J. Perinat. Med.
15 (1987) 523

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

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1 Introduction

Adrenergic receptor activity is of particular interest in pregnancy because of its influence both on the uterine circulation and uterine tone and contractility. Beta-sympathomimetic drugs as for example fenoterol are widely used in obstetrics for the treatment of premature labor and intrapartum fetal distress. The effects of tocolytic beta-sympathomimetic drugs on uterine and umbilical blood flow have been studied in non-laboring pregnant sheep.

The results from these studies on the reactions of the uterine vascular bed upon intravenous administration of beta-adrenergic drugs to the ewe are not one at all identical. In several studies [1, 9, 11] increases in uterine blood flow were reported while other studies [2, 3, 4, 6, 7, 8, 10, 12] showed no changes or even decreases in flow after beta-adrenergic drug infusion. Part of these differences might be explained by the fact that different beta-sympathomimetic drugs were used, but more important seems the site of flow measurement in the pelvic vascular bed. Some authors used the median uterine artery for flow measurements while others recorded blood flow in the main uterine or common internal iliac artery. These vessels do not have to react in the same way and/or degree upon vasoactive stimuli, as was recently pointed out by the group of ASSALI. The different reactions of the various vessels in the pelvic arterial bed to vasoactive stimuli might be explained by different autonomic innervation of the vessels [1, 9, 12]. In the present study we measured maternal pelvic blood flow at two locations, namely in the internal iliac artery and the median uterine artery. Objective of the study was to assess whether any difference in flow reactions between the vascular beds of the two vessels existed during fenoterol infusion to the ewe.

Furthermore the effects of maternal fenoterol 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 seven pregnant sheep of the Dutch Texel breed. Surgical instrumentation was performed under aseptic conditions and under general anesthesia induced with pentobarbital 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. An in vitro 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 in vivo assessment of zero blood flow. This procedure often produces

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spasm of the vessels with slow return to the normal situation. The experimental protocol was started after full recovery of the vessel from spasm for a period of at least 30 minutes.

The fetal lambs were approached by a 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 atery (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) [5]. 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) in 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 43.5 + 3.4 kg (range 36 – 47 kg). Some animals were also subjected to infusion protocols with norepinephrine and acetylcholine. The interval between two subsequent infusion experiments was at least 24 hours.

Fenoterol 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 selected drug solution prior to 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 doses of the drug were increased during the infusion period by doubling 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. Two testing periods of each 30 minutes then followed, during which fenoterol was infused intravenously in a dose of 2 respectively 4 micrograms per minute. Fetal acid base balance was determined at the end of the drug infusion period.
3. A post infusion period of 30 minutes was allowed. 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 15 experiments in 4 animals, median uterine artery blood (QMUA) flow during 18 experiments in 6 animals and finally umbilical venous blood flow (QUV) during 20 experiments in 7 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 an interval of five minutes in the control period and during the last

five minutes of both thirty minute infusion periods and of the thirty minute recovery period. The following intervals during infusion and recovery period were therefore analyzed: the intervals 25 to 30 (= 30), 55 to 60 (= 60) and 85 to 90 (= 90) minutes after the start 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 analysed by a paired students t-test.

Only data derived from experiments without uterine contractions or contractures as judged from the amniotic pressure recording which affect uterine blood flow were included in the study.

3 Results

The mean blood flow in the internal iliac artery increased during the infusion period and was still elevated at the end of the thirty minute recovery period.

Only the 10.5% increase in blood flow at the end of the infusion period with 4 microgram per minute differed significantly ($p < 0.05$) from control (table I). The individual data of each experiment showed an increase in blood flow at the end of each infusion period in 9 experiments. Blood flow was lower than control value at the end of each infusion period in three experiments, while in the remaining three experiments the blood flow response was varying, that is to say either lower or higher than the control value at the end of both infusion periods. Mean median uterine artery blood flow showed no significant changes, although an incremental trend during the infusion period was found. Analysis of the individual data of each experiment showed a consistent increase in blood flow at the end of each infusion period in 10 experiments. Blood flow was lower than the control value at the end of each infusion period in five experiments, while in the remaining three experiments the effect on blood flow was varying, namely either lower or higher than the control value at the end of both infusion periods. Fetal umbilical venous blood flow and arterial blood pressure did not change. Fetal heart rate showed no changes except for a slight decrease at the end of the infusion period ($p < 0.02$). The fetal pH and blood gas values are shown in the next slide (table II). Fetal Pco_2 was significantly ($p < 0.005$)

Table I. Effect of continuous intravenous administration of fenoterol 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 ± SEM (↓ start of the infusion).

