Umbilical and uterine blood flow in pregnant sheep

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UMBILICAL AND UTERINE BLOOD FLOW IN PREGNANT SHEEP

Proefschrift

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Thomas Hubertus Maria Hasaart

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Promotor: Prof.Dr. J. de Haan, Rijksuniversiteit Limburg, Maastricht

Referenten: Prof.Dr. C.B. Martin jr., Katholieke Universiteit, Nijmegen
Prof.Dr. F.I.M. Bonke, Rijksuniversiteit Limburg, Maastricht

Aan mijn ouders

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Tom Hasaart

CONTENTS

LIST OF ABBREVIATIONS

a.	artery
BE	base excess
bpm	beats per minute
C	control value
cm	centimeter
E	value measured at the end of the occlusion period
ECG	electrocardiogram
EFW	estimated fetal weight
FBP	fetal arterial blood pressure
FECG	fetal electrocardiogram
FHR	fetal heart rate
FIAP	fetal intraabdominal pressure
Fig.	figure
	gamma (1 = 1 microgram)
g.	gram
hr	hour
Hz	Herz
IU	international unit
IUFD	intrauterine fetal death
IUP	intrauterine pressure
Kg	kilogram
kPa	kilo Pascal (1kPa = 7.5 mm Hg)
l.	liter
M	mean
mEq	milliequivalent
mg	milligram
min	minute
ml	milliliter
mm	millimeter
mm Hg	millimeters of mercury
msec	millisecond
n	number
n anim.	number of animals

n exp.	number of experiments
p	tail probability
pCO_2	partial arterial carbon dioxide pressure
pH	degree of acidity; negative logarithm of hydrogen ion concentration in equivalents per liter
pO_2	partial arterial oxygen pressure
p.o.	post operation
QIIA	maternal internal iliac artery blood flow
QMUA	maternal median uterine artery blood flow
QUV	fetal common umbilical vein blood flow
SD	standard deviation
sec	second
SEM	standard error of the mean
TP	fetal intratracheal pressure

CHAPTER I

GENERAL INTRODUCTION

The normal development of the fetus during intrauterine life, its growth and wellbeing as its capacity to tolerate the stress of labor and delivery depend to a great extent upon the integrity of the fetoplacental circulation, a subject of study during centuries.

The present accumulated knowledge on fetal physiology in general and fetal circulation in particular, is mainly the product of work and thought in the twentieth century. The foundation however was laid in the discoveries of the Ancients and in the seventeenth century, when William Harvey first described the circulation of the adult as well as that of the fetus in his Exercitatio anatomica de motu cordis et sanguinis (1628). The unique anatomical features of the fetus had been described long before Harvey's publications. Galenus first described the foramen ovale and the ductus arteriosus in 1525, while Vesalius apparently was the first author who mentioned the ductus venosus in a work published posthumously in 1564.

The slow flowering process in the unraveling of the fetal physiology until modern times was amongst others due to the defective technical facilities while the methods of communication between investigators and the spread of knowledge were only a fraction of present-day possibilities.

For example, more than two hundred years elapsed between raising of the question of fetal respiration in utero by William Harvey in 1651 in his Exercitationes de Generatione Animalium and the final answer by Paul Zweifel, a Swiss obstetrician in 1876. Zweifel's demonstration, that the fetus respires via the placenta is one of the landmarks in the development of our understanding of life in utero. His findings were confirmed by Zuntz in 1877.

The exceedingly rapid developments of the past fifty years are related directly to the use of a wide range of technologies.
In the same time several animal models in different species as sheep, subhuman primates, goats, guinea-pigs and sows were developed for the study of fetomaternal physiology, from which animal models the chronic pregnant sheep preparation is the one mostly used in perinatal research. The combination of the pregnant sheep model in a chronic way and the available technology has yielded enormous information on fetomaternal physiology with a considerable impact on the modern management of pregnancy and especially labor.
The introduction of simultaneous monitoring of the fetal heart rate and uterine activity by Hon (1960), Hammacher (1962) and Caldeyro-Barcia et al (1963) has led to the recognition of various fetal heart rate patterns during pregnancy and labor and fetal hypoxemia can now be detected before fetal condition deteriorates.
Studies in the chronic sheep preparation varying from causing maternal and fetal hypoxemia to interruption of fetal and maternal placental circulation have revealed several of the mechanisms by which the fetus reacts to acute and chronic stress. The reflections of acute and chronic stress are found in the fetal heart rate patterns, which are nowadays a safe and reliable guideline for the judgement of fetal well being in utero.
Together with the introduction of fetal scalp blood sampling during parturition (Saling 1962), which makes it possible to determine the fetal acid-base balance, fetal heart rate monitoring is an indispensable tool in modern obstetrics. Fetal acidemia and hypoxemia both in pregnancy and labor can now be recognized and assessed and management of labor can be directed in those cases in such a way that irreversible damage to the fetus caused by hypoxia is avoided.
Continuous measurements of pO_2 with scalp electrodes are performed both in the human and in animal studies (Huch et al 1977, O'Connor and Hytten 1979, Aarnoudse 1980), but they are not directly applicable in routine obstetrical care, at least in their present technical state, whereas it is questionable whether they give useful additional information next to fetal heart rate monitoring.
The technical improvements of ultrasonography opened up new fields of

investigation as fetal behaviour in utero and the detection of congenital anomalies.

Simultaneous registration of fetal heart rate and fetal movements as a routine measurement is not easy to perform, but may add valuable information on fetal well-being in special cases.

Ultrasonographic observations of fetal body and breathing movements in utero can yield in the same way valuable information, among other things on congenital malformations.

Recent studies were directed to the relations between heart rate, breathing movements, fetal behavorial states and brain activity (Dawes et al 1972, Wheeler et al 1980, van der Wildt 1982).

Fetal and maternal placental blood flows have been under study in animal models for several decades with different methods of measurement.

Despite the increased knowledge on the regulation of the placental blood flows by the development of the chronic fetal sheep model in perinatal research, still relatively less is known about flow regulation to and from the placenta than about the regulation of flow in any other organ. Due to technical and ethical problems involved only scarce data on placental blood flow in the human are available.

Assali et al (1960) measured uterine blood flow by means of electromagnetic flow transducers in the first two trimesters in the human. Washout methods using 133 Xe in the human estimate the clearance from myometrium (Jansson 1969), but do not give absolute figures.

Recently a noninvasive method of flow measurement is used in the human consisting of a combination of pulsed Doppler ultrasound technique for flow velocity measurements and real time B-scan ultrasonography for localization and assessment of the diameter of the bloodvessels to be measured. Although this technique has several technical and methodological shortcomings, which make this method not yet available for routine hospital practice, the preliminary results are promising for the study of fetal hemodynamics in the near future (Eik-Nes et al 1980, Eik-Nes et al 1982, Jouppila et al 1983).

The earliest measurements of uterine blood flow were done by Barcroft et al (1933), who collected the uterine venous outflow of the rabbit over longer periods of time. This method was replaced by the discovery

of Kety and Schmidt in 1948 that an estimate of tissue blood flow could be obtained in man using a diffusible inert gas such as nitrous oxide. Assali et al (1953) measured with this method uterine blood flow in the human, later they compared it with the results obtained by means of electromagnetic flow transducers (Assali et al 1960).

4-amino-antipyrene instead of nitrous oxide was used by Huckabee et al in 1961 to measure the uterine blood flow in goats on the basis of the diffusion-equilibrium technique. Electromagnetic flowtransducers for the measurement of uterine blood flow are available since the late fifties. Kirschbaum et al (1967) demonstrated their usefulness in uterine flow measurement in pregnant sheep.

Radioactive microspheres, injected into the arterial circulation will be distributed in accordance with the arterial blood flow, if they are well mixed with the blood and if they are too large to pass through the precapillary arterioles. This technique was first used for uterine blood flow measurement in sheep by Makowski et al in 1968 after a modification of the technique by Rudolph and Heymann in 1967.

All the mentioned techniques have their disadvantages and limitations. The diffusion-equilibrium technique gives flow data in ml/min per kg of uterus and intrauterine tissue. The precise intrauterine tissues, in casu fetus and placenta, and the possible involvement of amniotic fluid however are not adequately defined with this method.

The diffusion-equilibrium technique gives a constant value for the blood flow to the uterus per unit weight from 90 days gestation onwards to term, but the absolute flow expressed in ml/min rises during the course of pregnancy due to the increasing mass of uterus and intrauterine tissues.

Electromagnetic flow transducers and the radioactive microsphere technique are now the two most used methods of flow determination, although each method has its specific problems which make them not suitable for every sort of experiment. The positioning of electromagnetic flow transducers around maternal and fetal vessels for chronic use requires extensive surgery. The flow transducer around the vessel may in itself produce artifacts by compressing or kinking the vessel, while the vessel can react upon the stripping of its perivascular attachments by vasoconstriction. Movements of the flow

transducer around the vessel can cause artifacts and it takes at least several days before the flowprobe is attached to the vessel wall by adhesions and a good steady contact between the inner surface of the flow transducer and the vessel wall is achieved. Other problems involve the calibration of the flow transducer and their influence upon each other if placed in each others proximity, which will be briefly discussed later on (paragraph 2.8.3).

The exact total flow to the uterus can not be assessed with electromagnetic flow transducers because the uterus has several arterial inputs and vessel anastomoses which cannot be measured all together, so flow measurements in the uterine artery reflect only part of total blood flow to the uterus. On the other hand, if one measures the blood flow in one of the major vessels from which the uterine blood supply arises, then flow measurement not only comprises the blood flow to the uterus but also part of the flow to other adjacent structures. And finally no differentiation can be made between placental blood flow and uterine muscle blood flow.

The radioactive microsphere method is an accurate way to measure blood flow and has the advantage of being able to measure the total uterine blood flow and its distribution over the various parts of the uterus and its contents. It is however also a technically cumbersome method and in general only one observation can be made in one animal unless microspheres with different radioactive labels are used. Furthermore this technique gives only an instantaneous flow measurement and continuous flow changes cannot be registrated.

When comparing the results of several techniques, one should always bear in mind the specific problems related to the method used. Another continuing problem in the evaluation of the literature on the regulation of placental blood flow is the effect of the condition of the animal during chronic experiments and the influence of anesthesia and surgical intervention in acute experiments upon the placental blood flow and its response to vasoactive agents.

The fetal side of the placental blood flow can be studied relatively easier since the whole of umbilical placental blood flow is contained in the umbilical cord. Cohnstein and Zuntz (1884) were the first who

studied umbilical blood flow in the living lamb fetuses. Studies in living fetuses in this period were troubled by technical limitations and rapid deterioration of the preparations. Technical developments and the use of anesthesia gave way to more sophisticated research on fetal hemodynamics.

Barcroft (1946) measured for the first time the course of blood through the principal vessels of the fetal lamb by rapid serial radioangiography. Cooper and Greenfield (1949) used a plethysmograph to measure the umbilical blood flow in the lamb, while retaining the integrity of the umbilical circulation. After immersion of the fetal lamb in a warm physiological saline bath, the umbilical veins were occluded and the rate of decrease of fetal volume was taken to represent umbilical blood flow, which was reported to amount 500 ml/min near term. Greenfield et al (1951) even used this method successfully in the human for umbilical blood flow measurement.

The application of electromagnetic induction to the measurement of blood flow in vivo was used by Dawes and Mott (1964) who inserted an electromagnetic flowprobe in a short external circuit between the cut ends of the abdominal umbilical vein. The observations were made after delivery of the near term fetal lamb by caesarean section with an intact umbilical circulation. Umbilical venous blood flow was reported to be 170 ml/min per kg of fetus. Kirschbaum et al (1967) found corroborative results in a similar experiment. They reported mean umbilical blood flow to be 138 ml/min per kg of fetus in the near term fetal lamb.

With the use of the Fick-principle and urea as test substance, Meschia et al (1966) found umbilical blood flow values of 233 ml/min per kg of fetus. Rudolph and Heymann (1967) proved the validity of this method with the simultaneous use of electromagnetic flow transducers. The difference between the results obtained by Dawes and Mott (1964) and Kirschbaum et al (1967) compared to the higher values reported by Meschia et al (1966) and Rudolph and Heymann (1967) (220 ml/min/Kg of fetus) is due to the fact that exteriorization of the fetus by delivery decreased the umbilical blood flow (Heymann and Rudolph 1967).

With the introduction of radioactive microspheres for flow measurements and the technical improvements of electromagnetic flow transducers,

more reliable and elegant methods are now available for measuring the umbilical blood flow. Makowski et al (1968) applied the radioactive microsphere method also to the measurement of the umbilical blood flows, as they did for uterine flow measurement. Since then reports have been published on umbilical and fetal organ blood flow under various conditions (Peeters 1978, Edelstone et al 1980b, Reuss and Rudolph 1980, Botti et al 1982).

The microsphere method employs catheters in fetal arteries and veins which in general can be done with simple surgical techniques without jeopardizing the fetus too much. However only relatively few determinations can be made in one animal and the processing methods afterwards are time consuming. The microsphere method might be the method of choice if one wants to separate the umbilical blood flow in that to the placenta and the part to the membranes and it is especially applicable for studies of umbilical flow distribution to different organs. The improvement of the reliability of electromagnetic flow transducers and their reduction in size have made them highly favorable in recent years for chronic measurements of umbilical blood flow in animal preparations. Oakes et al (1976a) have described a technique for implanting electromagnetic flow transducers around the common intraabdominal umbilical vein, while Berman et al (1975) developed a similar technique whereby the probe is placed around the common umbilical artery via a retroperitoneal approach. Both methods provide a direct and continuous measurement of umbilical blood flow in a chronic preparation over longer periods but they do not separate the flow into its components. Implantation of electromagnetic flow transducers in the chronic experimentP on the common umbilical vein or artery is not easily to perform and requires extensive fetal surgery with a concomitant considerable fetal loss even in experienced hands, while fetal recovery from surgery requires at least three days (Assali et al 1974, de Haan et al 1975, De Muylder et al 1983).

Ideally, the measurement of blood flow in vivo would be done noninvasively; that is to say, without any surgical intervention whatever. The Doppler flow systems might possibly fulfil some of these whishes for the field of perinatal research in the near future, as they already do in the human for the examination of peripheral arteries

(Baker et al 1974, Bodily et al 1981, Bruins Slot 1981, Breslau 1982). The placental circulation is vital to the fetus and its well functioning a conditio sine qua non for normal fetal development. Factors that influence fetal and/or maternal placental circulation as for example various drugs, cord compression and obstruction of uterine circulation can have a detrimental effect on the fetus. The regulation of the placental blood flows encompasses several sections including the neural regulation which has been reviewed by Bell (1972), secondly, the mechanical regulation with the problem of sluice flow and thirdly, the chemical factors that influence fetal and maternal placental flows. These chemical factors are not well defined and they comprise various substances such as angiotensin, renin, catecholamines, prostaglandins and steroids (Rankin and McLaughlin 1979).

The present study was undertaken to investigate some aspects of maternal pelvic and fetal umbilical blood flow and their possible influences upon each other.

The maternal part deals with reactions of the blood flow in the pelvic arterial bed, in casu the internal iliac artery and median uterine artery, to vasoactive stimuli by the cholinergic and adrenergic drugs acetylcholine, norepinephrine and fenoterol (=Partusisten^{R}) and their influence on fetal hemodynamics and acid-base balance. Adrenergic receptor activity is of particular interest in pregnancy because of its influence both on the uterine circulation and uterine tone and contractility. Beta-sympathicomimetic drugs as for example fenoterol are widely used in obstetrics for the treatment of premature labor and intrapartum fetal distress and by some even for the treatment of intrauterine growth retardation. Alpha-adrenergic activity can be caused by catecholamines and related vasoactive substances and it is a potential hazardous side effect of some drugs with the central nervous system as their target organ.

Pain and fear during labor increase the level of circulating catecholamines which can hamper uterine blood flow.

The effects of tocolytic beta-sympathicomimetic drugs on uterine and umbilical blood flow were studied in non-laboring pregnant sheep (Brennan et al 1977, Ehrenkranz et al 1976, 1977a, 1977b, Chez et al

1978, Oakes et al 1978b, Nuwayhid et al 1978, 1980). They obtained data 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 some studies increases in uterine blood flow were reported while others showed no changes or decreases in flow after beta-adrenergic drug infusion. Part of these differences might be explained by the fact that different beta-sympathicomimetic drugs are compared, 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 however 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 (Assali et al 1981, Erkkola et al 1981, Tabsh et al 1981). Fetal umbilical flow either showed no change or an increase during maternal infusion with beta-adrenergic agents (Brennan et al 1977, Ehrenkranz et al 1976, 1977a, 1977b, Chez et al 1978, Oakes et al 1976b).

General consensus exists on the vasoconstrictive effect of alpha-adrenergic agents on the median uterine artery and on the common internal iliac artery with a more marked effect on the median uterine artery (Greiss 1963, Greiss and Pick 1964, Tabsh et al 1981, Assali et al 1981). Fetal umbilical flow was not affected by maternal norepinephrine infusion in two studies (Chez et al 1978, Wilkening et al 1982). The effect of acetylcholine upon the pelvic vascular bed does not seem quantitively to be the same in the various vessels (Greiss et al 1967c, Erkkola et al 1981).

The possible influence of maternal acetylcholine infusion upon fetal umbilical blood flow is not known.

The fetal part of this investigation deals with the effects of subacute fetal distress caused by compression of the umbilical cord and by occlusion of the uterine blood supply on umbilical venous blood flow and in the case of umbilical cord compression also with its possible effects on the maternal uterine blood flow.

Subacute fetal distress can be mimicked by obstruction of the uterine

circulation. Subacute reduction of uterine blood flow can thus, as is generally accepted, imitate the clinical concept of subacute uteroplacental insufficiency. The hemodynamic sequelae as the changes in heart rate ("late decelerations"), the rise in blood pressure and the responsible reflex mechanisms have extensively been studied in sheep (Evers 1978, Martin et al 1979, de Haan et al 1979, Itskovitz et al 1982a, Künzel et al 1983). Scarce data however are available on the effects of uterine blood flow obstruction on umbilical blood flow.

Berman et al (1976) reported some data on umbilical arterial blood flow in a study of the relationship between pressure and flow in the umbilical and uterine circulations of the sheep. Data on arterial umbilical blood flow during obstruction of the maternal aorta in the hypoxic fetus were recently published by Harris et al (1982), while Parer et al (1980) gave data from the same sort of experiments in normoxemic fetuses. In these studies umbilical arterial blood flow was measured. It is expected that umbilical venous blood flow would show the same reaction patterns as the arterial side of the circulation.

Knowledge of the reactions of the umbilical venous flow to acute uteroplacental insufficiency by uterine blood flow obstruction is not merely of physiological interest, but might be essential in the near future with the further development of the Doppler-flowsystems for measurement in pregnant women.

Transient compression of the umbilical cord with the characteristic reactions of fetal heart rate deceleration and blood pressure rise is a common occurrence in clinical obstetrics, easily recognizable by fetal heart rate monitoring. The fetal responses to hypoxemia caused by umbilical cord occlusion have been well documented in several studies (de Haan et al 1976, Evers 1978, Towell et al 1978).

Much less is known about the effects of cord compression on the maternal placental circulation.

In 1973 Power and Longo proposed a theory about the maternal vascular pressure effects on fetal circulation, which they called "sluice flow in placenta". This theory is based on the assumption that the uterine vascular system surrounds the umbilical circulation in the placenta and generates a placental tissue pressure which affects umbilical blood flow by the waterfall mechanism.

Berman et al (1976) however showed in a study on pressure-flow relationships in the uterine and umbilical circulations that this waterfall-mechanism is absent in the placental circulation of the sheep. Part of their study was the obstruction of umbilical venous flow by inflating a balloon in the common umbilical vein, while concomitantly uterine flow was measured with an electromagnetic flow transducer.
They found no change in uterine blood flow during obstruction of umbilical venous flow. The accomplished umbilical flow obstruction was however only partial and of a very short duration. Moreover their definition of uterine blood flow was the flow in the common uterine artery, (=common internal iliac or common hypogastric artery), the terminal branch of the abdominal aorta, that also provides extrauterine structures with blood, and is not directly adjacent to the uterus.
Cottle et al (1982) reported a depression of uterine blood flow as measured in the median uterine artery in response to longer lasting (4 minutes) cord compression in sheep.

The fetuses of all so far studied mammals including the human make periodic thoracic and diaphragmatic movements during intrauterine life, which are called fetal breathing movements.
The first animal observations on fetal breathing movements were done by Béclard (1815) in dogs and cats with opened uterus, but intact membranes. Ahlfeld, a German gynecologist, described in 1888 rhythmical movements of the fetus seen on the intact maternal abdominal wall in the human, which he considered fetal breathing movements.
Breathing movements in fetal sheep under spinal anesthesia were observed by Barcroft in 1946. In the last two decades the influences of hypoxemia, hypoxia, hyperoxia, hypocapnia, hypercapnia, asfyxia, glucose, prostaglandins and their synthetase inhibitors, maternal smoking and many other items on fetal breathing movements have been investigated.
Rurak and Gruber (1983) described an increased oxygen consumption associated with breathing activity in fetal lambs, together with an increase in umbilical blood flow during fetal breathing movements. Umbilical blood flow was measured with an electromagnetic flow

transducer around the common umbilical artery in acute experiments and by means of the steady state diffusion technique in chronic experiments.

Rudolph (1976) reported the negative effect of a rise in intrathoracic pressure on umbilical arterial blood flow.

Chiba et al (1981) published observations on the relation between flow velocity measured with pulsed Doppler flow transducers in the human umbilical vein and fetal breathing movements.

The aim of this study was to investigate some aspects of the maternal pelvic and fetal umbilical circulation.
The following specific questions were studied:

1. What are the effects of late decelerations in the fetal heart rate pattern produced by uterine flow obstruction on umbilical venous blood flow ? (chapter 3)
2. What are the effects of cord compression on the instantaneous fetal umbilical blood flow pattern ? (chapter 4)
3. Does cord compression influences maternal uterine blood flow ? (chapter 4)
4. What are the effects of agonists and antagonists of the autonomic nervous system on umbilical venous blood flow ? (chapter 5)
5. What are the effects of maternal infusion with cholinergic and alpha-and beta-adrenergic agents on the blood flow in the maternal internal iliac and median uterine artery ? (chapter 6)
6. What are the effects of maternal infusions with cholinergic and alpha-and beta-adrenergic agents on fetal umbilical blood flow ? (chapter 6)
7. What are the influences of intermittently occurring fetal breathing movements on umbilical venous blood flow ? (chapter 7)
8. How does fetal gasping, occurring during acute fetal hypoxemia affects umbilical venous flow ? (chapter 7)

CHAPTER II

MATERIALS AND METHODS

2.1 Introduction

Pregnant sheep have been widely used in fetal physiological research and considerable information on fetal and maternal cardiovascular function is available at the moment.

After the first description of the fetal circulation by William Harvey in 1628, further hypotheses of the circulation of blood in the fetus were for almost 300 years after Harvey's publication solely based on anatomic observations.

Physiological studies in living fetuses were first reported by Cohnstein and Zuntz in 1884, who measured umbilical arterial pressure in exposed lamb fetuses and by Pohlman in 1907 and 1909, who studied fetal circulation through the heart in pig fetuses.

After that, Barcroft in the mid-thirties and forties made his classic observations on the umbilical placental circulation in fetal sheep in an acute manner while the ewe was under general or spinal anesthesia and the fetus mostly exteriorized from the uterus (Barcroft 1946).

Dawes and coworkers in Oxford, England (1968a) and Assali and colleagues in Los Angeles, U.S.A. (1965, 1974) reported extensive studies on fetal circulation in exteriorized fetal lambs.

Although these acute studies have yielded enormous information with respect to fetal physiology, one has become aware during the last 15-20 years of the disturbing effects of maternal anesthesia, fetal exteriorization and manipulation on fetal cardiovascular function (Heymann and Rudolph 1967) and other regulatory mechanisms. This has led in different centers to the development of chronic animal preparations with the fetus in utero, which allow fetal studies without

the influence of anesthetic agents.

Several mammalian species (sheep, goat, primate, pig) have been used in intact animal preparations. Since the mammalian fetus is surrounded by amniotic fluid within the membranes, which are covered by the uterine wall, access to the fetus can only by obtained by incising the maternal abdominal wall, the uterine muscular wall and the membranes.

These procedures may to an unknown extent interfere with uterine activity and fetal physiology.

In contrast to primates, for instance, which have a thick muscular uterine wall, sheep and goats possess a thin uterine musculature which on incision only shows local contractions which do not interfere usually in such an extent with uterine circulation, that the fetus becomes hypoxemic or even asphyxiated.

Another advantage of the sheep uterus in relation to surgical procedures is the fact that the sheep placenta is polycotyledonous, which makes it possible to incise the uterine wall in an area free of placental attachments. Furthermore there is little tendency to separation of the placental attachment after surgery and postoperative abortion due to placental abruption or circulatory disturbance is very low in sheep. The circulation of the fetal lamb has the same three shunts that also exist in the human fetus: foramen ovale, ductus arteriosus Botalli, and ductus venosus Arantii.

Major anatomical differences consist of the number of umbilical veins which are two in fetal sheep. Furthermore the sheep placenta is of the epitheliochorial type in contrast to the human hemochorial placenta.

The uterus of the sheep is an uterus bicornis unicollis with a thinner muscular wall than the uterus of primates and the human. The non pregnant uterine horn is much smaller than the pregnant horn and is filled with amniotic fluid. The inner surface of the pregnant horn is covered by the chorionic membrane which encompasses the amniotic sac, containing the fetus and the allantoic sac which extends from the urachus in the umbilical cord and which fills part of the uterine cavity. The blood supply to the uterus in sheep is also different from the situation in the human as will be pointed out later on (paragraph 2.4.1).

2.2 The animal

All experiments were carried out in primigravid ewes of the Dutch sheep (Texel breed). First pregnancies in ewes are mostly singleton pregnancies which was in all the experimental animals but one (no 8315, twins) the case.

The pregnant ewes were obtained from the Praktijkschool at Horst.

The conception dates of 11 of the animals used in this study was well known, but in 4 instances however no exact date was known. In these cases duration of pregnancy was estimated during operation by using the criteria of Naaktgeboren and Stegeman (1969) for the fetuses of Dutch sheep of the Texel breed. At least three days before surgery the animals were transported to the animal laboratory, where they stayed in a small mobile cart in order to get used to their new surroundings.

Food was withheld twenty-four hours prior to operation and water twelve hours preceding operation.

After the operation the ewe was allowed to recover for at least 72 hours before experiments were performed. Immediately after operation the ewe got food and water ad libitum. During the recovery and experimentation period maternal rectal temperature was controlled daily as was fetal arterial blood gas balance.

During the 72 hours recovery period only steady state registrations of fetal and maternal parameters were recorded without any experimentation.

The period of time between operation and the end of each series of experiments ranged between 5 and 35 days.

The experiment ended when the fetus died in utero or was stillborn, and also in those cases in which the ewe developed labour which ended either spontaneously vaginally or by caesarean section.

Seven fetuses were born alive either vaginally or by caesarean section.

All the fetal instrumentation was removed after birth.

The maternal transducers and occluders were removed at caesarean section or by relaparotomy after birth of the lamb.

2.3 Anesthesia

All surgical procedures were performed during general anesthesia. The anesthetic procedures were started by 0.5 ml xylazine (Rompun^{R}) intravenously and 0.03 mg/kg body weight scopolamine hydrobromidum 0.025% intramuscularly. Induction was performed with pentobarbital (Narcovet^{R}), 15 mg/kg intravenously and the ewe was then intubated, while she was lying on her back on the operation table.
The tube was connected to an artificial respirator (type Dräger Pulmomat 19.1) and general anesthesia was continued with halothane in a concentration of 3-5% initially in a 2:1 mixture of nitrous oxide (N_2O) and oxygen. The halothane concentration was reduced during the further procedure from 5% to 1% - 1.5%.
The ewe was monitored by E.C.G. registration (Schwarzer C3600, Monitor Knott SG 4100) and by CO_2 measurements in a capnograph (capnolog Dräger) to detect ventilation disturbances.
In order to prevent distended rumen and bowel to interfere with diaphragmatic movements and to avoid protrusion from the abdominal incision, a tube was inserted into the rumen via the oesophagus. The mostly gaseous distension of the rumen could then be diminished.
An 0.9% NaCl solution was administered intravenously to the ewe during operation at an infusion rate of 250 ml/hour.

Skin preparation

The abdominal wall and left flank of the ewe were shaven and thoroughly cleaned with an iodine solution (Betadine^{R}) several times. The animal was placed in a left tilted Trendelenburg position to avoid caval compression by the pregnant uterus and the legs were fastened upon the operating table.

Recovery

At the end of the operation the halothane ventilation was replaced by oxygen and the ewe was kept in supine position on the operating table until she breathed spontaneously.

The ewe was placed in the same mobile cart as which she stayed in before operation and she received food and water ad libitum immediately after operation.

2.4 Surgical procedures

2.4.1 Anatomy

For a good understanding of the procedures used and the problems encountered, a description of the anatomy of the pelvic arterial blood supply in the pregnant ewe is essential (fig. 2.1).
There is a lot of confusion in the literature in regard to the anatomy and nomenclature of the arterial blood supply to the uterus and related pelvic organs. Moreover the arterial blood supply is a rather complex one.
The abdominal aorta in sheep has another branching at its end compared to the human. After the origin of the external iliac artery on both sides, which supplies the hindlegs, the external genitals and the mammae, the vessel continues as the common internal iliac artery, sometimes called the common uterine artery or middle sacral artery (Berman et al 1976), which gives rise to the two internal iliac arteries, which in turn give rise to the medial sacral arteries which supply the regio presacralis.
These sacral arteries receive only 5% of the blood flow of the common internal iliac artery in pregnancy (Fuller et al 1975, Tabsh et al 1981). Their origin however can vary considerably. Mostly they arise from the internal iliac artery about 1-2 cm after its origin from the common internal iliac artery. Sometimes they are seen arising directly from the common internal iliac artery in a caudodorsal direction. The part of the internal iliac artery after the rise of the sacral arteries and before its further branching in the various uterine arteries has several names in literature: internal iliac artery, hypogastric artery or main uterine artery.

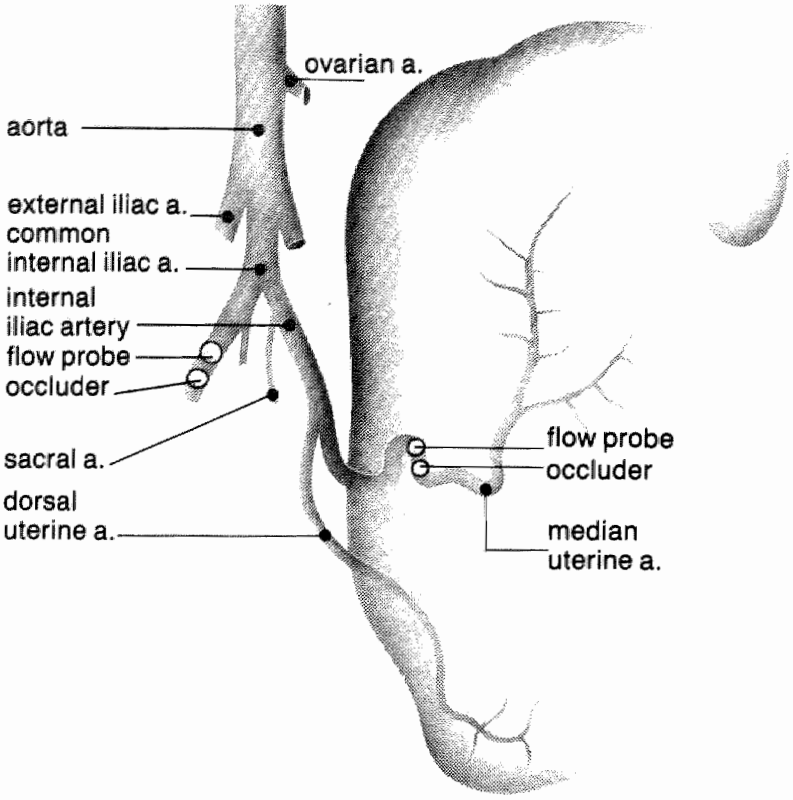


Fig.2.1 The anatomy of the pelvic arterial tree
The position of the occluders and
flow probes is indicated by open
circles (modified from tabsh et al 1981)

In this study the name internal iliac artery is used for this vessel from its origin from the common internal iliac artery till its branching in the different uterine arteries, regardless of the site of origin of the sacral arteries. The internal iliac artery then gives rise to the median uterine artery, which supplies the uterine horns and a large part of the uterine body and to a smaller vessel, the dorsal or caudal uterine artery, which enters the uterus at the cervicoisthmic

junction. From its entry site it subdivides to send three to four branches longitudinally over the ventral and dorsal surfaces as well as several smaller branches to the cervix. It forms collaterals with the median uterine artery over the ventrolateral surface of the corpus uteri (Fuller et al 1975, Fuller et al 1978, Evers 1978).
The dorsal uterine artery supplies the lower part of the uterus, the cervix, the bladder and the upper part of the vagina.
The common internal iliac artery supplies therefore the entire uterus with blood apart from the possible smaller anastomoses via the ovarian artery and extrauterine cervical arteries. It forms furthermore the vesical plexus and finally part of its blood flow is destined for other extra uterine structures via the spatium ischiadicum majus (Evers 1978).

2.4.2 Maternal instrumentation

A left or right paramedian abdominal incision was made, lateral to the mammary vein on that side.
- Common internal iliac artery occluder.
The uterus was lifted out of the true pelvis and outside the abdominal cavity. The intestines were held away with a soaked gauze and the trifurcation of the aorta deep in the true pelvis was exposed. The retroperitoneal space over the trifurcation (fig. 2.1) was opened and the vessels exposed by sharp and blunt dissection. A balloon type cuff occluder with a diameter of 6 mm, which was always large enough to avoid partial obstruction of the vessel, was placed around the vessel and secured with a linen tie (fig. 2.2).
The uterus was lifted out of the true pelvis not longer than ninety seconds after which it was replaced and a recovery period of three minutes was observed to let restore uterine blood flow.
- Internal iliac artery occluder and flow transducer.
With the uterus lifted out of the true pelvis and abdominal cavity the internal iliac artery (=hypogastric artery) at the side of the pregnant horn was dissected free from its perivascular attachments over a distance of 4 to 5 centimeters.

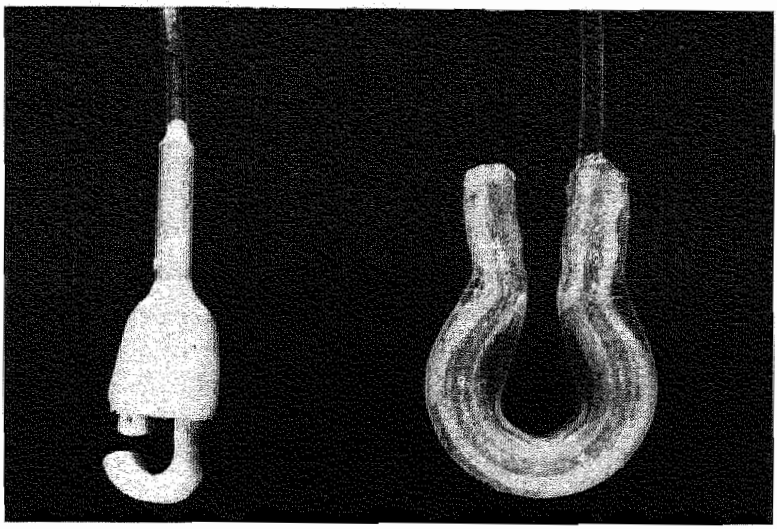


FIG. 2.2 EXAMPLE OF A SMALL INFLATABLE OCCLUDER (INTERNAL DIAMETER 4 MM, ON THE LEFT SIDE) AND A LARGE ONE (INTERNAL DIAMETER 6 MM, ON THE RIGHT SIDE).

The estimated diameter of the vessel at the point of instrumentation varied between 4.0 to 5.5 millimeters. An inflatable balloon occluder with an internal diameter of 4 to 5 mm was placed around the vessel and its ends tied together (fig. 2.2). Care was taken that the device could not obstruct the blood flow.

Proximal to the occluder a cuff type flow transducer with an internal diameter of 3.5 to 5.0 mm was placed around the vessel and the opening in the flow transducer was locked with a slide-slot or with a small piece of polyvinyl tubing. Special attention was given to the size of the flow transducer with a preferred 10% smaller internal diameter of the flow transducer than the external diameter of the vessel (Gordon 1971, Charbon and van der Mark 1981).

Also in this procedure the uterus was lifted out of the abdominal cavity not longer than ninety seconds with a rest pause of at least

three minutes to let restore the blood flow to the uterus.

- Median uterine artery flow transducer and occluder.

The median uterine artery at the side of the pregnant horn was exposed before it splits into two or more branches (Soma et al 1971).

The peritoneum was opened 2 centimeters medial to the vessel, after which the vessel was freed from its fine attachments. An inflatable balloon occluder with an internal diameter of 4 to 4.5 mm was placed around the vessel and its end tied together. The internal diameter of the flow transducer ranged from 3.0 to 4.0 mm. The flow transducer was locked with a slide-slot or with a small piece of polyvinyl tubing. The internal diameter of the flow transducer was chosen 10% smaller than the external diameter of the vessel to obtain a good vessel contact.

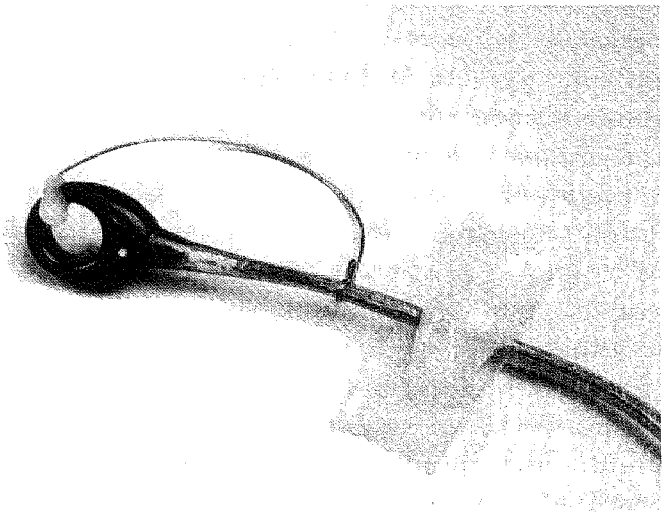


FIG. 2.3 FLOW TRANSDUCER WITH AN INTERNAL DIAMETER OF 6 MM. AND A SLIDE SLOT. A SMALL POLY-VINYL WING IS ATTACHED TO THE CABLE OF THE FLOW TRANSDUCER TO GUARANTEE A PERPENDICULAR POSITION OF THE FLOW TRANSDUCER AROUND THE BLOOD VESSEL.

The cables were passed through a tunnel under the round ligament and

the peritoneum over the vessel was closed. A small wing of polyvinyl (fig. 2.3) was attached to the cable of the flow transducer at a distance of 3 to 5 centimeters of the flow transducer. This polyvinyl attachment made it possible to position the cable and the flow transducer at a right angle to the vessel. The attachment was fixed to the uterine wall with sutures.

- External venous catheter.

After closing of the abdominal wall a venous catheter was inserted in a maternal vein, either a jugular vein, a mammary vein or a hindleg vein. The catheter was fixed to the maternal skin and continuously flushed with a heparine solution.

2.4.3 Fetal instrumentation

- Femoral artery catheter.

The position of the fetus within the pregnant horn was assessed.
The uterine wall over the fetal pelvic region was stretched between two Babcock clamps and the incision was made parallel with the intramural vessels. Care was taken to avoid cotyledons in the area of the incision. The uterine wall was opened by means of electrocautery over a distance of 8 to 10 centimeters. The membranes were sharply opened and blood vessels in it coagulated. The uterine muscle and membranes were clamped with Babcock forceps at four sides. Both hindlimbs were extracted from the uterine horn and the fetal pelvis was exposed.
The incision was then covered with a soaked gauze which was also grasped with the Babcock clamps, preventing further rupturing of the uterine wall.
The fetal femoral artery was approached through a groin incision and cannulated with a polyvinyl catheter (outer diameter 1.6 mm; inner diameter 0.8 mm; length 150 cm), which was advanced into the fetal abdominal aorta. The catheter was fixed and filled with a heparin solution and the skin closed with a continuous suture.

- E.C.G. electrodes.

Three E.C.G. electrodes (length 150 cm) were placed subcutaneously on one of the hindlimbs and on either side of the thorax respectively and fixed.

-Umbilical cord occluder.

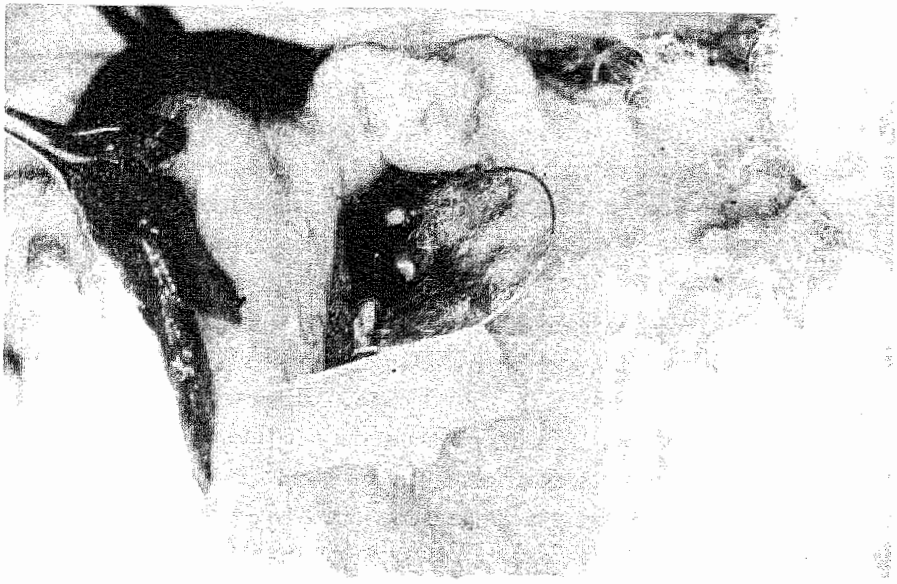
The fetus was then extracted a little further from the uterus until the umbilical insertion was exposed. An inflatable balloon type occluder with an internal diameter ranging from 10 to 14 cm was placed around the total umbilical cord in a rather loose fit to prevent obstruction. The occluder was secured with a linen tie and fixed to the fetal abdominal skin with stitches.

- Common intraabdominal umbilical vein flow transducer.

The two umbilical veins fuse immediately after entering the abdomen to form the common intraabdominal umbilical vein which was approached through an incision cranial to the umbilicus and parallel to the right costal margin (Soma et al 1971, Oakes et al 1976a) (fig. 2.4). An electromagnetic flow transducer with an internal diameter of 5 to 8 mm was placed around the vein and the flow transducer was locked with a slide-slot or a small piece of polyvinyl tubing. The flow transducer cable was provided with a polyvinyl wing (fig 2.3) at a distance of 3 to 4 cm from the flow transducer. This attachment was then sutured to the fetal abdominal wall with the flow transducer perpendicular to the umbilical vein. The peritoneal cavity and abdominal wall were closed with sutures.

- Amniotic cavity catheter.

A polyvinyl catheter (length 150 cm, outer diameter 1.6 mm, inner diameter 0.8 mm) with side holes at its end was placed into the amniotic cavity. The fetus was then carefully replaced in the uterus and in case much amniotic fluid was lost during surgery, it was supplemented with 0.9% NaCl solution. The uterine wall and membranes were closed in two layers with a continuous suture. The exteriorized cable bundle was secured with a purse string suture through the uterine wall.



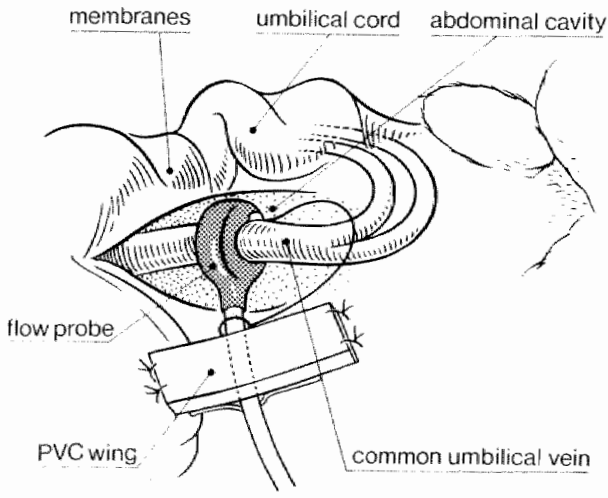


FIG. 2.4 FLOW PROBE AROUND THE INTRAABDOMINAL COMMON UMBILICAL VEIN IN SITU AND THE SCHEMATIC REPRESENTATION OF ANATOMY.

- Tracheal catheter.

For access to the trachea a second incision was necessary. The fetal head was with gentle manipulation positioned against the uterine wall within an area without cotyledons. With the uterine wall stretched between two Babcock clamps, the uterus was opened with electrocautery over a distance of 4 to 6 cm. The tracheal area was then either manipulated towards the incision opening and the skin grasped with Babcock clamps or the head was delivered through the opening after which the uterine wall, the membranes, a soaked gauze and the fetal skin were all together grasped with Babcock forcipes to avoid spilling of amniotic fluid. A transverse incision was made over the trachea below the cricoid cartilage. After exposure of the trachea by blunt dissection a polyvinyl catheter (outer diameter 1.6 mm, inner diameter 0.8 mm, length 150 cm) was inserted through a small stab incision into the trachea over a distance of 5 to 7 cm, depending on the size of the lamb, so that the catheter was situated above the tracheal bifurcation and within the thoracic cavity. The catheter was fixed with a suture on the cartilage rings and after closure of the incision also to the fetal skin. After reposition of the fetal head the incision was closed in two layers with a continuous suture. The uterine incision through which the catheters were diverted, was secured with a purse string suture.

- Intraabdominal catheter.

In two fetuses a polyvinyl catheter (outer diameter 1.6 mm; inner diameter 0.8 mm; length 150cm) was advanced into the abdominal cavity through the incision made for application of the flow transducer around the umbilical vein. This catheter allowed intraabdominal pressure measurements during fetal breathing movements.

2.5 End of the operation

The catheters, electrodes and flow transducer leads were exteriorized via a small incision on the ewe's left flank. The abdominal wall was closed in two layers with mattress sutures. A pouch was attached to the skin on the ewe's left flank, in which the catheter and cable bundle was protected.

2.6 Post-operative care

2.6.1 Prophylactic administration of antibiotics

Although all surgical procedures took place under sterile conditions, there are numerous sources of infections in chronic preparations with exteriorized catheters. Therefore in all cases antibiotics were given to the ewe according the following scheme:

-Together with premedication: 1 gram ampicillin intravenously to the ewe

-a. During surgery : ampicillin 500 mg intraabdominally
ampicillin 500 mg in the amniotic cavity

-b. The first three days after surgery : procain penicillin 2.000.000 I.U and dihydrostreptomycin 2000 mg intramuscularly

In four cases in which there were clinically signs of maternal or fetal intrauterine infection the antibiotics were continued in the same or in another regimen after the third day postoperatively. In the latter case ampicillin 1000 mg or ticarcillin 1000 mg was injected intraamniotically while the ewe received additionally metronidazol 500 mg intravenously or gentamycin 40 mg intravenously.

