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Tiina Erkinaro

FETAL AND PLACENTAL HAEMODYNAMIC RESPONSES TO HYPOXAEMIA, MATERNAL HYPOTENSION AND VASOPRESSOR THERAPY IN A CHRONIC SHEEP MODEL

FACULTY OF MEDICINE,
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DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY,
UNIVERSITY OF OULU

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Abstract

Knowledge of the effects of maternally administered vasopressors on human fetal and placental haemodynamics is sparse and limited to elective Caesarean deliveries in uncomplicated pregnancies. We hypothesized that, after short-term fetal hypoxaemia, which activates fetal cardiovascular compensatory mechanisms, treatment of maternal hypotension with ephedrine or phenylephrine results in divergent responses in fetal and placental haemodynamics.

Chronically instrumented near-term sheep fetuses with either normal placental function or increased placental vascular resistance following placental embolization were exposed to two subsequent periods of decreased fetal oxygenation caused by maternal hypoxaemia and epidural-induced hypotension. The fetuses that underwent placental embolization were also chronically hypoxaemic.

Fetal and placental haemodynamics were assessed by invasive techniques and by noninvasive Doppler ultrasonography. Our results show that umbilical artery blood flow velocity waveforms cannot be used to derive information of fetal cardiac function. Furthermore, the changes in placental volume blood flows and vascular resistances caused by maternal vasopressor treatment cannot be reliably recognized based on uterine and umbilical artery pulsatility index values.

In response to acute hypoxaemia, a fetus with normal placental function redistributes its right ventricular cardiac output from the pulmonary to the systemic circulation and is able to increase its combined cardiac output, with a concomitant relative decrease in the net forward flow through the aortic isthmus. However, fetal haemodynamic responses to subsequent hypoxaemic insults may vary. Furthermore, the compensatory responses of fetuses with increased placental vascular resistance differ from those of normal fetuses. In these fetuses, repeated episodes of a further decrease in oxygenation lead to lactataemia.

The effects of ephedrine on uteroplacental and umbilicoplacental circulations were more favourable than those of phenylephrine. Ephedrine restored the changes in fetal cardiovascular haemodynamics caused by maternal hypotension to the baseline conditions in both embolized and nonembolized fetuses. Phenylephrine did not reverse fetal pulmonary vasoconstriction or the relative decrease in the net forward flow through the aortic isthmus. Moreover, fetal left ventricular function was impaired by phenylephrine. Although no significant differences in fetal acid-base status were observed in fetuses with normal placental function, the lactate concentrations of the embolized fetuses increased further when maternal hypotension was treated with phenylephrine.

Keywords: cardiovascular physiology, Doppler ultrasonography, ephedrine, epidural anaesthesia, fetus, phenylephrine, placental circulation, pregnancy, sheep

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Abbreviations

α	Alpha
β	Beta
AoI	Aortic isthmus
A-wave	Atrial contraction wave
BE	Base excess
CCO	Combined cardiac output
CI	Cardiac index
CSA	Cross-sectional area
CVP	Systemic venous pressure
DA	Ductus arteriosus
DAo	Descending aorta
DV	Ductus venosus
EDV	End-diastolic velocity
E-wave	Early filling wave
FO	Foramen ovale
G	Gauge
HR	Heart rate
ICT	Isovolumetric contraction time
I.m.	Intramuscular
IRT	Isovolumetric relaxation time
I.v.	Intravenous
IVC	Inferior vena cava
LHV	Left hepatic vein
LVCO	Left ventricular cardiac output
LVeFo	Left ventricular ejection force
LVFS	Left ventricular fractional shortening
MAP	Mean arterial pressure
Pco_2	Partial pressure of carbon dioxide
PCWP	Pulmonary capillary wedge pressure
PI	Pulsatility index
PI_{UA}	Umbilical artery pulsatility index

PI_{UtA}	Uterine artery pulsatility index
PIV	Pulsatility index for vein
Po_2	Partial pressure of oxygen
PPA	Proximal branch pulmonary artery
PSV	Peak systolic velocity
PV	Pulmonary vein
Q_{UA}	Umbilicoplacental volume blood flow
Q_{UtA}	Uteroplacental volume blood flow
R_{UA}	Umbilicoplacental vascular resistance
R_{UtA}	Uteroplacental vascular resistance
RVCO	Right ventricular cardiac output
RVeFo	Right ventricular ejection force
RVFS	Right ventricular fractional shortening
SD	Standard deviation
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
TAMXV	Time-averaged maximum velocity
TVI	Time-velocity integral
V_{mean}	Mean velocity

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Acharya G, Erkinaro T, Mäkikallio K, Lappalainen T & Räsänen J (2004) Relationships among Doppler-derived umbilical artery absolute velocities, cardiac function, and placental volume blood flow and resistance in fetal sheep. Am J Physiol Heart Circ Physiol 286: H1266-H1272.

II Mäkikallio K*, Erkinaro T*, Niemi N, Kavasmaa T, Acharya G, Päkkilä M & Räsänen J (2006) Fetal oxygenation and Doppler ultrasonography of cardiovascular hemodynamics in a chronic near-term sheep model. Am J Obstet Gynecol 194: 542-550. *Equal contribution

III Erkinaro T, Mäkikallio K, Kavasmaa T, Alahuhta S & Räsänen J (2004) Effects of ephedrine and phenylephrine on uterine and placental circulations and fetal outcome following fetal hypoxaemia and epidural-induced hypotension in a sheep model. Br J Anaesth 93: 825-832.