	−30′	0′	30′	60′	90′
Fenoterol	Control	↓ 2 µg/min	4 µg/min	Recovery	
FHR (BPM) N = 24	167 ± 3.6	163 ± 3.2	159 ▲ ± 3.9	164 ± 3.5	
FBP (mm.Hg) N = 21	36.3 ± 1.9	36.4 ± 1.9	36.3 ± 2.1	35.6 ± 1.8	
QUV (ml/min) N = 20	635 ± 59	631 ± 51	637 ± 64	628 ± 59	
QIIA (ml/min) N = 15	389 ± 50	402 ± 39	430 □ ± 59	454 ± 74	
QMUA (ml/min) N = 18	324 ± 43	331 ± 46	338 ± 41	317 ± 43	

▲P < 0.02 □P < 0.05

Table II. Fetal pH and blood gas values before, during and after the administration of fenoterol to the ewe (mean ± SD; N = 24; C = Control value). pH is expressed in units, Po_2 and Pco_2 are expressed in kPa.

Fenoterol	Control	60 min	90 min
pH	7.35 ± 0.04	7.36 ± 0.04	7.35 ± 0.03
Pco_2	4.96 ± 0.57	4.67 ± 0.61 ★	4.61 ± 0.64 ★
Po_2	3.57 ± 0.44	3.52 ± 0.49	3.59 ± 0.53

★$P < 0.005$

reduced at the end of the infusion and recovery period. Fetal pH and Po_2 did not significantly change.

4 Discussion

Although the changes in blood flow were small, and except for one value not significant, a distinct difference between the flow changes in the internal iliac artery and median uterine artery was observed. The internal iliac artery blood flow showed a relatively greater increase than the median uterine artery blood flow, while the former still was increased at the end of the post infusion period in contrast to the latter. This finding suggests a greater sensitivity of the internal illiac artery than the median uterine artery or the vascular beds supplied by them to beta-adrenergic receptor stimulation.

These changes in blood flow upon beta-adrenergic receptor stimulation are in agreement with the results of TABSH et al. [12] and ERKKOLA et al. [9]. ERKKOLA et al. [9] found an increase in blood flow in the common internal iliac artery while the median uterine artery flow decreased or did not change upon intra-arterial stimulation of beta-adrenergic receptors by isoproterenol administered directly into the aortic trifurcation. TABSH et al. [12] also found a difference in response. Common internal iliac artery blood flow remained unchanged while the blood flow in the median uterine artery progressively decreased during intravenous infusion of the beta adrenergic agonist isoxsuprine, which drug has also alpha-adrenergic properties.

TABSH et al. [12] suggested that the different functions of the tissues supplied by respectively the median uterine artery and the dorsal uterine artery, which is one of the other great branches of the internal iliac artery, required different neurohumeral mechanisms for hemodynamic adjustments. The middle uterine artery supplies the fundus and corpus uteri, the contractile part of the uterus, while the dorsal uterine artery supplies the lower uterine segment, the cervix and the vagina, the more passive part of the uterus, and furthermore part of the bladder. The remainder of the internal iliac artery flow is destined for extragenital structures.

A difference in adrenergic receptor sensitivity of the vascular bed of the median and dorsal uterine artery might explain the difference in flow changes between dorsal uterine artery (as they are reflected in the flow of the common internal iliac artery) and median uterine artery.

BRENNAN et al. [3] measured blood flow in the main uterine artery, a terminal branch of the internal iliac artery, giving rise to the median and dorsal uterine arteries, during continuous intravenous infusion of fenoterol to the ewe. The observed small increases in flow are in agreement with the concept of TABSH et al. [12].

The data from the present study also fit into the concept that the vascular bed of the internal iliac artery can be divided in that of the median uterine artery with a relatively small beta-adrenergic sensitivity, and in that of the dorsal uterine artery and other nongenital structures which react with a blood flow increase upon beta-adrenergic receptor stimulation.

Fetal heart rate, arterial blood pressure and umbilical venous blood flow were not affected by the maternal fenoterol infusion, except for a very small but significant decrease in heart rate at the end of the infusion period. This finding is somewhat curious, because if an effect had to be present, then a fetal tachycardia would be expected. In some instances however, a decrease in fetal heart rate was noted, associated with flushing of the aortic catheter after sampling of fetal blood for blood gas analysis. This decrease in heart rate might be caused by baroreceptor stimulation and could account for observed differences in heart rate compared to the control value.