2.6.2 Flushing of the catheters

The fetal arterial and maternal venous catheter were connected to a calibrated infusion pump (B.Braun, Melsungen, type 871100), by means of an external extension catheter, which allowed a continuous flushing during the entire postoperative period at a flushing rate of 1.2 ml/hr. The flushing fluid was a 0.9% NaCl solution containing 1000 I.U. heparin/100ml.

2.6.3 Recovery period

The arterial and venous infusion catheters were led through the eye of a 50 cm long spring attached to the ewe's cart which prevented possible biting of the catheters by the ewe. All animals showed a remarkably fast recovery period and were found to be eating and drinking already two or three hours after surgery with no disadvantageous side effects. The total recovery period lasted 72 hours. The ewe stayed in the transportable cart during the experimentation period and was taken in principle every day after the recovery period to the laboratory where the catheters and cables were connected to the registration equipment and where experiments were done.

2.7 Fully equipped animal

A short overlook of the used instrumentation in one animal is given, if all the equipment had been applied (fig. 2.5).

Ewe:

1. Balloon occluder around the common internal iliac artery.
2. Balloon occluder around the internal iliac artery at the side of the pregnant horn.
3. Electromagnetic flow transducer around the internal iliac artery at the side of the pregnant horn.
4. Balloon occluder around the median uterine artery at the side of the pregnant horn.
5. Electromagnetic flow transducer around the median uterine artery at the side of the pregnant horn.
6. Intravenous catheter in either a jugular vein, mammarian vein or a hindleg vein.

Fetus:

1. Femoral artery catheter.
2. 3 subcutaneous E.C.G. electrodes.
3. Tracheal catheter.
4. Balloon occluder around the umbilical cord.
5. Electromagnetic flow transducer around the intraabdominal common umbilical vein.
6. Amniotic cavity catheter.
7. Intraabdominal catheter.

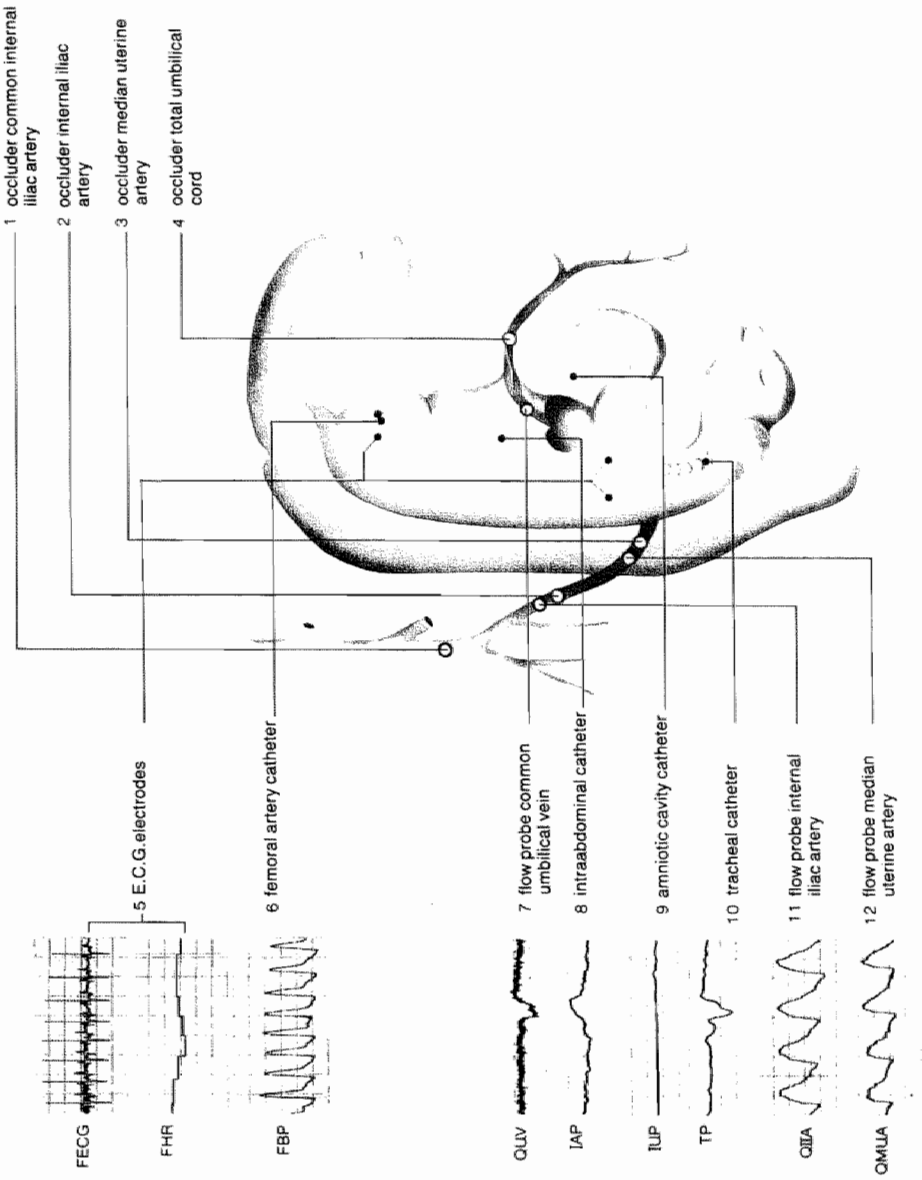


Fig. 2.5 Schematic representation of the applied maternal and fetal instrumentarium and the recorded signals

2.8 Registration equipment

2.8.1 Electrocardiogram and cardiotachogram

The three E.C.G. electrodes were connected to a junction box, fixed to the cart in which the ewe was stabled after the operation. The signals were led in to a bio-electric amplifier (Hewlett Packard 8811 A), where they were filtered and amplified. From the three electrodes two were chosen which gave the best E.C.G. signal in regard to the relative amplitudes of the different E.C.G. peaks. The third electrode was used as a reference electrode. The signal was displayed on a neonatal monitor (Hewlett Packard 78801 A) with storage facilities and on a six channel monitor (Hewlett Packard 78309 A). The fetal cardiotachogram was obtained from the E.C.G. by means of a signal coupler (Hewlett Packard 8809 A) and displayed on the six channel monitor. The electrocardiogram and the calculated heart rate were displayed on an eight channel strip chart recorder (Hewlett Packard 7758 A) and stored on the magnetic tape of an eight channel instrumentation recorder (Hewlett Packard 3968 A).

2.8.2 Pressure registration

The fetal arterial, tracheal and amniotic catheters were connected to an extension catheter of polyethylene (length 200 cm, outer diameter 2.0 mm, inner diameter 1.0 mm), which material gives less dampening of the pressure wave than the softer polyvinyl. The extension catheters were connected to a stopcock on the pressure transducer (Hewlett Packard 1293 A) from where the signals were led to a pressure amplifier (Hewlett Packard 8805 D), displayed on the monitors and strip chart recorder and stored on magnetic tape. In order to obtain a fixed reference point for pressure measurements in the same animal, all pressure transducers were located at the level of the ewe's spine, when she was standing. Each registration was started with an electronic calibration signal, which was in turn in regular intervals calibrated with a mercury column.

2.8.3 Arterial and venous blood flow measurements

The electromagnetic flow transducer connectors were attached to an adapter box, which contained a preamplifier (Skalar Transflow 601 system) from where they were led to a recorder module (Skalar Transflow 601 system, mdl 400). From the recorder output connection the signal was led to a low gain DC amplifier (Hewlett Packard 8801 A), displayed on monitor and strip chart recorder and stored on magnetic tape. All flow measurements concerned pulsatile measurements. An external ground reference wire, which needle end was inserted subcutaneously into the ewe's skin, was connected with the flow transducer adapter boxes. Distal to the maternal arterial flow transducers an inflatable occluder was placed around the vessel which allowed total obstruction of the blood flow and assessment of the baseline reference for zero flow (Reneman et al 1970). Complete occlusion of the umbilical vein was obtained with an inflatable occluder placed around the umbilical cord. Electromagnetic flow transducers have been used in various forms under experimental conditions (Greiss 1962, Westersten et al 1969, Wyatt 1982) and they have the advantage of instantaneous flow measurements even during rapid flow changes. For a correct flow measurement however several conditions have to be fulfilled and their sensitivity may change with implant duration (Astley et al 1979).

We observed in preliminary chronic studies considerable differences in flow measurements between subsequent days, which could no longer be attributed to the stabilization of the flow transducer to the vessel wall because they also happened incidently several weeks after surgery. These differences in mean flow were especially seen in experimental animals which were provided with two or three flow transducers, which raised the suspicion that interference or "cross talk" between these flow transducers in each others proximity occurred with a subsequent base line shift, which experience has been reported by others (Assali et al 1981).

But also flow signals from only one flow transducer in an experimental animal varied sometimes on different days. Mechanical total occlusion of the bloodvessel with a balloon occluder distal to the flow transducer, to keep the vessel distended and its wall in contact with

the electrodes showed that in those cases a base line shift of the in vitro assessed electronic zero flow reference level had occurred which needed readjustment of the zero balance. It was concluded, that the in vitro assessment of the electronic zero flow reference level could show baseline shifts in these chronic experiments with one to three flow transducers simultaneously implanted. Apart from that, mechanically assessing of the zero flow level had a practical advantage too. The zero-balance of electromagnetic flow transducers which are used simultaneously must also be set in vitro simultaneously.

Because all flow transducers had to be sterilized for operation and connecting the flow transducer to the recording equipment was not possible during surgery, theoretically the zero-balance of all the available flow probes which might be used during operation should be set in vitro before sterilization in each possible usable combination, because the size of the flow transducer that is going to be implanted, is dependable of the vessel size, an unknown factor before operation. Numerous combinations of the in vitro assessed zero balance had then to be made, which seemed at least impractical.

The mechanical zero-balance of the flow transducers took place at the beginning of each registration and was generally checked at the end of the experimentation session and sometimes during experimentation.

The vessel occlusions were performed simultaneously for all flow transducers in use and during the occlusion the zero-balance of the flow transducers was adjusted in such a way that all flows were at the zero-level; after this procedure the occlusion was discontinued and steady state registration began.

The blood flow in the median uterine artery could be considerably diminished after an occlusion due to vasospasm. This was seldom the case for the internal iliac artery flow. If necessary the steady state period was prolonged till flow had returned to normal values over a period of at least 30 minutes.

The above mentioned base line shifts did not occur in all experiments. In many cases the mechanically obtained zero flow balance was rather stable in subsequent experiments, several days after implantation when the flow transducers were attached to the vessel wall by adhesions.

2.8.4 Blood sample analysis

Fetal arterial blood samples were withdrawn from the indwelling femoral artery catheter in an anaerobic way. A total amount of 0.3 ml was sampled for each analysis. After the sampling procedure the catheter and stopcock were flushed with a small amount of heparinized physiological saline solution. The samples were immediately analysed with an automatic blood gas analyser (AVL 940 automatic gas check). The blood gas analyser had the possibility of presetting the desired temperature and the choice between adult and fetal Hb preset. Sheep have a higher body temperature (38.5° -39°C) than human beings and since temperature influences pH, pCO_2 and pO_2 it would not be correct to analyse blood samples at 37°C. The samples were therefore analysed at 39°C and with the hemoglobin switch in the HbF position. One should bear in mind the differences in pH, pCO_2 and PO_2 analysed at 37° or 39°C, when comparing the results of studies done in different research centers. The sampling protocol for the various experiments will be explained later on.

2.8.5 Display and storage of the signals

All signals were displayed on an eight channel strip chart recorder (Hewlett Packard 7758 A) running at a paper speed of 3 cm/min or 25 mm/sec. A marker signal was added for recognition of begin and end of an experimental event. All signals were stored on magnetic tape by means of an eight channel instrumentation recorder (Hewlett Packard 3968 A) at a running speed of 15/32 inches/sec.

2.9 Signal analysis

2.9.1 Data processing

The analog signals stored on magnetic tape were subsequently converted to digital signals and processed by a computer (Digital VAX 11/780). The sampling rate for each parameter was 250 Hz. All data were stored on disk and magnetic tape after conversion.

2.9.2 Data reduction

Before statistical analysis could be performed, means and standard deviations of each appropriate variable were calculated during a steady state period preceding the experimental event, during the experimental event and during a period following the event.
In case of an umbilical cord occlusion or an internal iliac artery occlusion the steady state period lasted 40 seconds, followed by a varying occlusion period and a recovery period of 120 seconds. Means and standard deviations of the fetal parameters were calculated over this total epoch in intervals of 10 seconds each.
The same procedure was followed in the experiments with agonists and antagonists of the autonomic nervous system administered to the fetus, but the total duration of the postinfusion period varied for each specific drug (chapter 5).
In the maternal infusion experiments means and standard deviations were calculated over intervals of five minutes at various moments during the experiment, as will be elucidated in chapter 6.

2.9.3 Artefact identification

Maternal and fetal movements can cause disturbances in the recorded signals.
This is most obvious in the recordings of the pressure signals. Each change in intra or extra uterine pressure from either fetal or maternal side is superimposed on the pressure wave propagated by the catheters. The amniotic cavity pressure was therefore subtracted from the fetal arterial pressure to minimize pressure artefacts.
Those cases in which no reliable amniotic cavity pressure was obtained due to blocking or kinking of the catheter, were discarded from the study. Also the occlusion experiments in which the arterial pressure signal was lost as the result of blood sampling procedures immediately following the occlusion were excluded from the analysis of the hemodynamic changes of the variables. Interference with the ECG-signal by electrical muscular activity with fetal movements was neglected,

because no electromechanical time intervals or heart rate indices derived from RR intervals had to be calculated.
Fetal movements sometimes disturbed the blood flow signal from the common umbilical vein, most likely caused by displacement of the flow transducer around the vessel. If this was the case in the short lasting occlusion experiments or the experiments with drug administration to the fetus, they were excluded from analysis.
Changes in the maternal blood flow measurements can occur when the ewe is frightened by e.g. unexpected movements of the investigator, which may decrease uterine blood flow (Hasaart and de Haan 1983b). Cautious behaviour of the investigator helped to prevent these reactions, otherwise they were excluded from analysis.
Postural changes of the ewe may also lead to slight changes in pelvic blood flow (Hasaart and de Haan 1983b).
The ewe was permitted to stand or lie as pleased, a condition important in longer lasting experiments with ruminants.

2.9.4 Statistical analysis

Comparison of the mean values of the variables was done by means of the Wilcoxon matched-pairs signed-ranks test or by means of a paired student's t-test.
All p values were calculated for two tailed tests.

2.10 Experiments

A total number of 15 animals was used in this study (table 2.1).
Experimental sessions were not started before the third day after surgery. The experiments took place between 103 and 142 days' gestation. Fetal postoperative survival ranged from 5 days to 35 days with a mean of 17.1 days (SD $\pm$ 3.1 days).
Maternal body weight at the time of surgery ranged form 36 to 47 kilograms with a mean of 42 kg (SD $\pm$ 1.9 kg).

SHEEP NO	MATERNAL WEIGHT AT THE TIME OF SURGERY (KG.)	GESTATIONAL AGE AT THE TIME OF SURGERY (DAYS)	DAYS OF INTRA-UTERINE SURVIVAL	FETAL OUTCOME AND ROUTE OF DELIVERY	FETAL WEIGHT AT BIRTH (GR.)
8204	38	109	27	BORN ALIVE VAGINALLY	2000
8205	37	"100"	19	I.U.F.D. VAGINALLY	1800
8208	38	"110"	7	I.U.F.D. VAGINALLY	1650
8210	38	125	10	FETAL DEATH DURING LABOR, VAGINALLY	3100
8215	45	139	7	FETAL DEATH DURING LABOR, VAGINALLY	4350
8216	36	"100"	35	BORN ALIVE VAGINALLY	4100
8303	46	"110"	8	BORN ALIVE VAGINALLY	2000
8304	42	128	15	BORN ALIVE VAGINALLY	3200
8308	44	117	17	I.U.F.D. VAGINALLY	2500
8309	46	105	23	BORN ALIVE SECTIO CAESAREA	1800
8310	43	112	5	I.U.F.D. VAGINALLY	1900
8311	44	114	17	I.U.F.D. SECTIO CAESAREA	3600
8312	45	110	11	I.U.F.D. SECTIO CAESAREA	3300
8315	47	114	27	BOTH BORN ALIVE VAGINALLY	I 2600 ; II 3300 (II:NOT OPERATED)
8317	42	110	29	BORN ALIVE SECTIO CAESAREA	2500

TABLE 2.1. MATERNAL BIOGRAPHICAL DATA AND FETAL OUTCOME OF THE SHEEP WHICH WERE INCLUDED IN THIS STUDY. DATA BETWEEN "QUOTATION MARKS" REFER TO THE ESTIMATED GESTATIONAL AGE AT THE TIME OF SURGERY.

	MEAN	SD	RANGE	N
GESTATIONAL AGE AT THE TIME OF SURGERY IN DAYS	113.5	± 3.2	100 - 139	15
GESTATIONAL AGE AT THE TIME OF DELIVERY IN DAYS	130.8	± 3.2	117 - 146	15
FETAL POSTOPERATIVE SURVIVAL IN DAYS	17.1	± 3.1	5 - 35	15
FETAL BODY WEIGHT AT THE TIME OF DELIVERY (GRAMS)	2690	± 30	1650-4350	15
MATERNAL BODY WEIGHT AT THE TIME OF SURGERY (KG.)	42	± 1.9	36 - 47	15

TABLE 2.2 BIOGRAPHICAL DATA OF THE ANIMALS INCLUDED IN THIS STUDY
(SD = STANDARD DEVIATION)
(N = NUMBER OF ANIMALS)

Fetal body weight at the time of delivery ranged from 1650 grams to 4350 grams with a mean of 2690 grams (SD $\pm$ 30 grams) (table 2.2).
Not all animals were fully equipped with the devices listed in paragraph 3.6, since not all identical measurements were performed in all animals. Moreover, it was not always possible to place all devices, for example due to the size of the fetus (table 2.3).
The experiments which were performed are divided in different groups which will be subsequently discussed.

SHEEP NO	APPLIED INSTRUMENTARIUM.
8204	1.2.3.5.6.9.11.12.
8205	1.2.4.5.6.7.9.11.
8208	1.2.3.4.5.6.7.9.11.12.
8210	1.2.3.4.5.6.7.9.11.12.
8215	1.2.3.5.6.9.11.12.
8216	1.2.3.4.5.6.7.9.11.12.
8303	1.2.3.4.5.6.7.9.10.11.12.
8304	3.4.5.6.7.9.10.12.
8308	1.2.3.4.5.6.7.9.10.11.12.
8309	1.2.3.4.5.6.7.9.10.11.12.
8310	1.2.3.4.5.6.7.8.9.10.11.12.
8311	1.2.3.4.5.6.7.8.9.10.11.12.
8312	1.2.3.4.5.6.7.9.11.12.
8315	1.2.3.4.5.6.7.9.11.12.
8317	1.2.3.4.5.6.9.10.11.12.

TABLE 2.3. LISTING OF THE APPLIED MATERNAL AND FETAL INSTRUMENTARIUM IN EACH ANIMAL. THE NUMBERS CORRESPOND WITH THOSE IN FIG. 2.6. , INDICATING THE CATHETER FLOWMETER,OCCLUDER OR ELECTRODE IN QUESTION.

Only those fetal lambs were included in the study, whose pH and pO_2 were within the normal range (mean $\pm$ 2 SD) for this laboratory (table 2.4).

The normal ranges were determined by averaging the steady state values within a previous group of 18 fetal sheep operated in the set up phase of this chronic animal model, from the third day after operation onwards with exclusion of the day of delivery.

Mean pH values were assessed by averaging the negative antilogarithm of each pH value, and subsequently converting this mean negative

antilogarithm (=mean hydrogen ion concentration) into the mean pH to avoid arithmetic errors (Bretscher 1966).

pH (UNITS)	+ 2 SD	: 7.433
	MEAN	: 7.338
	- 2 SD	: 7.231
PO_2 (kPA)	+ 2 SD	: 4.82
	MEAN	: 3.20
	- 2 SD	: 1.58
PCO_2 (kPA)	+ 2 SD	: 6.52
	MEAN	: 5.35
	- 2 SD	: 4.18

TABLE 2.4 NORMAL RANGES FOR FETAL pH, PO_2 AND PCO_2 IN THIS LABORATORY.

2.10.1 Umbilical cord occlusions

An inflatable balloon occluder was placed around the total umbilical cord in 8 fetuses which were also provided with an electromagnetic flow transducer around the intraabdominal common umbilical vein. The balloon was inflated with saline solution until no further filling of the balloon could be obtained. The occlusion period ranged from 20 to 90 seconds. In most experiments several occlusions after each other were performed with intervals of three to four minutes.
The umbilical cord occlusions with simultaneous registration of the blood flow in the internal iliac and/or median uterine artery are shown in table 2.5.

	OCCLUSION OF THE UMBILICAL CORD	
	N EXP.	N ANIMALS
INTERNAL ILIAC ARTERY	69	7
MEDIAN UTERINE ARTERY	69	7

TABLE 2.5 SUMMARY OF THE PERFORMED UMBILICAL CORD OCCLUSIONS WITH SIMULTANEOUS MEASUREMENT OF THE BLOOD FLOW IN THE MATERNAL ILIAC ARTERY AND/OR MEDIAN UTERINE ARTERY.

2.10.2 Common internal iliac artery occlusions

Fetal hypoxemia can be established in several ways. One of the two mostly used techniques of producing fetal hypoxemia in the chronic animal model are causing maternal hypoxemia and hence fetal hypoxemia by lowering the oxygen content of the inspired air by placing a bag around the ewe's head and ventilating it with low oxygen mixtures.
The other method is interrupting the maternal placental blood flow to the fetus by occlusion of the supplying arteries. This blood flow obstruction can be established at different levels in the arterial tree from the abdominal aorta onwards to the uterine arteries. One of the important effects of the uterine contraction, namely the transient reduction of the maternal placental blood flow can thus be mimicked. Occlusion of the maternal abdominal aorta by an indwelling balloon occluder via the femoral artery can obstruct the maternal placental circulation almost completely, but rupture of the aorta is a dangerous complication of this method. Occlusion of even both median uterine arteries does in general not result in the desired fetal hypoxemia (Evers 1978).
Occlusion of the common internal iliac artery by a balloon occluder which surrounds the vessel is a safe method and causes also a nearly

complete obstruction of maternal placental flow.
This method was used in this study. The completeness of the blood flow obstruction could be judged by the decrease of the flow in the internal iliac artery or median uterine artery to zero measured with an electromagnetic flow transducer. The occlusion period ranged between 30 and 250 seconds, except in three experiments after propranolol administration, in which the occlusion time was extended up to 340 seconds before an effect could be noted. Several subsequent occlusions were performed with intervals of three to four minutes. Blood samples for analysis of fetal pH, pO_2 and pCO_2 were drawn at the end of the steady state period before the beginning of the occlusion experiments and immediately after the last occlusion. The experiments are listed in table 2.6.

	TOTAL OCCLUSION OF THE MATERNAL COMMON INTERNAL ILIAC ARTERY	
	N EXP.	N ANIM.
INTACT AUTONOMIC NERVOUS SYSTEM	75	9
AFTER CHOLINERGIC BLOCKADE WITH ATROPINE	17	6
AFTER α-ADRENERGIC BLOCKADE WITH PHENTOLAMINE	19	6
AFTER β-ADRENERGIC BLOCKADE WITH PROPRANOLOL	16	5

TABLE 2.6 SUMMARY OF THE COMMON INTERNAL ILIAC ARTERY OCCLUSIONS WITH AND WITHOUT THE ADMINISTRATION OF AUTONOMIC ACTING AGENTS TO THE FETUS.
(N EXP. = NUMBER OF EXPERIMENTS PERFORMED)
(N ANIM. = NUMBER OF ANIMALS INVOLVED)

2.10.3 Occlusion experiments after selective autonomic nervous system blockade

The influence of various parts of the autonomic nervous system upon umbilical venous blood flow during acute hypoxemia caused by occlusion of the maternal common internal iliac artery was studied by blocking

the different parts of the autonomic nervous system with antagonistic drugs. The drugs were administered to the fetus via the indwelling femoral artery catheter in a bolus injection.
The given doses were related to the estimated fetal weight according to Naaktgeboren's fetal development scales (Naaktgeboren and Stegeman 1969). The completeness of the autonomic blockade with the used doses has been proven by Evers (1978), who found inhibition of the effects of their respective agonists.

2.10.3.1 Parasympathetic or cholinergic blockade with atropine

Seventeen occlusion experiments of the maternal internal iliac artery were performed in six animals. Seven occlusion experiments of the total umbilical cord were done in four animals. Atropine was administered in a dosage of 1.0 mg/kg estimated fetal weight.

	AGONIST	DOSE MICROG./KG.	NUMBER OF EXP.	NUMBER OF ANIM.
CHOLINERGIC	ACETYLCHOLINE	5 - 25	45	5
ALPHA-ADRENERGIC	NOREPINEPHRINE	2 - 5	28	7
BETA-ADRENERGIC	FENOTEROL	0.5 - 1.0	8	3

TABLE 2.7 SUMMARY OF THE EXPERIMENTS PERFORMED IN THE FETAL LAMB WITH AGONISTS OF THE AUTONOMIC NERVOUS SYSTEM.

2.10.3.2 Beta-adrenergic blockade with propranolol

Sixteen occlusion experiments of the maternal common internal iliac artery were performed in five animals. Eight occlusion experiments of the total umbilical cord were performed in four animals. Propranolol was administered in a dose of 1.0 mg/kg estimated fetal weight.

2.10.3.3 Alpha-adrenergic blockade with phentolamine

Nineteen occlusion experiments of the maternal common internal iliac artery were performed in six animals. Eleven occlusion experiments of the total umbilical cord were performed in four animals. Phentolamine was administered in a dose of 2.5 mg/kg estimated fetal weight.

2.10.4 Studies with autonomic acting agents

Apart from the occlusion experiments under selective autonomic nervous system blockade agonists and antagonists of the autonomic nervous system were administered to the fetus to study their effects on umbilical venous blood flow. All drugs were administered by bolus injections to the fetus via the femoral artery catheter (table 2.7 and 2.8).

	ANTAGONIST	DOSE MG./KG.	NUMBER OF EXP.	NUMBER OF ANIM.
CHOLINERGIC	ATROPINE	1.0	7	6
ALPHA-ADRENERGIC	PHENTOLAMINE	2.5	9	6
BETA-ADRENERGIC	PROPRANOLOL	1.0	7	5

TABLE 2.8 SUMMARY OF THE EXPERIMENTS PERFORMED IN THE FETAL LAMB WITH ANTAGONISTS OF THE AUTONOMIC NERVOUS SYSTEM.

2.10.5 Maternal infusions with acetylcholine, norepinephrine and fenoterol

The blood flow responses of the pelvic vascular bed in the pregnant ewe to vasoactive stimuli and their possible effects on the fetal circulation were studied with the autonomic agonists acetylcholine, norepinephrine and fenoterol. These three drugs have different properties. Acetylcholine has a cholinergic effect, while norepinephrine has mainly alpha-adrenergic activity with very little beta-1 activity on the heart. Fenoterol is a beta-adrenergic acting drug with mainly beta-2 activity. Fenoterol was chosen to cover the beta-adrenergic part because of the fact that this drug is also used in the human for tocolysis (Fenoterol=Partusisten^{R}). With the use of these three drugs the various parts of the autonomic nervous system were influenced. A total number of 58 infusion experiments were performed in 12 pregnant sheep between 104 and 146 days gestation.

	FENOTEROL		NOREPINEPHRINE		ACETYLCHOLINE	
	N EXP.	N ANIM.	N EXP.	N ANIM.	N EXP.	N ANIM.
MATERNAL INTERNAL ILIAC ARTERY	15	4	7	5	7	4
MATERNAL MEDIAN UTERINE ARTERY	18	6	13	8	15	5
FETAL COMMON UMBILICAL VEIN	20	7	13	9	12	6

TABLE 2.9 NUMBER OF EXPERIMENTS IN WHICH THE BLOOD FLOW IN RESPECTIVELY THE INTERNAL ILIAC ARTERY, MEDIAN UTERINE ARTERY AND COMMON UMBILICAL VEIN WAS MEASURED DURING THE ADMINISTRATION OF FENOTEROL, NOREPINEPHRINE AND ACETYLCHOLINE TO THE EWE.

The internal iliac artery and median uterine artery blood flow at the side of the pregnant horn were not simultaneously measured in all

experiments. The reasons for the fact that in part of the experiments only the flow in one maternal vessel was measured were twofold. Either only one flow transducer was placed or one of the flow transducers around the maternal vessels lost its grip on the vessel during the experimental period and subsequently no signal was obtained.
A detailed list of the various experiments with the number of blood flow measurements in each vessel is given in table 2.9.

2.10.5.1 Infusion protocol

The drugs were 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 (B.Braun Melsungen, type 871100).
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 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 doses of the drug were increased during the infusion period by increasing the infusion rate, which varied between 1.2 ml/hour and 60 ml/hour.
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 then followed, during which the selected drug was infused intravenously in progressively increasing dose, each infusion lasting 15 minutes, but in the cases with fenoterol infusion, the infusion period amounted 30 minutes. Doses, infusion periods and the number of experiments for each drug are enlisted in table 2.10.

	DOSE (MICROGR./MIN)	INFUSION TIME (MINUTES)	NUMBER OF EXPERIMENTS	NUMBER OF ANIMALS
FENOTEROL	2 4	30 30	24	7
NOREPINEPHRINE	4 8 20 40	15 15 15 15	17	10
ACETYLCHOLINE	20 50 100 200	15 15 15 15	17	7

TABLE 2.10 DOSES AND INFUSION TIMES OF FENOTEROL, NOREPINEPHRINE AND ACETYLCHOLINE AND THE NUMBER OF EXPERIMENTS PERFORMED WHICH EACH DRUG.

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 was allowed during which flows and fetal parameters were recorded continuously. 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.

Only one drug was studied in each animal on any one day.

The absolute drug doses used in this study were the same for each animal and not related to the bodyweight of the ewe. The reasons therefore were several. First of all it was not the aim of the experiments to assess dose-response curves. Secondly the bodyweight of the ewes did not vary that much with a mean body weight of 42.8 $\pm$ 1.9 kg (mean $\pm$ SD ; n=12 ; range 36-47 kg).

Moreover the bodyweight of the ewe was not constant over the experimental period with advancing gestation and it was rather

impractical if not impossible to perform daily weight measurements without severing the indwelling catheters.
The doses of norepinephrine and acetylcholine were in the range that other investigators have used for these kind of experiments in sheep. The infused amount of fenoterol per kg maternal body weight corresponded with the drug doses per kg maternal body weight used in the human for tocolysis.

2.10.6 Fetal breathing movements, fetal intraabdominal pressure and common umbilical vein flow

The influences of fetal breathing movements on the blood flow of the common umbilical vein was studied by simultaneous registration of tracheal pressure, amniotic fluid pressure and common umbilical vein blood flow in 6 fetal lambs from the third postoperative day onwards. Periods with and without fetal breathing movements were discerned by inspection of the analog record.
The effects of acute hypoxemia caused by occlusion of the maternal common internal iliac artery and the fetal umbilical cord on fetal breathing movements could be studied in relation with umbilical venous blood flow.
The relation between fetal breathing movements, intraabdominal pressure and amniotic fluid pressure was studied in two fetal lambs.

CHAPTER III

COMMON INTERNAL ILIAC ARTERY OCCLUSIONS AND UMBILICAL VENOUS BLOOD FLOW

3.1 Introduction

Late decelerations in the fetal heart rate are generally considered to be a sign of fetal hypoxemia. The fetal heart rate pattern of late deceleration in the human is characterized by a uniform specific fetal heart rate pattern, whose shape reflects the shape of the associated uterine contraction curve and whose onset is late in the contracting phase of the uterus (Hon 1968). The major factor in the production of late decelerations is a transient decrease in uterine blood flow during contractions and a concomitant decrease of fetal oxygenation below the limit of fetal tolerance. Late decelerations mostly occur in conditions in which the duration of uterine contractions is too much for the fetus that is already at the limits of its reserves, as e.g. in pre-eclampsia or chronically impaired placental exchange. They also occur in instances in which uteroplacental perfusion is acutely diminished as a result of, for example, uterine hypertonus, maternal cardiovascular shock and partial abruptio of the placenta.

Fetal hypoxemia can be established in several ways as has been shown in paragraph 2.10.2. Producing maternal and fetal hypoxemia by letting the ewe inspire a low oxygen content gas mixture differs in two aspects substantially from the production of fetal hypoxemia by means of uterine blood flow obstruction. The latter method namely implies also major hemodynamic changes in the uterine vascular bed, comparable to those occurring during uterine contractions. The first technique not only leads to fetal hypoxemia but general maternal hypoxemia is established too.

Periodic uterine contractions which lead to fetal hypoxemia are

difficult to produce in a controllable way in the chronic sheep preparation, so that most of the animal studies concerning late decelerations are performed by blood flow obstruction in the maternal abdominal aorta or somewhere downstream in the uterine vascular bed (Parer 1976). Although the effects of hypoxemia and acidemia on umbilical blood flow under several conditions are well known, all these experiments took place with the ewe breathing low oxygen content mixtures (Cohn et al 1974, 1980, 1982). Only scarce data are available on the influences of acute uterine flow decrease on arterial umbilical blood flow (Berman et al 1976, Parer et al 1980, Harris et al 1982). No data exist to our knowledge on the effects on umbilical venous blood flow as measured with an electromagnetic flow transducer.
The literature on the late decelerations in the fetal heart rate and especially its relation with umbilical blood flow will be briefly reviewed.

3.2. Literature

The late deceleration fetal heart rate pattern in the human was ascribed by Hon (1962) to hypoxemic depression of the myocardium. As evidence for this mechanism Hon showed that late decelerations in human fetuses could be modified by the administration of 100% oxygen to the mother. However data from both Hon (1962) and Mendez-Bauer et al (1963) suggested that there was also a vagal reflex component to the mechanism of late deceleration. They observed that parasympathetic blockade with atropine, injected into human fetuses with late decelerations, could modify but not completely eliminate this phenomenon in the fetal heart rate pattern. Later animal studies were directed upon the hypoxic depression of cardiac performance.
James et al (1972) observed in anesthetized subhuman primates that the severity of the late decelerations was lessened as the fetal arterial oxygen tension was increased. The same results were obtained by Meyers et al (1973) who showed in acute monkey preparations in which late decelerations were provoked by transient maternal aortic occlusion, that the severity of the late deceleration was related to the degree of fetal hypoxemia. Boddy et al (1974) showed on the other hand in the

chronically catheterized fetal lamb that the initial bradycardia, associated with acute hypoxemia can be abolished by vagotomy. The hypoxemic bradycardia can also be converted to a tachycardia by cholinergic blockade (Parer 1977, Evers 1978).

Martin et al (1979) and de Haan et al (1979) described the mechanisms of late decelerations in fetal lambs in a study performed with autonomic blocking agents. The late decelerations were induced by periodic occlusion of the maternal common internal iliac artery for 30-60 seconds. The nonacidemic fetuses in their study responded to periodic reductions in uterine blood flow by periodic hypertension and fetal heart rate decelerations. Elimination of the fetal hypertensive response by alpha-adrenergic blockade markedly modified the fetal heart rate decelerations, but did not eliminate them completely. Cholinergic blockade converted the periodic decelerations to accelerations, which in turn could be blocked by propranolol. When the alpha-adrenergic, cholinergic and beta-adrenergic parts of the autonomic nervous system were blocked simultaneously, the nonacidemic fetuses showed essentially no heart rate response to periodic hypoxemia, indicating that the heart rate deceleration during hypoxemia is mediated by the autonomic nervous system.

In contrast, blockade of the efferent limb of the cardiodecelerator reflex (by cholinergic blockade) did not alter the degree of fetal heart rate deceleration in response to periodic occlusion of the maternal common internal iliac artery in fetuses made severely acidotic by a long series of such occlusions. They concluded that the dominant reflex-mechanism involved in "acute" late decelerations would be chemoreceptor-mediated reflex vasoconstriction (Dawes et al 1968b, 1969), producing hypertension and, in turn, baroreflex-induced cardiac slowing (Shinebourne et al, 1972). Martin et al (1979) furthermore state that chemoreceptor (peripheral or central) stimulation by hypoxemia can also activate a cardiodecelerator reflex primarily, as is suggested by the frequent onset of heart rate deceleration several seconds before the appearance of any blood pressure increase in the unblocked fetuses in their experiments.

The interpretation of Harris et al (1982) and Itskovitz et al (1982a) of the conclusions of Martin and coworkers that the decrease in fetal

heart rate was primarily due to a baroreflex mechanism is therefore not correct.

Martin et al concluded moreover that the reflex component of the late deceleration was absent or minimal under conditions of severe fetal acidosis, and direct hypoxic depression of myocardial rhythmicity seemed to be the major determinant of the late deceleration during hypoxic acidosis.

Hypoxemia decreases the rate of spontaneous impulse initiation in the sinoatrial node (Senges et al 1979) with slowing of the heart rate as result and may furthermore affect contraction force of the myocardium resulting in a decrease of the heart minute volume.

Berman et al (1976), in a study on pressure flow relationships in the umbilical and uterine circulations of the sheep, reduced uterine arterial pressure and thus flow to the placenta by inflating a Swan-Ganz catheter in the descending aorta of the ewe. Umbilical arterial blood flow was measured continuously during this procedure by means of an electromagnetic flow transducer around the common umbilical artery of the fetus (Berman et al 1975). They concluded that uterine blood flow decreased instantaneously after reduction of uterine arterial pressure, whereas umbilical bloodflow did not change initially. A variable and delayed fall in umbilical blood flow subsequent to fetal hypoxemia could result from the reduced uterine arterial flow. They supposed that the bradycardia due to fetal hypoxemia (Cohn et al 1974) might be responsible for the late fall in umbilical blood flow, because the prevention of the bradycardia by atropine abolished the decrease in umbilical blood flow associated with the hypoxemic response.

Parer et al (1980) produced late decelerations in the fetal heart rate by abruptly decreasing uterine blood flow to zero for 20 seconds in chronically instrumented normoxemic sheep. Uterine flow reduction was accomplished by inflation of a balloon in the maternal abdominal aorta. Fetal O_2 consumption, O_2 content and O_2 tension in umbilical blood decreased significantly before the decline in heart rate. Fetal arterial blood pressure either showed no change (nine experiments), an increase (fifteen experiments) or a decrease (five experiments) following aortic occlusion. The mean value of fetal arterial blood

pressure actually showed a slight, though nonsignificant, decline with aortic occlusion. Only minor changes in umbilical blood flow were found with aortic occlusion and no value was significantly different from control. After complete vagal blockade with atropine the late deceleration disappeared and a late acceleration was uncovered, which was due to beta-adrenergic activity. No change in mean fetal arterial blood pressure occurred, but a substantial decline in umbilical venous oxygen tension was present during aortic occlusion. Their final conclusion is therefore that these late decelerations caused by short lasting obstruction of the aortic blood flow in normoxemic fetal sheep are primarily vagally mediated and due to chemoreceptor rather than baro-receptor activity. Further evidence for the primary roll of the chemoreceptors in the onset of fetal bradycardia during late decelerations is the abolishment of fetal bradycardia during short lasting maternal aortic occlusion after denervation of the fetal aortic and carotid chemoreceptors (Itskovitz 1982b).

In a continuation of the study by Parer et al (1980), Harris et al (1982) published the results of a study into the mechanism of late decelerations of the fetal heart rate in fetal lambs which were already made hypoxemic before the obstruction of uterine blood flow. The ewes were made hypoxemic by breathing a low oxygen gas mixture through a mask placed over their faces. Transient maternal aortic occlusion during 20 seconds in these hypoxemic ewes resulted in a delayed and transient deceleration of the fetal heart rate in the hypoxemic fetuses, associated with a significant decrease in mean fetal arterial pressure and umbilical arterial blood flow as measured with an electromagnetic flow transducer. Parasympathetic blockade of the fetus with atropine modified but did not abolish the fetal heart rate response with aortic occlusion nor did it restore umbilical blood flow completely. The conclusion was that late decelerations result from two mechanisms: a chemoreceptor mediated vagal reflex and hypoxic myocardial depression. Itskovitz et al (1982a) studied the responses of fetal heart rate and blood pressure to a transient reduction in uterine blood flow during 10 or 20 seconds in normoxemic and chronically hypoxemic fetal lambs. Uterine flow reduction was established by inflating a balloon in the maternal abdominal aorta. In normoxemic

fetuses, a reduction in uterine blood flow, if prolonged sufficiently, produced reflex bradycardia mediated through chemoreceptors. The bradycardia was associated with a marked decrease in left ventricular output as measured by an electromagnetic flow transducer around the ascending fetal aorta. Both phenomena, the bradycardia as well as the decrease in left ventricular output were abolished by atropine, indicating that hypoxemic depression of the sinoatrial node did not occur.

In chronically hypoxemic fetuses, a reduction in uterine blood flow produced a late deceleration in heart rate, which consisted of three components: reflex bradycardia due to chemoreceptor stimulation, baroreceptor-mediated reflex bradycardia associated with the hypertensive period, which involved the slow and late recovery of the heart rate, and nonreflex bradycardia which was probably secondary to hypoxic depression of the sinoatrial node. No data on left ventricular output upon uterine flow reduction in the hypoxemic animals were available in these study. Their conclusion is that the response of fetal heart rate to a transient reduction in uterine blood flow is related to the duration of the reduction and to the status of fetal oxygenation prior to the reduction in uterine blood flow. The same flow changes as occur in the ascending aorta might be expected in the common umbilical artery, but the effects of flow redistribution ("Sparschaltung") during these events must be taken into account when comparing the flow changes in these two vessels.

3.3 Summary

Summarizing the studies from different research centers, there seems to be little disagreement on the mechanism of the late deceleration. The most important factor which determines the reaction in the fetal heart rate pattern during uterine blood flow reduction is the oxygenation of the fetus prior to the decrease in uterine flow (Itskovitz et al 1982a), as was already descibed by Meyers et al in 1973, and furthermore the degree of hypoxemia which is reached as the flow reduction advances.

The primary mechanism in the fetal heart rate decline in normoxemic

fetuses is vagally mediated by chemoreceptors in response to the decrease in arterial pO_2. As the uterine flow reduction advances then an indirect vasoconstriction-baroreceptor mechanism during fetal hypertension reinforces the bradycardia. If hypoxemia becomes severe then a non-reflex bradycardia due to direct depression of cardiac rhythmicity is eventually added.

Itskovitz et al (1982a) suggested that direct hypoxic myocardial depression occurred with an arterial pO_2 around 10 torr. Martin et al (1979) supposed myocardial depression to play a role rather early in the course of fetal acidemia at a pH between 7.25 and 7.30. This nonreflex bradycardia due to direct hypoxic myocardial depression plays a substantial role in the development of bradycardia in hypoxemic fetuses and may occur from the beginning of the heart rate deceleration in severe hypoxemic and acidemic fetuses.

The changes in the arterial umbilical blood flow that accompany the heart rate decelerations seem also to be dependent on fetal oxygenation. Short reductions of maternal aortic blood flow to zero up to 20 seconds did not affect umbilical arterial blood flow in the experiments by Berman et al (1976), Rudolph (1976) and Parer et al (1980) in normoxemic fetuses. Berman et al and Rudolph however reported a decrease in umbilical blood flow as fetal hypoxemia and bradycardia developed with advancing flow obstruction. Umbilical arterial blood flow always decreased upon a short lasting maternal aortic flow reduction in fetuses which were already hypoxemic before the onset of the uterine flow reduction and this fall in umbilical flow could not be prevented by atropine (Harris et al 1982).

No data are available on the umbilical venous blood flow during late decelerations, nor are the umbilical blood flow reactions known during longer lasting uterine blood flow obstruction with the subsequent deterioration of fetal oxygenation.

In order to study the effects of late decelerations on umbilical venous blood flow, periodic occlusions of the maternal common internal iliac artery were performed. The roles of the fetal parasympathetic, alpha-and beta-adrenergic systems were determined by blockade of each of these brances of the fetal autonomic nervous system.

3.4 Materials and methods

A total number of one hundred twenty seven occlusions of the maternal common internal iliac artery in nine fetuses were analysed.
Seventy five occlusions were performed in nine fetuses with an intact autonomic nervous system, while the remaining fifty two occlusions were done in seven fetuses with a selective blockade of a part of the autonomic nervous system. The distribution of the occlusions over the several groups is given in table 2.6.
The occlusion time for the total group ranged from 30 to 340 seconds.
The occlusions were performed in series ranging from two to seven occlusions per experimental session.

3.5 Results

3.5.1 Changes in fetal arterial pH and blood gases

Table 3.1 shows the values for arterial pH, blood gases and base excess during the control period prior to the start of the occlusions.

pH ± SD (UNITS)	7.36 ± 0.036
pO_2 ± SD (kPA)	3.23 ± 0.81
pCO_2 ± SD (kPA)	5.24 ± 0.67
BE ± SD (mEq/L.)	-2.6 ± 1.4

TABLE 3.1 FETAL ARTERIAL pH, BLOOD GASES AND BASE EXCESS DURING THE CONTROL PERIOD IN 31 EXPERIMENTAL SESSIONS.

The data of the fetal acid-base balance immediately after the last occlusion of each experimental session are shown in table 3.2. The repetitive short lasting occlusions of the maternal common internal iliac artery resulted in a decrease in fetal pH and pO_2, while fetal pCO_2 increased.

PH ± SD (UNITS)	7.31 ± 0.05
pO_2 ± SD (KPA)	2.76 ± 0.79
pCO_2 ± SD (KPA)	5.70 ± 0.90
BE ± SD (MEQ/L.)	-4.8 ± 1.6

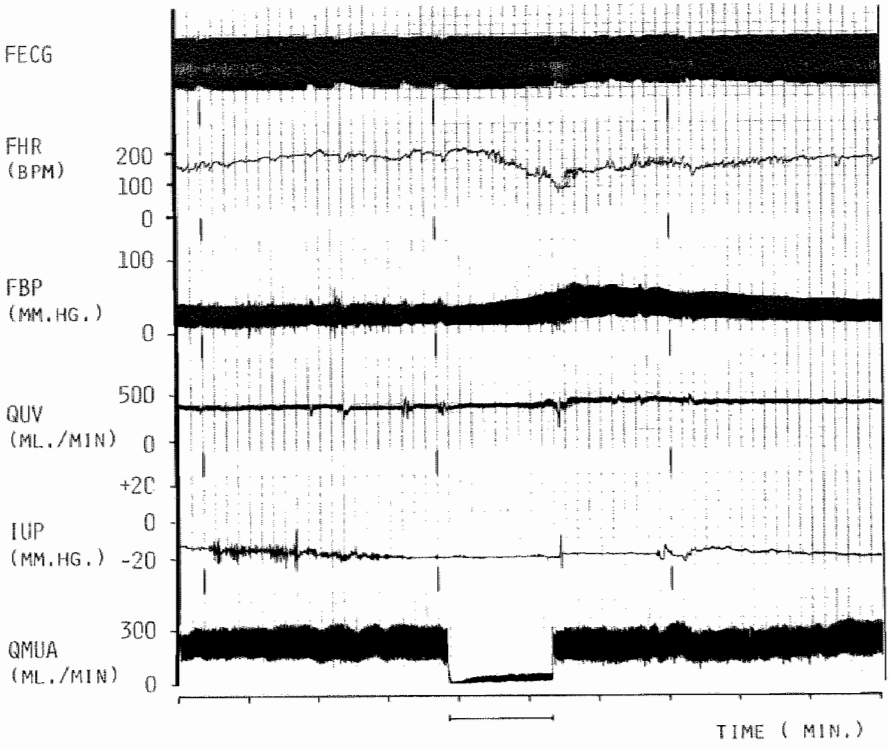
TABLE 3.2 FETAL ARTERIAL PH, BLOOD GASES AND BASE EXCESS IMMEDIATELY FOLLOWING THE LAST OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY OF EACH EXPERIMENTAL SESSION (N = 28).

