac and median uterine artery blood flow which gradually but certainly not completely abates with time despite continued drug administration.

This adaption in time might be caused by local factors involving prostaglandin production and/or by the phenomenon of down-regulation. This concept of down-regulation implies that after a prolonged exposure to the adrenergic drug the concentration of adrenergic receptors decreases, parallel with the declining response to continued drug administration [10].

Fetal heart rate and arterial blood pressure did not change significantly during infusion in contrast to the results obtained by CHEZ et al [3], who found a slight increase in blood pressure and a small decrease in fetal heart rate. Fetal arterial blood pressure did show an incremental trend in the present data. Umbilical venous blood flow showed an increase but a great variation in flow existed without any significant change. No significant changes in fetal acid base balance occurred and the meaning of the observed increase in P_{CO_2} and P_{O_2} during the recovery period is not clear. Although cer-

tain trends in effect could be observed, most of the changes in maternal blood flow were not statistically different from control.

The results are compatible with blunting of the effects of autonomic vasoactive drugs on the

utero-placental and pelvic vascular beds during pregnancy. This latter phenomenon is potentially protective for the fetus. Possibly other mechanisms than the influences of the autonomic nervous system are more important in the regulation of utero-placental blood flow.

Summary

The effect of continuous maternal intravenous infusion with norepinephrine on the blood flow in the maternal internal iliac and the median uterine artery was studied in ten chronically instrumented pregnant sheep between 104 and 146 days gestation. Furthermore the effects on umbilical venous blood flow, fetal heart rate and acid-base balance were analyzed.

Maternal and fetal blood flows were measured with electromagnetic flow transducers. Norepinephrine was administered to the ewe via a continuous intravenous infusion in increasing sequential doses of 15 minutes duration from 4 to 40 micrograms per minute. Variations of often considerable magnitude associated with e. g. micturition, defecation and fear of the ewe occurred in the maternal pelvic blood flow during the steady state

period. The blood flow in the maternal vessels substantially decreased immediately following the onset of the norepinephrine infusion but gradually returned towards the preinfusion level despite the continued drug infusion and except one no significant changes in blood flow were found at the end of each sequential infusion period. Umbilical venous blood flow did not change. No significant changes in fetal arterial blood pressure, heart rate and acid base balance were found. It is concluded that the decrease in maternal pelvic blood flow associated with continuous norepinephrine administration gradually abates with time, possibly by the involvement of local factors such as prostaglandin formation and/or by the phenomenon of down-regulation.

Keywords: Fetal acid-base balance, maternal pelvic blood flow, norepinephrine, umbilical blood flow.

Zusammenfassung

Einfluß einer kontinuierlichen Noradrenalininfusion auf den maternalen pelvinen und fetalen umbilikalen Flow beim trächtigen Schaf

Wir untersuchten den Einfluß einer kontinuierlichen, intravenösen Noradrenalininfusion auf den Flow in der mütterlichen Arteria iliaca interna und Arteria uterina bei 10 permanent überwachten, trächtigen Schafen zwischen dem 104. und 146. Tag der Tragzeit. Darüberhinaus wurde der Einfluß auf den Flow in der Nabelvene, die fetale Herzfrequenz und den Säure-Basen-Status analysiert.

Der maternale und fetale Flow wurde mit elektromagnetischen Transducern gemessen. Noradrenalin wurde dem Muttertier über eine kontinuierliche Infusion in steigender Dosierung von 4 bis 40 µg/min intravenös verabreicht, wobei die Dosis nach jeweils 15 Minuten erhöht wurde. Kam es beim maternalen, pelvinen Flow in der Steady-state-Phase zu bedeutsamen Schwankungen,

waren diese assoziiert mit Miktion, Defäkation und Ausdruck von Angst beim Schaf. In den mütterlichen Gefäßen war der Flow hauptsächlich unmittelbar nach Beginn der Noradrenalininfusion reduziert; trotz kontinuierlicher Gabe erfolgte schrittweise ein Absinken auf den Ausgangswert vor Infusionsbeginn. Mit einer Ausnahme wurden keine signifikanten Veränderungen des Flows am Ende einer Infusionsphase von 15 Minuten gefunden. Der Flow in der Nabelvene änderte sich nicht. Auch der fetale, arterielle Druck, die Frequenz und die Parameter im Säure-Basen-Status wiesen keine Veränderungen auf. Wir schließen aus unseren Ergebnissen, daß die Reduktion des Flows in den mütterlichen, pelvinen Gefäßen nach kontinuierlicher Noradrenalininfusion in Abhängigkeit von der Zeit aufgehoben wird. Hieran können lokale Faktoren wie z. B. Prostaglandinfreisetzung und/oder ein Regulationsmechanismus im Sinne einer Anpassung beteiligt sein.

Schlüsselwörter: Fetalen Säure-Basen-Status, maternalen pelvinen Flow, Noradrenalin, umbilikalen Flow.

Résumé

Effet d'une perfusion continue de norépinéphrine sur le débit sanguin pelvien maternel et ombilical du fœtus chez la brebis gravide

On a étudié chez dix brebis gravides installées chroniquement les effets d'une perfusion maternelle continue de

norépinéphrine sur le débit sanguin au niveau de l'artère iliaque interne maternelle et de l'artère utérine médiane entre 104 et 146 jours de gestation. En outre, on a analysé les effets sur le débit sanguin dans la veine ombilicale, sur le rythme cardiaque fœtal et l'équilibre

acido-basique. Les débits sanguins maternels et fœtaux ont été mesurés à l'aide de capteurs de flux électromagnétiques.

La norépinéphrine était injectée à la brebis par une perfusion continue avec des doses progressivement croissantes toutes les 15 minutes depuis 4 jusqu'à 40 microgrammes par minute. Pendant la période d'état calme, au niveau du débit sanguin maternel pelvien surviennent des variations souvent d'amplitude considérable en rapport avec par exemple la miction, la défécation ou des épisodes de peur de la brebis. Le débit sanguin dans les vaisseaux maternels diminue de façon substantielle immédiatement après le début de la perfusion de norépinéphrine mais revient progressivement

vers les taux antérieurs à la perfusion malgré la poursuite de la perfusion; sauf une fois, on n'a pas trouvé de modifications significatives du débit sanguin à la fin de chaque période successive de perfusion. Le débit sanguin ombilical ne s'est pas modifié. On n'a pas mis en évidence de modifications significatives de la pression artérielle fœtale, de la fréquence cardiaque ni de l'équilibre acido-basique. On en conclut que la diminution du débit sanguin pelvien maternel qui accompagne l'injection continue de norépinéphrine se modère progressivement dans le temps, peut-être du fait de l'implication de facteurs locaux tels que la formation de prostaglandines et/ou du fait d'un phénomène de Feed-back.

Mots-clés: Débit sanguin maternel pelvien, débit sanguin ombilical, équilibre acido-basique du fœtus, norépinéphrine.

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