EHRENKRANZ et al. [7] and CHEZ et al. [4] did not find any significant change in fetal heart rate, blood pressure or umbilical venous blood flow.

Fetal pH and Po_2 did not change, whereas fetal Pco_2 was significantly decreased at the end of the infusion period and the recovery period.

A significant decrease in fetal P_{CO_2} together with an increase in fetal pH was found by BRENNAN et al. [3] during infusion of ritodrine to the ewe, while no changes were observed during fenoterol administration. An explanation for the decrease in fetal P_{CO_2} found in this study could be a concomitant decrease in maternal P_{CO_2} during hyperventilation, associated with beta-sympathomimetic drug infusion.

It indicates that fenoterol infusion to the mother at least did not adversely affect fetal acid-base balance.

Summary

The results from studies on the reactions of the uterine vascular bed upon intravenous administrations of beta-adrenergic drugs to the ewe are not all identical. This can be partly explained by different reactions of the pelvic vasculature on beta-adrenergic receptor stimulation. In order to assess whether any differences in flow reactions existed between the vascular beds of two maternal pelvic vessels upon beta-adrenergic receptor stimulation, we studied the effect of continuous maternal intravenous infusion with fenoterol on the blood flow in the maternal internal iliac and the median uterine artery in seven chronically instrumented pregnant sheep between 104 and 142 days gestation.

Furthermore, the effects on umbilical venous blood flow, fetal heart rate, blood pressure and acid-base balance were analyzed. Maternal and fetal blood flows were measured with electromagnetic flow transducers. Fenoterol was administered to the ewe via a continuous intravenous infusion in two sequential periods of 30 minutes duration in a dose of 2 respectively 4 micrograms per minute.

The blood flow in the internal iliac artery showed an increase of 10.5% ($p < 0.05$) at the end of the infusion period and was still but not significantly elevated during the postinfusion period. No significant changes in median uterine artery blood flow were found during the fenoterol infusion, although an incremental trend was present.

Fenoterol infusion to the mother had no effect on umbilical venous blood flow. Fetal pH and P_{O_2} did not change, while fetal P_{CO_2} was reduced ($p < 0.005$) at the end of the infusion and recovery period, probably as a result of the concomitant maternal hyperventilation.

The data from the present study fit into the concept of a different beta-adrenergic sensitivity between the vascular bed of the median uterine artery with a relatively small beta-adrenergic sensitivity and the vascular bed of other branches of the internal iliac artery with a higher beta-adrenergic responsiveness. Fenoterol infusion to the mother has no effect on the fetal umbilical circulation.

Keywords: Fenoterol, fetal acid-base balance, maternal pelvic blood flow, umbilical blood flow.

Zusammenfassung

Der Einfluß einer Fenoterol-Dauerinfusion auf die mütterliche Becken- und die kindliche Nabelschnurdurchblutung bei trächtigen Schafen

Die Studienergebnisse über die uterinen Gefäßreaktionen auf i. v. Applikation von Beta-Sympathomimetika beim Schaf sind nicht einheitlich. Dies kann teilweise durch die unterschiedlichen Reaktionsmöglichkeiten der Becken-Gefäßmuskulatur auf Beta-Rezeptorenstimulation erklärt werden.

Um festzustellen, ob irgendwelche Unterschiede in den Strömungsreaktionen zweier mütterlicher Beckengefäße auf beta-adrenerge Rezeptorenstimulation nachweisbar sind, haben wir den Effekt von einer Fenoterol-i. v.-Dauerinfusion auf die Strömungsverhältnisse in der mütterlichen A. iliaca interna und in der medialen Uterusaterie unter dauernder instrumenteller Ableitung bei sieben trächtigen Schafen zwischen dem 104. und dem 142. Tag der Schwangerschaft gemessen.

Außerdem wurden die Wirkungen auf die venöse Nabelschnurdurchblutung, auf die fetale Herzfrequenz, auf den Blutdruck und den Säure-Basen-Status untersucht.

Maternale und fetale Durchblutung wurden mit elektromagnetischer Fluß-Übertragung gemessen. Das Fenoterol wurde den Schafen per i. v. Dauerinfusion gegeben, und zwar in zwei aufeinander folgenden Perioden von je 30 Minuten Dauer, in einer Dosierung von 2 bzw. 4 Mikrogramm/Minute.