The differences between the values from the control period and the values obtained at the end of each series of occlusions were significant at the $p<0.01$ level for pH, pO_2 and base excess and at the $p<0.02$ level for pCO_2 (student's t-test for paired observations).

3.5.2 Intact autonomic nervous system

In sixty nine of the seventy five occlusions a deceleration in the fetal heart rate occurred. In the remaining six occlusions in two sheep no heart rate deceleration was seen (occlusion time 60-120 seconds), nor a change in arterial blood pressure and umbilical venous blood flow. The minimal occlusion time causing heart rate decrease showed a great interanimal variation, but the intraanimal variation with different occlusions was quite small.

The overall effect was a fetal heart rate decrease after an initial delay during each occlusion and a gradual recovery after the occlusion period (fig. 3.1). Fetal arterial blood pressure however showed a varying response during the occlusion, namely either an increase or a decrease in mean arterial pressure.



EWE 8308 GESTATIONAL AGE 119 3 DAYS P.O.

FIG 3.1 GRADUAL INCREASE IN ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟝⟞) IN A FETUS WITH AN INTACT AUTONOMIC NERVOUS SYSTEM.

To investigate the factors, e.g. fetal pO_2, which were involved in this varying blood pressure response and to establish the relationships of arterial blood pressure with the other cardiovascular data, further analysis was performed in two groups.
The individual data of the sixty nine occlusions were therefore divided in two groups with the arterial pressure response at the end of the occlusion period as criterion.
In thirty six occlusions mean arterial blood pressure was increased at the end of the occlusion compared with the control value preceding the occlusion (group I). In the remaining thirty three occlusions a decrease in mean arterial blood pressure was found at the end of the occlusion compared with the value of the control period (group II).
The mean values of fetal heart rate, arterial blood pressure and umbilical venous blood flow over an interval of 10 seconds were pooled for each group and statistically analysed. The control values (=C) were obtained from a period 10 seconds before the start of the occlusion. Control values were then compared with the mean values calculated from the last 10 seconds of the occlusion (=E), the interval 10 to 20 seconds after the occlusion (=10), the interval 30 to 40 seconds after the occlusion (=30), the interval 60 to 70 seconds after the occlusion (=60) and finally with the mean value about two minutes after occlusion (=120), calculated over the interval 110-120 seconds after the occlusion.
Data were expressed as percent change $\pm$ SEM with control values as the 100% reference level.
Statistical analysis was performed by means of Wilcoxon's matched-pairs signed ranks test. All p-values were calculated for two tailed tests.

In twelve experimental sessions an increase in mean arterial blood pressure was found during all the performed occlusions (n=19). In eleven experimental sessions arterial blood pressure invariably decreased during all occlusions (n=17).
In the remaining eight experimental sessions blood pressure either increased (n=17) or decreased (n=16) during the occlusions. In the latter eight remaining experimental sessions with mixed blood pressure responses, the same trend in time was found in five experimental

sessions: an increase in blood pressure was associated with the first occlusions (n=13), while a decrease in blood pressure was noted in the following occlusions (n=12). Figures 3.2 and 3.3 show such an example of the reversal in blood pressure response in an occlusion performed early in the experimental session compared with an occlusion performed after seven foregoing occlusions.

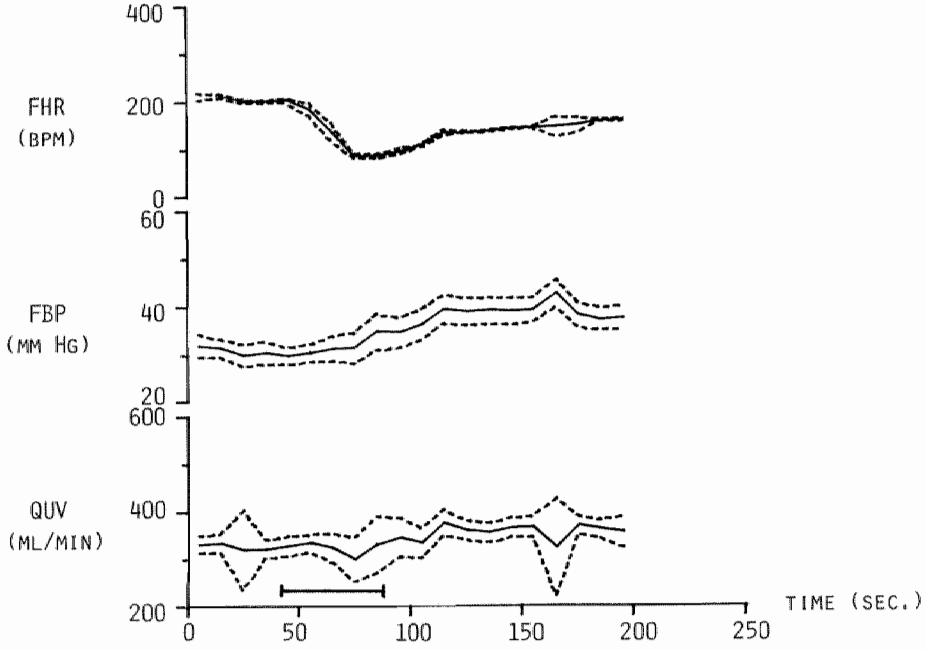


FIG. 3.2 INCREASE IN ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟷) EARLY IN THE EXPERIMENTAL SESSION. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

Either increase or decrease in mean arterial blood pressure started after an initial delay period from the beginning of the occlusion.

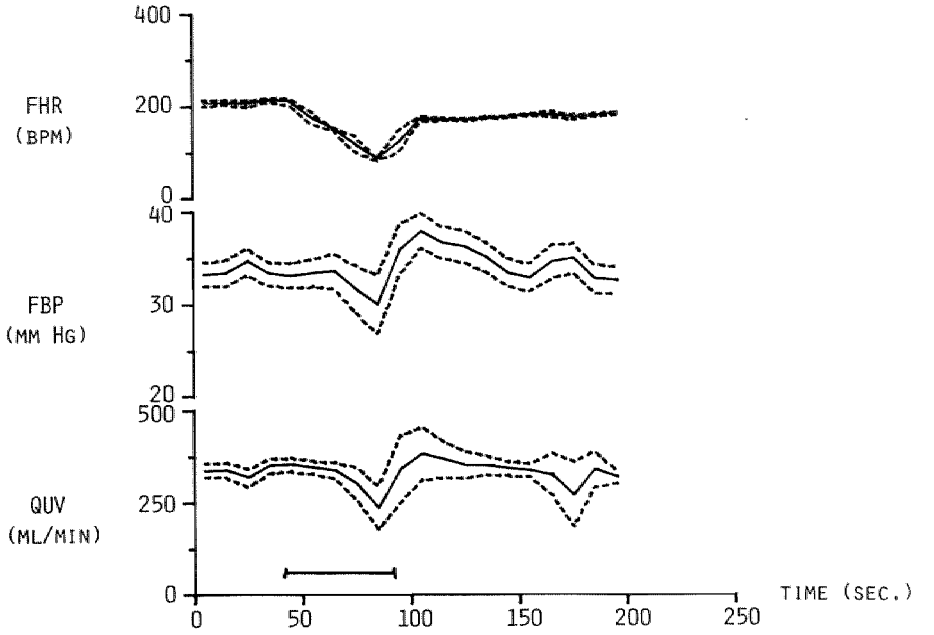


FIG. 3.3 DECREASE IN ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟝⟞) LATER IN THE SAME EXPERIMENTAL SESSION AS IN FIG. 3.5. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

Figure 3.4 shows mean values ± SD for heart rate, arterial blood pressure and umbilical venous blood flow of an occlusion in an animal reacting with a hypertensive response, while fig. 3.5 shows the same parameters of an occlusion in an animal whose mean arterial blood pressure decreased.

If hypertension was present then fetal blood pressure returned towards control levels after the occlusion (fig. 3.4). In the case of a hypotensive response however, blood pressure increased again after the end of the occlusion with often a hypertensive response during the recovery phase (fig. 3.5).

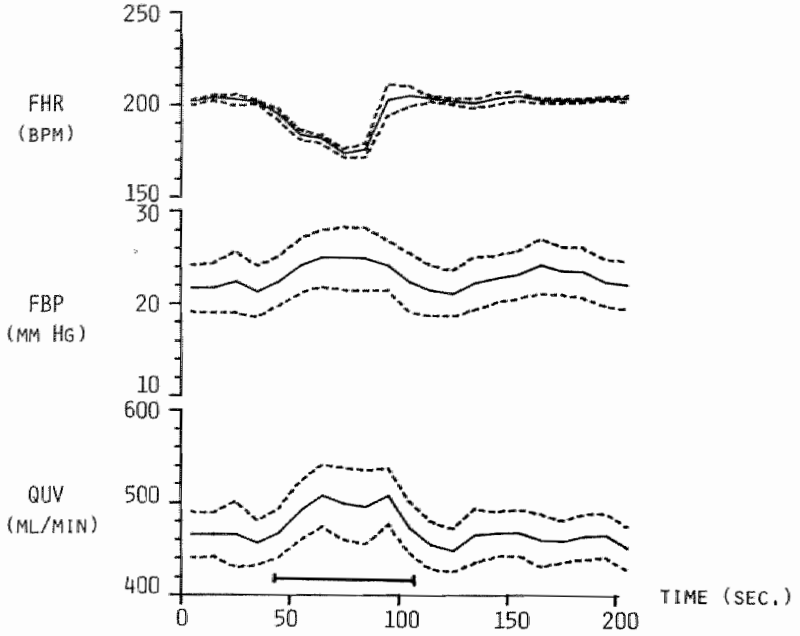


FIG. 3.4 INCREASE IN ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⊢—⊣) IN AN EXPERIMENT BELONGING TO GROUP I WITH AN INTACT AUTONOMIC NERVOUS SYSTEM. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

Umbilical venous blood flow showed the same reaction pattern as the changes in arterial pressure. If arterial blood pressure increased during the occlusion then umbilical blood flow either did not change or also increased. A marked decrease in umbilical blood flow was found however when arterial blood pressure decreased.

A typical recording of the cardiovascular parameters during an occlusion, showing a decrease in arterial blood pressure and umbilical blood flow is shown in fig. 3.6.

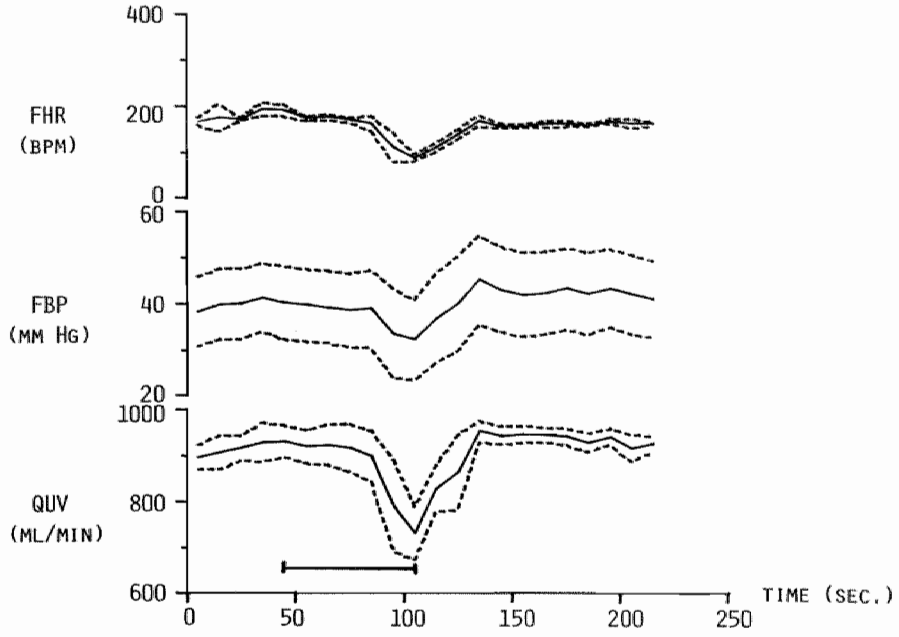


FIG. 3.5 DECREASE IN ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⊢—⊣) IN AN EXPERIMENT BELONGING TO GROUP II WITH AN INTACT AUTONOMIC NERVOUS SYSTEM. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

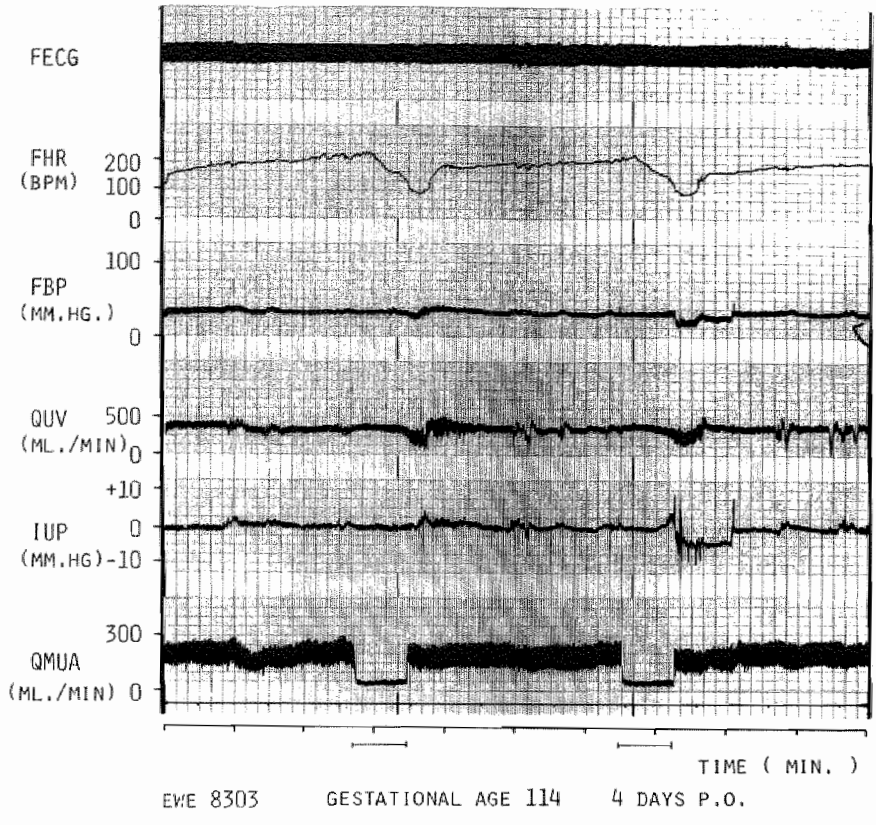


FIG. 3.6 DECREASE IN UMBILICAL VENOUS BLOOD FLOW AND ARTERIAL BLOOD PRESSURE DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶) IN A FETUS WITH AN INTACT AUTONOMIC NERVOUS SYSTEM.

The fetal acid-base balance in the control period and immediately after the last occlusion in that particular series of experiments in which mean arterial blood pressure invariably increased during the occlusions is shown in table 3.3. The same data are given in table 3.4 for the group experiments in which mean arterial blood pressure decreased. The fetuses from group II had a higher starting and ending pH and pO_2 value than the fetuses from group I. The starting and ending pCO_2 value was higher in group I than in group II.

	pH (UNITS)	pO_2 (kPA)	pCO_2 (kPA)	BE (mEq/L.)
CONTROL PERIOD (N = 10)	7.34±0.03	2.81±0.81	5.44±0.65	-3.6±1.5
AFTER THE LAST OCCLUSION (N = 7)	7.29±0.03	2.49±0.81	5.83±0.83	-5.5±1.6

TABLE 3.3 FETAL ACID-BASE BALANCE DURING THE CONTROL PERIOD AND IMMEDIATELY AFTER THE LAST OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN THE SERIES OF EXPERIMENTS IN WHICH ARTERIAL BLOOD PRESSURE INCREASED AT THE END OF THE OCCLUSION (GROUP I).

	pH (UNITS)	pO_2 (kPA)	pCO_2 (kPA)	BE (mEq/L.)
CONTROL (N = 10)	7.37±0.02	3.90±0.76	4.84±0.62	-2.7±1.2
AFTER THE LAST OCCLUSION (N = 7)	7.34±0.03	3.29±0.65	5.21±0.79	-4.5±1.3

TABLE 3.4 FETAL ACID-BASE BALANCE DURING THE CONTROL PERIOD AND IMMEDIATELY AFTER THE LAST OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN THE SERIES OF EXPERIMENTS IN WHICH ARTERIAL BLOOD PRESSURE DECREASED AT THE END OF THE OCCLUSION (GROUP II).

Table 3.5 shows the data on gestational age, and number of days after surgery at the time of the occlusion experiment and the duration of the occlusion for group I.

GROUP I	MEAN ± SD	RANGE
GESTATIONAL AGE (DAYS)	119.3 ± 2.7	110 - 138
TIME AFTER SURGERY(DAYS)	10 ± 2.7	3 - 28
OCCLUSION TIME (SECONDS)	78 ± 6.6	30 - 200

TABLE 3.5 GESTATIONAL AGE, TIME AFTER SURGERY AND OCCLUSION TIME OF THE 36 OCCLUSIONS OF THE COMMON INTERNAL ILIAC ARTERY , PERFORMED IN 8 ANIMALS IN GROUP I.

A composite analysis of the data on fetal heart rate, arterial blood pressure and umbilical venous blood flow from group I (n=36) is given in fig. 3.7.
The double vertical bars between control and end of the occlusion values represent the variation in occlusion time.

Fetal heart rate was significantly ($p<0.001$) reduced from the control value with 25.2% by the end of the occlusion (179 to 134 bpm). After the end of the occlusion fetal heart rate gradually returned towards the control level. There was a significant reduction ($p<0.001$) at 10, 30 and 60 seconds after the occlusion of respectively 21.7%, 12.8% and 5.6%.
Two minutes after the occlusion fetal heart rate was 169 bpm, which was still significantly ($p<0.05$) lower than the control value of 179 bpm.
Fetal arterial blood pressure was significantly increased ($p<0.001$) with 5.7% (40.3 mm Hg) above the control value (38.1 mm Hg) at the end

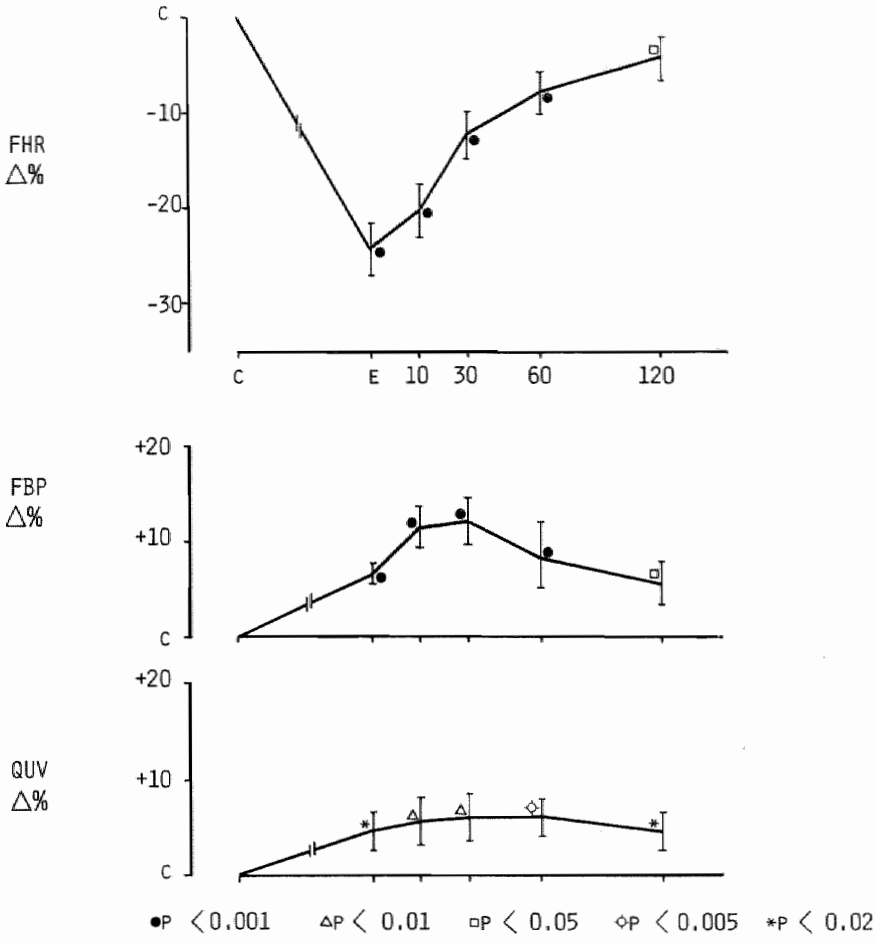


FIG 3.7 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN GROUP I WITH INTACT AUTONOMIC NERVOUS SYSTEM. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

of the occlusion. Arterial blood pressure rose further to reach its maximum increase (11.8%) at 30 seconds after the end of the occlusion ($p<0.001$). Thereafter a gradually returning of blood pressure towards control level occurred but it still was significantly higher (4.7%) than control level at two minutes after the end of the occlusion ($p<0.05$).

Umbilical blood flow paralelled with the increase in arterial blood pressure.

Umbilical blood flow was significantly higher (408 ml/min; $p<0.02$) at the end of the occlusion with an increase of 4.6% above the control value (390 ml/min). The maximum blood flow increase (5.9%; $p<0.01$) was also found at 60 seconds after the occlusion. At two minutes umbilical blood flow was still significantly higher ($p<0.02$) than the control value.

Table 3.6 shows the data on gestational age and number of days after surgery at the time of the occlusion experiment and the duration of the occlusion for group II.

GROUP II	MEAN ± SD	RANGE
GESTATIONAL AGE (DAYS)	116.2 ± 2.3	110 - 136
TIME AFTER SURGERY (DAYS)	6.7 ± 2.2	3 - 26
OCCLUSION TIME (SECONDS)	68 ± 5.7	30 - 180

TABLE 3.6 GESTATIONAL AGE, TIME AFTER SURGERY AND OCCLUSION TIME OF THE 33 OCCLUSIONS OF THE COMMON INTERNAL ILIAC ARTERY, PERFORMED IN 7 ANIMALS IN GROUP II.

A composite analysis of the data on fetal heart rate, arterial blood pressure and umbilical venous blood flow from group II (n=33) is given in fig. 3.8. The double vertical bars between control and end of the occlusion values represent the variation in occlusion time.

The reduction in fetal heart rate was greater than in group I.

Fetal heart rate fell to 63.8% (113 bpm) from the control value (177 bpm) at the end of the occlusion, which decrease was highly significant ($p<0.001$).

The return of fetal heart rate towards control level was slower than in group I with a significant decrease ($p<0.001$) of respectively 27.1%, 14.1%, 10.1% and 6.8% at 10, 30, 60 and 120 seconds after the end of the occlusion.

Fetal arterial blood pressure showed in contrast to the changes in group one a decrease which was maximal at the end of the occlusion time. Blood pressure was at that time significantly ($p<0.001$) diminished to 90.8% (35.6 mm Hg) of the control value (39.2 mm Hg).

Blood pressure had already returned to nearly the control value at 10 seconds from the end of occlusion. At 30 and 60 seconds after the occlusion blood pressure was increased with 3.1% resp. 3.5% above control value. These changes were not significant. At 2 minutes after the occlusion no difference from the control level was found. Umbilical venous blood flow also significantly ($p<0.001$) decreased in this group with 10.7% from 466 ml/min at control period to 417 ml/min at the end of the occlusion.

Umbilical blood flow was still significantly ($p<0.02$) decreased at 10 seconds post occlusion with 5.4%. There after no significant difference from the control value was present.

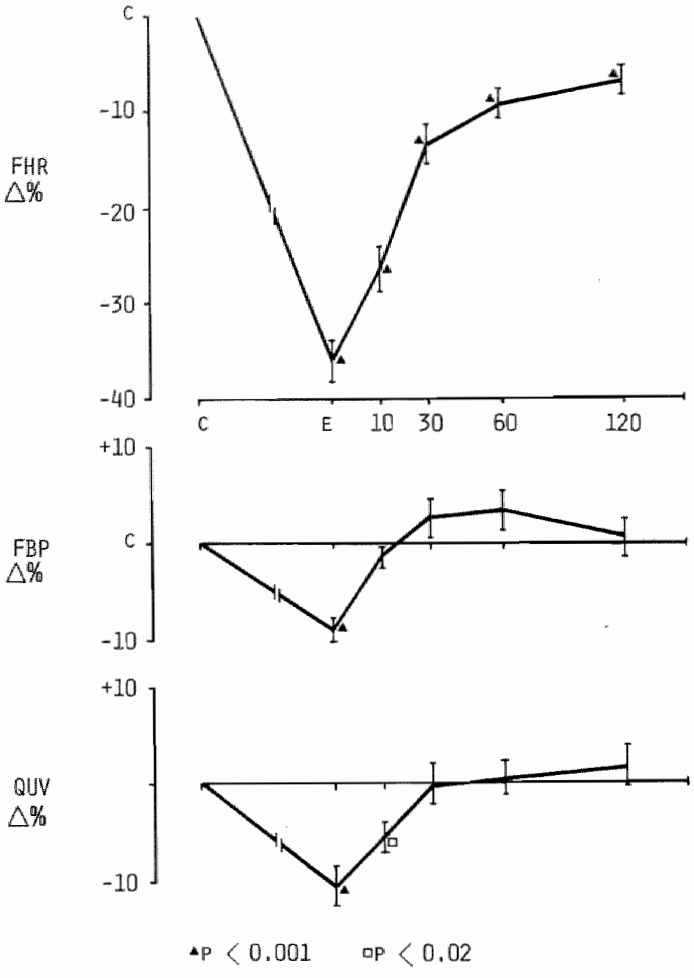


FIG.3.8 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN GROUP II WITH INTACT AUTONOMIC NERVOUS SYSTEM. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

3.5.3 Selective blockade of a part of the autonomic nervous system

The data of each series of occlusions after respectively cholinergic, alpha-adrenergic and beta-adrenergic blockade were analysed as total group and in two subgroups.

Before the occlusions during autonomic blockade were performed, one to three "control" occlusions without blockade were performed. The data of the occlusions after autonomic blockade were pooled in subgroup 1, if the foregoing "control" occlusions had led to an increase in mean arterial blood pressure at the end of the occlusion and in subgroup 2 if on the contrary a decrease in mean arterial blood pressure had occurred during the "control" occlusions.

Statistical analysis was done by means of Wilcoxon's matched-pairs signed-ranks test. All p-values were calculated for two tailed tests. Data are expressed in the composite analyses as percent change $\pm$ SEM from control as 100% reference level. The occlusion time in the experiments during autonomic blockade was in the same order of magnitude as with the "control" occlusions except after propranolol, in which case often a longer occlusion was necessary to establish heart rate changes.

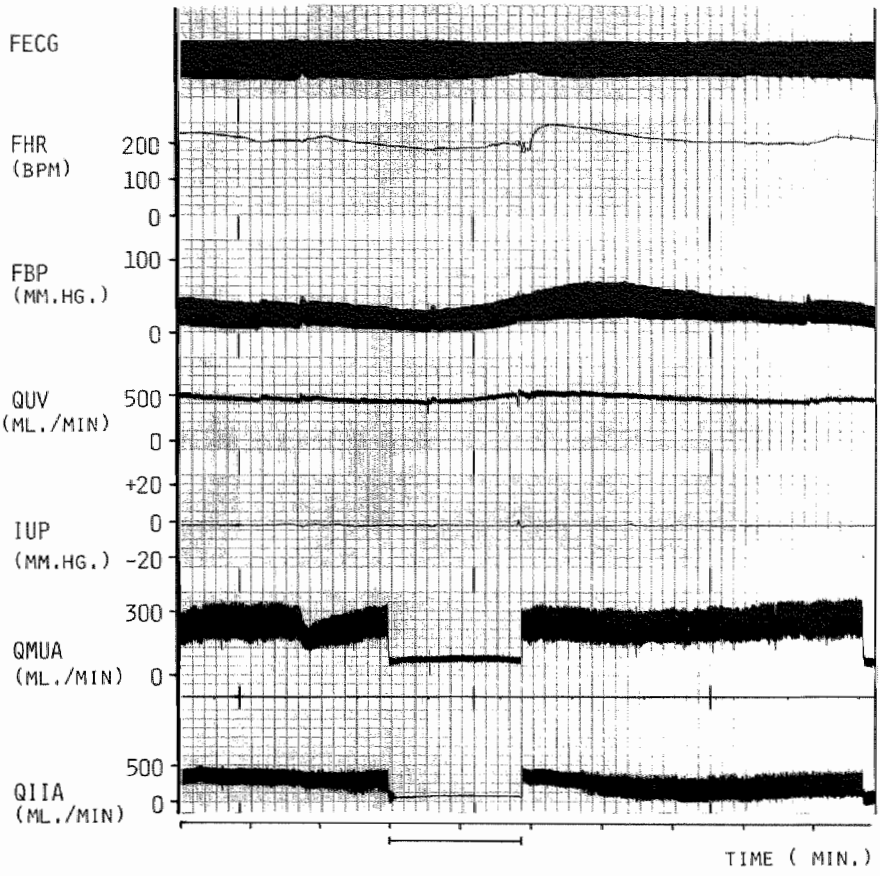
3.5.3.1 Cholinergic blockade with atropine

The data on gestational age and number of days after surgery at the time of the experiment and the duration of the occlusion for the total group are depicted in table 3.7.

CHOLINERGIC BLOCKADE	MEAN ± SD	RANGE
GESTATIONAL AGE (DAYS)	118.5 ± 2.1	114 - 130
TIME AFTER SURGERY (DAYS)	5.5 ± 2.1	3 - 19
OCCLUSION TIME (SECONDS)	78 ± 4.8	30 - 120

TABLE 3.7 GESTATIONAL AGE, TIME AFTER SURGERY AND OCCLUSION TIME OF THE 17 OCCLUSIONS OF THE COMMON INTERNAL ILIAC ARTERY, PERFORMED IN 6 ANIMALS AFTER CHOLINERGIC BLOCKADE.

Fig. 3.9 shows a typical recording of an occlusion response after atropine administration: no decrease in heart rate and an increase in arterial blood pressure and umbilical venous blood flow. Mean values ± SD of fetal heart rate, arterial blood pressure and umbilical venous blood flow in a single occlusion experiment are given in fig. 3.10.
A composite analysis of the data on fetal heart rate, arterial blood pressure and umbilical venous blood flow from the total group of occlusions during cholinergic blockade is given in fig. 3.11.
An increase in fetal heart rate of 7.7% from 209 bpm to 225 bpm was seen at the end of the occlusion ($p<0.02$), followed by the maximum response (9.1%) at 10 seconds after the occlusion ($p<0.05$), after which a slow return towards control level occurred at two minutes.
Arterial blood pressure also increased with a maximum response of 9.2% (from 40.3 to 44 mm Hg) at the end of the occlusion, after which a fast decrease to the control value was found at 2 minutes.



EWE 8308 GESTATIONAL AGE 120 4 DAYS P.O.

FIG. 3.9 CHANGES IN HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶) AFTER CHOLINERGIC BLOCKADE WITH ATROPINE.

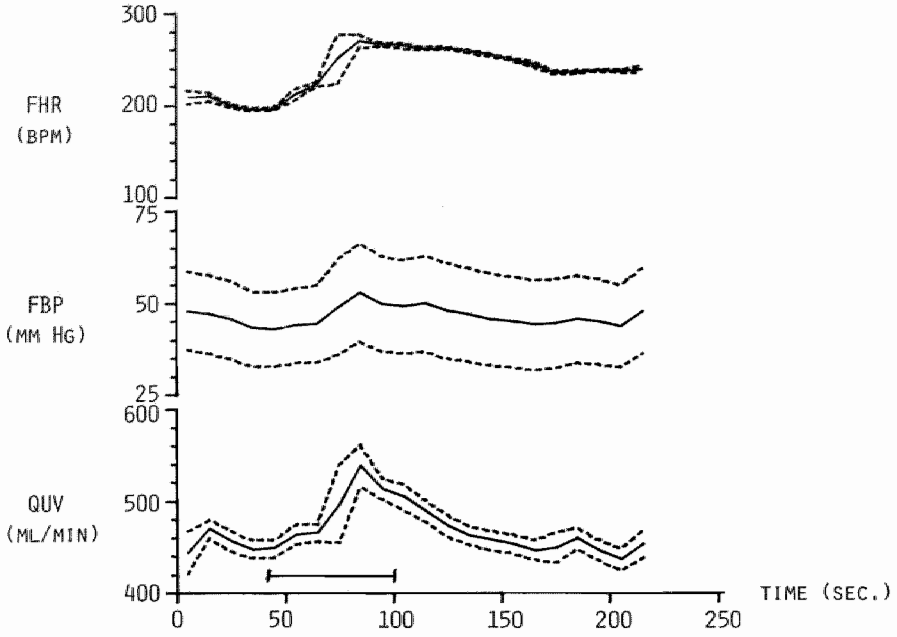


FIG. 3.10 THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶) AFTER CHOLINERGIC BLOCKADE WITH ATROPINE. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

Umbilical venous blood flow followed the increase in heart rate and blood pressure with a significant increase ($p<0.002$) of 9.6% from 503 ml/min at control to 551 ml/min at the end of the occlusion. Umbilical blood flow was also significant higher than the control value at 10 seconds post infusion. By 2 minutes umbilical blood flow had completely returned to pre-occlusion values.

The composite analysis (fig. 3.12) of the fetal cardiovascular parameters of subgroup 1 (5 occlusions in 3 animals) did not differ in general from that of the total group, except that only the increase in blood flow (8.6%) was significantly different from control ($p<0.05$). This is probably due to the small number of observations (5 occlusions in 3 animals).

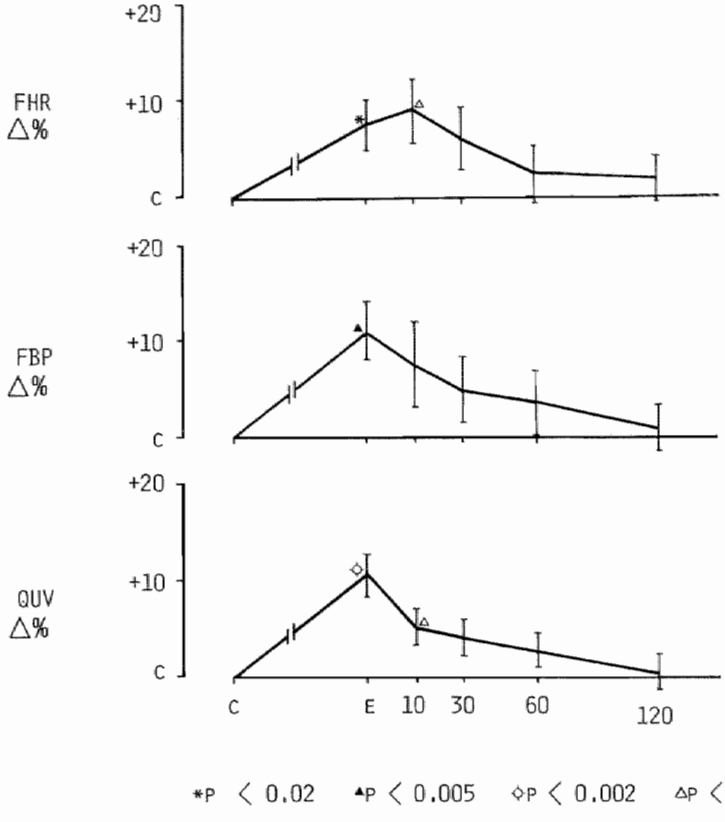


FIG 3.11 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN THE TOTAL GROUP OF OCCLUSIONS AFTER CHOLINERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

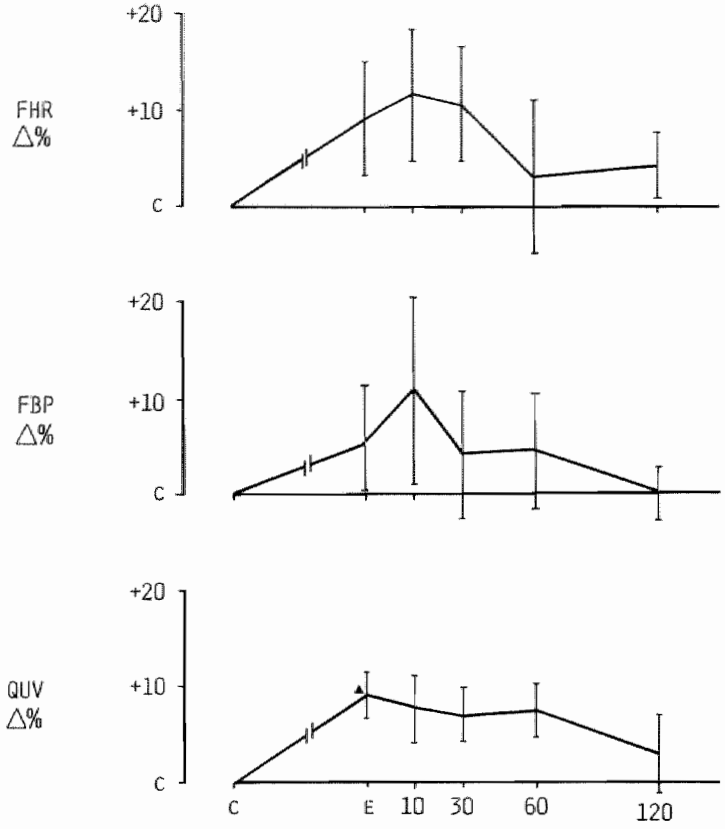


FIG 3.12 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN SUBGROUP I WITH CHOLINERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

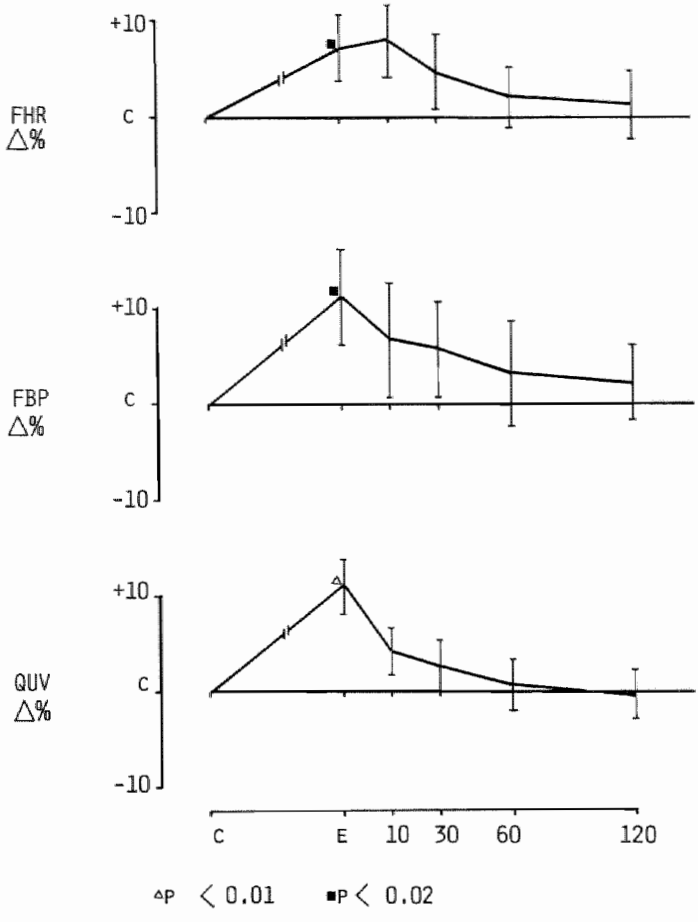


FIG 3.13 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN SUBGROUP II WITH CHOLINERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

The same changes in fetal heart rate, arterial blood pressure and umbilical venous blood flow were also seen in subgroup 2 (12 occlusions in 4 animals). Both heart rate and blood pressure and also umbilical blood flow increased with a significant increase in heart rate of 6.9% ($p<0.05$), in blood pressure of 11.1% ($p<0.02$) and in umbilical blood flow of 10.1% ($p<0.01$) at the end of the occlusion (fig. 3.13).
In 4 of the individual 12 occlusions of subgroup 2 still a deceleration in the heart rate was seen, although it was small.
The increase in umbilical blood flow was more prolonged in group I than in group II.

3.5.3.2 Alpha-adrenergic blockade with phentolamine

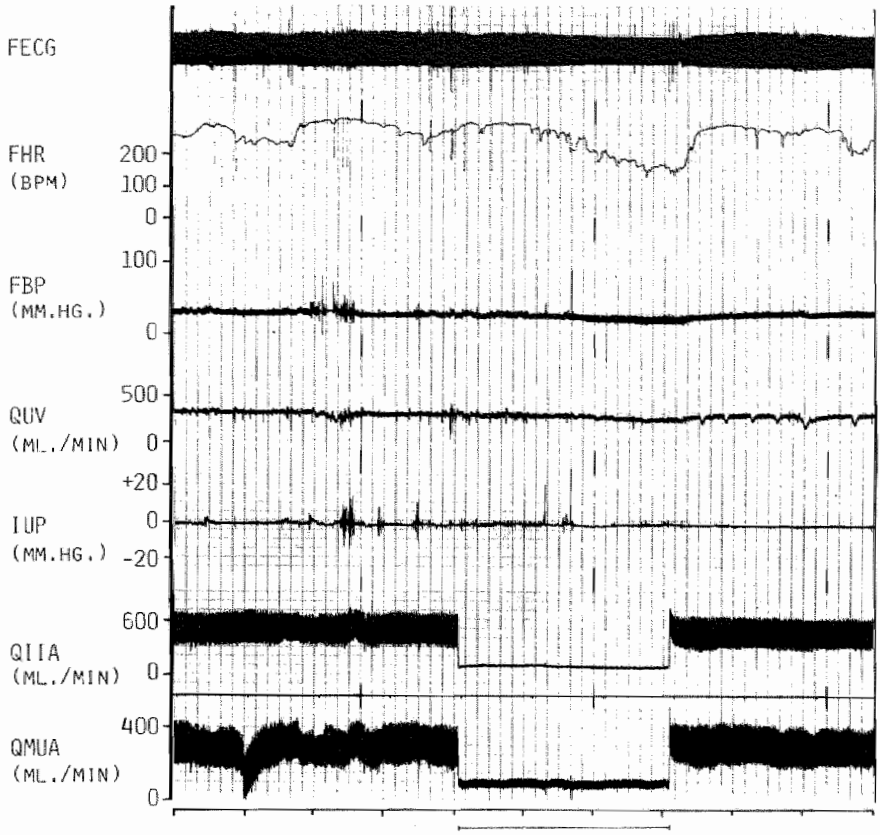
Table 3.8 shows the data on gestational age and number of days after surgery at the time of the experiment as well as the duration of the occlusion for the total group.

ALPHA-ADRENERGIC BLOCKADE	MEAN ± SD	RANGE
GESTATIONAL AGE (DAYS)	117.9 ± 2.3	115 - 138
TIME AFTER SURGERY (DAYS)	8.9 ± 2.7	3 - 28
OCCLUSION TIME (SECONDS)	106.8 ± 7.9	50 - 250

TABLE 3.8 GESTATIONAL AGE, TIME AFTER SURGERY AND OCCLUSION TIME OF THE 19 OCCLUSIONS OF THE COMMON INTERNAL ILIAC ARTERY , PERFORMED IN 6 ANIMALS AFTER ALPHA-ADRENERGIC BLOCKADE.

The decrease in fetal heart rate upon interruption of the uterine blood supply after alpha-adrenergic blockade varied in magnitude from very small decreases in heart rate followed by accelerations to deep decelerations. Figure 3.14 shows an example of a typical recording of a

deep deceleration after alpha-adrenergic blockade.



EWE 8317 GESTATIONAL AGE 115 5 DAYS P.O.

FIG. 3.14 CHANGES IN HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶) AFTER ALPHA-ADRENERGIC BLOCKADE WITH PHENTOLAMINE.

Figures 3.15 and 3.16 show the calculated means ± SD over intervals of 10 seconds in respectively an experiment without and with a deceleration during occlusion.
Fetal blood pressure decreased in all instances upon a common internal iliac artery occlusion.

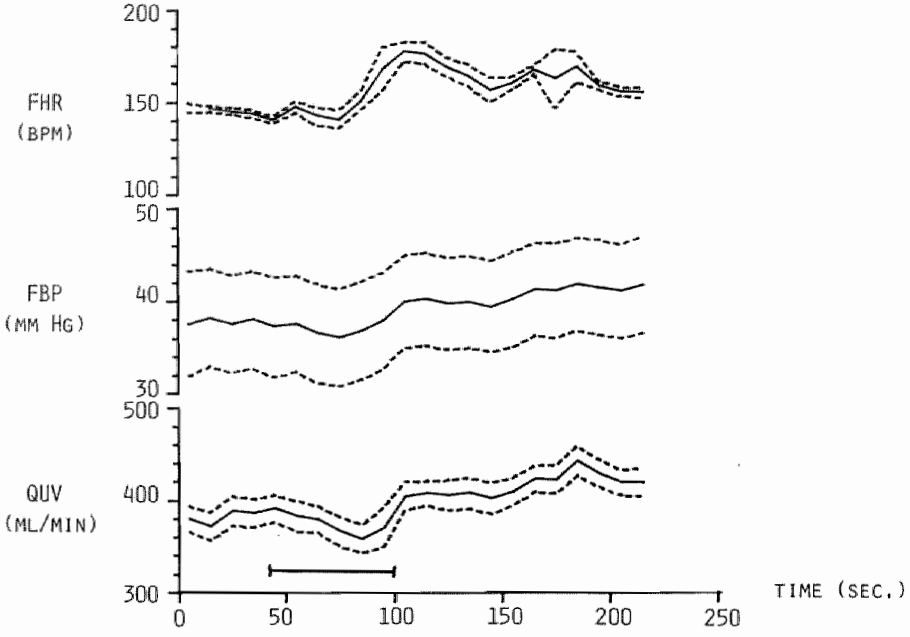


FIG. 3.15 THE ABSENCE OF A FETAL HEART RATE DECELERATION DURING OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶) AFTER PHENTOLAMINE ADMINISTRATION TO A FETUS OF GROUP I. NOTE THE DECREASE IN BLOOD PRESSURE WITH THE CONCOMITANT FALL IN UMBILICAL BLOOD FLOW. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

A composite analysis of the fetal cardiovascular variables of the total group of occlusions during alpha-adrenergic blockade is given in figure 3.17.
Fetal heart rate decreased significantly ($p<0.01$) from 206 bpm to 169 bpm (=82% of control) at the end of the occlusion after which a fast return occurred to the control value.

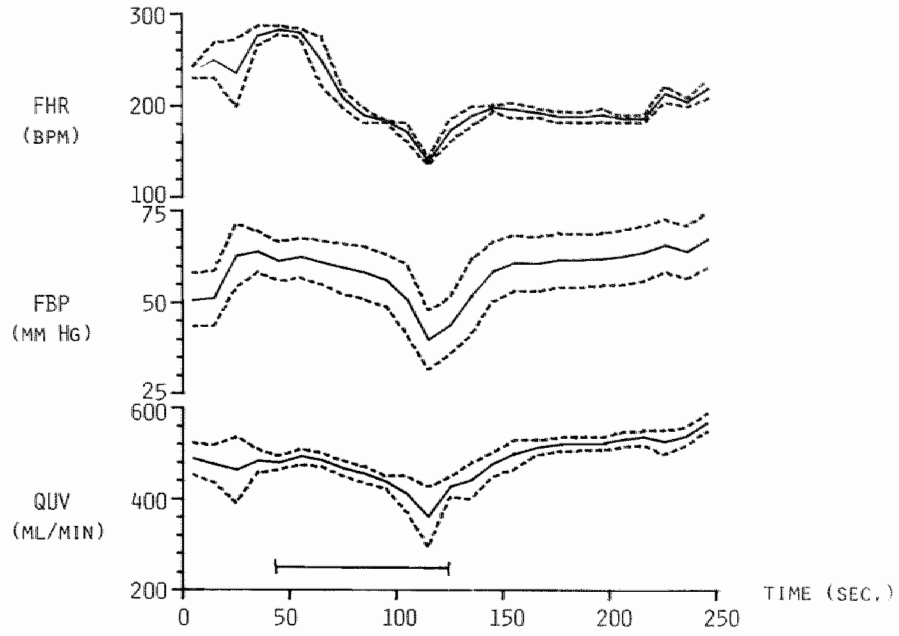


FIG. 3.16 A DECREASE IN FETAL HEART RATE DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⊢—⊣) AFTER PHENTOLAMINE ADMINISTRATION TO A FETUS OF GROUP II. NOTE THE DEEP FALL IN BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

Arterial blood pressure showed a marked decrease at the end of the occlusion from 39.6 mm Hg to 34.2 mm Hg (=86.4% of control), followed by a slower return to and above the control value at two minutes.
Umbilical venous blood flow also decreased (9.6%) with its nadir at the end of the occlusion, at which time blood flow had decreased from 458 ml/min to 409 ml /min ($p<0.002$).
At two minutes after the end of the occlusion umbilical blood flow was significantly higher (7.6%) than its control value ($p<0.01$).

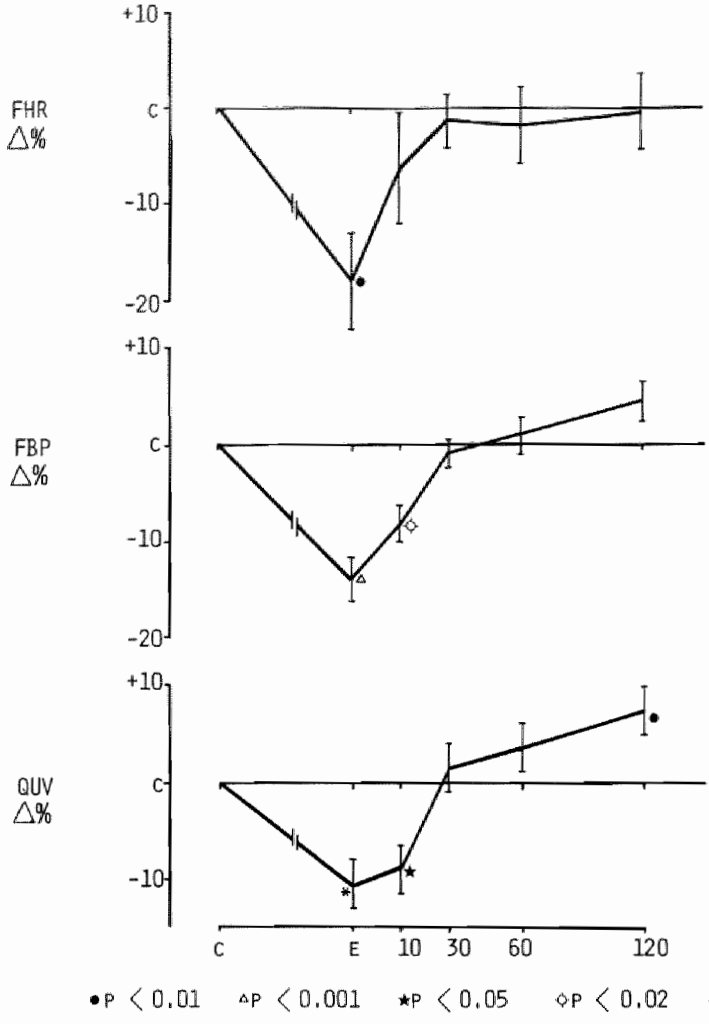


FIG. 3.17 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN THE TOTAL GROUP OF OCCLUSIONS AFTER ALPHA-ADRENERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

Dividing the total group into its two subgroups 1 and 2 according to the criteria summoned in paragraph 3.4.3 revealed a remarkable distinction between these two subgroups.

In subgroup 1 (10 occlusions in 3 animals) only a small decrease in heart rate was found at the end of the occlusion followed by a marked although not significant increase of 11.5% over control level at 10 seconds post occlusion, followed by a return to the control value at two minutes (fig. 3.18).
Arterial blood pressure decreased and reached its nadir (29.7 mm Hg = 88.7% of the control value) at the end of the occlusion ($p<0.01$).
Blood pressure was slightly but not significantly elevated over control level at two minutes post occlusion.
Umbilical venous blood flow showed only a slight but nonsignificant decrease at the end of the occlusion after which a slight increase over control level followed parallel with the changes in heart rate and blood pressure (fig. 3.18).

Figure 3.19 shows the composite analysis from the same fetal hemodynamic variables from subgroup 2 (9 occlusions in 3 animals). There is an obvious difference in magnitude of the changes between the two subgroups. The decrease in heart rate at the end of the occlusion is much greater in subgroup 2 than in subgroup 1. Fetal heart rate decreased from 212 bpm to 150 bpm (=71 % of control ; $p<0.01$) at the end of occlusion. Fetal heart rate was also significantly ($p<0.01$) decreased at 10 seconds post occlusion, at which time an acceleration occurred in subgroup 1. At two minutes post occlusion the control value had been reached again.
Fetal blood pressure decreased from 46.3 mm Hg to 39.1 mm Hg (=84.4% of control) at the end of the occlusion ($p<0.02$). A small overshoot in pressure was seen at 2 minutes post occlusion.
Umbilical venous blood flow parallelled these pressure changes. The lowest flow value (460 ml/min =84.0% of control; $p<0.02$) was recorded at the end of the occlusion followed by a rapid return to control value at 30 seconds whereafter a significant ($p<0.02$) increase (10.4%) in blood flow over control level was found at two minutes post occlusion.

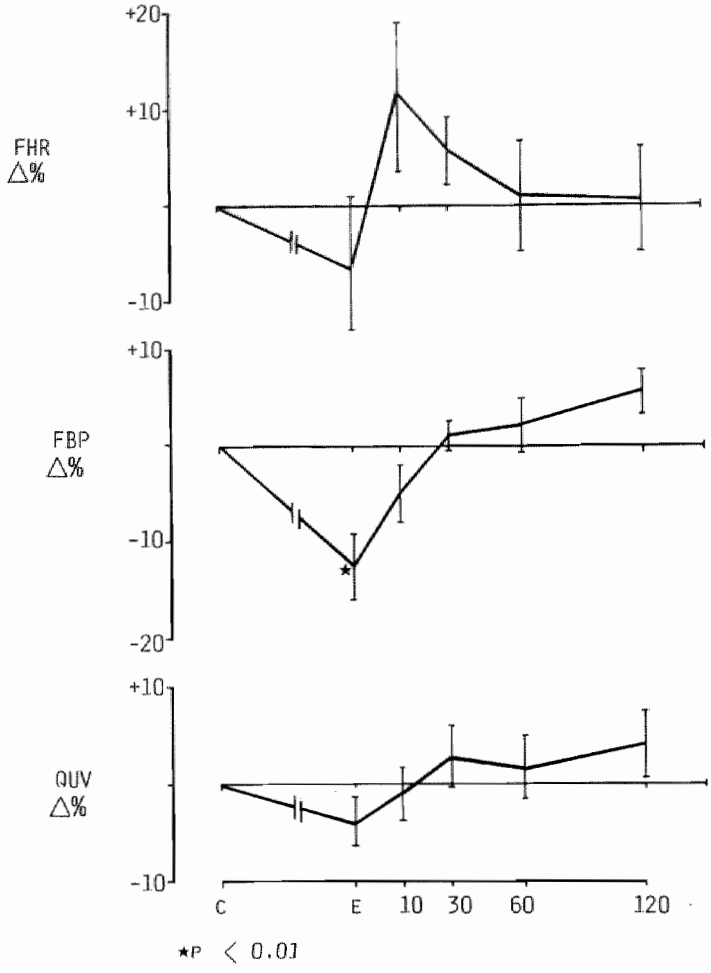


FIG. 3.18 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW, DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN SUBGROUP I WITH ALPHA-ADRENERGIC BLOCKADE THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

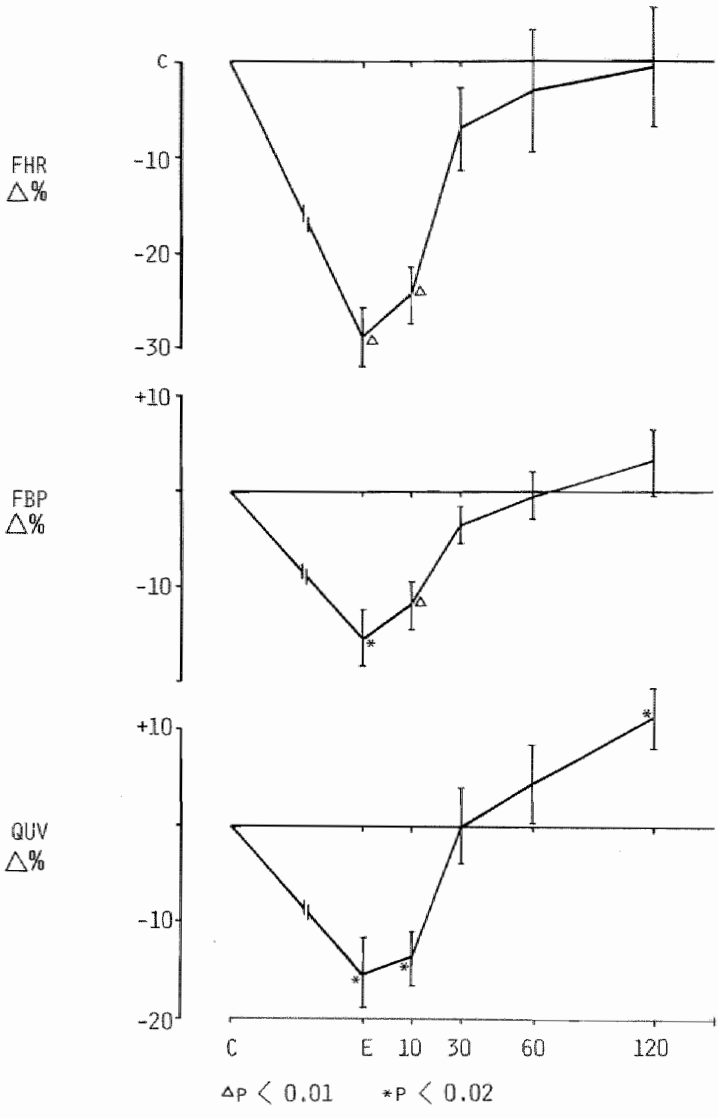


FIG 3.19 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN SUBGROUP II WITH ALPHA-ADRENERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

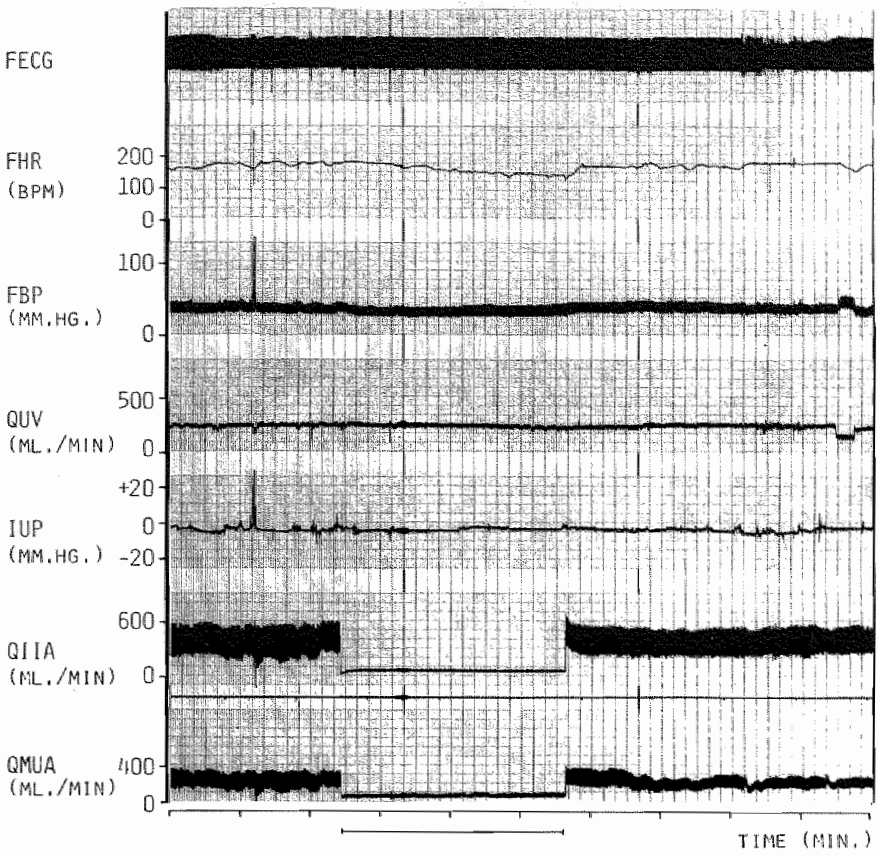
3.5.3.3 Beta-adrenergic blockade with propranolol

Table 3.9 shows the data on gestational age, number of days after surgery at the time of the experiments as well as the duration of the occlusion time in the total group. The occlusion time in the propranolol group was longer than in the other groups for two reasons. Firstly the onset and the progress of the heart rate decrease was more gradual after beta-adrenergic blockade which made the early recognition of the deceleration during experimentation more difficult and secondly the occlusions took place in animals in which in general a longer occlusion time was needed to establish any heart rate change (fig. 3.20).

BETA-ADRENERGIC BLOCKADE	MEAN ± SD	RANGE
GESTATIONAL AGE (DAYS)	119.1 ± 2.4	114 - 136
TIME AFTER SURGERY (DAYS)	7.8 ± 2.5	4 - 26
OCCLUSION TIME (SECONDS)	161 ± 9.7	50 - 340

TABLE 3.9 GESTATIONAL AGE, TIME AFTER SURGERY AND OCCLUSION TIME OF THE 16 OCCLUSIONS OF THE COMMON INTERNAL ILIAC ARTERY , PERFORMED IN 5 ANIMALS AFTER BETA-ADRENERGIC BLOCKADE.

The composite analysis of the cardiovascular parameters of the total group of occlusions during beta-adrenergic blockade in fig. 3.21 show a maximum decrease in heart rate of 19.2% ($p<0.002$) at the end of the occlusion (from 167 bpm to 136 bpm).
Blood pressure increased from the end of the occlusion onwards to a peak at 30 seconds (6.5% increase above control from 40.1 to 42.8 mm Hg; $p<0.02$).



EWE 8317 GESTATIONAL AGE 114 4 DAYS P.O.

FIG. 3.20 A DISTINCT DECREASE IN HEART RATE DURING A PROLONGED OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶) AFTER BETA-ADRENERGIC BLOCKADE WITH PROPRANOLOL. NOTE THE SLIGHT INCREASE IN BLOOD PRESSURE AND THE SMALL DECREASE IN UMBILICAL BLOOD FLOW AT THE END OF THE OCCLUSION.

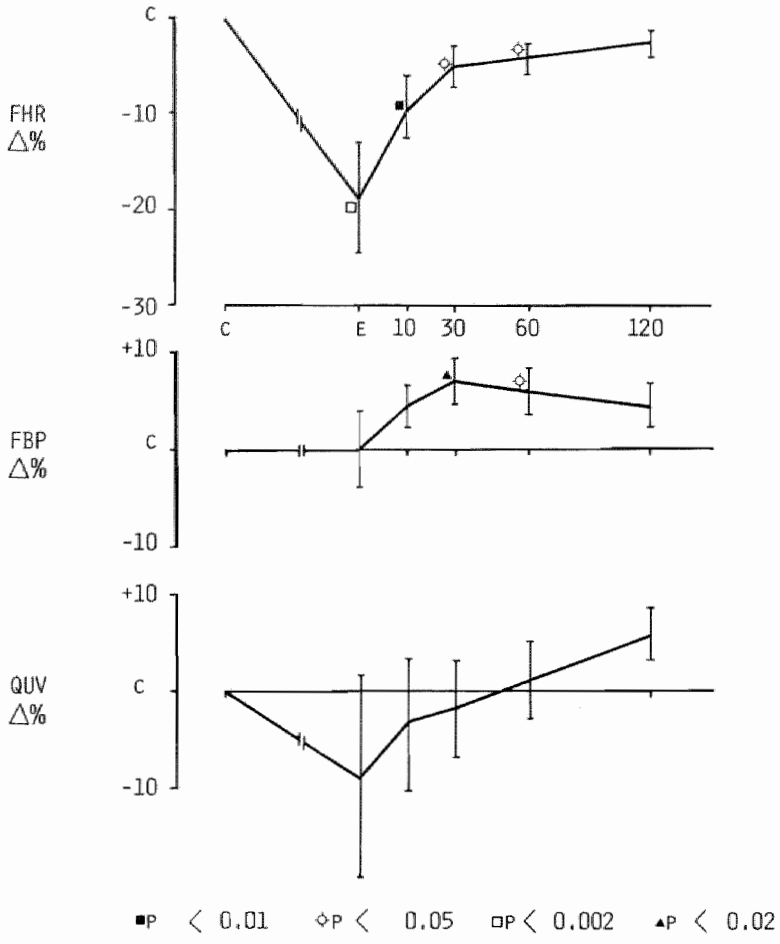


FIG 3.21 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN THE TOTAL GROUP OF OCCLUSIONS AFTER BETA-ADRENERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

Umbilical venous blood flow was slightly decreased at the end of the occlusion, followed by a return to control value at 30 seconds and a small overshoot above control level at two minutes. The changes in umbilical venous blood flow reached no level of significance.

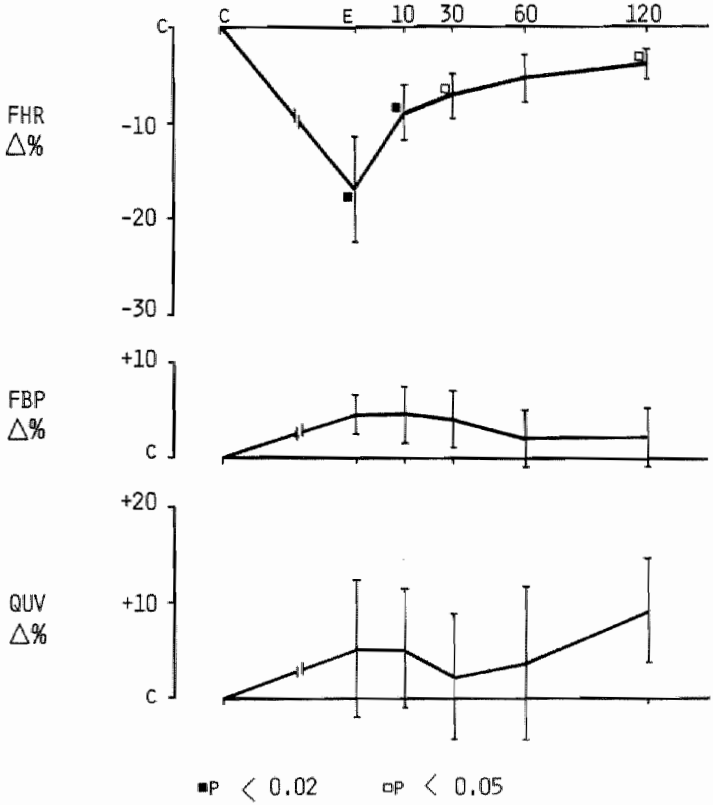


FIG 3.22 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN SUBGROUP I WITH BETA-ADRENERGIC BLOCKADE. THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

Again a difference was seen in the reaction patterns after dividing the total group in its two subgroups 1 and 2 (figures 3.22 and 3.23).
Subgroup 1 (8 occlusions in 4 animals) reacted with a deceleration in heart rate and an increase in both arterial blood pressure and umbilical blood flow.
The fetal heart rate changes were significant at the $p<0.02$ level at the end of the occlusion and at 10 seconds post occlusion. The nadir in heart rate was seen at the end of the occlusion (82.6% of control, a decrease from 173 to 143 bpm).
The changes in umbilical blood flow and arterial blood pressure did not reach any level of significance (fig. 3.22).
The composite analysis of subgroup 2 (7 occlusions in 2 animals) shows the same degree and course in the heart rate change as with subgroup 1. Arterial blood pressure however decreased at the end of the occlusion (from 38.6 mm Hg to 36.6 mm Hg), parallel with a decrease in umbilical venous blood flow of 23.1% to 338 ml/min at the end of the occlusion ($p<0.05$).
Arterial blood pressure increased in the recovery period to 9.6% ($p<0.05$) and 9.8% ($p<0.05$) above control at respectively 30 and 60 seconds post occlusion.
Umbilical blood flow slowly returned to pre occlusion values at 2 minutes after the end of the occlusion (fig. 3.23).
The changes in heart rate failed to reach a significant level. This was probably due to the small number of observations with a great standard deviation of the calculated mean.
Heart rhythm disturbances were seen in both subgroups especially during longer lasting occlusions.

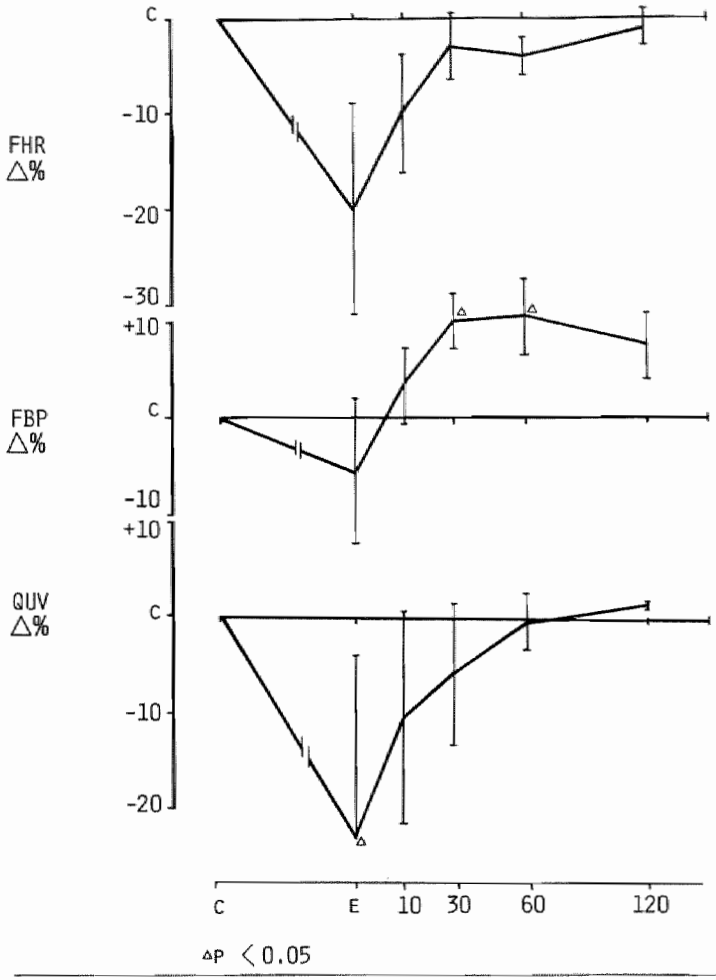
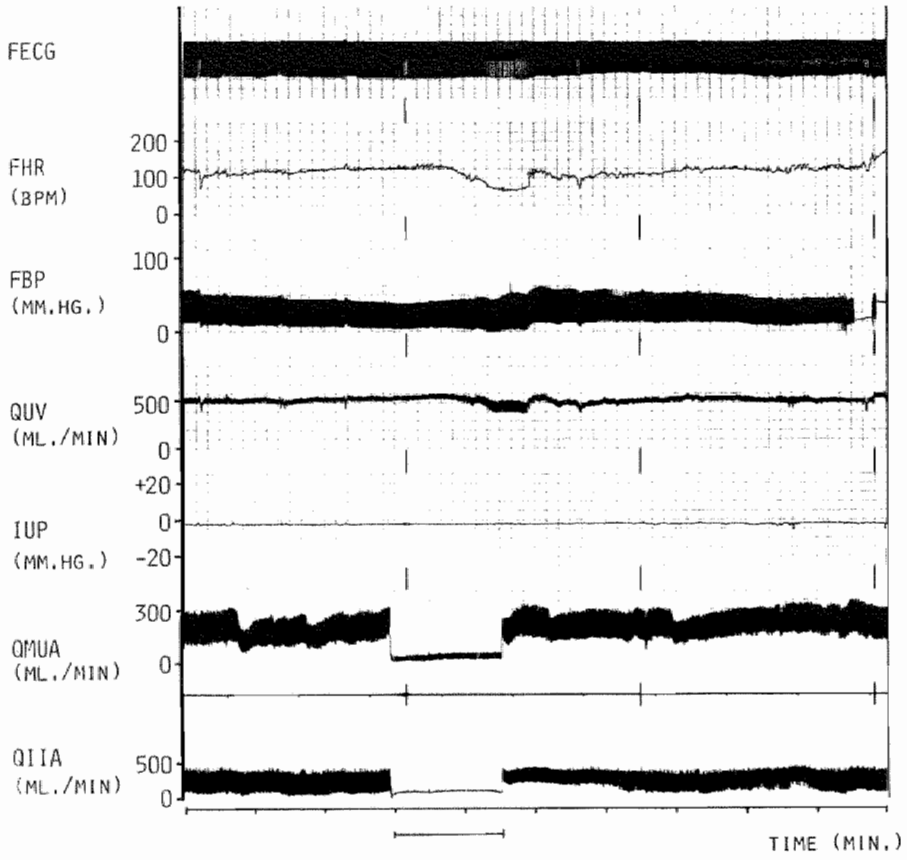


FIG 3.23 A COMPOSITE ANALYSIS OF THE CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING AND AFTER THE OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY IN SUBGROUP II WITH BETA-ADRENERGIC BLOCKADE THE VERTICAL BARS BETWEEN C AND E REPRESENT THE VARIATION IN OCCLUSION TIME.

3.6 Instantaneous umbilical venous blood flow patterns during occlusions of the maternal common internal iliac artery

During the fetal bradycardia associated with the maternal common internal iliac artery occlusion, biphasic pulsations in line with fetal heart rate occurred in the phasic umbilical venous blood flow pattern. These pulsations occurred both in the group with a hypertensive response as well as in the group with a hypotensive response during the occlusion (fig. 3.24). These pulsations were in line with fetal heart

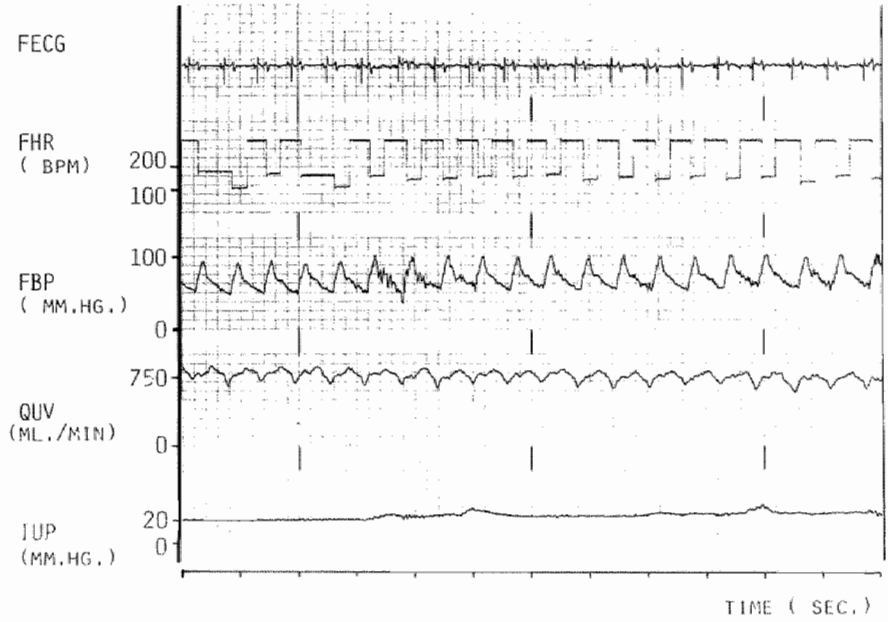


EWE 8308 GESTATIONAL AGE 120 4 DAYS P.O.

FIG. 3.24 THE OCCURRENCE OF PULSATIONS IN THE UMBILICAL VENOUS BLOOD FLOW PATTERN DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY (⟵⟶).

rate and consisted of two forward surges of venous flow, one smaller simultaneous with the ventricular systole and a component greater in amplitude during ventricular diastole. After the diastolic flow surge a decrease in flow occurred followed by an increase during the following ventricular systole (fig. 3.25).

These biphasic pulsations gradually decreased and eventually disappeared during the recovery phase in the fetal heart rate deceleration and thereafter.



EWE 8210 GESTATIONAL AGE 134 9 DAYS P.O.

FIG. 3.25 THE OCCURRENCE OF BIPHASIC PULSATIONS IN THE COMMON UMBILICAL VEIN FLOW IN LINE WITH FETAL HEART RATE DURING AN OCCLUSION OF THE COMMON INTERNAL ILIAC ARTERY. NOTE THE DIFFERENCE IN SYSTOLIC AND DIASTOLIC FLOW SURGE.

3.7 Discussion

3.7.1 Intact autonomic nervous system

Occlusion of the common internal iliac artery caused in sixty nine of the seventy five occlusions with an intact fetal autonomic nervous system a late deceleration in the fetal heart rate. These interruptions of the uterine blood flow led to a decrease in the fetal oxygen status from normoxemia to a very mild hypoxemia at the end of each series of occlusions, together with the development of a mild hypercapnia and a decrease in fetal arterial pH. The degree of hypoxemia which was reached during each individual occlusion is not known in these experiments, but may have varied substantially.

The fetal cardiovascular reaction pattern upon the decline in uterine blood flow could be divided in a group with an increase in arterial blood pressure and umbilical venous blood flow and a group with a decrease of these parameters during a late deceleration. If the reduction in uterine blood flow was associated with an increase in fetal arterial blood pressure, then also a significant increase in umbilical blood flow was present. This indicates that the fetus who is capable of increasing its blood pressure during a late deceleration is also capable of increasing its umbilical blood flow thereby probably safeguarding its oxygen needs.

Increases in arterial blood pressure during late decelerations in normoxemic fetal lambs under chronic experimental conditions have also been reported by others (Evers 1978, Martin et al 1979, de Haan et al 1979).

Parer et al (1980) found in a study with short reductions in maternal aortic blood flow of 20 seconds duration in normoxemic fetal lambs (pO_2 = 20 mm Hg) no significant changes in fetal arterial blood pressure. No significant change in umbilical arterial blood flow was found as measured with an electromagnetic flow transducer around the common umbilical artery in that study. This might be explained by the absence of a blood pressure response with the late decelerations.

In the group which showed a decrease in arterial blood pressure (=group two, paragraph 3.5.2) the deceleration of the heart rate was greater

than in the group which showed an increase in arterial blood pressure during the late decelerations (=group one, paragraph 3.5.2). In contrast to the increase in umbilical blood flow in group I, a highly significant reduction in umbilical blood flow was noted together with a decrease in arterial blood pressure in this group II.

A decrease in arterial blood pressure during late decelerations can be seen in hypoxemic and/or acidemic fetuses, followed by a secondary late increase in blood pressure during the recovery period (de Haan et al 1979, Martin et al 1979, Harris et al 1982, Itskovitz et al 1982a).

The induced hypoxemia in such a condition may lead to a decrease in myocardial oxygen supply with a negative effect on the sinoatrial node (Senges et al 1979) which condition is in part responsible for the bradycardia of the late deceleration (Itskovitz et al 1982a, Harris et al 1982) and with a negative influence on the contraction force of the myocardium.

A diminished cardiac performance during the bradycardia may then be responsible for the decrease in arterial blood pressure and the subsequent fall in umbilical blood flow, as it has been shown that umbilical blood flow is positively correlated with arterial perfusion pressure (Berman et al 1976).

Although the fetuses from both the group (I) with an increase in umbilical blood flow as well as the group (II) with a decrease in flow had acid-base balances in the normal range, while in fact that part of group II whose blood gases could be analysed even had higher pO_2 and pH values, the degree of fetal hypoxemia during the occlusion is not known. It is likely in view of the present knowledge that fetal hypoxemia reached during the occlusion was more severe in the group with the umbilical flow decrease.

The overall condition of the fetuses from group I might furthermore have been better. Indirect evidence for this assumption is the fact that the delay between the start of the occlusion and the beginning of the fetal heart rate decline was longer in group I than in group II, which can also be inferred from the longer mean occlusion time in group I.

Another difference is the interval between surgery and the moment of the experiment, which was much longer (10 $\pm$ 2.7 days) for group I than

group II (6.7 ± 2.2 days). A better "physiological" condition of the fetus might be expected after a longer recovery from surgery. Furthermore the transition of a reactive hypertension during the first occlusions towards a decrease in blood pressure during the last occlusions in five experimental sessions also indicates a relation between the blood pressure response and the fetal condition during an occlusion of the common internal iliac artery.

An alternative explanation of the difference in blood pressure and flow responses between the 2 groups might be that a lesser degree of hypoxemia in group II (in keeping with the higher starting and ending pH and pO_2 values) might have caused less stimulation of the chemoreceptors and failed to activate other mechanisms such as vasopressin release (Iwamoto et al 1979), resulting in cardiodeceleration with minimal vasoconstriction and blood flow redistribution. Besides the higher pH and pO_2 values, the more rapid return of arterial pressure and umbilical blood flow to control levels in group II would seem to support this explanation. Against this concept, however, are the shorter occlusion-deceleration delay time in group II (Itskovitz et al 1982a), and also the fact that when transitions in response pattern occurred during an experiment, they were always from the hypertensive to the hypotensive pattern (see also 3.7.2 and 3.7.3).

As the fetuses from both groups were studied in the same period of gestation, no specific differences in the development of reflex mechanisms are to be expected between the two groups, especially since the autonomic control of the fetal circulation is fully operational at the time of gestation at which the fetuses were studied (Vapaavouri et al 1973, Nuwayhid et al 1975a).

Decreases in arterial umbilical blood flow and arterial blood pressure were reported by Harris et al (1982) during late decelerations accomplished by short reductions (20 seconds duration) of maternal aortic blood flow in hypoxemic fetuses.

No significant changes in umbilical vascular resistance during late decelerations produced by short lasting maternal aortic occlusion were found by Parer et al (1980) in normoxemic fetal lambs. General maternal and fetal hypoxemia induced by breathing of a low oxygen gas mixture by

the ewe, on the other hand caused a small increase in umbilical vascular resistance in the study by Cohn et al (1982), while umbilical blood flow was maintained by redistribution of cardiac output and increased arterial blood pressure.
The changes in the umbilical venous blood flow during the heart rate decelerations parallelled the changes in the arterial driving pressure. Whether umbilical vascular resistance changed during the common internal iliac artery occlusions in this study is not known, as umbilical venous pressure was not measured.
It is however obvious that possible changes in umbilical vascular resistance associated with the internal iliac artery occlusions had no serious adverse effect on umbilical venous blood flow, if fetal arterial blood pressure increased towards the end of the occlusion (group 1). Although the decrease in umbilical venous blood flow at the end of the occlusion period in group 2 can be explained by the concomitant fall in arterial blood pressure, an increased umbilical vascular resistance might possibly have added to this fall in blood flow. It is known, that umbilical vascular resistance increases during a more severe degree of hypoxemia (Cohn et al 1982), a supposed causative factor in the hemodynamic changes occurring in group 2 of this study.

3.7.2 Cholinergic blockade with atropine

The composite analyses of both subgroups show that cholinergic blockade with atropine abolished the late deceleration in both subgroups and instead a delayed acceleration in heart rate occurred.
The fact that the late deceleration could completely be blocked by atropine in all individual occlusions belonging to subgroup 1 shows that the vagal mediated cardiodecelerator reflexmechanism was still present in this group. The mean data of all occlusions from subgroup 2 also show the absence of a fetal heart decrease. In 4 individual occlusions of the 12 occlusions from this group however the occurrence of a bradycardia was not completely prevented by atropine although the degree of heart rate slowing was reduced. This indicates that hypoxic myocardial depression was a serious causative factor in the heart rate

deceleration associated with these occlusions, otherwise the heart rate depression would have been completely blocked after cholinergic blockade (Martin et al 1979, de Haan et al 1979, Harris et al 1982).
Arterial blood pressure increased in both subgroups. This was expected in the experiments of subgroup 1. However no decrease but also a small increase in blood pressure was found in the experiments belonging to subgroup 2.
This was probably the result of the increased heart rate in combination with the arterial blood pressure raising effect of atropine in higher doses (Goodman and Gilman 1975).
The changes in umbilical venous blood flow are caused by the concomitant increases in heart rate and arterial blood pressure in both subgroups.

3.7.3 Alpha-adrenergic blockade with phentolamine

Alpha-adrenergic blockade with phentolamine prevented the peripheral chemoreceptor mediated reflex vasoconstriction.
Blood pressure thus fell in both subgroups but this decrease was more severe in subgroup 2. Any decrease in heart rate was minimal in subgroup 1 and was followed by an acceleration after the occlusion, but a severe and prolonged deceleration with a slow recovery of the heart rate was seen in subgroup 2.
After the primary vagally mediated heart rate decrease due to chemoreceptor activity, a second causative step is the hypertension associated baroreflex induced cardiac slowing. The absence of a hypertensive response after alpha-adrenergic blockade explains the absence of heart rate decelerations in subgroup 1. The deep heart rate deceleration in subgroup 2 suggests then that in this group a chemoreceptor mediated cardiac slowing response was present and probably an additional direct depression of myocardial chronotropism, which is in accordance with the assumption that fetal hypoxemia during the occlusion was more severe in subgroup 2. The difference in heart rate between the two groups during and after the occlusion explains the more depressed umbilical blood flow in subgroup 2 with a nearly equal fall in blood pressure in both groups.

An increase in umbilical vascular resistance can not be ruled out, but if this had happened, then it would be associated with the developing fetal hypoxemia as alpha-adrenergic blockade per se does not influence umbilical vascular resistance (see paragraph 5.4.1.2).

3.7.4 Beta-adrenergic blockade with propranolol

Beta-adrenergic blockade with propranolol did not essentially alter the hemodynamic responses in the two subgroups. Umbilical blood flow and arterial blood pressure increased during the heart rate deceleration under beta blockade. It has been suggested that the basal flow in the umbilical vascular bed is under a tonic beta- adrenergic influence (Chez et al 1978, Cohn et al 1982) and decreases after beta-adrenergic blockade with propranolol (see also paragraph 5.4.1.3). Beta-adrenergic blockade however did not prevent umbilical venous blood flow to increase parallel with arterial blood pressure during the heart rate deceleration in subgroup 1. The fall in umbilical blood flow in subgroup 2 was relatively great in view of the concomitant changes in heart rate and blood pressure.

A much greater increase in umbilical vascular resistance after beta-adrenergic blockade with propranolol was found by Cohn et al (1982) and Parer et al (1983) during fetal hypoxemia than with beta-adrenergic blockade or fetal hypoxemia alone. Their findings suggest that beta-adrenergic activity is increased during hypoxemia, probably in order to maintain fetal heart rate and umbilical blood flow. The relatively great decrease in umbilical blood flow in subgroup 2 can then be explained on the basis of a considerably increased umbilical vascular resistance, provided that the assumption of a more severe fetal hypoxemia in subgroup 2 is correct.

3.7.5 Changes in the instantaneous umbilical venous blood flow during occlusions of the common internal iliac artery

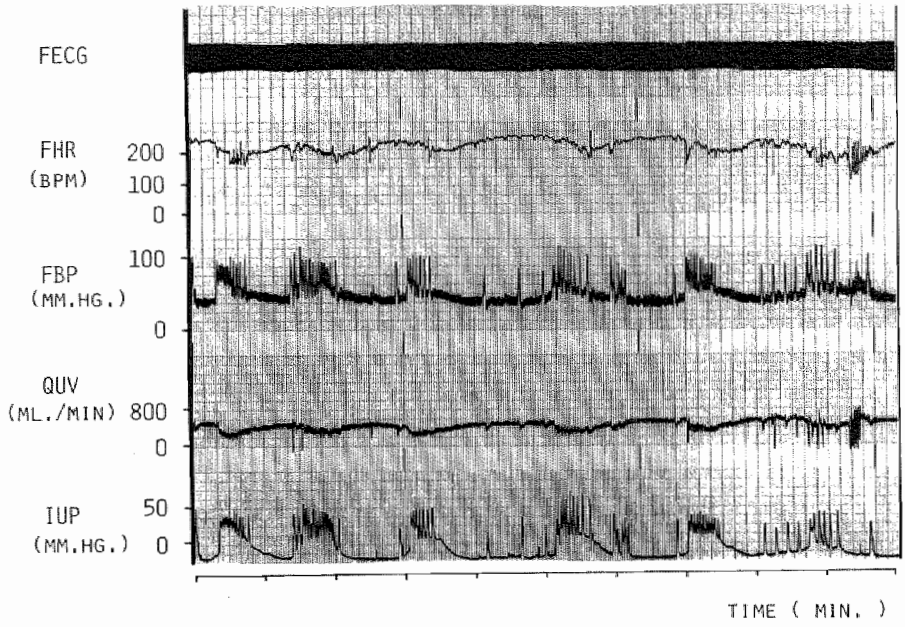
Umbilical venous blood flow shows no or only minimal pulsations unless fetal respiratory or other activity is present.

Situations which increase the amplitudes of the always pulsatile flow pattern in the venae cavae (Reuss et al 1983), may provoke pulsations in the common umbilical vein by backward propagation through vena cava inferior and ductus venosus Arantii to the common umbilical vein. The nature of these pulsations, the circumstances under which they occur and their possible consequence for fetal hemodynamics will be discussed in chapter 5.
In this paragraph it suffices therefore to say that the greater flow surge during ventricular diastole can be explained by the slow heart rate, allowing a longer atrial filling phase during diastole.

The results of this study show that fetal umbilical venous blood flow may increase or decrease during late decelerations of the fetal heart rate caused by uterine blood flow obstruction.
The direction of the blood flow change is mainly determined by the concomitant change in perfusion pressure, and to a lesser extent by the magnitude of the heart rate change. The influence of possible changes in umbilical vascular resistance is not known from this study. The occurrence of a blood pressure decrease during a late deceleration in spite of the very fast appearing chemoreceptor mediated peripheral reflex vasoconstriction implies a decrease in cardiac output, probably resulting from hypoxic myocardial depression. Redistribution of cardiac output which is an important fetal mechanism to provide high-priority tissues as heart and brain with enough blood at the expense of low-priority organs as e.g. viscera and musculoskeletal system, and which mechanism is associated with hypertension, is then endangered.

Observations in 4 animals who got into spontaneous labor and whose fetuses showed late decelerations in their heart rate learnt that umbilical blood flow could be maintained early in the course of labor, when fetal hypertension was present during the heart rate decrease. When fetal condition was however deteriorating in a later stage of labor, arterial hypotension ensued during the late deceleration instead of hypertension and umbilical blood flow decreased.

Figure 3.26 shows part of such a recording with decrease of umbilical blood flow during a late deceleration. After correction for the superimposed intrauterine pressure it is clear that fetal arterial blood pressure decreases during the deceleration. Figure 3.27 shows the mean values ± SD calculated over intervals of 10 seconds of part of the recording shown in fig 3.26.



EWE 8301 GESTATIONAL AGE 143 3 DAYS P.O.

FIG 3.26 LATE DECELERATIONS OF THE FETAL HEART RATE DURING SPONTANEOUS LABOR. UMBILICAL VENOUS BLOOD FLOW DECREASES DURING THE DECELERATIONS. COMPARE WITH FIG. 3.27

Conclusions from animal studies are not automatically applicable to the human, although observations from fetal lamb studies have contributed considerably to the understanding of cardiovascular reaction patterns in the human fetus.

The occurrence of a late deceleration in a human fetus is always an ominous sign, but between a warning signal and danger of life lies a scale of possibilities. The presence of heart rate variability, accelerations upon fetal movements etcetera all qualify the seriousness of the late deceleration to a certain degree. Quantitative analysis of the components of the late deceleration as has been done by Meyers et al (1973) in acute monkey preparations, might in combination with fetal umbilical blood velocity measurements by means of pulsed Doppler systems, open a new approach to the study and the judgment of the late deceleration heart rate pattern in the human.