Der Blutdurchfluß in der A. iliaca interna nahm bis zum Ende der Infusionsperiode um 10.5% ($p < 0.05$) zu und war immer noch, wenn auch nicht deutlich, während der Postinfusionsperiode erhöht. Keine prägnante Änderung des Blutdurchflusses gab es während der Infusion in der medianen Uterusarterie, wenn auch eine ansteigende Tendenz vorhanden war. Die Fenoterol-Infusion der Mutter hatte keinen Einfluß auf die Nabelvenendurchblutung. Der fetale pH und P_{O_2} veränderten sich nicht, währen der fetale P_{CO_2} für die Dauer der Infusion und in der Erholungsphase wahrscheinlich als Reaktion auf die begleitende mütterliche Hyperventilation abnahm ($p < 0.0005$).

Die Ergebnisse dieser Studie passen in das Konzept von unterschiedlicher beta-adrenergen Sensibilität, und zwar

mit einer relativ geringen beta-adrenergen Sensibilität der medianen Uterusarterie, und einer höheren Ansprechbarkeit auf beta-adrenerge Stimuli der anderen Zweige der A. iliaca interna. Eine der Mutter gegebene Fenoterol-Infusion hat keinen Effekt auf die fetale Nabelschnurdurchblutung.

Schlüsselwörter: Fenoterol, fetaler Säure-Basen Status, mütterliche Beckendurchblutung, Nabelschnurdurchblutung.

Résumé

Effet de la perfusion continue de fénotérol sur les débits sanguins pelviens maternels et ombilicaux du fœtus chez la brebis gravide

Les résultats des études sur les réactions du lit vasculaire utérin à l'injection intraveineuse de médicaments béta-adrénergiques chez la brebis ne sont pas tous identiques. Cela peut, en partie, être expliqué par des réactions différentes de la vascularisation pelvienne sur la stimulation des récepteurs béta-adrénergiques.

Afin d'apprécier s'il exists des différences au niveau des réactions des débits entre les lits vasculaires de deux vaisseaux pelviens maternals sur la stimulation des récepteurs béta-adrénergiques, nous avons étudié l'effet d'une perfusion intraveineuse maternelle continue de fénotérol sur les débits de l'artère illiaque interne maternelle et de l'artère utérine moyenne chez 7 brebis gravides préparées chroniquement entre 104 et 142 jours de gestation.

En outre nous avons analysé les effets sur les débits sanguins veineux ombilicaux, sur le rythme cardiaque fœtal, la pression sanguine et l'équilibre acido-basique. La mesure de sdébits sanguins maternels et fœtaux a été effectuée par des capteurs de débit électromagnétiques. Le fénotérol a été administré aux brebis par une perfusion intraveineuse continue au cours de deux périodes séquentielles de 30 minutes aux doses respectives de 2 et de 4 microgrammes par minute.

Le débit sanguin de l'artère illiaque interne s'est élevé de 10,5% ($p < 0,05$) à la fin de la perfusion et est demeuré élevé après la perfusion mais de façon non significative. On n'a pas trouvé de modifications significatives du débit sanguin dans l'artère utérine moyenne au cours de la perfusion de fénotérol, bien qu'une tendance à l'augmentation se soit manifestée.

La perfusion de fénotérol à la mère n'a pas d'effet sur le débit sanguin ombilical veineux. Le pH fœtal et la Po_2 ne se modifient pas, tandis que la Pco_2 diminue ($p < 0,005$) à la fin de la perfusion et à la période de rétablissement, il s'agit là probablement du résultat de l'hyperventilation maternelle simultanée.

Les données de cette étude sont en accord avec le concept d'une sensibilité béta-adrénergique différente entre le lit vasculaire de l'artère utérine moyenne qui a une sensibilité béta-adrénergique relativement faible, et le lit vasculaire des autres branches de l'artère illiaque interne qui ont une sensibilité béta-adrénergique plus élevée. La perfusion de fénotérol à la mère n'a pas d'effet sur la circulation ombilicale fœtale.

Mots-clés: Débit sanguin maternel pelvien, débit sanguin ombilical, équilibre acido-basique fœtal, fénotérol.

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Received July 29, 1985. Revised July 25, 1986. Accepted December 28, 1986.

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