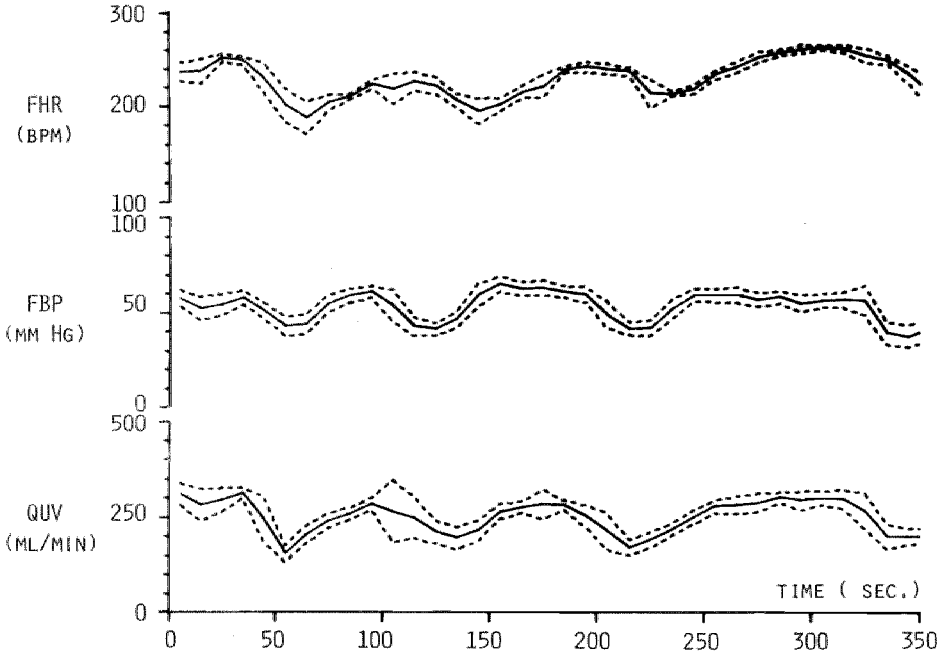


FIG. 3.27 FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING THE LATE DECELERATIONS DEPICTED IN FIG. 3.26. FETAL ARTERIAL BLOOD PRESSURE IS CORRECTED FOR INTRA UTERINE PRESSURE CHANGES. NOTE THE DECREASE IN BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING A LATE DECELERATION. DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS.

CHAPTER IV

UMBILICAL CORD OCCLUSIONS AND UMBILICAL VENOUS AND MATERNAL PELVIC BLOOD FLOW

4.1 Introduction

Transient occlusion of the umbilical cord, recognizable by variable decelerations in the fetal heart rate pattern in human fetuses, often occurs during labor. Entanglement of the cord is one of the major causes of cord occlusion during a contraction, but cord compression can occur in several ways in labor. Cord compression has striking effects on fetal hemodynamics, depending in severity upon the degree and the duration of the occlusion.

The umbilical vein with its relatively low pressure and its nonpulsatile flow is easily compressed by the uterine contraction force. Compression of the umbilical arteries takes more force because of their higher and pulsatile pressure, but complete obstruction of the umbilical cord can probably occur with an uterine contraction. The typical variable deceleration fetal heart rate pattern, that accompanies cord occlusions, is extensively described by Hon (1968).

Variable deceleration has the following characteristics. It varies markedly in shape from uterine contraction to uterine contraction, and does not reflect the shape of the associated uterine contraction curve. The onset of the deceleration bears a variable time-relationship to the beginning of the associated uterine contraction. The duration of the deceleration varies from a few seconds to minutes and the fall in heart rate is usually below 100 beats per minute and is frequently as low as 50-60 beats per minute or less.

The pattern of the variable deceleration probably varies with the degree of venous or venous and arterial umbilical flow obstruction, the

duration of the occlusion and fetal oxygen state before the occlusion.

4.2 Mechanisms of the variable decelerations

The various explanations of the mechanisms underlying the variable deceleration have been obtained largely from animal studies. Bauer (1937) studied the slowing of heart rate produced by clamping the umbilical cord in the fetal sheep and goat and noted a considerable delay in the slowing of fetal heart rate after sectioning of the cervical vagal nerves. Barcroft (1946) ascribed the initial fall in fetal heart rate to vagal stimulation and the residual bradycardia after vagotomy to direct hypoxic depression of the myocardium (see also paragraph 3.2). Partial occlusion of the umbilical cord or the isolated intraabdominal vein in near-term pregnant baboons and Rhesus monkeys resulted in the well-oxygenated fetus in transient acceleration of heart rate and a decrease in pulse pressure in a study by James et al (1976). This response was abolished after alpha-adrenergic blockade with dibenzyline or beta-adrenergic blockade with propranolol. In the hypoxic fetus however partial occlusion resulted in either bradycardia and hypotension or hypotension with no alteration in heart rate. James concluded that transient acceleration of the fetal heart rate can be explained on the basis of a sympathetic response to diminished venous return.

The same type of study was done by de Haan et al (1976, 1979) and Evers (1978) in the chronically instrumented fetal sheep. With the use of a special occluding device separate occlusions of the umbilical veins and/or arteries were performed. They found an initial decrease of systolic and diastolic arterial pressure after occlusion of the umbilical veins, followed by an increase during the rest of the occlusion. A small increase in fetal heart rate often preceded the following decrease. The initial decrease in arterial pressure following venous occlusion must be caused by an initial decreased venous return to the right heart due to a certain amount of blood trapped in the placental circulation, until arterial pressure is maintained in the rest of the circulation (de Haan et al 1976, 1979, Evers 1978).

Total occlusion of both umbilical arteries or the total umbilical cord

resulted in an immediate rise of systolic and diastolic pressure, followed by a second rise after a variable time to a certain steady-state level. The fetal heart rate decreased immediately after the occlusion to a certain level and was followed by a second decrease accompanying the second rise in fetal blood pressure. Complete occlusion of the umbilical arteries or total umbilical cord will lead to a sudden marked increase in peripheral vascular resistance since about 40% to 50% of fetal total cardiac output is umbilical blood flow (Cohn et al 1974, Peeters 1978, Rudolph and Heymann 1970). This leads to an immediate rise in arterial blood pressure, followed within 1 to 2 seconds by a decrease in fetal heart rate as a result of carotid baroreceptor stimulation which can be blocked by atropine in the fetal lamb (De Haan et al 1976, Evers 1978).

Mueller-Heubach and Battelli (1982) performed total umbilical cord occlusions for 15 or 39 seconds in Rhesus monkeys under anesthesia. They found an initial short-lasting rise in blood pressure with cord occlusion followed by a decrease in blood pressure which crossed in most experiments the baseline blood pressure present before cord occlusion. They concluded that the initial baroreceptor stimulation is of limited duration and the continued decline in fetal heart rate while fetal blood pressure decreases from a peak has to be attributed to chemoreceptor stimulation in view of the continuing linear fall of transcutaneous pO_2, which measurement has a high correlation with the pO_2 measured in arterial blood.

De Haan et al (1976, 1979) ascribed the second increase in arterial pressure during clamping of the cord to vasoconstriction based on a decrease in partial oxygen pressure, i.e also chemoreceptor mediated. It is likely that blood pressure would have been decreased with longer lasting occlusions causing a more severe fetal hypoxemia with direct myocardial depression in their experiments.

There are however differences in experimental conditions between the studies from de Haan et al (1976, 1979) and Mueller-Heubach and Battelli (1982), as the animal under study, the variation in occlusion time and chronic versus acute experiment.

The role of chemoreceptor activity, which exists during the latter third of gestation in fetal lambs (Dawes et al 1969), in fetal heart

rate changes caused by umbilical cord compression has been studied in delivered fetal lambs which were connected to a membrane oxygenator replacing the ventilatory function of the placenta by Siassi et al (1979). They showed that variation of arterial oxygen tension from 220 to 20 mm Hg, an after all unphysiological range as normal fetal arterial oxygen tension is in the range of 20 to 30 mm Hg, was associated with progressive increase in blood pressure and heart rate, indicating presence of chemoreceptor activity throughout this range of arterial oxygen tension. Cardiac decelerations and blood pressure rises were less in hyperoxemic fetuses which were in a state of reflex peripheral vasodilation compared to the responses in normoxemic fetuses which were in a state of reflex peripheral vasoconstriction. They postulate that heart rate deceleration as a result of umbilical cord occlusion is in part due to immediate chemoreflex-mediated bradycardia which acts in a synergistic manner with baroreflex responses. The chemoreceptor sensitivity may be increased at lowered levels of arterial oxygen tension, which can explain the greater deceleration elicited during fetal normoxemia in contrast to fetal hyperoxemia.

Künzel et al (1980) found in acute fetal lamb studies that the first response to total cord occlusion took place within 0.25 seconds, a very unlikely value, as the sum of the afferent, central and efferent conduction times of the vagally mediated baroreflex is 600 msec (Borst 1979). Their following conclusion is however not invalid by this difference. When taking the fetal circulation time from the umbilical vein to the carotid artery which is 1.9 $\pm$ 0.2 seconds (Power and Longo 1975) into account, then an initial chemoreceptor response due to hypoxia is excluded, so that the initial cardiovascular response has to be baroreceptor mediated.

In summary, the reflex mechanisms regulating fetal cardiovascular adaption to cord compression are primarily baroreflex mediated, followed by or in combination with a chemoreceptor response induced by hypoxemia, and eventually the effects of direct hypoxic myocardial depression on heart rate and arterial pressure are added. So the sequence of the reflex mechanisms underlying the variable deceleration is not the same in case of the late deceleration, in which the first part of the deceleration is chemoreceptor mediated, followed by a

baroreceptor response (paragraph 3.3).

4.3 Umbilical venous blood flow and cord compression

Total umbilical cord occlusion leads to exclusion of the placental circulation with a total stop of fetal umbilical circulation. The concomitantly occurring changes in heart rate and blood pressure have been described before. Mean umbilical blood flow is expected to become zero after total cord occlusion.
The flow pattern in the common umbilical vein shows normally no or minimal pulsations, in contrast to the flow patterns in the fetal superior and inferior venae cavae which have a phasic pulsatile character (Reuss et al 1983). The pulsatility in the venae cavae increases under several conditions like slower heart rates, hypoxemia and changes in ventricular afterload (Reuss et al 1983). These factors also evoke biphasic pulsations in the common umbilical vein, in line with fetal heart rate (Hasaart and de Haan 1983). The appearance of biphasic pulsations in the common umbilical vein and their relationship with heart rate and blood pressure was studied during total cord occlusion and the immediate post occlusion period.

4.4 Pelvic arterial blood flow and cord compression

It is evident that decreases in maternal uterine flow or vascular pressure influence the fetal circulation if the fetal oxygenation becomes compromised by the flow reduction, as has been outlined in chapter 3. Power and Longo proposed in 1973 that a placental tissue pressure is generated by the uterine vascular system surrounding the fetal placental circulation. This placental tissue pressure may be an important factor in the regulation of the umbilical flow. This sluice flow or waterfall mechanism, as it was referred to by Thornburg et al (1976), would enable changes in maternal uterine flow or vascular pressure to influence the fetal circulation. The sluice flow model states that blood flow through a system of collapsible channnels which are surrounded by a pressure exceeding venous outflow pressure is directly proportional to the difference between inflow pressure and

surrounding pressure, and inversely proportional to the resistance of the rigid vascular elements, but is unaffected by outflow pressure as long as outflow pressure is lower than surrounding pressure (Berman et al 1976).

The experiments in this respect by Power and Longo (1973) were performed in the fetal circulation of a single cotyledon of the sheep placenta, while Bissonnette and Farrell (1973) perfused the entire umbilical circulation of near-term fetal lambs after removal of the fetus. This concept implies that a rise in uterine venous pressure would increase placental tissue pressure surrounding the umbilical vascular bed with a greater resistance to fetal placental flow as result. Umbilical flow would then fall. The effects in the fetal circulation of the maternal hypotensive supine syndrome during human pregnancy could be explained in this way.

A fall in uterine arterial pressure or a flow reduction on the other hand would decrease the surrounding placental tissue pressure and therefore decrease umbilical placental vascular resistance with an increase in umbilical flow as result. However, Thornburg et al (1976) reinvestigated this problem in chronically instrumented near-term sheep. They report that changes in uterine venous pressure in the physiological range from 2 to 30 mm Hg did not affect the umbilical vascular resistance. The same results were obtained by Berman et al (1976), also in a chronic sheep preparation. They found that changes in maternal arterial and venous pressure within the physiological range did not alter umbilical blood flow.

According to these two series of experiments which were performed in a chronic preparation in a certainly better physiological condition than the acute perfused placenta preparations, there is no evidence that the placental waterfall phenomenon exists in the fetal sheep. In a continuation of their work from 1973 Power and Gilbert reported in 1977 however that changes in pressure on the maternal side of the placenta, caused by occlusion of the vena cava inferior or the distal aorta produced changes in fetal umbilical compliance. These experiments were done in the acutely perfused placenta preparation with cut umbilical vessels and moreover umbilical compliance was measured within a pressure range of 40 to 80 mm Hg, totally unphysiological values for

the umbilical veins.
Any valid conclusion for the intact in vivo situation cannot be drawn therefore from this latter study.
On the other hand the placental waterfall concept has also been used to propose that changes in pressure and flow in the fetal placental vasculature may conversely influence the maternal placental circulation. Berman et al (1976) and Rudolph (1976) however found no measurable effect on uterine blood flow upon an elevation of umbilical venous pressure or a reduction of umbilical arterial pressure.
Recently Cottle et al (1982) reported a decrease in median uterine blood flow in response to longerlasting (4 minutes) cord compression in a chronic sheep model.
In the experiments by Berman et al and Rudolph only partial and very short lasting flow obstructions in either the common umbilical vein, or the fetal distal aorta were performed possibly not sufficient enough to establish maternal flow changes, while Cottle et al (1982) performed long lasting occlusions of the total umbilical cord. Moreover in the former studies blood flow in the common internal iliac artery was measured, the terminal branch of the aorta, that also supplies the nonpregnant uterine horn and other extrauterine structures with blood. Possible changes in maternal placental blood flow might not be reflected in the mean flow of this vessel. The measurements by Cottle et al were performed in the median uterine artery, directly adjacent to the uterine wall and only providing the uterus and its contents with blood. They suggested that fetal release of catecholamines or increased fluid pressure in the fetal placental tissue or a combination of these mechanisms might be involved in the uterine flow depression during cord compression. The maternal uterine bed is highly sensitive for catecholamines and reacts with a vasoconstriction upon its administration (Greiss 1963, Greiss and Pick 1964). Catecholamines are released from the fetal adrenal medulla in response to hypoxemia (Comline et al 1965), and they may constrict the maternal vascular bed after transfer over the placenta from the fetal to the maternal side. Evidence of placental transfer of catecholamines is however conflicting. Jones and Robinson (1975) detected no labeled catecholamines of fetal origin in the maternal circulation in sheep

whereas reduced uterine blood flow after intravenous administration into sheep fetuses was reported by Chez et al (1978). Rankin and Phernetton (1976) also observed a fall in uterine blood flow subsequent to the injection of norepinephrine to the fetal lamb.
An increased tissue pressure in the fetal placenta during cord occlusion might alternatively or additionally heighten resistance in the maternal placental circulation with a flow reduction as result.

In this chapter the results of total umbilical cord occlusion upon the blood flow in the maternal internal iliac artery and median uterine artery will be presented as well as the instantaneous flow patterns in the common umbilical vein during and immediate after cord occlusion.

4.5 Materials and methods

A total number of 92 umbilical cord occlusions with simultaneous maternal flow measurements were performed in 8 animals. The maternal blood flow measurements were distributed as follows. The blood flow in the median uterine artery was measured during 69 cord occlusions in 7 animals. The blood flow in the internal iliac artery was also measured during 69 cord occlusions in 7 animals (see table 2.5). Simultaneous measurement of the internal iliac artery blood flow as well as the blood flow in the median uterine artery was possible in 46 cord occlusions in 6 animals.
Table 4.1 shows the data on gestational age, number of days after surgery at the time of the occlusion experiment and the duration of the occlusion.

	MEAN ± SD	RANGE
GESTATIONAL AGE (DAYS)	120±2.5	114 - 133
TIME AFTER SURGERY (DAYS)	7.6±2.5	3 - 26
OCCLUSION TIME (SECONDS)	40.1±3.3	20 - 90

TABLE 4.1 GESTATIONAL AGE, TIME AFTER SURGERY AND OCCLUSION TIME OF THE 92 UMBILICAL CORD OCCLUSIONS IN 8 ANIMALS.

The instantaneous umbilical venous blood flow pattern in the fetuses with an intact autonomic nervous system was studied during the cord occlusions of the above mentioned group.
The instantaneous umbilical venous blood flow pattern during umbilical cord occlusions was also analysed after selective blockade of the cholinergic, alpha-adrenergic and beta-adrenergic part of the autonomic nervous system of the fetal lamb.

The mean values of the blood flow in the internal iliac artery or the median uterine artery calculated over an interval of 10 seconds were pooled and statistically analysed.
The control values (=C) were obtained from a period 10 seconds before the start of the occlusion. Control values were then compared with the mean values calculated from the last 10 seconds of the umbilical cord occlusion (=E), the interval 0 to 10 seconds after the occlusion (=10), the interval 60 to 70 seconds after the occlusion (=60) and finally with the mean value about two minutes after occlusion (=120), calculated over the interval 110-120 seconds after the occlusion.
Data were expressed as percent change $\pm$ SEM with control values as the 100% reference level. Statistical analysis was done by means of Wilcoxon's matched-pairs signed-ranks test. All p-values were calculated for two tailed tests.

4.6 Results

4.6.1 Maternal internal iliac artery blood flow during umbilical cord occlusion

The blood flow in the maternal internal iliac artery was significantly ($p<0.001$) reduced at the end of the occlusion to 93.9% of the control value (=330 ml/min). Internal iliac artery blood flow was also significantly ($p<0.001$) less than the control value at the first 10 seconds after the end of the occlusion. The values at 60 and 120 seconds did not significantly differ from the control value. Table 4.2 shows the mean values $\pm$ SEM for the internal iliac artery blood flow expressed in percent change from control.

4.6.2 Maternal median uterine artery blood flow during umbilical cord occlusion

The blood flow in the median uterine artery was significantly ($p<0.001$) reduced at the end of the occlusion and at the first 10 seconds after the end of the cord occlusion to respectively 91.7 and 94.9% of the control value (=256 ml/min). A still significant decrease ($p<0.05$) in

	C N = 69	E N = 69	10 N = 69	60 N = 69	120 N = 69
INTERNAL ILIAC ARTERY	100	93.9±1.1 ☆	94.8±1.1 ☆	97.5±1.2	98.5±1.5

☆P < 0.001

TABLE 4.2 MATERNAL BLOOD FLOW IN THE INTERNAL ILIAC ARTERY DURING AND AFTER UMBILICAL CORD OCCLUSION. (MEAN± SEM, EXPRESSED AS PERCENT CHANGE FROM CONTROL.)

C = CONTROL
E = AT THE END OF OCCLUSION
10 = DURING FIRST 10 SECONDS AFTER OCCLUSION
60 = AFTER 1 MINUTE (INTERVAL 60-70 SECONDS IS USED FOR CALCULATION)
120 = AFTER 2 MINUTES (INTERVAL 110-120 SECONDS IS USED FOR CALCULATION)

uterine blood flow was found at 60 seconds after the end of the occlusion (97.2% of control value). Mean uterine blood flow at 120 seconds post occlusion did not differ significantly from the control value. Figure 4.1 shows the mean values ± SD calculated over intervals of 10 seconds of fetal umbilical blood flow and maternal median uterine artery blood flow in a single umbilical cord occlusion experiment. Table 4.3 shows the mean values ± SEM for the median uterine artery blood flow, expressed in percent change from control.

	C N = 69	E N = 69	10 N = 69	60 N = 69	120 N = 69
MEDIAN UTERINE ARTERY	100	91.7±1.1 *	94.9±1.1 *	97.2±1.3	97.2±1.5

*P < 0.001

TABLE 4.3 MATERNAL BLOOD FLOW IN THE MEDIAN UTERINE ARTERY DURING AND AFTER UMBILICAL CORD OCCLUSION. (MEAN±SEM, EXPRESSED AS PERCENT CHANGE FROM CONTROL). SEE ALSO LEGEND TABLE 4.2

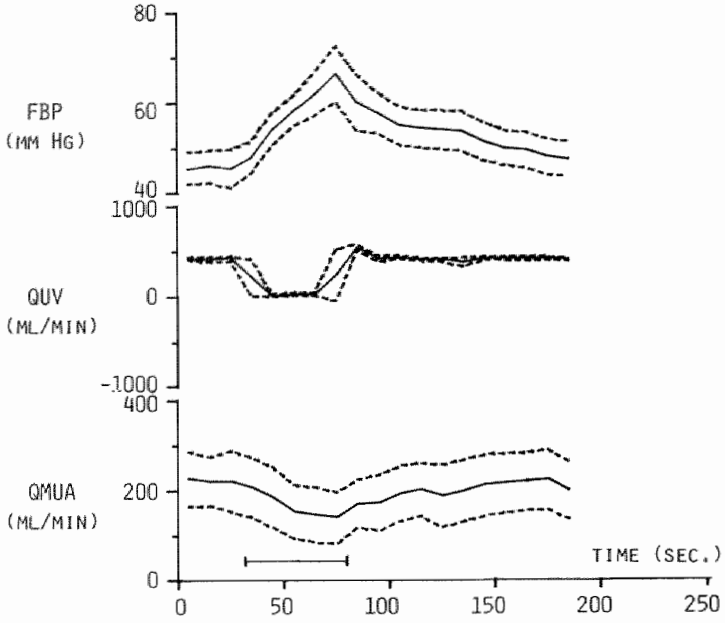


FIG. 4.1 CHANGES IN MEDIAN UTERINE ARTERY BLOOD FLOW DURING AN UMBILICAL CORD OCCLUSION (⟵⟶). DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS. THE GRADUAL CHANGES IN QUV AT THE BEGIN AND END OF THE OCCLUSION ARE DUE TO THE WAY OF GRAPHICAL EXPRESSION.

4.6.3 Simultaneous measurement of maternal internal iliac artery and median uterine artery blood flow during umbilical cord occlusion

The data of the blood flow changes in the internal iliac artery and median uterine artery during umbilical cord occlusion showed a greater reduction in median uterine artery blood flow than in the internal iliac artery flow.

Part of the data of these two groups were however obtained from different experiments. Therefore the data on the maternal blood flow during cord occlusion were also analysed in the 46 occlusions in which internal iliac artery and median uterine artery blood flow were

measured simultaneously. The blood flow in the maternal internal iliac artery was significantly reduced at the end of the occlusion and at first the 10 seconds after the end of the cord occlusion to respectively 94.3% ($p<0.001$) and 96.8% ($p<0.01$) of control value (=317 ml/min). A still significant ($p<0.05$) decrease in internal iliac blood flow was found at 60 seconds post occlusion.

Median uterine artery blood flow was also significantly reduced at the end of the occlusion and at the first 10 seconds after the end of the cord occlusion to respectively 93.6% ($p<0.001$) and 96.2% ($p<0.01$) of control value (=236 ml/min).

At 60 seconds post occlusion median uterine artery blood flow was still significantly ($p<0.02$) reduced to 96.6% of control value.

The absolute values of the flow decreases were about the same in both vessels. Figure 4.2 shows the mean values $\pm$ SD calculated over intervals of 10 seconds of fetal umbilical blood flow and maternal internal iliac and median uterine artery blood flow in such an Pexperiment.

Table 4.4 shows the mean values $\pm$ SEM for both maternal blood flows expressed in percent change from control.

	C N = 46	E N = 46	10 N = 46	60 N = 46	120 N = 46
INTERNAL ILIAC ARTERY	100±0	94.3±1.2 ▲	96.8±1.3 □	97.5±1.5 *	98.4±1.8
MEDIAN UTERINE ARTERY	100±0	93.6±1.1 ▲	96.2±1.2 □	96.6±1.3 ◇	97.5±1.8

▲P < 0.001 □P < 0.01 ◇P < 0.02 *P < 0.05

TABLE 4.4 MATERNAL BLOOD FLOW AS MEASURED SIMULTANEOUSLY IN THE INTERNAL ILIAC ARTERY AND THE MEDIAN UTERINE ARTERY DURING AND AFTER UMBILICAL CORD OCCLUSION (MEAN±SEM, EXPRESSED AS PERCENT CHANGE FROM CONTROL). SEE ALSO LEGEND TABLE 4.2

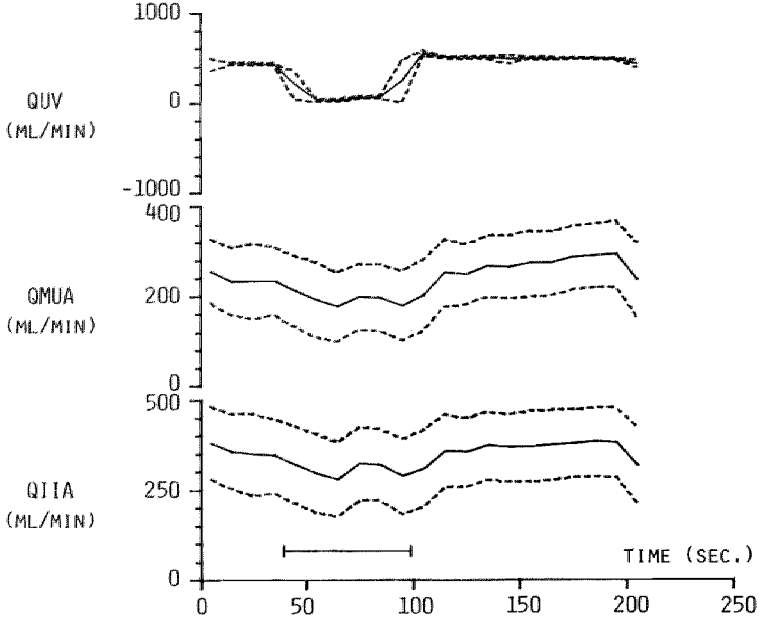


FIG. 4.2 CHANGES IN MEDIAN UTERINE AND INTERNAL ILIAC ARTERY BLOOD FLOW DURING AN UMBILICAL CORD OCCLUSION (⟷). DATA ARE EXPRESSED AS MEAN ± SD IN INTERVALS OF 10 SECONDS. THE GRADUAL CHANGES IN QUV AT THE BEGIN AND END OF THE OCCLUSION ARE DUE TO THE WAY OF GRAPHICAL EXPRESSION.

4.7 Instantaneous umbilical venous blood flow during occlusion of the umbilical cord

4.7.1 Intact autonomic nervous system

Inflation of the balloon occluder around the total umbilical cord led to an increase in mean arterial blood pressure and a decrease in heart rate, phenomena which have been described extensively (de Haan et al 1976, Künzel et al 1977, 1980, Evers 1978, De Haan et al 1979, Mueller-Heubach and Battelli 1982, Itskovitz et al 1983).

Umbilical venous blood flow abruptly decreased during cord occlusion and with complete inflation of the balloon, a total blockade of venous blood flow was accomplished.

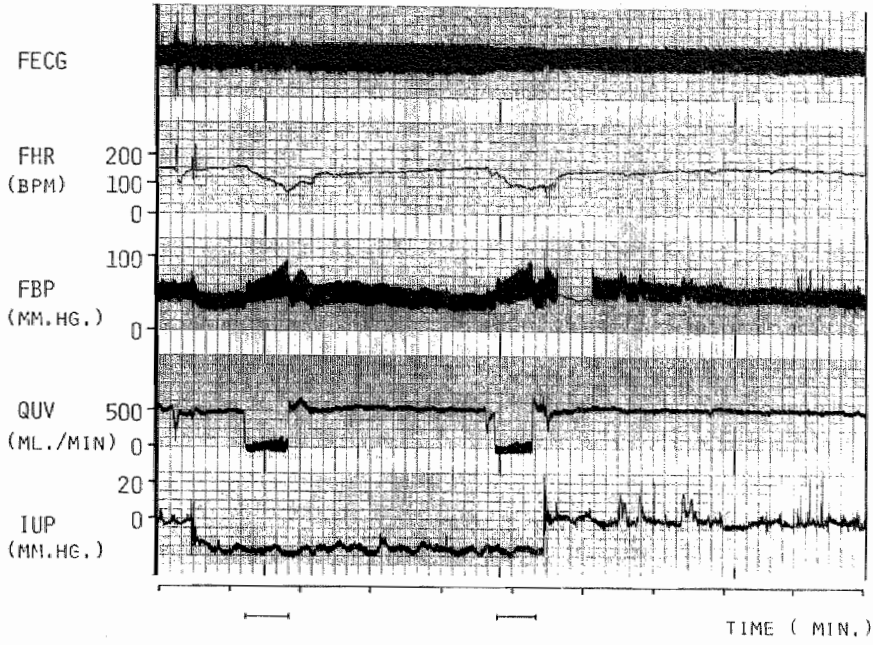


FIG. 4.3 THE OCCURRENCE OF PULSATIONS IN THE PHASIC FLOW PATTERN OF THE COMMON UMBILICAL VEIN. (⟵⟶ UMBILICAL CORD OCCLUSION) THE ABRUPT CHANGES IN IUP ARE CAUSED BY A POSTURAL CHANGE OF THE EWE.

The instantaneous flow pattern in the common umbilical vein which under steady-state conditions showed no pulsations, changed during cord occlusion to a pattern with biphasic pulsations in line with fetal heart rate. This change occurred both in the situations in which umbilical venous blood flow was only partially reduced by incomplete inflation of the occluder as well as in those experiments in which a complete blockade of venous blood flow was established (fig 4.3). In

the latter situation no mean forward flow was present of course, in contrast to the experiments with only partially reduced umbilical blood flow. The biphasic pulsations appeared after a certain delay after the beginning of the cord occlusion and gradually increased in amplitude to reach their maximum amplitude immediately before the end of the occlusion. Maximum pulsatility was seen with high blood pressure increases and deep bradycardia. An overshoot of umbilical venous blood flow was found after release of the cord occlusion. The pulsations were then abruptly diminished in size or had even disappeared (fig. 4.4).
If the pulsations were still present in a lesser degree after the occlusion, then they were extinguished within several seconds after the occlusion, unless fetal bradycardia and hypertension were still pronounced at that time.

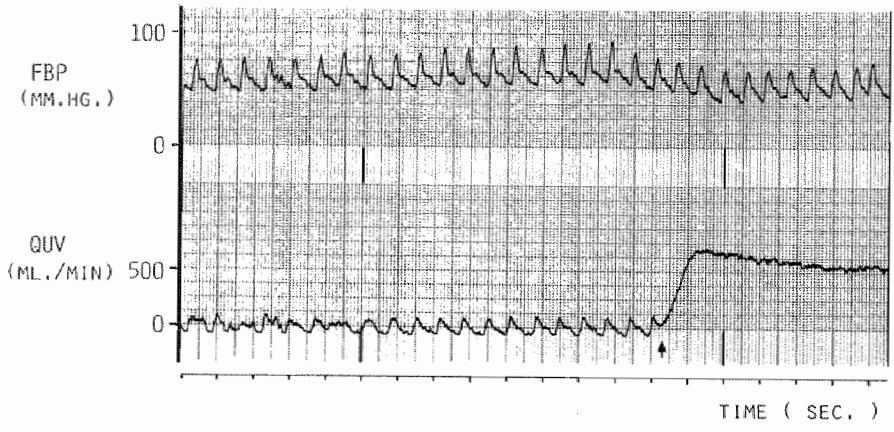
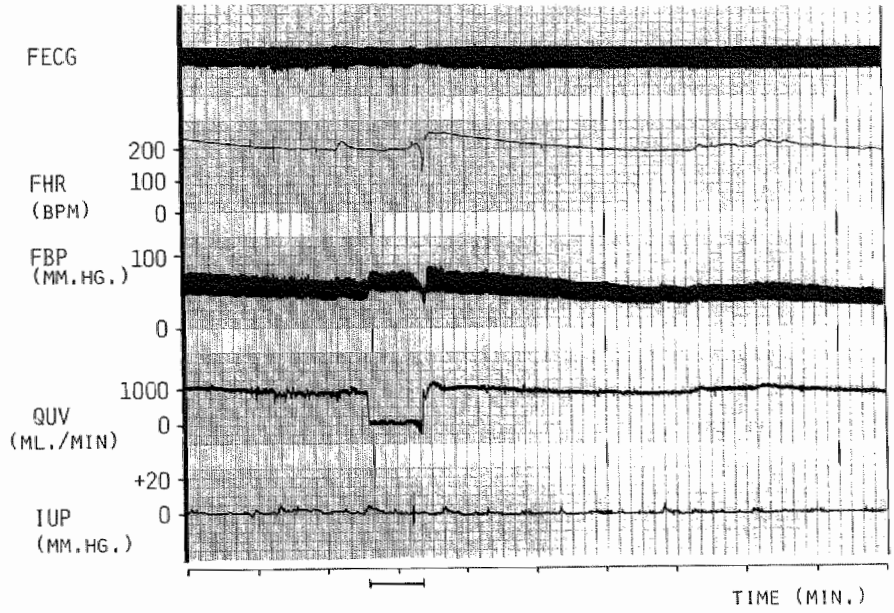


FIG. 4.4 THE OCCURRENCE OF BIPHASIC PULSATIONS IN LINE WITH FETAL HEART RATE DURING UMBILICAL CORD OCCLUSION.
(↑ END OF THE OCCLUSION)

These venous pulsations were biphasic with a systolic component occurring during ventricular systole and a diastolic component during ventricular diastole. The systolic component started parallel with the

arterial pressure rise, peaked and decreased again, after which a second diastolic flow "surge" was seen much smaller in amplitude and occurring during ventricular diastole. Thereafter a nadir occurred directly before the next rise in arterial blood pressure. During this nadir retrograde flow occurred in the experiments with complete blockade of umbilical venous blood flow.

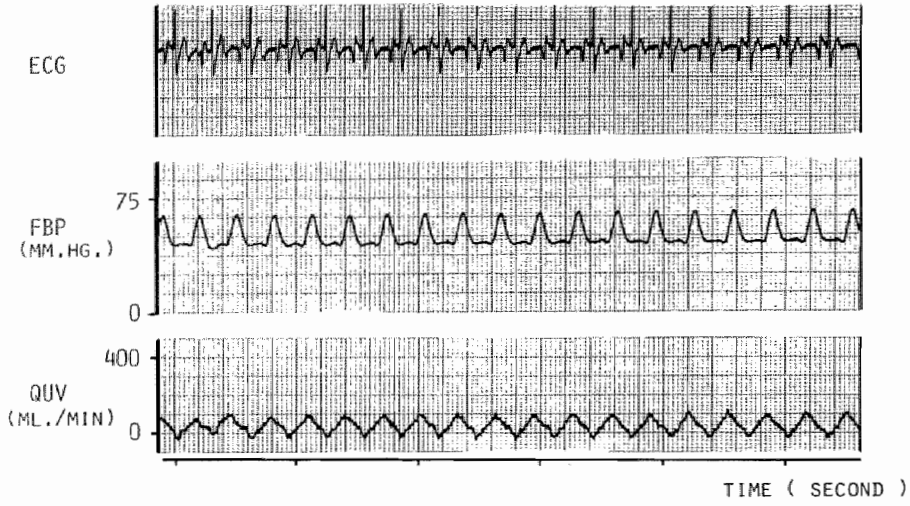


EWE 8315 GESTATIONAL AGE 119 5 DAYS P.O.

FIG 4.5 CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW DURING UMBILICAL CORD OCCLUSION (⟵⟶) AFTER CHOLINERGIC BLOCKADE WITH ATROPINE. NOTE THE VENOUS PULSATIONS AT THE END OF THE OCCLUSION.

4.7.2 Selective blockade of the cholinergic, alpha-adrenergic and beta-adrenergic part of the autonomic nervous system

Cholinergic blockade with atropine (7 cord occlusions in 4 animals) prevented or diminished the fetal heart rate deceleration during the cord occlusion, but did not preclude the occurrence of biphasic pulsations in the common umbilical vein flow (fig 4.5).

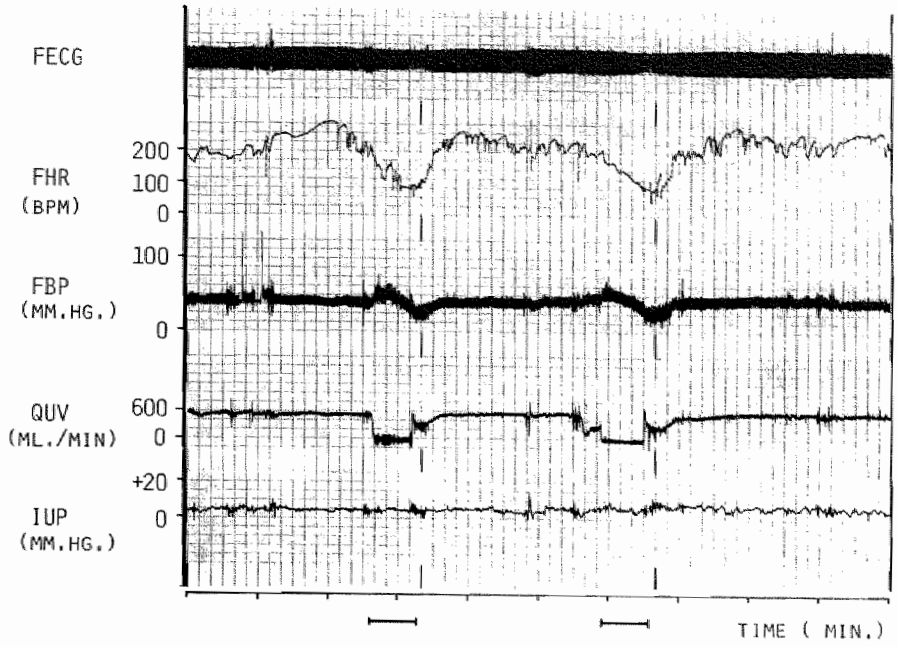


EWE 8308 GESTATIONAL AGE 123 6 DAYS P.O.

FIG 4.6. THE OCCURRENCE OF MONOPHASIC VENOUS PULSATIONS IN LINE WITH FETAL HEART RATE DURING UMBILICAL CORD OCCLUSION AFTER CHOLINERGIC BLOCKADE WITH ATROPINE.

Fetal arterial blood pressure invariably increased during the occlusion with a gradually decrease to preocclusion values after the end of the occlusion.

Cholinergic blockade did not preclude the occurrence of biphasic pulsations in the common umbilical vein, but their shape was monophasic instead of biphasic (fig 4.6). The diastolic component of the pulsation disappeared then.



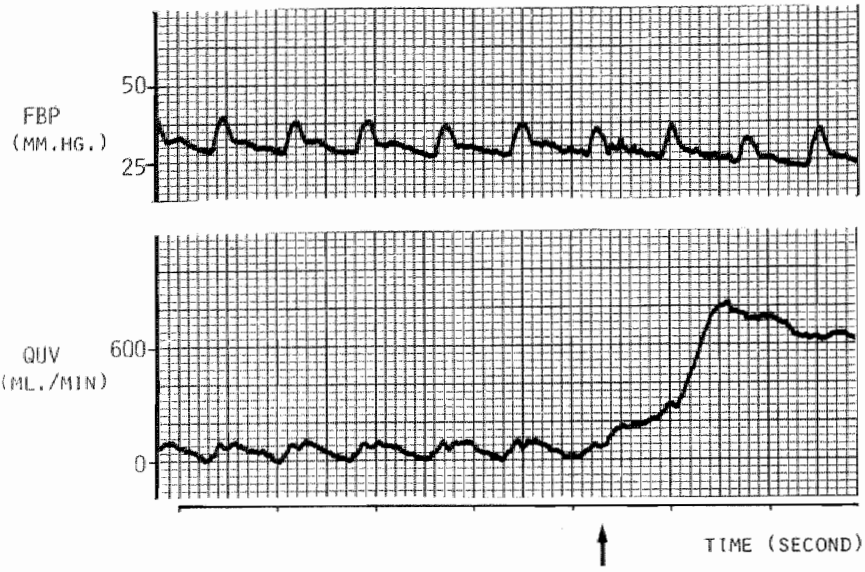
EWE 8310 GESTATIONAL AGE 115 3 DAYS P.O.

FIG 4.7 CHANGES IN FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL BLOOD FLOW DURING UMBILICAL CORD OCCLUSION (⟵⟶) AFTER ALPHA-ADRENERGIC BLOCKADE WITH PHENTOLAMINE NOTE THE BLOOD PRESSURE DECREASE AT THE END OF THE OCCLUSION.

After alpha-adrenergic blockade with phentolamine (11 occlusions in 4 animals) an initial rise in arterial blood pressure was seen followed by a decrease in pressure during the latter part of the occlusion (fig 4.7). Fetal heart rate decreased during the occlusion.

The magnitude of the venous pulsations during umbilical cord occlusions after alpha-adrenergic blockade did not differ from their appearance in the unblocked condition. With regard to the shape of the biphasic pulsation however a shift in the proportion of the systolic and diastolic component of the pulsation was observed during the latter

part of the occlusion when arterial blood pressure decreased. The diastolic component of the pulsation increased in amplitude at the cost of the amplitude of the systolic component (fig 4.8). This change in pattern of flow was only observed during a low arterial blood pressure.



EWE 8310 GESTATIONAL AGE 115 3 DAYS P.O.

FIG 4.8 BIPHASIC PULSATIONS IN THE COMMON UMBILICAL VEIN FLOW PATTERN AT THE END OF AN UMBILICAL CORD OCCLUSION AFTER ALPHA-ADRENERGIC BLOCKADE WITH PHENTOLAMINE. THE DIASTOLIC COMPONENT OF THE PULSATION IS MORE PROMINENT THAN IN FIGURE 4.4.(↑ END OF OCCLUSION).

Umbilical cord occlusion during beta-adrenergic blockade (8 occlusions in 4 animals) resulted in fetal bradycardia and hypertension. Fetal arrhythmia with collapse of blood pressure often occurred in the latter part of the occlusions.

The pulsatile umbilical venous flow pattern during umbilical cord occlusion after beta-adrenergic blockade was the same in magnitude and shape as during cord occlusion in the fetuses with an intact autonomic nervous system.

4.8 Discussion

4.8.1 Blood flow in the maternal internal iliac and median uterine artery during umbilical cord compression

The results from this study show that the maternal blood flow to the uterus is depressed during umbilical cord occlusion of short duration. The mechanism by which this decrease in maternal blood flow is brought about is not entirely clear.

The uterine circulation in pregnancy is considered as a low resistance, high flow vascular bed.

Minimal autoregulation of uteroplacental blood flow in response to changes in oxygen tension, carbon dioxide tension and perfusion pressure is present (Assali and Brinkman 1972, Clapp 1979) and a reduced uterine blood flow associated with a diminished oxygen uptake by the fetal blood can thus be ruled out as an explanation for this phenomenon.

Changes in perfusion pressure or autonomic tone of the uterine vascular bed also result in blood flow changes, but it is very unlikely that maternal hypotension would be responsible for the decrease in internal iliac and median uterine artery blood flow during umbilical cord compression. Changes in autonomic tone of the uterine vascular bed, which is highly sensitive to alpha-adrenergic receptor stimulation on the other hand could be caused by catecholamines from fetal origin.

Cottle et al (1982) suggested that fetal catecholamines released from the fetal adrenal medulla in response to hypoxemia (Comline et al 1965, Jones and Robinson 1975) and crossing the fetal maternal placental barrier, would at least be in part responsible for the reduced uterine blood flow during umbilical cord occlusion. He was the first one who observed maternal uterine blood flow reductions during long lasting (4 min) partial occlusions of the umbilical cord.

In a recent study however Cottle et al (1983) found evidence that fetal catecholamines released in response to the hypoxemia caused by umbilical cord occlusion were not the major determinant of the uterine

blood flow reductions induced by cord occlusions. They found the same reductions in uterine blood flow during umbilical cord occlusion with and without the previous administration of promazine to the ewe. Promazine is an antiemetic drug with alpha-adrenergic blocking properties and therefore capable of alpha-adrenergic blockade in the maternal placenta. If maternal uterine blood flow during umbilical cord occlusion would have been mainly reduced by fetal catecholamines, then this reduction in flow should have been absent after maternal alpha-adrenergic blockade, which was however not the case.

The results from this study also give evidence that fetal catecholamines are not primarily involved in the mechanism of maternal flow reduction. Total umbilical cord occlusion namely reduces umbilical blood flow to zero thereby preventing fetal catecholamines to cross the placental barrier to the maternal side.

Furthermore one would have expected a sustained reduction in maternal uterine blood flow after the end of the cord occlusion, because of the relatively long lasting uterine vasoconstriction after alpha-adrenergic receptor stimulation.

The most likely explanation for the decrease in internal iliac and median uterine artery blood flow during umbilical cord occlusion refers to an increased pressure in the fetal placental tissue leading to a decreased maternal flow by elevating the resistance in the maternal uterine circulation. An increase in tissue pressure and possibly tissue fluid formation could develop during the umbilical cord occlusion as follows: The umbilical veins will first be compressed during inflation of the balloon occluder. After a lag time of several seconds, necessary for the complete filling of the balloon, the umbilical arteries are occluded too.

During this lag time the umbilical veins are completely compressed while the umbilical arteries are still totally or partially patent. A certain additional amount of arterial blood will then be pumped into the umbilical circulation and will eventually be trapped in the umbilical vascular bed under a high pressure after complete compression of the umbilical arteries. The elevated fetal capillary pressure in the placenta leads then to an increased fetal placental tissue pressure which in turn compresses the maternal placental capillaries resulting

in an increased vascular resistance and a decrease in uterine blood flow.
The umbilical placental circulation is capable of storing an extra amount of blood, which is shown in the study by de Haan et al (1979), who found that during selective occlusion of both umbilical veins a slowly decreasing mean flow can be measured in the umbilical arteries during the first seconds following the start of the occlusion. The results of a study by Jongsma et al (1979), in which an increase in placental blood volume of 34.8 ml after clamping of the umbilical veins was found, are in favor of this hypothesis.

The results from this study are in agreement with the report by Cottle et al (1982) who also found a decrease in the median uterine artery blood flow during long lasting (4 min) partial umbilical cord occlusion.
The greater decrease in median uterine artery blood flow than in internal iliac artery blood flow found in this study was in terms of percentage. The flow decrease in absolute values was the same in both vessels. The difference in percentage change between the two vessels is explained by the fact that part of the internal iliac artery blood flow is to non-uterine structures (paragraph 2.4.1), which should not show any change in blood flow during umbilical cord occlusion. It also makes clear why no changes in uterine blood flow during umbilical cord occlusions were found in the study by Berman et al (1976). They measured the maternal blood flow in the middle sacral artery which in the nomenclature used in this study is known as the common internal iliac artery. This vessel not only supplies the pregnant uterine horn but also the non pregnant uterine horn, the presacral region and other structures. It is conceivable that relatively small decreases in the blood flow in a part of the vascular bed of this artery do not lead to statistically significant changes in the blood flow of the common internal iliac artery, in which vessel the blood flow is much higher than in the median uterine artery. Another possibility might be that relatively small increases in the resistance to flow in a part of the vascular bed of this artery might easily be accounted for by shifting blood to other vessels in such a degree that the mean flow in the

common internal iliac artery is not affected.
It is concluded from these results that uterine blood flow is decreased during umbilical cord occlusion probably on the basis of an increased fetal placental tissue pressure.

4.8.2 Instantaneous umbilical blood flow during occlusion of the umbilical cord in fetuses with an intact autonomic nervous system

The nature of the biphasic pulsations occurring in the common umbilical vein under various conditions and their possible consequence for fetal hemodynamics in general will be discussed in chapter 5.
The comment given here will therefore be restricted to this specific situation. Occlusion of the umbilical cord is associated with an increased systemic arterial pressure and peripheral vascular resistence. This increase in afterload augments the under normal circumstances always present biphasic pulsations in the venae cavae (Reuss et al 1983).
The higher end-diastolic ventricular pressure associated with the increase in peripheral vascular resistance and arterial blood pressure leads to an increased ventricular contraction force, resulting in a higher systolic component in the vena caval flow surge (Reuss et al 1983). This explains why the systolic component of the biphasic pulsation in the common umbilical vein is also greater than the diastolic component.
The retrograde flow occurring with complete umbilical cord occlusion during the deep through in between two biphasic pulsations was also found by Reuss et al for the flow pattern in the venae cavae during increased peripheral resistance and arterial blood pressure associated with fetal hypoxemia.
Forward flow in the venae cavae is normally impeded during atrial contraction. Conditions which result in an increase in atrial pressure as fetal bradycardia and increased ventricular afterload do, can eventually cause a retrograde flow in the venae cavae during atrial contraction.
This flow pattern is then reflected in the common umbilical vein after

backward propagation.

4.8.3 Instantaneous umbilical blood flow during occlusions of the umbilical cord after selctive blockade of the cholinergic, alpha-adrenergic and beta-adrenergic part of the autonomic system

The changes in heart rate and arterial blood pressure induced by umbilical cord occlusion during cholinergic, alpha-adrenergic respectively beta-adrenergic blockade have extensively been studied (de Haan et al 1976, 1979, Evers 1978). The data from the present study are in agreement with the results reported by them.

Cholinergic blockade prevented or diminished the heart rate deceleration associated with the umbilical cord occlusion. Higher heart rates shorten the diastolic filling time of the right atrium with a diminishing diastolic component of forward flow in the venae cavae as result. Biphasic caval flow becomes then monophasic (Reuss et al 1983), and the pulsations in the common umbilical vein, which are caused by backward propagation from the vena cava, follow this alteration.

Alpha-adrenergic blockade caused a blood pressure decrease in the latter part of the umbilical cord occlusion by preventing peripheral vasoconstriction.

This reduction in afterload allows for greater ventricular emptying and a decrease in end-diastolic pressure. A greater diastolic flow surge in the caval veins then occurs (Reuss et al 1983).

This explains the relative increase in the diastolic flow component during the blood pressure decrease in the latter part of the umbilical cord occlusion after alpha-adrenergic blockade.

Beta-adrenergic blockade with propranolol did not essentially change the fetal heart rate and blood pressure responses during umbilical cord occlusion except for the rhythm disturbances.

No qualitative differences in the umbilical venous flow pattern changes during cord occlusions were therefore observed compared with the unblocked condition.

The degree of fetal hypoxemia and acidemia caused by umbilical cord

occlusion is of course out of proportion to the possible role of the associated relatively small uterine blood flow depression for fetal oxygenation.

It is however conceivable that the uterine flow decrease may adversely contribute to the development of fetal hypoxemia and acidemia, especially during long lasting occlusions with a sustained depression of uterine blood flow (Cottle et al 1982), in fetuses who are already severely compromised and in those situations in which the umbilical vein alone is regularly compressed.

On the other hand when considering the relatively great short-term variations that can occur in maternal uterine blood flow rate in response to changes in perfusion pressure, maternal cardiac output and autonomic tone (Clapp 1979), which variations were also observed in this study, then it is obvious that a great safety margin exists in the uterine flow rate before the fetus becomes endangered.

Moreover results from animal studies cannot be transposed to the human without restriction and one should be aware of the differences in anatomical structure between the ovine and human placenta, especially when fetomaternal placental relationships are concerned.

CHAPTER V

EFFECTS OF AGONISTS AND ANTAGONISTS OF THE AUTONOMIC NERVOUS SYSTEM ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND THE BLOOD FLOW IN THE COMMON UMBILICAL VEIN

5.1 Introduction

After the umbilical veins enter the fetal body, they fuse to form the common intraabdominal umbilical vein, through which vessel well oxygenated blood from the placenta reaches the fetus. Part of the umbilical venous blood flow is destined for liver blood supply, while the remainder (53% according to Edelstone et al 1978) passes through the ductus venosus Arantii.

The ductus venosus Arantii is one of the circulatory shunts unique to the fetus that connects the common umbilical vein with the inferior vena cava: umbilical venous blood flow accounts for more than 95% of ductus venosus blood flow, the rest is supplied by portal blood (Edelstone et al 1978, 1980a).

From the inferior vena cava umbilical venous blood flow is transported either through the right atrium to the right ventricle or through the foramen ovale to the left atrium and left ventricle. The arterial circulation distributes this oxygenated blood then to the fetal organs. After the entrance of the ductus venosus with its well oxygenated blood into the inferior vena cava with poorly oxygenated blood from the lower part of the fetal body, their flows do not mix evenly in the normoxemic fetus but a certain preferential streaming exists.

The implications of streaming of venous blood are important in the fetus with its special anatomic connections that allow mixing of well oxygenated umbilical venous blood with poorly oxygenated systemic venous blood. Streaming occurs in the thoracic inferior vena cava of

fetal monkeys (Behrman et al 1970) and lambs (Edelstone and Rudolph 1979). Well oxygenated ductus venosus blood is preferentially delivered to the brain and myocardium in both species, as compared to distal inferior vena caval blood. Streaming of blood in the right atrium occurs in such a way that superior vena caval blood passes through the right atrium mainly to the right ventricle, whereas inferior vena caval blood, which contains well oxygenated umbilical venous blood, passes both to the right ventricle and through the foramen ovale to the left atrium and left ventricle (Rudolph and Heymann 1967).

The umbilical venous part of the thoracic inferior vena caval flow streams preferentially through the foramen ovale to the left atrium and left ventricle, whereas the poorly oxygenated distal inferior vena caval blood passes preferably through the tricuspid valve (Edelstone and Rudolph 1979, Reuss et al 1981). During fetal hypoxemia however Reuss et al (1981) found a significant decrease in preferential streaming. They attributed this decrease in preference to the pulsatile flow pattern in the vena cava.

The flow pattern in both superior and inferior vena cava is pulsatile with two forward surges of blood flow during ventricular systole and diastole and the intensity of the caval pulsations is enhanced during fetal hypoxia (Reuss et al 1983). This increased amplitude of pulsations might disrupt streaming and enhance mixing of ductus venosus blood with inferior vena cava blood. Although this interruption of preferential streaming may lead to the flow of less oxygenated blood to the left heart via the foramen ovale and therefore may impair oxygen delivery to the brain and myocardium, this is well compensated for by two mechanisms.

First, there is an increase in the percentage of umbilical venous flow that bypasses the liver through the ductus venosus, causing the proportion of umbilical venous blood contributing to the fetal cardiac output to increase from 27% during normoxemia to 39% during hypoxemia (Reuss and Rudolph 1980).

Secondly, a redistribution of cardiac output occurs during hypoxemia in fetal sheep with an increase in flow to the brain and even more to the myocardium, thereby guaranteeing oxygen delivery to these organs (Peeters 1978, Reuss and Rudolph 1980).

It was shown by Reuss et al (1983) that changes in heart rate, ventricular afterload and the volumes of blood returning to the heart altered the flow pattern in the venae cavae. The afore-mentioned changes were induced by administration of various autonomic acting agents and by causing fetal hypoxemia, factors that interact with systemic and umbilical-placental vascular resistance. It was concluded by Reuss et al (1983) that these changes in the fetal systemic circulation caused alterations in fetal vena caval flow patterns and influenced the right atrioventricular filling patterns.

It was suggested by them, based however on only one observation in a single fetus, that factors which increased pulsatility in the fetal venae cavae might also influence the flow pattern in the common umbilical vein, which shows under normal conditions no or only minimal pulsations. We observed pulsatile flow patterns under various conditions in twelve fetal lambs (Hasaart and de Haan 1983, also paragraph 3.6 and 4.7).

To investigate the flow patterns in the common umbilical vein, the effects of agonists and antagonists of the autonomic nervous system upon the instantaneous umbilical venous blood flow were studied.

Because the possible effects of these autonomic acting agents on the instantaneous umbilical venous blood flow pattern are closely related to their effects on the general circulation and must be judged in connection with them, the influences of these agents on mean fetal heart rate, mean arterial blood pressure and mean umbilical venous blood flow were also studied.

5.2 Materials and methods

The cholinergic, alpha-adrenergic and beta-adrenergic parts of the autonomic nervous system (see also appendix) were blocked by administration of respectively atropine, phentolamine and propranolol. Acetylcholine, norepinephrine and fenoterol were used as agonists of respectively the cholinergic, alpha-adrenergic and beta-adrenergic part of the autonomic nervous system.

The effects of these drugs on fetal heart rate, arterial blood pressure and umbilical venous blood flow were analyzed by comparing control data with values recorded at varying moments from the start of infusion of the drug to the fetus via the femoral artery catheter. All values were calculated over an interval of 10 seconds preceding the time moment depicted in the tables. That is to say that the values shown at, e.g., 30 seconds were calculated over the interval from 20 to 30 seconds post infusion. The same can be stated of the sampling interval of each other moment depicted in the tables.

The doses of the administered bolus infusions with acetylcholine, norepinephrine and fenoterol (table 2.7) were varied, in order to assess a possible different effect on instantaneous umbilical blood flow with different doses.

All data of the infusion experiments with each specific drug were pooled irrespectively of the administered dose. The reasons therefore were threefold.

Firstly, only small quantitative and qualitative changes in mean fetal heart rate, mean arterial blood pressure and mean respectively instantaneous umbilical venous blood flow were found with higher doses of acetylcholine and norepinephrine.

Secondly, the experiments were not directed upon the assessment of dose-response curves and thirdly, the exact fetal weight at the time of the experiment was of course not known so that the interanimal variation in total administered dose has certainly been considerable.

The Wilcoxon matched-pairs signed-ranks test was used for comparison of the parameters of the variables. All p-values were calculated for two tailed tests. Data are expressed as means $\pm$ SEM.

The total number of observations at the various moments after the start

of the infusion is not always the same due to interfering factors, not allowing calculations at that particular moment.

5.3 Results

5.3.1 The effects of agonists and antagonists of the autonomic nervous system on fetal heart rate arterial blood pressure and mean umbilical venous blood flow

5.3.1.1 Cholinergic blockade with atropine

The effect of the administration of atropine on fetal heart rate, arterial blood pressure and umbilical venous flow is shown in table 5.1. Seven studies were performed in six fetal lambs between 114 and 123 days gestation (mean ± SD = 118 ± 1.8 days) Mean fetal weight ± SD at birth was 3000 ± 28.5 grams with a range from 1900 to 4100 grams.

	CONTROL N = 7	30 SEC. N = 7	60 SEC. N = 7	120 SEC. N = 5	180 SEC. N = 5	240 SEC. N = 4
FETAL HEART RATE (BPM)	159±4.6	*181±10.4	*189±9.2	177±11.9	*186±7.8	195±11.1
FETAL ARTERIAL PRESSURE (MM.HG.)	40±2.5	41±2.6	43±2.9	42±3.9	41±3.7	44±5.0
UMBILICAL VENOUS BLOOD FLOW (ML./MIN.)	511±66	*556±81	546±80	585±113	569±101	476±34

*P < 0.05

TABLE 5.1 EFFECT OF ATROPINE ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. (MEAN ± SEM)
THE ADMINISTERED DOSE OF ATROPINE WAS 1.0 MILLIGRAM / KG EFW.

There was a significant increase in heart rate at 30, 60 and 180 seconds after atropine administration. Mean fetal arterial blood pressure did not change significantly.
A small increase in umbilical venous blood flow was found with a significant difference from control values only at 30 seconds post infusion.

5.3.1.2 Alpha-adrenergic blockade with phentolamine

The effects of alpha-adrenergic blockade with phentolamine are shown in table 5.2. Nine studies were performed in six fetal lambs between 115 and 138 days gestation (mean ± SD = 123 ± 3.1 days). Mean fetal weight ± SD at birth was 3000 ± 28.5 grams with a range from 1900 to 4100 grams.

	CONTROL N = 9	30 SEC. N = 9	60 SEC. N = 9	120 SEC. N = 8	180 SEC. N = 4
FETAL HEART RATE (BPM)	174±7.9	*212±13.9	188±14.2	177±10.1	180±17.2
FETAL ARTERIAL PRESSURE (MM.HG.)	40±4.3	*34±3.4	☆31±3.4	*31±3.2	35±4.5
UMBILICAL VENOUS BLOOD FLOW (ML./MIN)	442±63.0	415±62.9	*346±51.0	*335±60.8	430±106.4

* P < 0.05 ☆ P < 0.01

TABLE 5.2 EFFECT OF PHENTOLAMINE ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. (MEAN ± SEM)
THE ADMINISTERED DOSE OF PHENTOLAMINE WAS 2.5 MILLIGRAM / KG EFW.

Heart rate increased significantly after 30 seconds and returned to control levels thereafter. Mean fetal arterial blood pressure decreased significantly by 9 mm Hg at 60 and 120 seconds post infusion.
Umbilical venous blood flow decreased significantly by 107 ml at 120 seconds. The umbilical blood flow decrease was most marked with the lowest blood pressure measured.

5.3.1.3 Beta-adrenergic blockade with propranolol

The effects of propranolol on fetal heart rate, arterial blood pressure and umbilical venous blood flow are listed in table 5.3. Seven studies were performed in five fetal lambs between 114-136 days gestation (Mean ± SD = 121 ± 2.8 days). Mean fetal weight ± SD at birth was 2780 ± 26 gram with a range from 1900 to 3600 grams.
After beta-adrenergic blockade with propranolol a decrease in fetal

heart rate of 38 bpm was found at three minutes, which was however not statistically significant, possibly due to the small number of observations. Fetal arterial pressure showed no change.
Umbilical venous blood flow declined to significantly different levels at two and three minutes from the start of the infusion.

	CONTROL N = 7	30 SEC. N = 7	60 SEC. N = 7	120 SEC. N = 7	180 SEC. N = 7
FETAL HEART RATE (BPM)	188±9.1	177±2.8	166±4.1	159±6.8	150±11.9
FETAL ARTERIAL PRESSURE (MM./HG.)	38±2.6	39±3.6	38±2.6	38±2.4	38±2.0
UMBILICAL VENOUS BLOOD FLOW (ML./MIN.)	443±95.6	423±89.6	451±100.2	★356±93.7	★334±100

★ $P < 0.05$

TABLE 5.3. EFFECT OF PROPRANOLOL ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. (MEAN ± SEM)
THE ADMINISTERED DOSE OF PROPRANOLOL WAS 1.0 MILLIGRAM / KG EFW.

5.3.1.4 Cholinergic stimulation with acetylcholine

The effects of the administration of acetylcholine on fetal heart rate, arterial blood pressure and umbilical venous blood flow are shown in table 5.4. The variables were analyzed starting directly after the end of the administration, because of the immediate effect of acetylcholine when administered to the fetal arterial circulation.
Forty-five experiments were performed in five fetal lambs between 117 and 142 days gestation (mean $\pm$ SD = 127 $\pm$ 2.9 days). Mean fetal weight $\pm$ SD at birth was 3020 $\pm$ 223 grams with a range from 2500 to 3600 grams.
There was a small decrease in fetal heart rate of 6 bpm at 60 seconds, which was significant at the $p<0.05$ level. Acetylcholine resulted in a highly significant decline in arterial blood pressure of 5 mm Hg at 30 seconds, followed by a significant increase over control levels at 30 and 60 seconds after infusion of the drug.

Umbilical venous blood flow fell concomitantly with fetal blood pressure by 22% or 129 ml/min at 10 seconds, followed by a recovery to control levels at 2 minutes. Figure 5.1 shows an example of a typical recording.

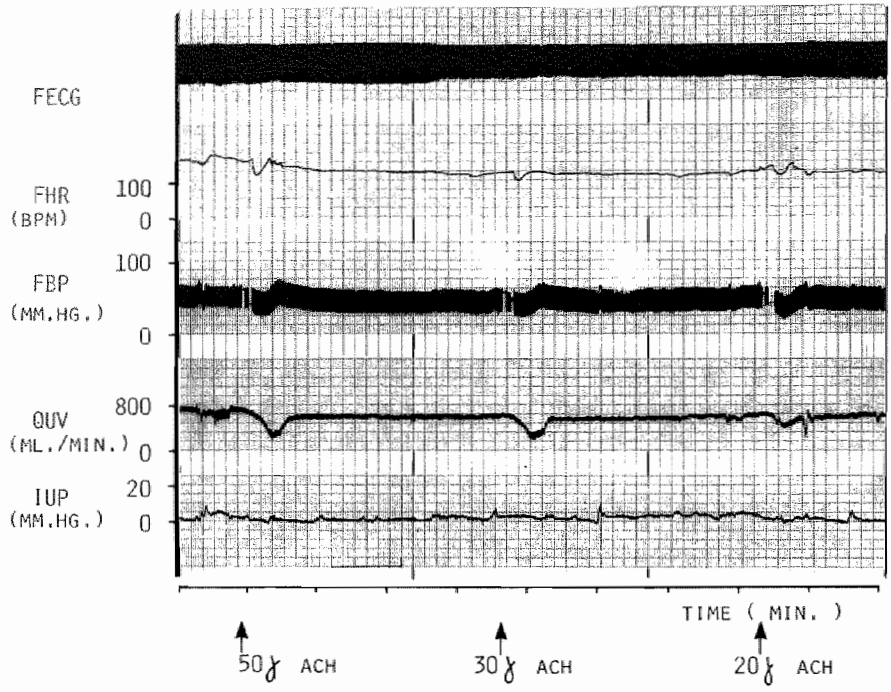


FIG. 5.1 THE EFFECTS OF BOLUS ADMINISTRATIONS OF ACETYLCHOLINE IN DIFFERENT DOSES TO THE FETUS UPON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW.

	CONTROL N = 45	10 SEC. N = 45	30 SEC. N = 45	60 SEC. N = 45	120 SEC. N = 38
FETAL HEART RATE (BPM)	168±3.6	173±4.1	169±4.2	☆162±3.1	167±3.9
FETAL ARTERIAL PRESSURE (MM.HG.)	39±1.3	★34±1.4	★42±1.2	★41±1.1	40±1.5
UMBILICAL VENOUS BLOOD FLOW (ML/MIN.)	595±46.5	★466±40.1	★525±40.3	☆562±42.4	586±49.9

★ $P < 0.001$ ☆ $P < 0.05$

TABLE 5.4 EFFECT OF ACETYLCHOLINE ON FETAL HEART RATE, FETAL ARTERIAL PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. (MEAN ± SEM)
THE ADMINISTERED DOSES OF ACETYLCHOLINE VARIED FROM 5 TO 25 MICROGRAM / KG EFW.

5.3.1.5 Alpha-adrenergic stimulation with norepinephrine

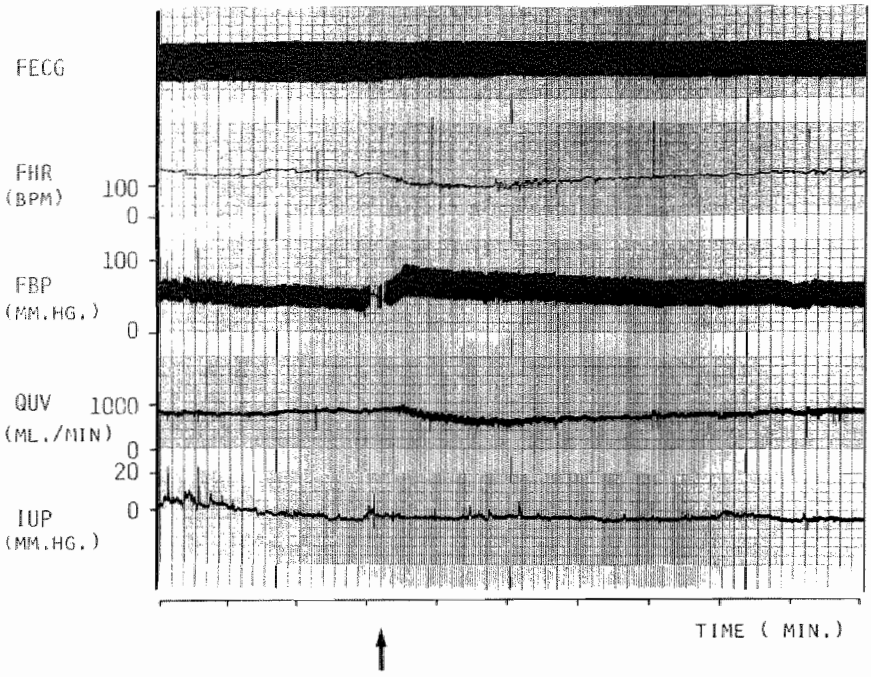
The effect of administration of norepinephrine on fetal heart rate, arterial blood pressure and umbilical venous flow is shown in table 5.5. Twenty-eight experiments were performed in seven fetal lambs between 115 and 140 days gestation (mean ± SD = 126 ± 2.7 days). Mean fetal weight ± SD at birth was 3028 ± 27 grams with a range from 2000 to 4100 grams.

Norepinephrine resulted in a marked significant decrease in the fetal heart rate over the first three minutes after the infusion. This decrease in heart rate is a reflex bradycardia in answer to the increased arterial blood pressure.

Arterial blood pressure showed an increase by 14 mm Hg at 1 minute whereafter blood pressure slowly returned to its control level at 5 minutes.

Umbilical venous blood flow showed a slight decrease during the first three minutes followed by a small increase at 4 and 5 minutes after infusion, but these differences were not statistically significant.

An example of the cardiovascular changes with norepinephrine administration is depicted in figure 5.2.



EWE 8304 GESTATIONAL AGE 135 7 DAYS P.O.

FIG. 5.2 EFFECT OF 10 γ NOREPINEPHRINE ADMINISTRATION TO THE FETAL LAMB UPON HEART RATE, BLOOD PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. NOTE THE OCCURRENCE OF PULSATIONS IN THE VENOUS FLOW DURING THE BRADYCARDIA.

	CONTROL N = 28	1 MIN. N = 28	2 MIN. N = 28	3 MIN. N = 27	4 MIN. N = 26	5 MIN. N = 24
FETAL HEART RATE (BPM)	169±4.8	*132±7.9	*142±5.6	☆158±5.6	169±5.9	170±5.3
FETAL ARTERIAL PRESSURE (MM.HG.)	42±2.3	*56±3.1	*52±2.8	*49±2.7	☆45±2.4	44±2.3
UMBILICAL VENOUS BLOOD FLOW (ML./MIN)	594±72.9	557±68.3	565±69.9	583±75.3	610±77.4	634±82.2

* P < 0.001 ☆P < 0.01

TABLE 5.5 EFFECT OF NOREPINEPHRINE ON FETAL HEART RATE, FETAL ARTERIAL PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. (MEAN ± SEM) THE ADMINISTERED DOSES OF NOREPINEPHRINE VARIED FROM 2 TO 5 MICROGRAM / KG EFW.

5.3.1.6 Beta-adrenergic stimulation with fenoterol

The effect of the administration of fenoterol on fetal heart rate, arterial blood pressure and umbilical venous flow is shown in table 5.6.

	CONTROL N = 8	1 MIN. N = 8	2 MIN. N = 8	3 MIN. N = 8	4 MIN. N = 7	5 MIN. N = 7
FETAL HEART RATE (BPM)	166±9.1	175±10.4	175±9.6	*184±10.9	178±10.6	163±9.8
FETAL ARTERIAL PRESSURE (MM.HG.)	44±4.4	43.4±3.8	46±4.5	45±3.9	46±5.6	46±5.1
UMBILICAL VENOUS BLOOD FLOW (ML./MIN.)	473±10.0	473±11.8	451±30.8	481±15.7	493±14.8	474±26.1

* P < 0.05

TABLE 5.6 EFFECT OF FENOTEROL ON FETAL HEART RATE, FETAL ARTERIAL PRESSURE AND UMBILICAL VENOUS BLOOD FLOW. (MEAN ± SEM) THE ADMINISTERED DOSES OF FENOTEROL VARIED FROM 0.5 TO 1.0 MICROGRAM / KG EFW.

Eight experiments were performed in three fetal lambs between 117 and 130 days gestation (mean ± S.D = 123 ± 3.1 days). Mean fetal weight ± SD at birth was 3367 ± 20 grams with a range from 3300 to 4100 grams.

Fenoterol resulted only in a significant increase in fetal heart rate of 18 bpm at 3 minutes. Arterial blood pressure and umbilical venous blood flow showed no significant changes.

5.3.2 The effects of agonists and antagonists of the autonomic nervous system on the instantaneous blood flow pattern in the common umbilical vein

Instantaneous umbilical venous blood flow showed in general no or only minimal pulsations without a recognizable pattern during the control registrations, unless fetal breathing movements were present which influenced instantaneous umbilical venous flow as will de discussed in chapter 7.

5.3.2.1 Cholinergic blockade with atropine

No changes were found in the instantaneous blood flow pattern of the common umbilical vein after cholinergic blockade with atropine (seven observations in six fetuses).

5.3.2.2 Alpha-adrenergic blockade with phentolamine

Administration of phentolamine to the fetus did not result in changes in the instantaneous blood flow pattern of the common umbilical vein (nine observations in six fetuses).

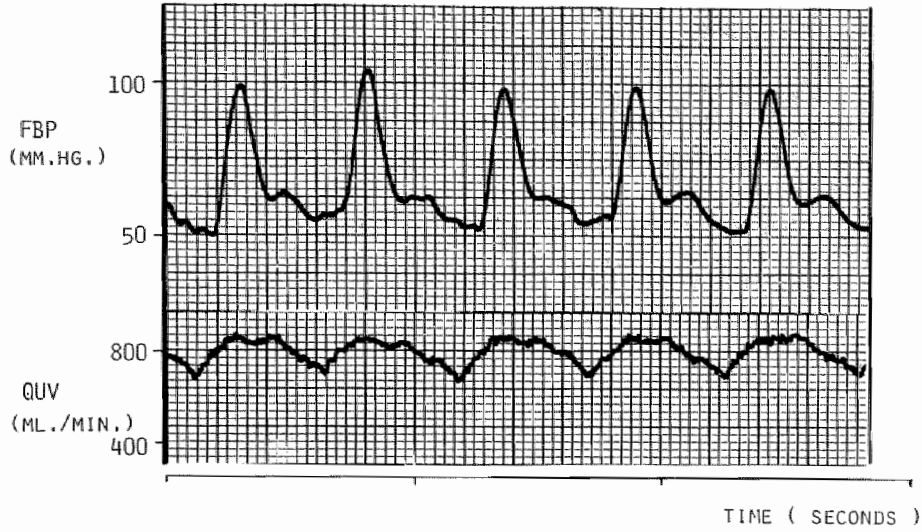
5.3.2.3 Beta-adrenergic blockade with propranolol

Also after propranolol infusion to the fetus no change in the instantaneous umbilical venous blood flow pattern was observed (seven observations in five fetuses).

5.3.2.4 Cholinergic stimulation with acetylcholine

Administration of acetylcholine to the fetus resulted in a decrease in mean umbilical venous blood flow and the occurrence of biphasic venous

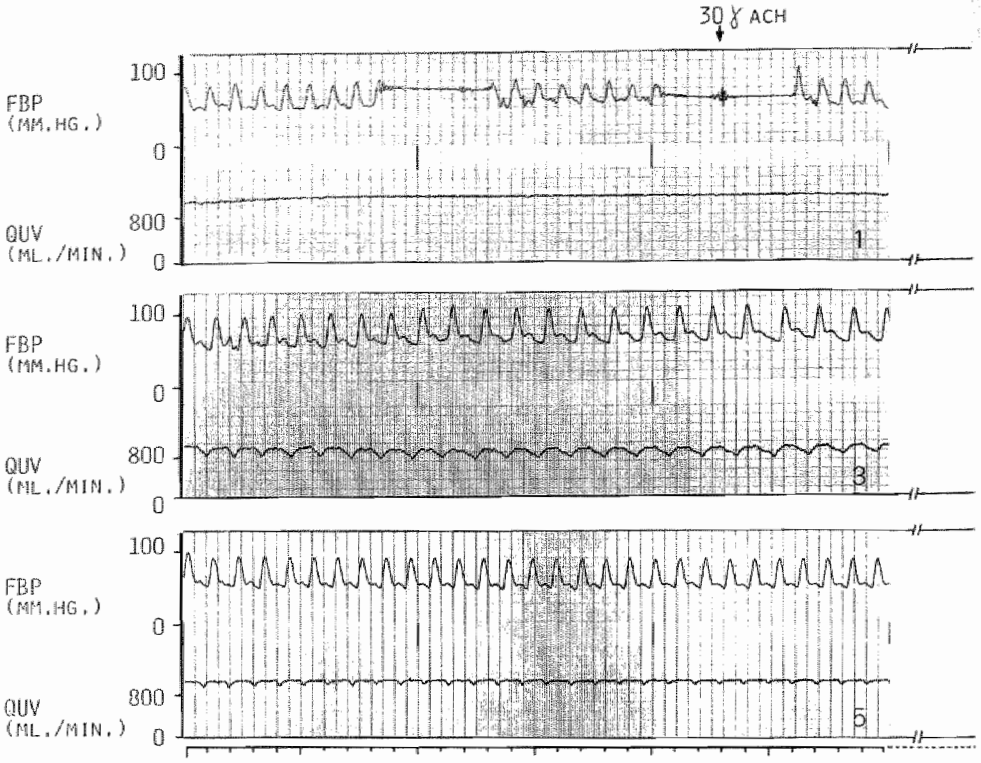
pulsations in the instantaneous blood flow in line with fetal heart rate (forty-five observations in five fetal lambs).
These pulsations consisted of two forward surges of venous blood, one occurring during ventricular systole and the second during ventricular diastole (fig. 5.3).



EWE 8304 GESTATIONAL AGE 133 5 DAYS P.O.

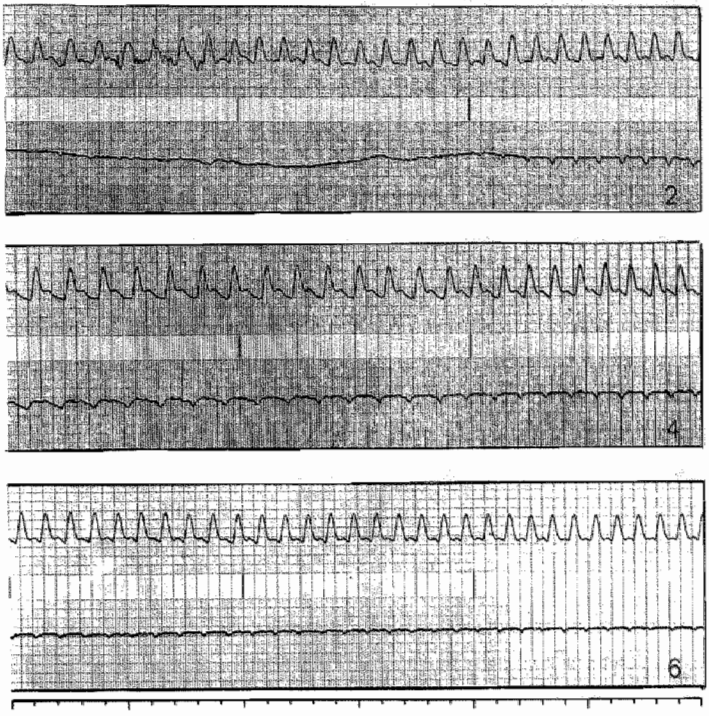
FIG 5.3 DETAIL OF THE RELATION BETWEEN THE FETAL ARTERIAL PRESSURE COMPLEX AND THE BIPHASIC UMBILICAL VENOUS PULSATIONS AFTER 30 γ ACETYLCHOLINE ADMINISTRATION TO THE FETUS.

Flow began to increase just before the beginning of the arterial pressure rise in the aorta with a peak during ventricular systole. Then a small dip occurred followed by a second increase in flow after which the flow slowly decreased and a marked reduction in flow occurred just before the beginning of the next ventricular systole. No clear difference was observed between the amplitude of the systolic and diastolic flow surge. The biphasic pulsations appeared when flow and arterial blood pressure were already returning from their nadir towards



EWE 8304 GESTATIONAL AGE 142 14 DAYS P.O.

FIG. 5.4 THE OCCURRENCE OF BIPHASIC UMBILICAL VENOUS FLOW PULSATIONS IN LINE WITH FETAL HEART RATE AFTER ACETYLCHOLINE ADMINISTRATION TO THE FETUS.


2
4
6
TIME (SECONDS)

normal values immediately after the acetylcholine administration. They increased in amplitude when fetal blood pressure began to rise above control values and gradually decreased and eventually disappeared as arterial blood pressure decreased to control values (see fig 5.4).
The amplitude of the pulsations varied from small undulations to large biphasic forms with higher doses of acetylcholine which caused more marked changes in arterial pressure and heart rate.

5.3.2.5 Alpha-adrenergic stimulation with norepinephrine

After administration of norepinephrine to the fetus mean arterial pressure rose and fetal heart rate fell. These changes were associated with the occurrence of biphasic flow patterns in the common umbilical venous blood flow which were in line with fetal heart rate. They also consisted of two small peaks during ventricular systole respectively diastole as judged by the arterial pressure curve, although their amplitude was smaller than the pulsations associated with acetylcholine administration. No distinct difference between the two flow peaks could be observed. They increased in amplitude as fetal blood pressure rose and heart rate decreased and gradually disappeared with fetal blood pressure and heart rate returning to control values.

5.3.2.6 Beta-adrenergic stimulation with fenoterol

Fenoterol administration to the fetus did not result in any change in the instantaneous flow pattern in the common umbilical vein.

5.4 Discussion

5.4.1 Effect of autonomic antagonists on heart rate, blood pressure and mean umbilical venous blood flow

5.4.1.1 Parasympathetic blockade with atropine

Parasympathetic blockade with atropine increased fetal heart rate. This change was consistent with previous reported effects (Vapaavouri et al 1973, Nuwayhid et al 1975b, Evers 1978, Harris et al 1979, Edelstone et al 1980b, Rankin et al 1980). Mean arterial blood pressure did not significantly change.

The increase in umbilical venous blood flow can be explained by the increased fetal heart rate after cholinergic blockade, since umbilical blood flow correlates positively with fetal heart rate and arterial blood pressure (Rudolph 1976). The increase in umbilical venous blood flow during cholinergic receptor blockade was therefore probably secondarily caused by the increase in fetal heart rate rather than by a specific effect of parasympathetic blockade on the placental vessels or common umbilical vein.

This latter supposition could only be true if cholinergic receptors sites were present in the umbilical vein. No clear evidence however exists of vasomotor control of extracorporal foetal umbilical cord flow, whereas data from histochemical studies identifying cholinergic neural fibers in the intraabdominal umbilical vein in man are conflicting. Ehinger et al (1968) recognized only adrenergic innervation in the intraabdominal vein and in the ductus venosus in the human fetus, whereas Pearson and Sauter (1969) found both cholinergic and adrenergic nerve fibers.

An increase in umbilical venous flow after cholinergic blockade was also found by Edelstone et al (1980b) and Rankin et al (1980) in a study with radioactive microspheres. Harris et al (1979) found a minimal nonsignificant increase in umbilical arterial blood flow after atropine administration to the fetus.

5.4.1.2 Alpha-adrenergic blockade with phentolamine

The considerable decrease in blood pressure after alpha-adrenergic blockade with phentolamine was accompanied by a fall in umbilical blood flow. The increase in fetal heart rate which was only noted immediately after the infusion of the drug might be regarded as a fetal compensatory mechanism for the ensued hypotension and decreased vascular resistance, but the direct sympathico-mimetic stimulating effect of phentolamine on cardiac tissue might also plays a role (Goodman and Gilman 1980).

The decrease in umbilical blood flow with a constant heart rate can be explained by the arterial hypotension. A change in umbilical placental resistance after alpha-adrenergic blockade could not be determined, because umbilical venous pressure was not measured. Edelstone et al (1980b) however showed that umbilical vascular resistance was not affected by alpha-adrenergic blockade with phentolamine. They found moreover no change in umbilical blood flow measured by means of the radioactive microsphere technique or in heart rate while mean arterial blood pressure decreased only 3 mm Hg in contrast to the observations (9 mm Hg) in this study.

Rankin and Phernetton (1978) also found no significant influence on umbilical vascular resistance and placental umbilical blood flow measured with microspheres after alpha-adrenergic blockade with phenoxybenzamine. Mean arterial pressure decreased 2 mm Hg in that study.

Vapaavouri at al (1973) measured a decrease of 7 mm Hg in systolic blood pressure after phentolamine in near-term fetal lambs, while heart rate showed a delayed increase of 15 to 80 beats/min.

Nuwayhid et al (1975b) found a 26% to 30% decrease in mean arterial blood pressure, but no change in heart rate after phenoxybenzamine in fetal lambs, part of which were however studied under anesthesia.

Chez et al (1978) found a 16% to 30% increase in fetal heart rate with no change in umbilical venous blood flow and arterial blood pressure with phenoxybenzamine administration.

In the investigations in which no change in umbilical blood flow was found, there was also a minor decrease in fetal arterial pressure.

Direct administration of phentolamine into the fetal descending aorta via the femoral artery catheter as was done in this study might provoke a more immediate and extensive vasodilatation than after administration to the fetal venous circulation, as was done in the studies by Rankin and Phernetton (1978), Chez et al (1978) and Edelstone et al (1980b). Although the doses of phentolamine (0.10 to 0.12 mg/kg EFW) were much smaller in the study by Edelstone et al than in the present study (2.5 mg/kg EFW), incomplete blockade was excluded by them by the absence of changes in heart rate or blood pressure in response to the agonist methoxamine. The influences of a different gestational age can also be excluded as a cause for the difference in results since in all studies near-term fetuses were used.
It is very likely that the fall in umbilical blood flow in the present study was caused by the considerable decrease in arterial blood pressure, although an increase in umbilical placental resistance cannot be excluded.

5.4.1.3 Beta-adrenergic blockade with propranolol

The decrease in fetal heart rate after beta-adrenergic blockade was of the same magnitude as that reported by Vapaavouri et al (1973), Nuwayhid et al (1975a), Llanos et al (1980) and Cohn et al (1982), while Harris et al (1979) reported only half of the decline in heart rate. Continuous infusion of propranolol also decreased fetal heart rate, as was shown by Oakes et al (1976b) and Ayromlooi (1983).
The absence of a blood pressure change is in agreement with the studies by Oakes et al (1976b), Harris et al (1979), Llanos et al (1980), Cohn et al (1982) and Ayromlooi (1983).
The 20% decrease in umbilical blood flow at 180 seconds is in agreement with the results of Oakes et al (1976b) and Cohn et al (1982) who also found significant decreases in umbilical blood flow of respectively 19% and 10% after propranolol.
Harris et al (1979) also reported a decrease in umbilical blood flow, although nonsignificant, of 23% after propranolol. No significant changes in umbilical vascular resistance were found in the study of Harris et al (1979), whereas Oakes et al (1976b) and Cohn et al (1982)

reported an increase in umbilical vascular resistance of 25% respectively 11% above control values.

The decrease in umbilical blood flow after beta-adrenergic blockade in the present study can be explained for the greater part by the concomitant fall in heart rate, but an increase in umbilical vascular resistance can not be excluded from the present data and might add to the decrease in umbilical blood flow.

Oakes et al (1976b) suggested that basal flow in the umbilical vascular bed is affected by a tonic beta-adrenergic activity, which conclusion was based on the increased umbilical vascular resistance after beta-adrenergic blockade.

Rudolph (1976) and Berman et al (1978) however pointed out that calculation of umbilical placental vascular resistance from the conventional formula based on the Poiseuille equation (umbilical resistance =(mean aortic - umbilical venous pressure) : umbilical blood flow) is not reliable if there are alterations in heart rate.

The present data do not allow a certain conclusion with respect to the presence of beta-adrenergic control of the umbilical circulation.

If the umbilical circulation is under control of the beta-adrenergic nervous system then the site of the variable resistance must be located in the intracorporal sections of the umbilical circulation, as no anatomical or histochemical evidence exists of vasomotor control of the extracorporal umbilical and placental vasculature.

5.4.2 Effect of agonists of the autonomic nervous system on heart rate, blood pressure and mean umbilical venous blood flow

5.4.2.1 Cholinergic stimulation with acetylcholine

The reduction in umbilical blood flow after cholinergic stimulation with acetylcholine resulted from the fall in arterial pressure, because acetylcholine probably does not change umbilical placental vascular resistance (Berman et al 1978).
The fall in arterial blood pressure after acetylcholine is caused by two mechanisms. There is a reduction in the vascular resistance in the systemic circulation (Berman et al 1978), leading to hypotension with a secondary fall caused by the decrease in the pulmonary vascular pressure (Nuwayhid et al 1975b).
The fall in blood pressure and umbilical blood flow were more obvious with higher doses of acetylcholine (25 microgram/kg EFW), which result is in agreement with the findings of Nuwayhid et al (1975b).

5.4.2.2 Alpha-adrenergic stimulation with norepinephrine

Norepinephrine causes an increase in the peripheral resistance due to vasoconstriction.
The decrease in heart rate after norepinephrine administration is a reflex bradycardia caused by the increased arterial blood pressure and initiated via the baroreceptors.
The responsiveness of the placental circulation in the near-term sheep to alpha-adrenergic stimulation has been shown by Barrett et al (1972) and was subsequently confirmed by other investigators (Rankin and Phernetton 1976, Chez et al 1978) indicating the existence of functional alpha receptors in the placental vascular bed.
The small decrease in umbilical blood flow in the face of a serious increase in perfusion pressure and a relatively small decrease in heart rate found in this study suggests that umbilical vascular resistance increased. This cannot be further proven, because fetal venous pressure was not measured. Whether norepinephrine and related cathecholamines

have a vasoconstricting effect on the umbilical circulation has been the subject of many discussions in the literature.

Novy et al (1974) found no change in umbilical placental vascular resistance after norepinephrine (1 to 2 microgram/kg EFW).

Rankin and Phernetton (1976) on the contrary found a 40% decrease in umbilical blood flow with a significant increase in placental vascular resistance with doses of 22 to 120 micrograms of norepinephrine kg/EFW.

Berman et al (1978) stated that norepinephrine (maximum total dose 2 microgram) altered umbilical blood flow secondary to changes in heart rate and placental perfusion pressure, but did not change umbilical placental vascular resistance. Their calculations of vascular resistance were done when there was no change in heart rate, because they questioned the validity of the Poiseuille equation for the calculation of umbilical vascular resistance when there were changes in heart rate (Rudolph 1976, Berman et al 1978). The calculations of umbilical resistance after norepinephrine administration were therefore done after fixing the heart rate by cholinergic blockade with atropine.

Rankin et al (1980) questioned these results and they concluded from their experiments with intravenous administration of 50 micrograms norepinephrine per minute that fetal heart rate is not a major determinant of umbilical blood flow and that high doses of norepinephrine cause vasoconstriction of the placental vascular bed of the near-term sheep fetus.

Zink and van Petten (1981) however found in a study done with radioactive microspheres that placental blood flow increased in proportion to the increment of arterial pressure in the fetus, showing that the placental bed was not appreciably constricted by norepinephrine in a dose of 1 microgram/kg/min.

Chez et al (1978) found a very small (<6%) decrease in umbilical blood flow with continuous infusion of 1 microgram/kg/min.

It can be inferred from the above mentioned studies that the vasoconstrictive effects of norepinephrine are dose related. Low doses (1-2 microgram Kg/ EFW) cause only minimal changes in umbilical blood flow and placental vascular resistance, while higher doses (>20 microgram Kg/ EFW) constrict the umbilical circulation and cause an increase in umbilical vascular resistance. The results from this study

indicate that placental vascular resistance may be already increased with doses of 2-5 microgram/Kg EFW.

5.4.2.3 Beta-adrenergic stimulation with fenoterol

Beta-adrenergic agonists have a stimulating effect on fetal heart rate without changes in arterial pressure after administration to the lamb (Chez et al 1978). The umbilical vessels are under normal circumstances fully dilated and beta-receptor stimulation does not lead to a decrease in umbilical vascular resistance (Berman et al 1978). The increases in umbilical blood flow after beta-adrenergic drugs are therefore probably directly related to the associated increases in heart rate.
In the small number of experiments from this study no changes in blood pressure or umbilical blood flow were found after a bolus injection of fenoterol, but only a small increase in heart rate, which result was to be expected.

5.4.3 Effect of agonists and antagonists of the autonomic nervous system on the instantaneous blood flow pattern in the common umbilical vein

Under normal conditions biphasic pulsations in line with fetal heart rate are absent in the sheep fetus. This is in contrast to the flow pattern in both venae cavae in the fetal sheep, in which vessels blood flow is always pulsatile, inversely related to venous pressure and influenced by the cardiac cycle and respiratory movements (Reuss et al 1983). These pulsations evidently are not big enough under normal circumstances to be propagated via the ductus venosus to the common umbilical vein. Those conditions which increase the pulsatility in the vena cava inferior as norepinephrine and acetylcholine administration (Reuss et al 1983) also provoke a biphasic pulsatile flow pattern in line with fetal heart rate in the common umbilical vein. The common finding with norepinephrine and acetylcholine administration was a decrease in fetal heart rate. The pulsations intensified after acetylcholine administration in the cases with slower heart rates. Slower heart rates allow for a longer diastolic atrial filling period

with a more prominent diastolic flow surge. This results in a higher atrial pressure development with the next contraction, which might have in turn an impeding effect on forward flow in the venae cavae leading to exaggerated biphasic pulsations.

The same phenomenon occurs with norepinephrine. In contrast to the biphasic flow pattern in the venae cavae there was only a small dip in between the systolic and diastolic component of the flow surge and no change was found in the magnitude of the systolic flow surge after either norepinephrine or acetylcholine. The flow pattern in the venae cavae showed an increased peak systolic flow after norepinephrine which Reuss et al (1983) explained by the increase in afterload associated with peripheral vasoconstriction and increased systemic arterial pressure. This leads to a higher end-diastolic pressure and an increase in ventricular contraction force which in turn could increase peak systolic flow.

The same mechanism is applicable to the increase in the diastolic component of the flow surge after acetylcholine. Acetylcholine reduces afterload by peripheral vasodilatation resulting in a greater ventricular emptying. Furthermore there is vasodilatation in the pulmonary vascular bed with acetylcholine (Nuwayhid et al 1975b) also allowing a greater ventricular emptying. End-diastolic atrial pressure is then reduced, permitting a greater diastolic flow surge.

The damping of the pulse waves in the propagation circuit from vena cava via ductus venosus to common umbilical vein is probably the reason that these differences in magnitude of the systolic and diastolic flow surges could not be seen in the flow pattern of the common umbilical vein.

It is concluded from these results that biphasic flow pulsations occur in the common umbilical vein under conditions which increase pulsatility in the venae cavae.

The influences of alterations in vena cava flow patterns on right atrioventricular filling patterns have been outlined by Reuss et al (1983).

It is very likely that flow pulsations in the common umbilical vein and thus also in the ductus venosus can increase the degree of mixing of systemic inferior vena cava and placental ductus venosus blood and thus

can interrupt preferential vena cava blood streaming leading to an alteration in the distribution of inferior vena cava blood in the fetal heart.

CHAPTER VI

EFFECTS OF FENOTEROL, NOREPINEPHRINE AND ACETYLCHOLINE INFUSION TO THE EWE ON MATERNAL PELVIC ARTERIAL AND FETAL UMBILICAL VENOUS BLOOD FLOW

6.1 Introduction

Since Barcroft et al (1933) first measured uterine blood flow in the pregnant rabbit, a significant amount of quantitative and qualitative knowledge on blood flow to the gravid uterus has accumulated. Among the various adjustments that take place in the maternal organism during pregnancy, the increase in maternal cardiac output and blood volume on the one hand and the rise in uterine blood flow on the other hand are considered to be of enormous importance for both the fetal and maternal homeostasis.

The increase in maternal cardiac output and blood volume begins early in pregnancy and amounts up to 42% over control values during the last part of gestation in sheep (Clapp 1978). The development of the uteroplacental circulation as a low resistance circulatory network causes a nearly tenfold decrease in uterine vascular resistance in sheep (Assali and Brinkman 1972).

The overall systemic vascular resistance of the mother falls approximately 30% during pregnancy due to this low placental vascular resistance. This decrease in the systemic vascular resistance helps to accommodate the increase in maternal cardiac output. At term uterine blood flow comprises approximately 80% of the pregnancy associated increase in cardiac output in the ewe (Clapp 1978).

In sheep, the uterine blood flow increases from about 1.5 ml/min per kilogram of the ewe's weight in the nonpregnant state to about 17 ml/min per kilogram of the ewe's weight near term pregnancy (Dilts et al 1969).

The mechanism underlying this massive sustained increase of uterine blood flow occurring during pregnancy could be merely a consequence of the increased cardiac output coupled with the development of the low resistance placental circulation, but there also might be active dilation of the uterine vasculature due to hormonal, chemical or nervous influences from the autonomic nervous system.

Evidence exists that the steroids oestrogen and progesterone influence the basal rate of uterine blood flow and its distribution throughout pregnancy in sheep (Rosenfeld et al 1975).

Support for the role of these steroids can be found in the fluctuations in uterine flow that occur in the cycling nonpregnant ewe, which reflect the cyclical hormonal changes (Greiss and Anderson 1969).

These changes can be reproduced by the administration of exogenous oestrogen and progesterone to the nonpregnant ewe (Greiss and Anderson 1970, Caton et al 1974).

Exogenous oestrogens also cause an increase in uterine blood flow in pregnant ewes (Greiss and Marston 1965).

As in most biological systems, there is not one single factor that regulates uterine blood flow, but this flow must be seen as the end result of many influences which among them also comprise the prostaglandins and the renin-angiotensin system (Rankin and McLaughlin 1979).

Regarding the presence of autoregulation of the maternal placental blood flow, which term is used for the ability of an organ to adjust and maintain its blood flow at a constant rate under changing perfusing pressure through adjustment in the intrinsic vascular resistance, Greiss (1966), Ladner et al (1970), and Assali and Brinkman (1972) have demonstrated that in the near term pregnant sheep autoregulation is absent in the maternal uterine circulation. Recent work by Greiss et al (1976) indicated however that autoregulation might be present in the myoendometrial or nonplacental vasculature but not in the placental cotyledons.

6.2 Nomenclature of the arterial pelvic vasculature

Blood flow measurements in the pelvic arterial bed of the ewe with

electromagnetic flow transducers have been performed on various anatomical sites. The following vessels have been used for continuous flow measurements:

1. the common internal or hypogastric iliac artery
2. the internal iliac or hypogastric artery
3. the main uterine artery
4. the middle or median uterine artery

The anatomy of the distal aortic trifurcation with the nomenclature of these branches has been described in paragraph 2.4.1 (fig 2.1).
One should bear in mind the anatomical location of the flow transducers when comparing the results of different studies. In the following review of the literature on the effects of various autonomic acting drugs on the pelvic arterial flow, attention will be paid to the particular flow transducer sites.

6.3 Blood flow responses of the maternal pelvic vascular bed to vasoactive stimuli

6.3.1 Alpha-adrenergic agents

The effects of the catecholamines on uterine blood flow were first studied by Robson and Schild in 1938. They found that epinephrine produced arterial vasoconstriction in both pregnant cats and castrated cats treated with estrone or estrone and progesterone.
The vasoconstrictive effects of epinephrine were further confirmed in pregnant dogs by Ahlquist and Woodbury (1947) and by Adams et al (1961) in pregnant ewes.
Extensive studies into adrenergic influences on uterine flow were done by Greiss et al in the sixties and early seventies. They found that norepinephrine and epinephrine caused a marked reduction in uterine blood flow during the last half of pregnancy after intravenous administration. This reduced uterine blood flow was almost exclusively due to increased vascular resistance with negligible changes in myometrial tension (Greiss 1963, Greiss and Pick 1964). Although his earlier studies indicated that only alpha adrenergic excitatory receptors were present in the ovine uterine vascular bed, later studies

showed the presence of beta adrenergic receptors in the myoendometrial bed too (Greiss 1971, 1972), but no evidence for their existence in the placental bed was found.

Ladner et al (1970) stimulated the alpha receptors in pregnant and nonpregnant ewes with intravenous and intraarterial administration of norepinephrine. They found a small increase in the flow of the median uterine artery with small intravenous doses of norepinephrine (0.5 microgram/kg/min) and a decrease with the larger doses. Direct intraarterial infusion via the uterine artery caused an immediate and striking fall in median uterine artery flow without significant alterations in arterial pressure. This vasoconstrictive effect of norepinephrine could be completely inhibited by the alpha blocker dibenzyline. The effects of norepinephrine were greater in nonpregnant than pregnant animals, which might be caused by a diminished alpha receptor activity during pregnancy related to the different hormonal environment.

Ladner et al (1970) ascribed the difference in response to vasoactive stimuli between pregnant and nonpregnant animals to the presence of the placenta which acts as a low resistance system, dampening the cardiovascular responses.

Assali et al (1981) also found a greater vasoconstriction in the common internal iliac artery in nonpregnant than in pregnant sheep upon intravenous administration of norepinephrine via the jugular vein and intraarterial administration via the distal aorta. They ascribed this difference in part to the greater dilution of a given dose of the drug in the greater blood volume in pregnant sheep, which would result in lower plasma levels in pregnant than in nonpregnant animals.

Rosenfeld et al (1976) showed in a study with radioactive microspheres that the vasculature of all three uterine tissues (endometrium, myometrium and placental cotyledons) are sensitive to the vasoconstrictive effects of epinephrine.

The flow in the main uterine artery also decreased after intravenous norepinephrine administration (Chez et al 1978). The vasoconstrictive effect of endogenous catecholamines were studied by Shnider et al (1979) who measured median uterine artery flow and endogenous norepinephrine plasma levels during application of stressing stimuli to

pregnant ewes. They concluded that maternal stress may decrease uterine flow secondary to release of endogenous norepinephrine.

6.3.2 Beta-adrenergic agents

Beta-adrenergic agents with preferential beta 2 activity are widely used in human obstetrics mainly for treatment of premature labor.
Several beta sympathicomimetic drugs such as fenoterol, salbutamol, ritodrine, terbutaline and isoxsuprine are nowadays available for tocolysis. They have in common associated cardiovascular and metabolic effects as well. In general they increase the maternal heart rate and decrease the maternal blood pressure and their use is accompanied by hyperglycemia. The magnitude of the cardiovascular effects vary with the drugs, which are infused. The effects of beta-adrenergic agents on uterine blood flow have been studied in several species including the pregnant sheep.
Greiss (1972) showed that beta-adrenergic receptors are present in the uterine vascular bed.
The group of Chez and Ehrenkranz studied uterine blood flow during continuous two hours intravenous administration of beta-mimetic drugs (Ehrenkranz et al 1976, 1977a, 1977b, Chez et al 1978). The uterine blood flow in their studies was measured with an electromagnetic flow transducer around the main uterine artery. They found a marked decrease in uterine blood flow with isoxsuprine and ritodrine, a minimal decrease with salbutamol and no change with fenoterol.
Similarly, mean maternal arterial pressure moderately decreased with isoxsuprine and ritodrine, decreased less with salbutamol and did not change with fenoterol. All four drugs were associated with maternal tachycardia. During the final 45 minutes of ritodrine and salbutamol infusion to the ewe, uterine blood flow began to return to control levels, while mean maternal arterial pressure remained decreased. During the subsequent control period there was a significant hyperemia after infusion of salbutamol and fenoterol, but not after ritodrine administration.
The initial depression of uterine blood flow and mean arterial pressure associated with administration of ritodrine or salbutamol was found to

abate with time despite continued drug infusion during prolonged infusions of these drugs (Brennan et al 1977). An increased uterine vascular resistance was found with ritodrine while salbutamol and fenoterol decreased uterine vascular resistance (Brennan et al 1977).
Nuwayhid et al (1980) studied the effect of continuous infusion of isoxsuprine and terbutaline on the flow in the maternal common internal iliac artery and median uterine artery in pregnant ewes.
Both agents caused an increase of the common internal iliac artery flow, but isoxsuprine decreased the uterine artery flow significantly, while terbutaline had only a small decreasing effect on uterine artery flow.
Milliez et al (1981) reported no change in median uterine artery flow during terbutaline infusion in the same dose as used by Brennan et al (0.40 microgram/kg /min) but in higher drug concentration (0.80 microgram/kg/min) a decrease in uterine flow was found.
Ayromlooi et al (1981) continuously infused isoxsuprine to pregnant ewes and found no significant change in median uterine artery flow.
Simultaneous measurements of common internal iliac artery and uterine artery blood flow were performed by Tabsh et al (1981). They found an insignificant effect on the common internal iliac artery blood flow but a decreased blood flow in the median uterine artery during continuous isoxsuprine infusion to pregnant ewes. They concluded that these contiguous vascular beds respond differently to isoxsuprine.
Erkkola et al (1981) stimulated beta-adrenergic receptors in the pelvic vascular bed of pregnant sheep by means of intraarterially administration of adrenergic drugs via a catheter located in the aortic trifurcation. Blood flow was measured in the common internal iliac and median uterine artery. After beta receptor stimulation with isoproterenol a profound vasodilatation occurred in the tissues served by the common internal iliac artery with an increase in blood flow, whereas the flow in the median uterine artery slightly but consistently decreased. They concluded that stimulation of beta-adrenergic receptors produced active vasodilatation in extra-uterine vascular beds with minor changes in uterine blood flow of the pregnant horn. They supposed the changes in uterine blood flow observed during beta-adrenergic stimulation to be secondary and related to a shift of blood from the

uterus to other vascular beds that were actively dilated.
Assali et al (1981) also found a consistent increase in blood flow in the common internal iliac artery in response to intravenous isoprotenerol administration. Maternal arterial pressure decreased and heart rate increased significantly during the infusion period.
The confusion in the literature regarding the effects of beta-adrenergic drugs on uterine blood flow can thus partially be explained by the different anatomical locations at which blood flow was measured by means of electromagnetic flow transducers. It is furthermore obvious that not all beta-adrenergic drugs have the same effect on pelvic arterial blood flow, probably due to differences in beta 1 and beta 2 activity as well as possible alpha-adrenergic and nonadrenergic effects. It is also clear from the above cited studies that the flow changes in the pelvic vascular bed elicited by beta-adrenergic agents in pregnant sheep are dose related.

6.3.3 Cholinergic agents

Ahlquist and Woodbury (1947) were among the first ones who reported increased uterine blood flow after acetylcholine administration to pregnant dogs and to dogs in the postpartum period. Greiss et al (1967c) showed that acetylcholine causes vasodilatation in the uterine vascular bed of the sheep, which effect was however many times greater in nonpregnant ewes than in pregnant ewes. Greiss measured the blood flow in the median uterine artery.
Assali et al (1981) reported that during intravenous administration of acetylcholine to the ewe, common iliac artery blood flow did not change significantly in pregnant animals but increased to about 100% in the nonpregnant sheep. After intraarterial injection of acetylcholine just above the aortic trifurcation, common iliac artery flow increased in both pregnant and nonpregnant ewes, but the increment in the latter was significantly greater than in the former.
This difference in reactivity between pregnant and nonpregnant sheep was attributed by them largely to the dilution of a given dose of the agent by the larger blood volume and blood flow that exist during pregnancy, rather than to the fact that the vessels were maximally

dilated during pregnancy due to hormonal influences.
Erkkola et al (1981) found that stimulation of cholinergic receptors by intraarterial acetylcholine administration produced active vasodilatation in extrauterine vascular beds with an increase in the common internal iliac artery flow and only minor changes in uterine flow of the pregnant horn, as measured in the median uterine artery.

6.4 Innervation of the uterine vascular bed

The uterine arteries in the sheep are supplied with nerve fibers that enter the uterus with the vessels. The uterine arteries are extremely sensitive to manipulation and they constrict intensively in the manipulated segment. The spasm of these vessels can be released by infiltration of the adventitia with anesthetic solutions suggesting a neurogenic nature of the vasoconstriction (Assali and Brinkman 1972).
There is a great interspecies difference in the nature of the innervation of the uterine vessels, while in the same species the hormonal status and gestational date also play a role in the degree of innervation and neural excitability (Bell 1972, 1974). The possible involvement of cholinergic vasodilator nerves in the maintenance of uterine blood flow in sheep was discounted by Greiss et al (1967c), because they were unable to produce increases in uterine blood flow by stimulation of either sympathetic or parasympathetic roots (Greiss and Gobble 1967, Greiss et al 1967b).
Bell (1971) confirmed the absence of cholinergic vasomotor nerves at least to the parametrial vessels in the sheep histochemically. Evidence for adrenergic nerve fibers in the parametrial arteries of sheep is indirect and not based on histochemical studies.
Greiss and Gobble (1967) found uterine vasoconstriction upon adrenergic sympathetic nerve stimulation in the pregnant sheep. The uterine vasculature reacts with a strong vasoconstriction upon alpha-adrenergic receptor stimulation (Barton et al 1974).
Greiss (1972) found a difference in reactivity of the myoendometrial and placental vasculature upon alpha-adrenergic stimulation with a pronounced flow reducing effect in the myoendometrium and a much smaller influence on the placental bed.

Beta-adrenergic receptor stimulation had a significant effect on myoendometrial vasculature, while no reaction in the placental vasculature occurred (Greiss 1971, 1972).

6.5 Effects of maternal infusion with alpha-adrenergic, beta-adrenergic and cholinergic agents upon umbilical blood flow

6.5.1 Influences of alpha-adrenergic agents

Chez et al (1978) found no change in umbilical venous blood flow upon maternal norepinephrine administration. Fetal arterial pressure mildly increased and fetal heart rate decreased. Wilkening et al (1982) also did not observe an appreciable effect on umbilical blood flow after uterine flow reduction by means of maternal norepinephrine infusion.

6.5.2 Influences of beta-adrenergic agents

The group of Chez and Ehrenkranz studied umbilical venous blood flow during maternal infusion with beta-adrenergic agents. They found a 15% increase above control in umbilical blood flow and a 50% increase in heart rate during maternal isoproterenol infusion. Isoxsuprine administration was asssociated with a moderate fetal tachycardia and a slight increase in umbilical blood flow. There were no significant changes in umbilical blood flow, mean fetal arterial pressure or fetal heart rate with ritodrine, salbutamol or fenoterol. However, incremental trends in both umbilical blood flow and fetal heart rate were observed when ritodrine or fenoterol were infused to the mother. But these trends were not significant because of inconsistency and variability from one fetus to another and the relatively small total number of animals (Ehrenkranz et al 1976, 1977a, 1977b, Chez et al 1978). Brennan et al (1977) found an increase in umbilical flow during long lasting maternal infusions with ritodrine and no significant change with fenoterol and salbutamol.

6.5.3 Influence of acetylcholine

No data exist to our knowledge on potential effects of maternal acetylcholine infusion on fetal umbilical blood flow.

6.6 Aim of the investigation

Aim of this part of the study was first to assess whether the vascular bed supplied by the internal iliac artery and the median uterine artery reacted with flow changes during maternal intravenous administration of adrenergic and cholinergic agonists. Secondly whether any difference in flow reactions between those two vascular beds existed during adrenergic and cholinergic receptor stimulation.

The fetal part encompasses the possible changes in fetal heart rate, arterial blood pressure, umbilical venous blood flow and acid-base balance during induced changes in maternal pelvic blood flow.

6.7 Materials and methods

Fifty eight maternal infusion experiments were performed in twelve animals. The infusion protocol for each drug has been described in paragraph 2.10.5.1, whereas the doses and infusion times of fenoterol, norepinephrine and acetylcholine are shown in table 2.10.

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 in case of an infusion with acetylcholine or norepinephrine the last five minutes of each sequential infusion period of fifteen minutes' duration.

The fetal and maternal parameters were therefore calculated during the infusion with acetylcholine or norepinephrine 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.

Other intervals were chosen to analyse the effects of the fenoterol infusions. Data were calculated over a five minute interval in the control period and during the last five minutes of both thirty minute infusion periods and of the thirty minute recovery period. Consequently the following intervals during infusion and recovery period were analysed: the intervals 25 to 30 (=30), 45 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 analysed 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. The distribution of the fetal and maternal blood flow measurements for each drug are given in table 2.9.

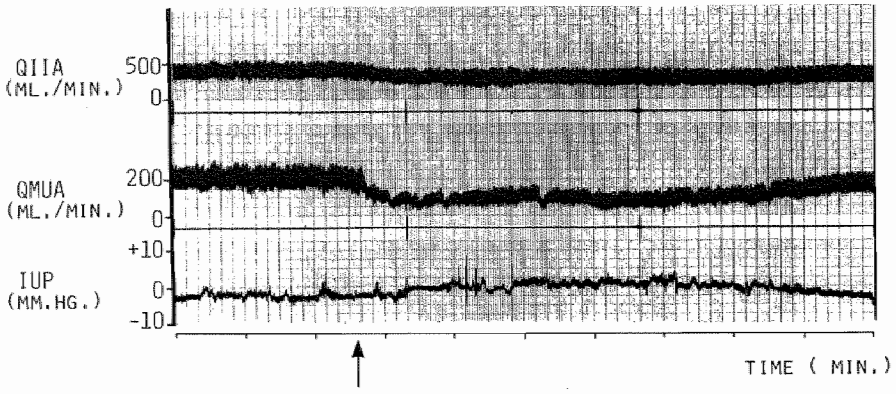
Fetal pH and blood gas values were determined during the control period (=C), and at the end of the infusion (=60) and recovery period (=90).

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 student's t-test.

6.8 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.

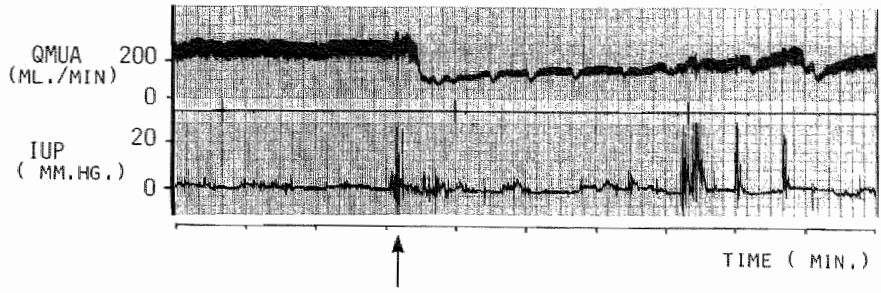


EWE 8303 GESTATIONAL AGE 113 3 DAYS P.O.

FIG. 6.1 DECREASES IN INTERNAL ILIAC AND MEDIAN UTERINE ARTERY BLOOD FLOW WHEN THE EWE WAS STARTLED (↑).

Short term variations of 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 in maternal internal iliac and median uterine artery blood flow is impressive. This is illustrated by the abrupt and often prolonged decreases in blood flow

sometimes occurring during micturition and defecation and also during moments when the ewe became frightened by sudden unexpected movements of the investigator (fig 6.1). Figure 6.2 shows an example of the decreases in maternal blood flow during micturition.



EWE 8207 GESTATIONAL AGE 129 3 DAYS P.O.

FIG. 6.2 THE INFLUENCE OF MICTURITION (↓) ON MEDIAN UTERINE ARTERY BLOOD FLOW.

Minor variations in blood flow were observed during postural changes of the ewe. There was a possible 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 analysed in this study. Small short lasting decreases in median uterine artery blood flow were also found during increases in uterine tone, as reflected in the amniotic pressure. Regular contractions were absent during the experiments.

Displacement of the flow transducers around the maternal vessels during e.g. micturition or maternal movements is a possible cause for the observed flow changes in the first days after implantation of the flow transducers. It is however unlikely that displacement of the flow transducers occurred several days after operation, because they were found to be firmly attached to the vessel wall by adhesions at that time.

The experiments with decreases in maternal blood flow associated with micturition, defecation and fright were excluded from the study.

6.8.1 Effect of continuous administration of fenoterol to the ewe on the maternal and fetal parameters

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. 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.

	-30'	0'	30'	60'	90'
FENOTEROL	CONTROL	↓ 2 γ /MIN.	4 γ /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 6.1 EFFECT OF CONTINOUS INTRAVENOUS ADMINISTRATION OF FENOTEROL TO THE EWE ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE, UMBILICAL VENOUS BLOOD FLOW AND MATERNAL INTERNAL ILIAC AND MEDIAN UTERINE ARTERY BLOOD FLOW. DATA ARE EXPRESSED AS MEAN ± SEM. (↓ START OF THE INFUSION).

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 ($p<0.02$). Table 6.1 shows the fetal and maternal parameters. The fetal pH and blood gas values are shown in table 6.2. Fetal pCO_2 was significantly ($p<0.005$) reduced at the end of the infusion and recovery period. Fetal pH and pO_2 did not significantly change.

FENOTEROL	C	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

TABLE 6.2 FETAL PH AND BLOOD GAS VALUES BEFORE, DURING AND AFTER THE ADMINISTRATION OF FENOTEROL TO THE EWE. (MEAN±SD ; N = 24).

6.8.2 Effect of continuous infusion of acetylcholine to the ewe on the maternal and fetal parameters

The mean blood flow in the internal iliac artery did not change significantly during acetylcholine administration to the ewe. A small (5.9%) but significant increase ($p<0.05$) in mean median uterine artery flow was found at the end of the first infusion period, but no significant changes occurred during the rest of the infusion period and thereafter (table 6.3).

	-30"	0	15"	30"	45"	60"	75"	90"
ACETYLCHOLINE	CONTROL	↓ 20γ/MIN.	50γ/MIN.	100 γ /MIN.	200 γ /MIN.		RECOVERY.	
FHR (BPM) N = 17	168±4.1	166±3.7	167±3.2	165±3.2	168±3.9	173±3.8	170±4.4	
FBP (MM.HG.) N = 15	40.9±2.3	40.0±2.9	41.3±2.5	39.6±2.9	41.6±3.5	42.5±2.7	40.1±2.0	
QUV (ML./MIN.) N = 12	562±76	591±68	617±72	594±73	548±71	562±85	603±90	
QIIA (ML./MIN.) N = 7	447±74	431±87	417±71	432±89	433±88	436±86	446±84	
QMUA (ML./MIN.) N = 15	323±44	342±47	305±40	320±46	331±43	318±41	362±44	

▲P < 0.05

TABLE 6.3 EFFECT OF CONTINUOUS INTRAVENOUS ADMINISTRATION OF ACETYLCHOLINE TO THE EWE ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE, UMBILICAL VENOUS BLOOD FLOW AND MATERNAL INTERNAL ILIAC AND MEDIAN UTERINE ARTERY BLOOD FLOW.
DATA ARE EXPRESSED AS MEAN±SEM (↓ START OF THE INFUSION.)

Analysis of the individual data of each experiment showed in the seven cases with internal iliac artery blood flow measurement a consistent increase in blood flow in one experiment and consistent decrease in blood flow in two experiments at the end of each infusion period. In the remaining four experiments no consistent change was found: blood flow either was lower or higher than the control value at the end of the infusion periods.

The same pattern was observed in the individual reactions in the fifteen experiments in which the median uterine artery blood flow was measured. A consistent increase in blood flow occurred in five

experiments and a consistent decrease in median uterine artery blood flow was seen in four experiments at the end of each infusion period. In the remaining six experiments median uterine artery blood flow response was varying, that is to say either lower or higher than the control, value at the end of the infusion periods.
Fetal heart rate, arterial blood pressure and umbilical venous blood flow did not change throughout the infusion and recovery period.
Fetal pH, pCO_2 and pO_2 neither showed any significant changes (table 6.4).

ACETYLCHOLINE	C	60 MIN.	90 MIN.
pH	7.34±0.04	7.33±0.06	7.34±0.04
pCO_2	4.76±0.61	4.64±0.82	4.65±0.67
pO_2	3.56±0.53	4.13±1.64	3.69±0.67

TABLE 6.4 FETAL pH AND BLOOD GAS VALUES BEFORE, DURING AND AFTER THE ADMINISTRATION OF ACETYLCHOLINE TO THE EWE (MEAN±SD ; N = 17).

6.8.3 Effect of continuous infusion of norepinephrine to the ewe 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 6.3, together with a fall in maternal heart rate. Blood flow gradually returned towards the preinfusion 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 6.5. 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 ($p<0.05$).

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

*P < 0.05

TABLE 6.5 EFFECT OF CONTINOUS INTRAVENOUS ADMINISTRATION OF NOREPINEPHRINE TO THE EWE ON FETAL HEART RATE, ARTERIAL BLOOD PRESSURE, UMBILICAL VENOUS BLOOD FLOW AND MATERNAL INTERNAL ILIAC AND MEDIAN UTERINE ARTERY BLOOD FLOW. DATA ARE EXPRESSED AS MEAN ± SEM . (↓ START OF THE INFUSION).

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

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 6.6), which latter values showed a great standard deviation.

NOREPINEPHRINE	C	60 MIN.	90 MIN.
pH	7.32±0.06	7.30±0.06	7.29±0.05
pCO_2	5.11±0.64	5.72±1.84	6.33±2.31
pO_2	3.55±0.59	4.26±2.41	5.13±3.09

TABLE 6.6 FETAL pH AND BLOOD GAS VALUES BEFORE, DURING AND AFTER THE ADMINISTRATION OF NOREPINEPHRINE TO THE EWE (MEAN±SD ; N = 17).

6.9 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 important they show the relatively great short term variations occurring in uterine blood flow. The same phenomenon has been described by Clapp (1979). 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 the 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 (Clapp 1979, Assali et al 1981) 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.

6.9.1 Effect of continuous administration of fenoterol to the ewe on the maternal and fetal parameters

Although the changes in blood flow were small and except 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 iliac 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 (1981) and Erkkola et al (1981).
Erkkola et al (1981) 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 isoprotererol administered directly into the aortic trifurcation. Tabsh et al (1981) also found a difference in response. Common internal iliac artery blood flow remained unchanged while the blood flow in the median uterine artery progessively decreased during intravenous infusion of the beta adrenergic agonist isoxsuprine, which drug has also alpha-adrenergic properties.
Tabsh et al (1981) 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 extra-genital 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 (1977) 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 (1981).
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. Ehrenkranz et al (1977a) and Chez et al (1978) 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 pCO_2 together with an increase in fetal pH was found by Brennan et al (1977) during infusion of ritodrine to the ewe, while no changes were observed during fenoterol administration. An explanation for this decrease in fetal pCO_2 could be a decrease in maternal pCO_2 during hyperventilation, associated with beta-sympathicomimetic drug infusion.
It indicates that fenoterol infusion to the mother at least did not adversely affect fetal acid-base balance.

6.9.2 Effect of continuous administration of acetylcholine to the ewe on the maternal and fetal parameters

Acetylcholine is known as a peripheral vasodilator. No indication was found from the present data that cholinergic stimulation via intravenously administered acetylcholine has an effect on the blood flow in the internal iliac artery. The same can be said about the median uterine artery blood flow since only one value showed a weak significant increase over the control level, whereas the flow values from the sequential infusions with higher doses of acetylcholine thereafter did not change. The meaning of this single significant increase is therefore questionable.
The absence of any increase in blood flow in the internal iliac artery is in agreement with the results from Assali et al (1981) who also

found no change in blood flow in the common internal iliac artery upon intravenous acetylcholine infusion. Bolus injections directly into the aortic trifurcation (2 to 64 gamma) on the other hand caused a small increase in the blood flow in the common internal iliac artery (Erkkola et al 1981, Assali et al 1981), but no changes in the median uterine artery flow (Erkkola et al 1981).

Erkkola et al (1981) suggested the existence of cholinergic receptors in the vascular bed of the common internal iliac artery and the absence of a strong cholinergic control of the median uterine artery. The conclusions of Greiss et al (1967c) that acetylcholine caused vasodilatation in the uterine vascular bed were questioned by them on the basis of the magnitude of the reported uterine blood flow changes and on the fact that central circulatory changes could have attributed to the flow increases.

Important evidence for the lack of cholinergic control of uterine blood flow is the absence of cholinergic vasomotor nerves to the parametrial vessels in the sheep (Bell 1971) and the absence of any change in uterine blood flow upon direct stimulation of the pelvic parasympathetic nerves (Greiss 1967b).

With regard to the fetal parameters, the absence of any changes indicates that acetylcholine was not or only minimally transferred via the placenta to the fetus.

No indications for any cholinergic influence on the blood flow in the internal iliac or median uterine artery were obtained from the results of these experiments.

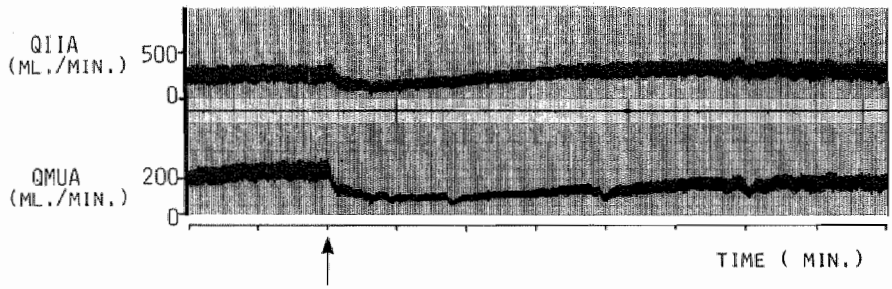
6.9.3 Effect of continuous administration of norepinephrine to the ewe on the maternal and fetal parameters

The magnitude of the decreases in internal iliac and median uterine artery blood flow were except during one interval not significant and were much smaller than those reported by others (Greiss 1963, Barton et al 1974, Chez et al 1978, Tabsh et al 1981, Assali et al 1981).

In each of these studies the maximum response upon norepinephrine administration either in a bolus injection intraarterially or intravenously (Greiss 1963, Chez et al 1978, Assali et al 1981) or in a

continuous systemic intravenous or local intraarterially infusion (Barton et al 1974, Rosenfeld et al 1976, Tabsh et al 1981) were assessed.

As can be seen in figure 6.3 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 sustained 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.



EWE 8303 GESTATIONAL AGE 117 7 DAYS P.O.

FIG. 6.3 INITIAL DECREASES IN INTERNAL ILIAC AND MEDIAN UTERINE ARTERY BLOOD FLOW FOLLOWED BY A SLOW RECOVERY DURING CONTINUOUS INTRA VENOUS ADMINISTRATION OF 4 γ-NOREPINEPHRINE PER MINUTE TO THE EWE.
(↑ START OF THE INFUSION)

This adaption in time might be caused by compensatory autonomic reflexes and/or local factors involving prostaglandin production.

Fetal heart rate and arterial blood pressure did not change significantly during infusion in contrast to the results obtained by

Chez et al (1978), 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 a great variation without any significant change.
The small but significant increase in fetal heart rate and the small decrease in arterial pH during the recovery period suggest a certain adverse effect of the diminished uterine blood flow on the fetal condition.

6.10 Final remarks

The recordings of the internal iliac and median uterine artery blood flow learnt that maternal pelvic vascular blood flow showed great fluctuations in time not only induced by several stimuli but also "spontaneously" occurring.
Furthermore considerable differences in absolute flow between the animals existed and the degree or direction of flow changes upon drug infusions in various animals was not always identical.
Although certain 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 uteroplacental 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 uteroplacental blood flow.

CHAPTER VII

FETAL BREATHING MOVEMENTS AND UMBILICAL VENOUS BLOOD FLOW

7.1 Introduction

Fetal breathing movements refer to fetal chest wall and diaphragmatic movements which mimic in utero the respiratory movements of postnatal life. In contrast to the situation after birth, gaseous exchange and alveolar expansion do not occur during intrauterine life, and in this respect the name fetal breathing movements is somewhat misleading.
Fetal breathing movements exist in fetuses of all mammals studied thus far, including the human. An extensive review on fetal breathing movements is given by Wilds (1978) and Lewis and Boylan (1979). Acute studies of fetal breathing movements in animals have a much longer history than observations of human fetal breathing movements. Béclard (1815) described in his often cited studies rhythmic movements of the fetal thorax and abdomen in dogs and kittens after opening of the uterine wall but with intact fetal membranes. The same movements were already observed by Winslow in 1781 (cited by Wilds 1978) after exposure of the uterus in dogs and cats.
Rhythmic breathing movements of the intrauterine human fetus were first described by Ahlfeld, a German gynecologist in 1888. He observed periodic and rhythmic intrauterine fetal movements in the periumbilical area of the intact abdomen of pregnant women, which he later ascribed to fetal respiratory movements. His observations were regarded by his contemporaries with scepticism, and the nowadays general accepted view that intrauterine breathing movements are necessary for a proper respiratory adaption after birth was denied. Ahlfeld himself however was convinced of this necessity: "Ich behaupte aber mit Bestimmtheit:

ich halte es für ganz unmoglich, dass ein Organ in Thätigkeit tritt, wenn es geboren ist, welches vorher noch nicht thätig gewesen ist. Ein Muskel kann nur leben, wenn er in Thätigkeit ist; nur wenn er sich zusammenzieht, kann er sich entwickeln" (Ahlfeld 1888).

It is now clear from animal studies that fetal breathing movements are not only necessary for a proper development of intercostal and diaphragmatic musculature but also establish the transport and spread of surfactant from the alveolar type II-cells over the total lung area. Surfactant is essential for the prevention of postnatal alveolar collapse. Clinical observations of severe respiratory distress syndrome and lung hypoplasia in newborns with abnormalities of the respiratory muscles (as, for example, in arthrogryposis multiplex congenita) underline this view. The occurrence of fetal breathing movements under experimental conditions in animals was until 1970 regarded as a consequence of fetal tactile stimulation or asphyxia during the acute experiment.

In 1970 however both Dawes et al in Oxford and Merlet et al in Paris reported the existence of spontaneous fetal breathing movements of the fetus in utero. Two breathing patterns were recognized in both intrauterine and exteriorized lamb fetuses. The first was a predominant, rapid, shallow, usually irregular breathing activity up to 50 percent of the time, characterized by varying rates of 1 to 4 Herz with interspersed episodes of apnea. The second pattern consisted of sporadic, deep inspiratory efforts at a rate of two to four per minute during about 5 percent of the time. The existence of breathing movements in the sheep fetus was confirmed by the findings of the two aforementioned groups and these breathing movements were seen to be a spontaneous physiologic phenomenon.

Since 1970 numerous investigations on fetal breathing movements and the factors which affect them have been published.

It is beyond the scope of this section to review the literature on this topic but a short and certainly not complete summary of the factors that affect fetal breathing movements is given in table 7.1.

The relations between breathing movements and brain activity have recently been studied by van der Wildt (1982).

DECREASE	INCREASE
HYPOGLYCEMIA	HYPERGLYCEMIA
HYPOXIA	HYPERCAPNIA
MATERNAL ACTIVITY	CAFFEINE
UTERINE ACTIVITY	THEOPHYLLINE
MATERNAL ABDOMINAL PALPATION	DOXAPRAM
FETAL TACTILE STIMULATION	EPINEPHRINE
FETAL TEMPERATURE CHANGE	TETRABUTALINE
SUPINE HYPOTENSION	INDOMETHACIN
CIGARETTE SMOKING	MECLOFENAMATE
ALCOHOL	
BARBITURATES	
PETHIDINE	
DIAZEPAM	
PROSTAGLANDINE E_2	
PARTURITION	

TABLE 7.1 FACTORS WHICH AFFECT FETAL BREATHING MOVEMENTS (MODIFIED FROM HILL,1983).

7.2 Fetal breathing and chest wall movements

The primordium of the respiratory system first appears during the third to fourth embryonic week as an outgrowth from the ventral wall of the foregut and by the tenth week of life, all of the characteristic features of the respiratory tract are present. Fetal breathing movements have been detected from the eleventh week by an A-scan ultrasound system (Boddy and Robinson 1971). Fetal breathing movements increase in rate, depth and incidence and become more organized as pregnancy advances and repiratory neuroregulatory control matures. Breathing movements in the fetal lamb are associated with contractions of the diaphragmatic and lower intercostal muscles (Dawes et al 1972, Maloney et al 1975, Harding et al 1977, Chapman et al 1980). Dawes et al (1972) showed that rapid irregular breathing movements which were observed after delivery of fetal lambs with intact umbilical circulation into a warm saline bath were characterized by inward

movements of the thoracic wall and outward movements of the abdomen. Marsal (1978) found the same phenomena in the human, as did Poore and Walker (1980) in fetal lambs. Poore and Walker implanted pairs of ultrasonic transducers on opposite sides of the thorax of fetal lambs provided with a tracheal catheter and they recorded changes in chest wall dimension associated with tracheal pressure changes.

The fetal chest wall responds to the pull of the diaphragm by an inward movement, which is maximal at the level of the xiphisternum (Marsal 1978). The relation between diaphragmatic activity and negative deflections in the intratracheal pressure recordings was demonstrated by Maloney et al (1975).

Fetal breathing movements are paradoxical (Bots 1977): contraction of the diaphragm and other respiratory muscles in the adult leads to an enlargement of the thoracic cavity which allows lung expansion during inspiration. In the fetus however, the attempts to enlarge the fetal thoracic cavity during inspiratory movements, are counteracted by the large airway resistance of the fluid-filled lungs and possibly by the high tonus of the laryngeal muscles (Maloney et al 1975). The inspiratory phase is therefore prolonged and exceeds the expiratory phase by 3 to 1 with a small tidal volume and a tracheal fluid flow of approximately 0.5 ml, but during maximum inspiratory gasping efforts in asphyxial states, however, the tidal liquid flow may exceed 10 ml.

Although the antero-posterior diameter of the chest diminishes during an inspiratory movement with the diaphragm moving downwards during contractions, the net result is a small enlargement of the thoracic cavity as is obvious from the pressure fall in the thorax during inspiration.

The concomitant outward movement of the abdominal wall may be a passive movement caused by the reduction in size of the abdominal cavity caused by the downward movement of the diaphragm.

It is likely that the pressure in the abdominal cavity increases during inspiration with the outward movement of the abdominal wall as a corresponding result.

7.3 Cardiovascular effects of fetal breathing movements

The cardiovascular effects of fetal breathing movements in long term experiments in lambs have been described in several studies. Fouron et al (1975) reported episodes of fetal tachycardia often followed by elevations of systolic and diastolic blood pressure to 50% above base line levels, associated with breathing episodes. The hypertensive episodes often coincided with transient increases in the rate and depth of breathing movements. A cardiac arrhythmia synchronous with respiratory activity was also seen.

Dalton et al (1977) observed a consistent increase in heart rate variability during breathing episodes in chronic lamb studies, and the degree of heart rate variability was related to the amplitude and the frequency of the tracheal pressure changes.

Rurak and Gruber (1983) found in chronically instrumented fetal lambs transient increases and decreases in blood pressure during fetal breathing movements and no significant changes were found compared to the blood pressure before or after the breathing episode.

Martin et al (1974) also observed increased heart rate variability and a respiratory arrhythmia during fetal breathing activity in chronic Rhesus monkey experiments.

Van der Wildt (1982) quantitated the beat to beat heart rate variability by means of the interval difference index and he found a strong relation with the presence or absence of rapid irregular fetal breathing movements, which occur only during low voltage electrocortical states.

It was suggested by Fouron et al (1975) that the cardiovascular effects of fetal breathing movements resulted from increased secretion of catecholamines by the fetus during breathing movements. Undoubtedly more factors are involved, as e.g. the influence of fetal breathing movements upon umbilical venous and vena caval blood flow and right atrial filling patterns.

7.4 Umbilical blood flow and fetal breathing movements

Rurak and Gruber (1983) found an increase in umbilical flow of 52 $\pm$ 12

ml/min/kg during breathing activity in 9 of 16 samples in their experiments in chronically instrumented fetal lambs while in the other 7 it decreased by 23 ± 9 ml/min/kg. The umbilical blood flow was measured using the steady-state diffusion technique with antipyrine as the test substance. They ascribed this increase to the general tendency for heart rate and arterial pressure to increase. A strong possitive correlation between heart rate and umbilical blood flow was reported by Rudolph (1976).

Dawes et al (1972) observed an increased descending aortic blood flow in association with tachycardia and hypertension during breathing episodes which might suggest that umbilical blood flow also would increase. An increase in left ventricular output however does not automatically imply an increase in umbilical blood flow. During vigorous breathing movements, Rurak and Gruber observed a fall in umbilical blood flow, but no concomitant data on fetal heart rate during those episodes were available. They suggested that the large intrapleural pressure changes (5-30 mm Hg) associated with vigorous breathing could cause phasic reductions in ventricular output with consequent decreases in umbilical blood flow.

The instantaneous effect of inspiratory movements upon umbilical venous blood flow was measured by Chiba et al (1981) in the human fetus, using a pulse-Doppler flow transducer in combination with real-time B-scan echography. They found that fetal breathing movements changed the flow velocity in the umbilical vein. When the abdominal wall was moving inwards, which movement they erroneously considered "inspiration", an increase in umbilical venous flow was found, while during "expiration" a decrease in flow occurred. However their definition of inspiration and expiration is confusing and it seems that they did not take into account the paradoxical breathing pattern of the fetus.

Gough and Poore (1977) used an ultrasound transducer in the tip of a catheter in chronic lamb studies to record fluctuations in venous return in the inferior vena cava during fetal breathing movements. Doppler shift fluctuations in time with fetal breathing movements were present in the inferior vena cava at the level of the diaphragm, especially at the juncture of the hepatic and diaphragmatic veins with

the vena cava. These signals may be generated from flow changes in the umbilical vessels coincident with breathing movements (Goodman and Mantell 1978).
In a study on the basic flow patterns in the superior and inferior venae cavae, Reuss et al (1983) showed striking changes in flow patterns occurring with fetal breathing movements. A decrease in tracheal or intrapleural pressure during an inspiratory movement caused an increase of venous forward flow. This increase in flow was in general proportional to the decrease in pressure. When large negative pressures were generated by regular deep breathing movements, marked venous pulsations occurred sometimes doubling or tripling the amplitude of the venous flow patterns. Fetal breathing movements also affect the instantaneous flow pattern in the common umbilical vein (Hasaart and de Haan 1982, 1983a).

7.5 Aim of the study

It is known that fetal breathing movements influence the occurrence of the short term irregularity in the fetal heart rate pattern. The short term irregularity is regarded in human obstetrics as a parameter for the estimation of fetal well being.
Bots et al (1978), Dawes et al (1981), Campogrande et al (1982) and Nijhuis et al (1982) showed that fetal heart rate decreases together with an increase in the short term variability during fetal breathing movements. This increased short term variability might in part be caused by changes in the venous blood flow returning to the fetal heart during breathing movements.
This part of the study was undertaken to investigate the effects of spontaneously occurring fetal breathing movements upon instantaneous umbilical venous blood flow. Furthermore the effects of fetal gasping during fetal asphyxia, as accomplished by transient occlusion of the maternal common internal iliac artery or the fetal umbilical cord, upon umbilical venous flow were studied.

7.6 Materials and methods

The fetal breathing movements were recorded by means of an intratracheal fluid-filled catheter, connected with a pressure transducer (see chapter 2). Since the fetal thorax contains no gas, the pressure changes resulting from breathing movements are transmitted relatively undamped to the other intrathoracic structures and are superimposed on circulatory and oesophageal pressure changes. Amniotic pressure changes are in the same way superimposed on the intrathoracic pressures and must be subtracted or otherwise accounted for in relating pressure changes to fetal breathing movements.

Periods with fetal respiratory movements were observed in six fetal lambs provided with a intratracheal catheter. Gestational age ranged from 106 to 143 days. Fetal breathing movements were identified visually comparing the tracheal and amniotic pressure registrations on the recording paper.
Instantaneous umbilical venous blood flow was studied during rapid irregular breathing movements, unusually vigorous breathing movements, gasping and expiratory efforts.

7.7 Results

7.7.1 Rapid irregular breathing and instantaneous umbilical venous blood flow

During rapid irregular breathing movements with an amplitude of 3 to 12 mm Hg and a frequency of 1 Hz and higher, instantaneous umbilical venous blood flow showed a marked increase in amplitude (fig. 7.1), which was caused by the occurrence of a flowpattern with undulations in line with the frequency of the breathing movements (fig. 7.2).
The undulatory pulsations in the tracheal pressure recording and the umbilical venous flow recording were slightly out of phase (fig.7.2). The time delay caused by propagation of the pulse wave of the tracheal pressure change to the pressure transducer must be accounted for when comparing the pressure changes with the electromagnetically recorded

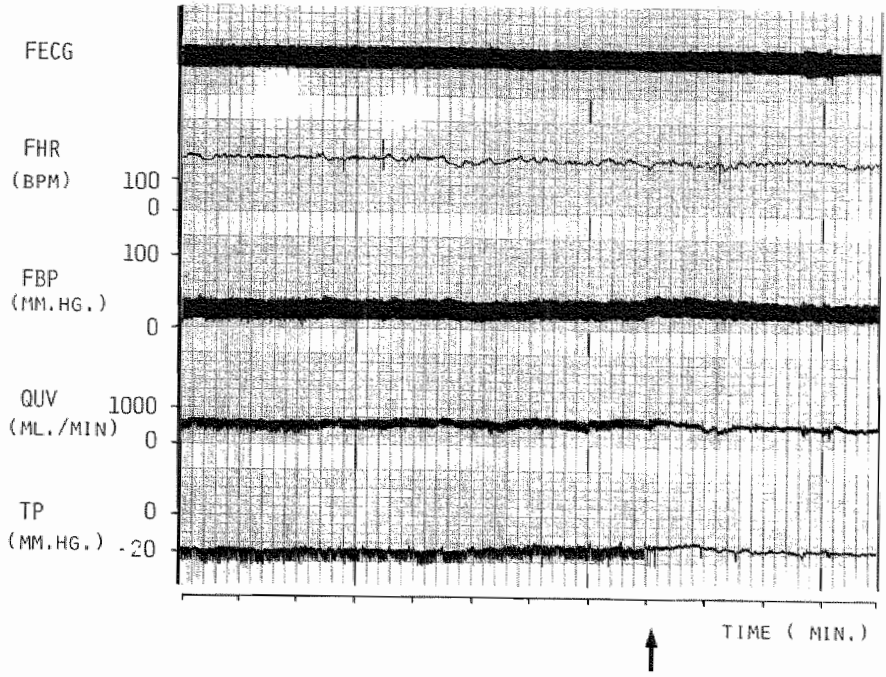
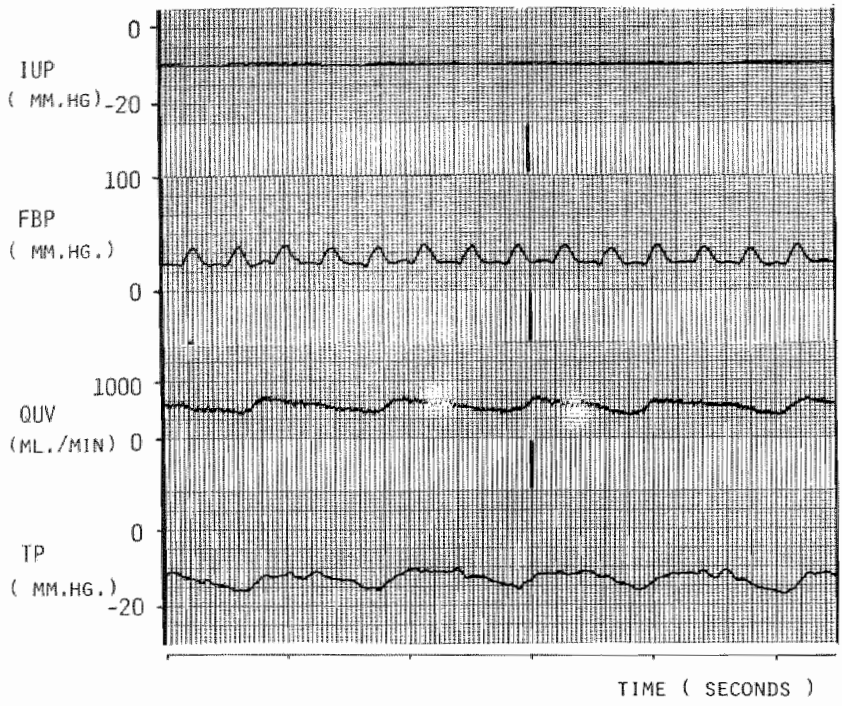


FIG. 7.1 TRANSITION (ARROW) FROM A PERIOD WITH RAPID IRREGULAR FETAL BREATHING MOVEMENTS AND UNDULATORY UMBILICAL VENOUS BLOOD FLOW TO A PERIOD WITHOUT FETAL BREATHING MOVEMENTS AND WITHOUT AN UNDULATORY UMBILICAL VENOUS BLOOD FLOW PATTERN.

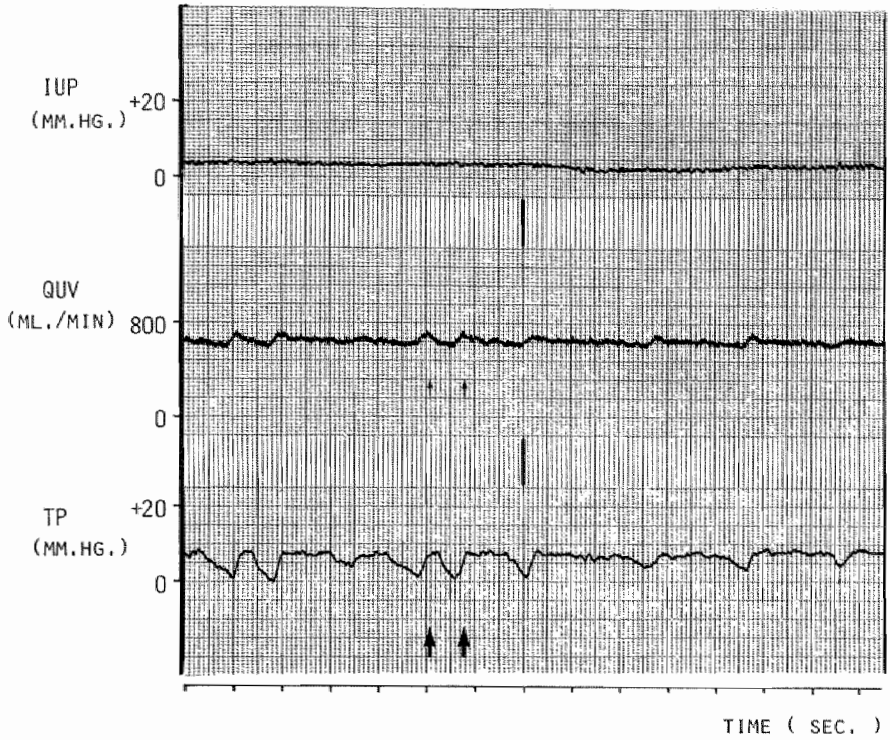
flow changes. Two kinds of variables add to the delay time in pulse wave propagation. First there is a technical factor namely the delay in pulse wave propagation caused by the intratracheal inserted polyvinyl catheter, the connecting polyethyleen catheter and the stopcocks.
The total delay in pulse wave propagation amounts 40 msec for the catheter and connecting system used in this study (Evers 1978). The second important physiological factor is the probably high compliance of the fluid filled tracheal system, which has an open connection with



EWE 8311 GESTATIONAL AGE 128 14 DAYS P.O.

FIG. 7.2 TIME RELATIONSHIP BETWEEN FETAL BREATHING MOVEMENTS AND THE THEREBY CAUSED UNDULATORY CHANGES IN UMBILICAL VENOUS BLOOD FLOW.

the oral cavity. A high compliance decreases the pulse wave velocity, adding a second time delay to the propagation of the pressure wave. The magnitude of this second time delay is unknown, but may amount up to 20 msec according to the total time delay found in most cases. The time delay caused by the electromagnetic circuit of the flow transducer system is negligible. The total time delay between the onset of the umbilical flow decrease and the onset of inspiration was in the range of 40-60 msec in most instances, and did not exceed 100 msec. The relation between tracheal pressure and umbilical venous flow recordings



EWE 8311 GESTATIONAL AGE 120 6 DAYS P.O.

FIG 7.3 OVERSHOOT OF UMBILICAL VENOUS BLOOD FLOW AFTER A FETAL INSPIRATORY MOVEMENT (ARROWS)

can then after correction for the time interval be described as follows.

During inspiration characterized by a drop in tracheal pressure, umbilical venous blood flow decreases. Umbilical venous blood flow returns to its baseline with the expiratory part of the breathing cycle (fig. 7.2). Sometimes a small overshoot in the umbilical blood flow was observed at the end of the expiration (fig. 7.3). The undulatory pulsations varied with the magnitude of the breathing amplitude. Greater pulsations were observed with deeper tracheal pressure drops.

Incidentally periods with unusual vigorous breathing movements were present with large changes in the umbilical venous flow pattern. Although heart variability was not quantified in this study, the impression of an increased heart rate variability during periods with fetal breathing movements existed on visual inspection of the analog recordings. This is in agreement with the findings by others (Martin et al 1974, Dalton et al 1977, van der Wildt 1982).

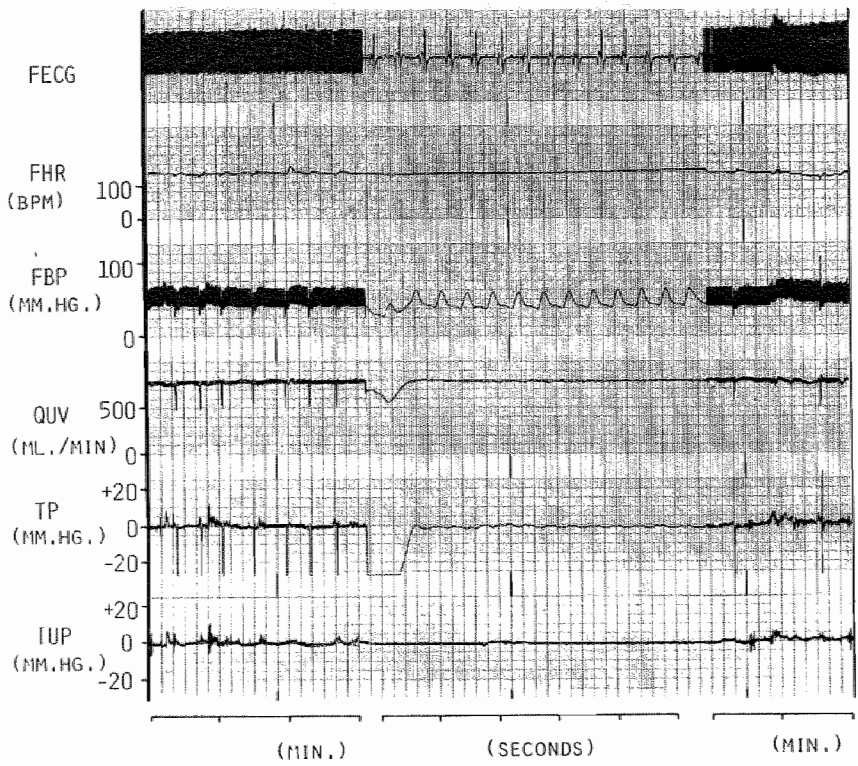


FIG. 7.4 EFFECT OF ISOLATED FETAL HICCUPS ON HEART RATE, ARTERIAL BLOOD PRESSURE AND UMBILICAL BLOOD FLOW.

7.7.2 Fetal hiccups and instantaneous umbilical venous blood flow

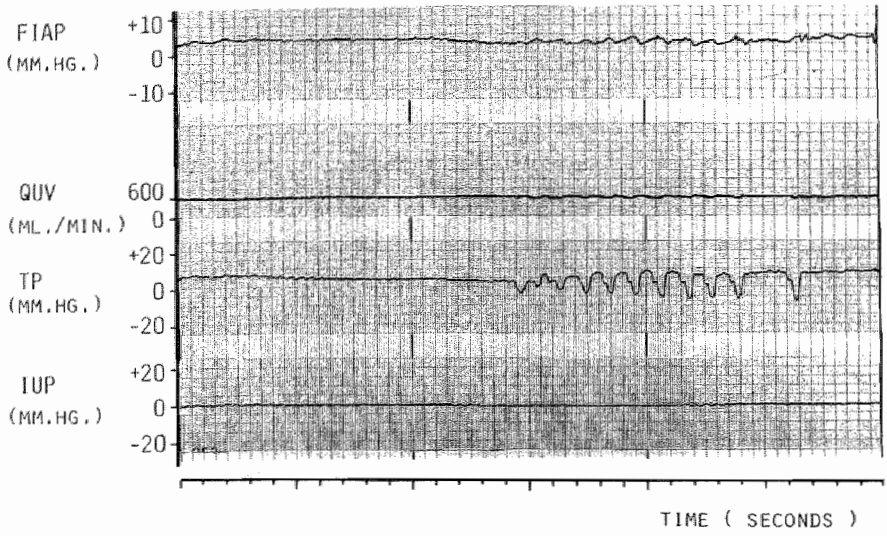
Fetal hiccups, characterized by single brief and relatively deep inspiratory efforts recurring irregularly at a much slower rate (1-4 /min) than rapid breathing movements, resulted in a much greater decrease in instantaneous umbilical venous blood flow than occurred with rapid irregular breathing movements (fig. 7.4). Arterial blood pressure decreased during hiccups followed by a small overshoot. The same decrease and increase was found in the fetal heart rate (fig 7.4). These deep inspiratory efforts are probably hiccups but might also be isolated deep breaths, or respiratory movements associated with bringing up material from the rumen.

7.7.3 Expiratory efforts and instantaneous umbilical venous blood flow

Inspection of the tracheal pressure recordings also showed incidentally brief rises in tracheal pressure during a period without other breathing movements. No inspiratory component was associated with these expiratory efforts. Umbilical venous blood flow decreased during such an expiratory effort. No changes in amniotic fluid pressure were seen at those moments. Fetal heart rate showed a slight decrease during such an expiratory effort (fig. 7.7).

7.7.4 Fetal intraabdominal and intratracheal pressure during fetal respiratory movements

The intraabdominal pressure was measured in two fetuses, also provided with an intratracheal pressure catheter.
The intra abdominal pressure also changed with fetal breathing movements but in the opposite direction as tracheal pressure: during a fall in tracheal pressure with inspiration there was a rise in the intra abdominal pressure, while intra abdominal pressure decreased again with the rise in intracheal pressure during expiration (fig. 7.5 and 7.6).



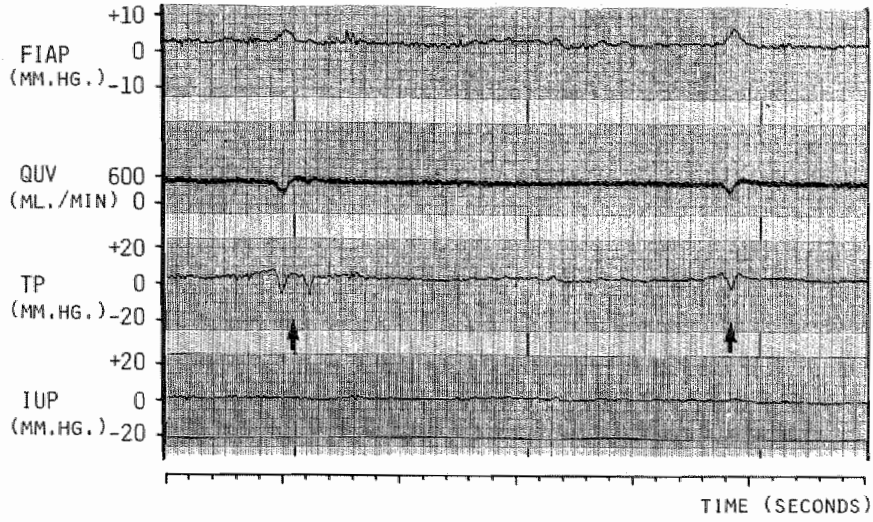
EWE 8310 GESTATIONAL AGE 116 4 DAYS P.O.

FIG. 7.5. THE INFLUENCE OF REGULAR FETAL BREATHING MOVEMENTS ON INTRA-ABDOMINAL PRESSURE AND UMBILICAL VENOUS BLOOD FLOW.

Deep tracheal pressure drops during fetal hiccups were accompanied by marked increases in intra abdominal pressure.
Fetal expiratory efforts without any inspiratory component as described in 7.7.3 caused a change in tracheal and intra abdominal pressure in the same direction: both pressures increased while umbilical venous blood flow decreased (fig. 7.7).

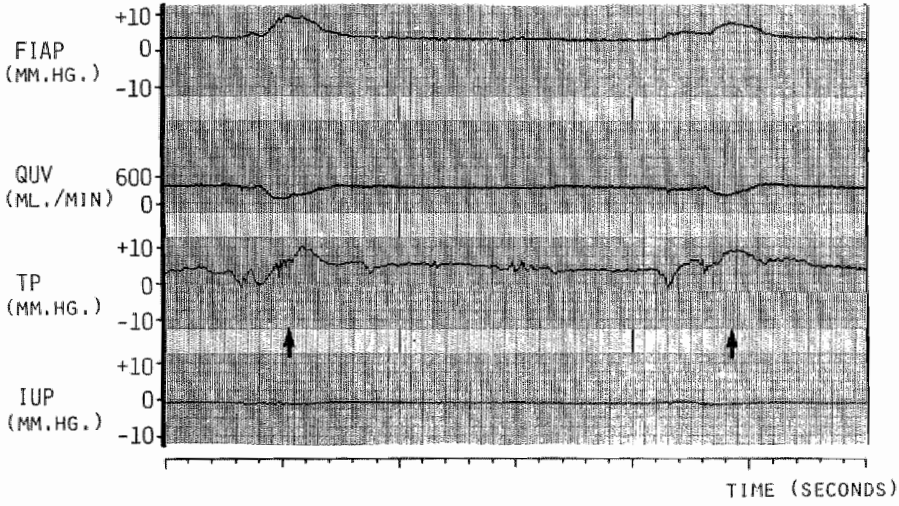
7.7.5 Fetal gasping and instantaneous umbilical venous blood flow with umbilical cord occlusions

Temporary occlusion of the total umbilical cord may lead to fetal asphyxia and fetal gasping can occur under such circumstances (Dawes et al 1972). These gasping efforts may have a much greater amplitude than those "spontaneously" occurring (fig. 7.8).



EWE 8310 GESTATIONAL AGE 116 4 DAYS P.O.

FIG. 7.6. EFFECT OF ISOLATED INSPIRATORY MOVEMENTS (ARROWS) ON INTRAABDOMINAL PRESSURE AND UMBILICAL VENOUS BLOOD FLOW.



EWE 8310 GESTATIONAL AGE 115 3 DAYS P.O.

FIG.7.7 EFFECTS OF FETAL EXPIRATORY EFFORTS, GRUNTING OR VALSAVA LIKE MANOEUVERS (ARROWS), ON INTRAABDOMINAL PRESSURE AND UMBILICAL VENOUS BLOOD FLOW.

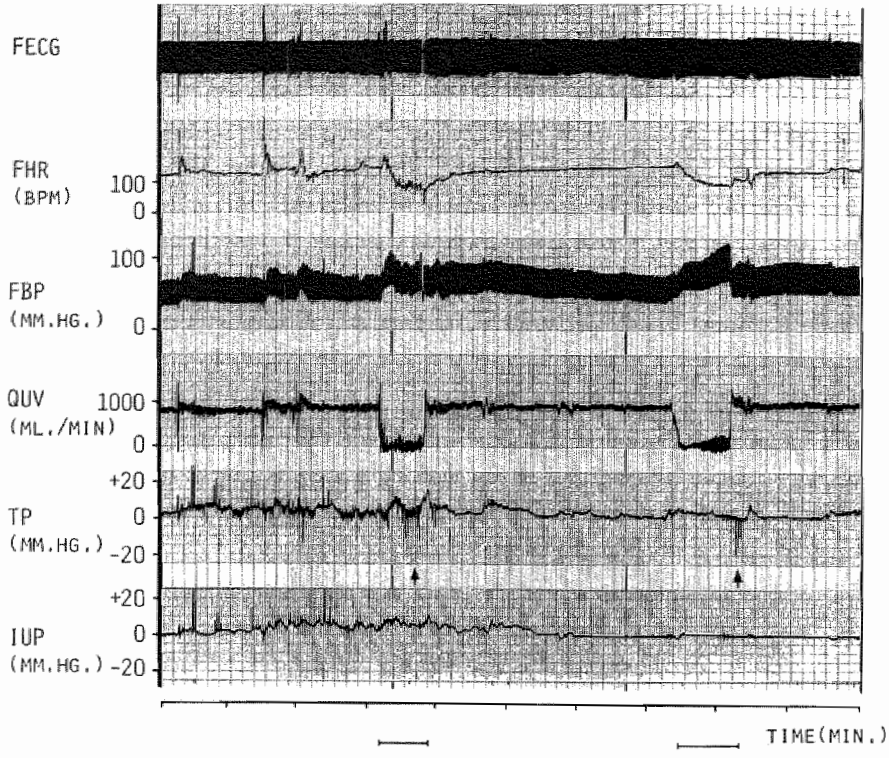
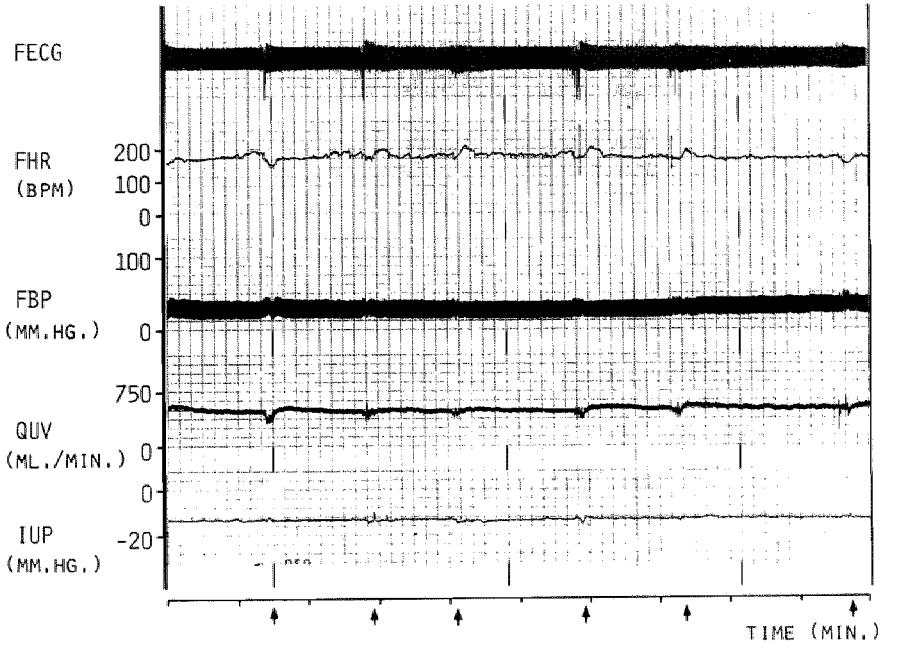


FIG. 7.8 FETAL GASPING MOVEMENTS (ARROW) DURING AND AFTER TOTAL UMBILICAL CORD OCCLUSION (⟵⟶)

The umbilical venous flow changes, occurring with the fetal gasping movements, were then superposed on the already present biphasic venous pulsations, which were caused by backward propagation of the increased pulsatility in the vena cava inferior to the common umbilical vein (see chapter 4). Fetal gasping with umbilical cord occlusion occurred towards the end or immediately following the occlusion.

These gasping movements had an overriding effect on the already present biphasic venous pulsations.

Also in cases with biphasic venous pulsations caused by other events than umbilical cord occlusion as e.g. acetylcholine administration to the fetus or occlusion of the maternal common internal iliac artery, fetal gasping efforts were sometimes observed. The influence of fetal gasping on the pulsatory umbilical venous blood flow had the same effect then as during umbilical cord occlusion.



EWE 8311 GESTATIONAL AGE 128 14 DAYS P.O.

FIG. 7.9 CHANGES IN UMBILICAL VENOUS BLOOD FLOW PROBABLY CAUSED BY FETAL MOVEMENTS AND THE CONCOMITANT CHANGES IN THE HEART RATE PATTERN (ARROWS).
FETAL BREATHING MOVEMENTS WERE ABSENT.

7.8 Discussion

These data show that fetal breathing movements influence the blood flow pattern in the common umbilical vein.

The decrease in umbilical venous flow during a decrease in tracheal pressure can be explained by the concomitant increase in intraabdominal pressure, caused by the downward movement of the diaphragm during inspiration. This increase in intraabdominal pressure partly compresses the intraabdominal common umbilical vein with a decrease in flow as result.

This flow change is different from the flow alterations occurring in the thoracic cavity. The fall in the intrathoracic pressure with inspiration acts as a certain suction force on the vena cava flow: a decrease in tracheal pressure causes an increase in forward flow in both the superior and inferior vena cava, which is proportional to the decrease in intratracheal pressure (Reuss et al 1983).

Phasic descending aortic flow on the other hand shows brief decreases in flow commensurate to the brief falls in arterial pressure occurring with each decrease in intrathoracic pressure (Dawes et al 1972). The phasic aortic flow immediately after the tracheal pressure fall shows a small increment, as can be seen in the figures from the article by Dawes et al (1972). This increment may not only be caused by the increase in arterial pressure after inspiration, but might also be the result of a greater ventricular ejection force caused by the increased filling of atrium and subsequent ventricle with the preceding forward flow surge in the venae cavae during inspiration.

This variability in cardiac filling with fetal breathing movements may partly account for the increased heart rate variability found during fetal breathing movements (Dalton et al 1977, van der Wildt 1982). It is very likely that these venous pulsations disrupt the preferential streaming pattern that exists in the vena cava inferior (paragraph 5.1), resulting in a greater mixing of the systemic venous blood from the vena cava and the umbilical venous blood at the juncture of the ductus venosus and the inferior vena cava.

Isolated increases in intrathoracic pressure, referred to as expiratory effects by Dawes et al (1972), were accompanied by rises in intraabdominal pressure and decreases in umbilical venous flow and heart rate. They are in fact Valsalva-like manoeuvres, present e.g. during micturition, meconium discharge or grunting.

Many factors determine the variability in the fetal heart rate pattern. Figure 7.9 for example shows a relation between changes in umbilical venous blood flow and fetal heart rate pattern. The decreases in flow are probably caused by fetal movements, which may partially compress the umbilical vein. These periodic accelerations are in the human fetus regarded as a sign of a good fetal condition. Maybe the fetus is touching or even pulling its umbilical cord at such a moment.

The observations from this study show that fetal respiratory movements influence the blood flow pattern in the common umbilical vein. The hemodynamic changes associated with fetal respiratory movements help to explain the phenomena occurring in the human fetal heart rate patterns during breathing movements.

CHAPTER VIII

EPILOGUE

A retrospective view at the end of this study on the questions addressed in chapter I is suitable not only to judge whether an answer to the questions is obtained from the results but it also offers an opportunity to suggest directives for future research.

The results reported in chapter III clearly show that umbilical venous blood flow during late decelerations in the fetal heart rate produced by uterine blood flow obstruction depends on the mean arterial blood pressure changes occurring during the late decelerations. The fetus which is capable of increasing its blood pressure and thus maintaining or even increasing its umbilical blood flow despite the fall in heart rate probably has a greater reserve than the fetus who reacts with a fall in blood pressure and umbilical blood flow.
It is very likely that the decrease in fetal pO_2 reached during the late deceleration is one of the major determinants of the fetal cardiovascular response.
Continuous measurement of fetal arterial pO_2 by means of an intravascular catheter might be a good method in future experiments to assess the "critical" pO_2 level, at which the fetus is no longer capable of maintaining its arterial blood pressure and umbilical blood flow during artificially produced late decelerations. Another important research item is the placental vascular resistance. Additional measurement of umbilical venous pressure or vena cava inferior pressure is necessary for resistance calculations.
Qualification and quantification of the fetal heart rate pattern during late decelerations with umbilical venous blood flow increase respectively decrease might furthermore possibly yield information of clinical interest in human obstetrics.The fact that instantaneous

umbilical blood flow is pulsatile under various circumstances has been shown in chapter III, IV and V.
This phenomenon is interesting from a physiological point of view in that interference with preferential streaming in the vena cava might occur during pulsations in the venous flow possibly leading to an enhanced mixing of oxygen poor blood from the lower part of the fetal body with oxygen rich blood from the placental side.
A more intriguing finding is the decrease in uterine blood flow during umbilical cord occlusions. Selective occlusions of either both umbilical veins or both umbilical arteries by means of a special occluding device (de Haan at al 1976) will probably shed more light on the mechanism involved.

The effects of agonists and antagonists of the autonomic nervous system on umbilical blood flow are described in chapter V. The need for placental vascular resistance calculations was felt during the discussion of the blood flow changes. Future studies should be directed to the influence of clinically important drugs as betasympathicomimetic tocolytic agents and betasympathicolytic antihypertensive drugs upon umbilical blood flow and placental vascular resistance.

The question concerning the effect of acetylcholine, norepinephrine and fenoterol on the maternal pelvic blood flow cannot be answered satisfyingly from the obtained results, nor can a certain answer be derived from the results whether any difference in the reaction pattern between internal iliac and median uterine artery blood flow exists. However a trend in the blood flow responses during the drug infusions was ascertained. More experiments are necessary to answer this question.
Relatively little is known about the effects of continuous administered beta-adrenergic blocking drugs (propranolol, atenolol, timolol, etcetera) on uterine and umbilical blood flow.
It might be worthwile to study the effects of these group of drugs as well as the influences of other betasympathicomimetic drugs on the maternal and fetal blood flow. Maternal arterial pressure and heart rate measurements as well as fetal venous pressure measurements must be

included in the design of such a study.

The great influences of any form of fetal respiratory movement on umbilical venous blood flow is shown in the observations described in chapter VII.
Simultaneous measurements of umbilical venous blood flow, fetal venous and arterial pressure, heart rate and tracheal pressure over longer periods of time might bring in valuable information for the understanding of the mechanisms involved in the regulation of fetal heart rate variability.

APPENDIX

The autonomic nervous system

The autonomic nervous system can be divided into its two classical components, the sympathetic and parasympathetic nervous systems, distinguished by differences in anatomy, distribution, chemistry and function. The sympathetic nervous system is concerned with adaption to emergencies, the application of certain reflexes and the maintenance of sympathetic tone, while the parasympathetic tone is thought to be involved predominantly with the normal running of bodily functions, particularly digestion (Jones 1983).

The preganglionic neurons of both the sympathetic and parasympathetic system secrete acetylcholine as a transmitter and this is true, too, of the parasympathetic postganglionic neurons. A few of the postganglionic endings of the sympathetic nervous system also secrete acetylcholine and these fibers are cholinergic. By far the majority of the sympathetic postganglionic endings secrete norepinephrine, and these are said to be adrenergic.

The sympathetic component of the autonomic nervous system can be further subdivided by the concept of alpha and beta receptors, introduced by Ahlquist (1948). Ahlquist proposed that alpha receptors mediated primarily excitation (contractile) responses such as vasoconstriction, excitation of the ureters and uterus and also one inhibitory response, gut relaxation. Beta receptors on the other hand were proposed to account mainly for inhibitory responses such as vasodilatation, uterine relaxation and one excitatory response, cardiac stimulation.

Closely related adrenergic agents as norepinephrine, epinephrine and isoprenaline differ in their effects: norepinephrine acts mainly on alpha receptors, epinephrine acts roughly equally on both alpha and beta receptors whereas isoprenaline is almost wholly active at beta receptor sites. Lands et al (1967) made a subclassification of the beta receptors in beta 1 and beta 2 receptors by comparing effector responses to a variety of catecholamines, which were active at the

adrenergic receptor site.

Beta 1 receptors mediate in the human for example relaxation of the intestinal smooth muscle, whereas beta 2 receptors mediate relaxation of vascular smooth muscle, relaxation of trachea and bronchi and also relaxation of the uterus. The difference in proportion of beta 1 and beta 2 receptor sites of for example the uterus enabled the development of beta 2 sympathicomimetic agents which can accomplish relaxation of the uterine smooth muscle with less adverse side effects towards predominantly beta 1 receptor containing organs.

These agents are now widely used as uterine relaxant in threatening premature labor in the human.

SUMMARY

The present study deals with several aspects of maternal uterine and fetal umbilical blood flow in a chronic lamb preparation in the latter third part of gestation.

In **chapter** I a general introduction is given on the various techniques in use for uterine and umbilical blood flow measurement. The possibilities and limitations of the diffusion-equilibrium technique, the radioactive microsphere method and electromagnetic flow transducers for uterine and umbilical blood flow measurements are described.
The questions to be addressed in this study are formulated, preceded by introductory remarks from the literature on the topics involved.

In **chapter** II the surgical procedures used in this study in the chronic fetal sheep preparation are described as well as the methods of data acquisition, signal analysis and the experimental plan.

In **chapter** III the effects of simulated late decelerations in the fetal heart rate caused by intermittent occlusion of the maternal common internal iliac artery on umbilical venous blood flow in normoxemic fetal lambs are presented.
Late decelerations in fetal heart rate are generally considered to be a sign of fetal hypoxemia in human obstetrics and mostly occur in conditions in which the duration or the force of uterine contractions is too much for the fetus that is already at the limits of its reserves, as e.g. in pre-eclampsia or chronically impaired placental exchange.
The results of this study show that fetal umbilical venous blood flow may increase or decrease during late decelerations of the fetal heart rate caused by uterine blood flow obstruction.
The direction of the umbilical blood flow change is mainly determined by the concomitant change in arterial perfusion pressure, and to a lesser extent by the magnitude of the heart rate decrease.
The fetus which is capable of increasing its blood pressure and thus

maintaining or even increasing its umbilical blood flow probably has a greater reserve than the fetus which reacts with a fall in blood pressure and umbilical blood flow.
The occurrence of a blood pressure decrease during a late deceleration in spite of the very fast appearing chemoreceptor mediated peripheral reflex vasoconstriction implies a decrease in cardiac output, probably resulting from hypoxic myocardial depression, involving the sinoatrial node and heart muscle.Redistribution of cardiac output which is an important fetal mechanism to provide high-priority tissues as heart and brain with enough blood at the expense of low-priority organs as e.g. viscera and musculoskeletal system, and which mechanism is associated with hypertension, is then endangered.
The determining factor in the fetal cardiovascular response may be the degree of fetal hypoxemia which is reached during the uterine blood flow obstruction.

Chapter IV deals with the effects of umbilical cord occlusions on umbilical venous and maternal pelvic blood flow.
Transient occlusion of the umbilical cord often occurs during labor in the human and leads to considerable changes in fetal hemodynamics.
The results from the present study show that umbilical cord occlusion also affects the maternal uterine blood flow. Shortlasting umbilical cord occlusions are accompanied by a decrease in the blood flow in the maternal median uterine and internal iliac artery at the side of the pregnant horn.
Gradual occlusion of the umbilical cord first leads to occlusion of the easy compressible umbilical veins. After a certain lag time during which the surrounding pressure is increased, complete occlusion of the umbilical arteries is accomplished too. During this lag time a certain additional amount of arterial blood will be pumped into the umbilical circulation and will eventually be trapped in the umbilical vascular bed under a high pressure after complete occlusion of the umbilical arteries.
The elevated fetal capillary pressure in the placenta may lead to an increased fetal placental tissue pressure which in turn compresses the maternal placental capillaries resulting in an increased vascular

resistance and a decrease in uterine blood flow.
A section of this chapter deals with the instantaneous umbilical flow pattern during and after umbilical cord occlusion.
The normally non-pulsatile blood flow in the common umbilical vein changes to a flow pattern with biphasic pulsations in line with fetal heart rate during umbilical cord occlusion.
The pulsations are caused by backward propagation of the increased pulsatile flow pattern in the vena cava inferior during changes in heart rate and ventricular afterload. They may interfere with the mixing of umbilical venous and inferior vena caval blood and alter the distribution of oxygen-rich and oxygen-poor blood in the fetal heart.

Chapter V presents the influences of autonomic acting agents on umbilical venous blood flow. Various drugs which are related to the autonomic nervous system are used in human obstetrics (betamimetic and beta blocking drugs e.g.). The effects of these drugs on fetal and maternal blood flow are only partly known.
Parasympathetic blockade with atropine increases umbilical venous blood flow which is probably secondarily caused by an increase in fetal heart rate. Alpha-adrenergic blockade with phentolamine causes peripheral vasodilatation with fetal hypotension and a decrease in umbilical blood flow as result.
Beta-adrenergic blockade with propranolol is accompanied by a fall in umbilical blood flow which for the greater part can be explained by the concomitant fall in heart rate, although an increase in placental vascular resistance cannot be excluded.
Cholinergic stimulation with acetylcholine causes peripheral vasodilatation with short lasting hypotension and a fall in umbilical blood flow.
Alpha-adrenergic stimulation with norepinephrine results in a small decrease in umbilical blood flow in the face of a serious increase in perfusion pressure and a relatively small decrease in heart rate suggesting that umbilical vascular resistance increases.
Beta-adrenergic stimulation with fenoterol does not influence umbilical blood flow.
Changes in fetal heart rate and peripheral resistance occurring after

acetylcholine and norepinephrine administration result in biphasic pulsations in line with fetal heart rate in the instantaneous umbilical venous blood flow pattern. These pulsations may interfere with preferential streaming in the vena cava inferior and thus influencing the filling of the right heart.

In **chapter** VI the effects of fenoterol, norepinephrine and acetylcholine infusion to the ewe on maternal pelvic and fetal umbilical blood flow are described.
Beta-adrenergic receptor stimulation with fenoterol does in general not lead to significant changes in maternal blood flow although a relatively greater increase in maternal internal iliac than median uterine blood flow is observed, suggesting a greater sensitivity of the internal iliac artery than the median uterine artery or the vascular bed supplied by them to beta-adrenergic receptor stimulation.
Alpha-adrenergic receptor stimulation with norepinephrine causes a initial decrease in blood flow in both maternal vessels, which for the greater part abates with time despite continued drug infusion.
No changes in maternal pelvic blood flow are observed during cholinergic receptor stimulation.
None of the infused drugs influences fetal umbilical blood flow.
The results are compatible with blunting of the effects of autonomic vasoactive drugs on the uteroplacental and pelvic vascular beds during pregnancy. This latter phenomenon is potentially protective for the fetus.

Chapter VII deals with the influences of fetal breathing movements on umbilical venous blood flow. Fetal breathing movements causes undulatory changes in umbilical venous blood flow.
An inspiratory movement, characterized by a fall in tracheal pressure is accompanied by a decrease in umbilical venous blood flow. This decrease in umbilical venous blood flow during inspiration is caused by the concomitant increase in intraabdominal pressure associated with the paradoxical fetal breathing movement. Other fetal respiratory movements as isolated deep breaths and gasping as well as other phenomena as

grunting, Valsalva-like manoeuvres or hiccups which are associated with intrathoracic and intraabdominal pressure changes also have a marked influence on umbilical venous blood flow.
Instantaneous changes in the blood flow returning to the fetal heart may lead to a variability in cardiac filling partly accounting for the increased heart rate variability during fetal breathing movements. Knowledge on the hemodynamic changes associated with fetal respiratory movements help to explain the phenomena occurring in the human fetal heart rate pattern.

In **chapter** VIII a retrospective view is given on the adressed questions in the present study and some directives for future research are suggested.

SAMENVATTING

In dit proefschrift worden verschillende aspecten van de maternale uteriene en foetale umbilicale bloed flow in het chronisch schapepreparaat beschreven.

In **hoofdstuk I** wordt een algemene beschouwing gegeven over de diverse technieken die gebruikt worden voor het meten van de uteriene en umbilicale bloed flow. De mogelijkheden en beperkingen van de diffusie-equilibrium techniek, de radio-actieve microsfeer methode en van de electromagnetische flow meting worden besproken.
Enige discussiepunten uit de literatuur welke van belang zijn voor de vraagstellingen van het onderzoek worden aangehaald.

In **hoofdstuk II** worden de gebruikte chirurgische technieken in dit chronisch schapemodel besproken evenals de methode van dataverwerking en signaalanalyse en het experimentele plan.

In **hoofdstuk III** worden de effecten van gesimuleerde late decelaraties in het foetale hartfrequentiepatroon, veroorzaakt door intermitterende afsluiting van de maternale arteria iliaca interna communis, op de umbilicale veneuze flow in normoxemische foetale lammeren beschreven.
Late decelaraties bij de mens worden beschouwd als een teken van foetale hypoxemie. Zij komen veelal voor in situaties waarin de foetus de extra belasting die weeënactiviteit vormt voor het placentaire zuurstoftransport niet meer kan opvangen zoals bij acute of chronische placenta insufficientie.
De resultaten van dit onderzoek laten zien dat de foetale umbilicale flow tijdens late decelaraties kan toenemen dan wel afnemen.
Deze toe- of afname in umbilicale flow is hoofdzakelijk afhankelijk van de tegelijkertijd optredende veranderingen in de foetale arteriële perfusie druk en in mindere mate van de hartfrequentiedaling.
De foetus die zijn bloeddruk kan verhogen en derhalve zijn umbilicale bloed flow kan handhaven of zelfs doen toenemen, heeft waarschijnlijk een grotere reserve dan de foetus die reageert met een bloeddrukdaling

en een afname van de umbilicale flow.
Een bloeddrukdaling tijdens een late deceleratie ondanks de snel in werking tredende perifere vasoconstrictie houdt een afname van het hartminuut volume in, waarschijnlijk tengevolge van hypoxemische depressie van het myocardium, waaronder sinusknoop en hartspiervezels. Het belangrijke foetale adaptatie mechanisme, namelijk de redistributie van het hartminuutvolume, welke de foetus in staat stelt om belangrijke organen als hart en hersenen van voldoende bloed te voorzien ten koste van organen als de ingewanden,de spieren en het skelet, mist dan de noodzakelijke bloeddrukstijging. De foetale hypoxemie die bereikt wordt tijdens de obstruktie van de uteriene bloed voorziening is waarschijnlijk de belangrijkste factor bij het bepalen van de foetale cardiovasculaire respons.

In **hoofdstuk IV** worden de effecten van navelstreng afklemmingen op de umbilicale veneuze en maternale bloed flow in het kleine bekken beschreven.
Afklemming van de navelstreng is een veel voorkomend verschijnsel tijdens de baring bij de mens dat aanzienlijke veranderingen in de foetale circulatie veroorzaakt.
De gepresenteerde resultaten laten zien dat navelstrengafklemming ook leidt tot veranderingen in de moederlijke uteriene bloed flow.
Kortdurende navelstrengafklemmingen gaan gepaard met een afname in de flow in de maternale arteria uterina mediana en iliac interna aan de zijde van de drachtige uterushoorn.
Geleidelijke afklemming van de navelstreng veroorzaakt eerst een afklemmen van de gemakkelijk samendrukbare navelstrengvenen. Een zekere tijdspanne is nodig voor het opbouwen van voldoende druk om ook de navelstrengarteriën dicht te drukken.
Een bepaalde hoeveelheid arterieël bloed zal extra in de umbilicale circulatie worden gepompt in deze tijdspanne en deze hoeveelheid wordt uiteindelijk onder hoge druk gevangen in het umbilicale vaatbed na complete afklemming van de navelstrengarteriën.
Er ontstaat een verhoogde foetale capillaire druk in de placenta met een toegenomen foetale placentaire weefseldruk welke op zijn beurt de maternale placentaire capillairen samendrukt met een verhoogde

vaatweerstand en een daling van de maternale uteriene flow als gevolg. Verder wordt in dit hoofdstuk het flowpatroon in de vena umbilicalis communis beschreven tijdens en na navelstrengafklemmingen.
De flow in de vena umbilicalis communis welke gewoonlijk zonder pulsaties is, vertoont tijdens navelstrengafklemming bifasische pulsaties in lijn met de foetale hartfrequentie.
De pulsaties worden veroorzaakt door het voortgeleiden van flowpulsaties in de vena cava inferior welke toenemen in amplitudo tijdens veranderingen in hartfrequentie en perifere vaatweerstand. Deze pulsaties kunnen interfereren met de menging van het veneuze umbilicale en vena cava inferior bloed en op deze wijze de verdeling van zuurstofrijk en zuurstofarm bloed in het foetale hart beïnvloeden.

In **hoofdstuk V** wordt de invloed van agonisten en antagonisten van het autonome zenuwstelsel op de umbilicale veneuze bloed flow beschreven.
In de humane obstetrie wordt veel gebruik gemaakt van aan het autonome zenuwstelsel gerelateerde medicamenten (betamimetica,beta-blokkers). De effecten van deze medicamenten op de foetale en maternale bloed flow zijn grotendeels onbekend.
Blokkade van het parasympatische zenuwstelsel met atropine veroorzaakt een toename van de umbilicale veneuze flow waarschijnlijk secundair aan de toename in hartfrequentie.
Beta-adrenerge blokkade met propranolol gaat gepaard met een daling van de umbilicale flow. Deze afname in flow kan voor een groot deel veroorzaakt worden door de gelijktijdige hartfrequentie daling, hoewel een toename van de placentaire vaatweerstand niet kan worden uitgesloten.
Stimulatie van het parasympatische zenuwstelsel met acetylcholine veroorzaakt perifere vasodilatatie met een kort durende hypotensie en een afname in umbilicale flow.
Alpha-adrenerge stimulatie met noradrenaline resulteert in een geringe afname van de umbilicale flow. Het gelijktijdig optreden van een aanzienlijke toename in de perfusiedruk en een relatief geringe daling van de hart frequentie suggereert dat de placentaire vaatweerstand toeneemt.
Beta-adrenerge stimulatie met fenoterol heeft geen invloed op de

umbilicale flow.
Veranderingen in foetale hartfrequentie en perifere weerstand na toediening van acetylcholine en noradrenaline gaan gepaard met bifasische pulsaties in het umbilicale flow patroon met dezelfde frequentie als de hartslag. Deze pulsaties kunnen de voorkeursstroming in de vena cava inferior beinvloeden en derhalve het vullingspatroon van het foetale hart.

In **hoofdstuk VI** worden de effecten van continue toediening van fenoterol, noradrenaline en acetylcholine aan de ooi op de moederlijke bloed flow in het kleine bekken en op de foetale umbilicale flow beschreven.
Beta-adrenerge receptor stimulatie met fenoterol veroorzaakt in het algemeen geen significante veranderingen in de maternale flow hoewel een relatief grotere toename in de flow optreedt in de arteria iliaca interna dan in de arteria uterina mediana, hetgeen een grotere gevoeligheid van de arteria iliaca uterina dan van de arteria uterina mediana en hun beider vaatbed voor beta-adrenerge receptor stimulatie suggereert.
Alpha-adrenerge receptor stimulatie met noradrenaline veroorzaakt aanvankelijk een daling in de flow in beide vaten, doch de flow herstelt geleidelijk ondanks het continueren van de noradrenaline infusie.
Cholinerge receptor stimulatie met acetylcholine leidt niet tot verandering in de moederlijke flow.
De umbilicale flow vertoont geen veranderingen tijdens maternale infusie met een der drie farmaca.
De resultaten zijn in overeenstemming met een verminderde gevoeligheid van het vaatbed van het kleine bekken tijdens de zwangerschap voor vasoactieve farmaca welke het autonome zenuwstelsel beinvloeden. Mogelijk gaat hiervan een beschermend effect voor de foetus uit.

In **hoofdstuk VII** wordt de invloed van foetale ademhalingsbewegingen op de umbilicale veneuze bloed flow gepresenteerd.
In de humane obstetrie worden de foetale ademhalingsbewegingen mede gebruikt voor het bepalen van de foetale conditie.Tevens is het bekend

dat de ademhalingsbewegingen invloed hebben op de snelle variaties in het foetale hartfrequentiepatroon.
Foetale adembewegingen veroorzaken golfbewegingen in de umbilicale veneuze bloed flow. Een inademingsbeweging welke gekarakteriseerd wordt door een daling van de druk in de trachea, gaat gepaard met een afname in de umbilicale veneuze flow. Deze afname in umbilicale veneuze flow tijdens inspiratie wordt veroorzaakt door de gelijktijdige toename van de intraabdominale druk tijdens de paradoxe foetale adembewegingen. Andere foetale respiratoire bewegingen zoals geisoleerde diepe adembewegingen en gaspen evenals fenomenen als Valsalva-achtige manoeuvres, hikken en meconium lozen die geassocieerd zijn met intrathoracale en intraabdominale drukveranderingen beinvloeden de umbilicale veneuze flow eveneens.
Veranderingen in de veneuze flow naar het foetale hart kunnen leiden tot schommelingen in de vulling van de rechter harthelft, welke gedeeltelijk verantwoordelijk kunnen zijn voor de toegenomen variabiliteit in het foetale hartfrequentiepatroon tijdens foetale adembewegingen. Kennis van de haemodynamische veranderingen tijdens foetale respiratoire bewegingen geven meer inzicht in de fenomenen die optreden in het antenale hart frequentie patroon.

In **hoodfstuk VIII** vindt een korte terugblik plaats op de vraagstellingen en worden suggesties gedaan voor toekomstig onderzoek.

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CURRICULUM VITAE

27-05-1953	Geboren te Brunssum
1971	Eindexamen Gymnasium beta aan het R.K. Gymnasium Rolduc te Kerkrade
1971	Aanvang studie geneeskunde aan de Gemeentelijke Universiteit van Amsterdam
1974-1975	Kandidaatassistentschap in het laboratorium voor Fysiologie, Jan Swammerdam Instituut te Amsterdam
1978	Artsexamen aan de Gemeentelijke Universiteit van Amsterdam
1978	Aanvang opleiding tot gynaecoloog in het Sint Annadal Ziekenhuis te Maastricht (opleider Prof. Dr. J. de Haan)
1983	Inschrijving specialistenregister
1983	Verbonden als gynaecoloog aan de afdeling obstetrie en gynaecologie van het Sint Annadal Ziekenhuis te Maastricht