IV Erkinaro T, Kavasmaa T, Päkkilä M, Acharya G, Mäkikallio K, Alahuhta S, Räsänen J (2006) Ephedrine and phenylephrine for the treatment of maternal hypotension in a chronic sheep model of increased placental vascular resistance. Br J Anaesth 96: 231-237.

V Erkinaro T, Mäkikallio K, Acharya G, Päkkilä M, Kavasmaa T, Huhta JC, Alahuhta S, Räsänen J (2006) Effects of ephedrine and phenylephrine on cardiovascular hemodynamics of near-term fetal sheep exposed to hypoxemia and maternal hypotension. (Submitted).

Contents

References

Original publications

1 Introduction

Maternal hypotension is a common complication of regional anaesthesia for Caesarean delivery. It is associated with a sympathetic block that increases venous capacitance and decreases systemic vascular resistance (SVR), resulting in reduced cardiac preload and afterload (Littleford 2004). It causes uncomfortable maternal symptoms such as dizziness, nausea and vomiting (Datta *et al.* 1982) and, more importantly, may impair uteroplacental perfusion (James *et al.* 1970; Wright *et al.* 1992). If prolonged, it may lead to fetal hypoxaemia, acidaemia and low Apgar scores (Datta *et al.* 1982) as well as neonatal neurobehavioural changes lasting for several days (Hollmen *et al.* 1978). Conservative measures in the prevention of hypotension include routine left uterine displacement (Clark *et al.* 1976; Alahuhta *et al.* 1994) and more controversial volume preloading (Rout *et al.* 1993; Jackson *et al.* 1995; Karinen *et al.* 1995; Ueyama *et al.* 1999; Gogarten *et al.* 2005). These precautions may be insufficient in 53−85% of cases (Clark *et al.* 1976; Rout *et al.* 1993; Karinen *et al.* 1995; Shearer *et al.* 1996; Chan *et al.* 1997; Desalu and Kushimo 2005), necessitating the use of sympathomimetic drugs.

The mixed alpha (α) and beta (β) adrenoceptor agonist ephedrine has been the most commonly used vasopressor in obstetric practice (Burns *et al.* 2001) because of its sparing effect on uteroplacental perfusion found in animal experiments (James *et al.* 1970; Ralston *et al.* 1974; Sipes *et al.* 1992; McGrath *et al.* 1994). This effect has been explained by its partial β-agonism that increases cardiac output (Ralston *et al.* 1974) and by its decreased tendency to constrict uterine arteries during pregnancy (Tong and Eisenach 1992; Li *et al.* 1996). The pure α-agonist phenylephrine has been avoided during pregnancy because experimental data suggest that it may compromise uterine blood flow (Greiss and Crandell 1965; Sipes *et al.* 1992; McGrath *et al.* 1994). Recently, however, ephedrine has been associated with lower umbilical artery pH values compared with phenylephrine when used for the prevention or treatment of maternal hypotension during elective Caesarean delivery in uncomplicated pregnancy (Mercier *et al.* 2001; Cooper *et al.* 2002; Ngan Kee and Lee 2003). In addition, the efficacy of prophylactic ephedrine in preventing maternal hypotension may be limited (Lee *et al.* 2004), whereas a combination of ephedrine and phenylephrine (Mercier *et al.* 2001) or phenylephrine alone (Ngan Kee *et al.* 2004a; Ngan Kee *et al.* 2005) seems to be more effective. Furthermore, the incidence of maternal nausea and vomiting is higher with ephedrine than with phenylephrine (Mercier *et al.* 2001; Cooper *et al.* 2002). On the basis of these findings, phenylephrine has been suggested as the first-line treatment strategy for maternal hypotension (Ngan Kee *et al.* 2004b).

It is important to realize that, in addition to indirect effects on fetal well-being mediated by changes in uteroplacental perfusion, sympathomimetic amines may also have direct effects on the fetus. Recently, it has been speculated that increased fetal metabolic rate secondary to β-adrenergic stimulation is the mechanism for lower umbilical artery pH values with ephedrine (Cooper *et al.* 2002; Ngan Kee and Lee 2003). Both ephedrine (Räsänen *et al.* 1991) and phenylephrine (Alahuhta *et al.* 1992) have also been shown to modify fetal cardiovascular haemodynamics. However, knowledge of the effects of maternally administered ephedrine and particularly phenylephrine on human fetal and placental haemodynamics is sparse.

Furthermore, ephedrine and phenylephrine have been studied only during elective Caesarean deliveries in uncomplicated pregnancies. During a planned vaginal delivery, however, labour may prolong or abnormalities in fetal heart rate tracings may appear, necessitating Caesarean delivery under regional anaesthesia. Even healthy fetuses become relatively hypoxaemic during the first stage of uncomplicated labour (Aarnoudse *et al.* 1981; Dildy *et al.* 1994). A hypoxaemic stimulus triggers cardiovascular compensatory mechanisms in the fetus, including redistribution of fetal arterial circulation in favour of the brain, heart and adrenal glands (Bocking *et al.* 1988; Iwamoto *et al.* 1989; Block *et al.* 1990). Under these circumstances, fetal haemodynamic responses to maternal hypotension and vasopressor therapy may become unpredictable. In placental insufficiency, Caesarean delivery is frequently performed to minimize fetal morbidity and mortality. As placental insufficiency can also lead to circulatory adjustments in the fetus (Hecher *et al.* 1995; Ferrazzi *et al.* 2002; Mäkikallio *et al.* 2002a), it may further modify fetal responses to these intrapartum incidents.

In the present study, the chronically instrumented fetal sheep model (Rudolph and Heymann 1967) was used to investigate the effects of short-term fetal hypoxaemia, a subsequent period of maternal epidural-induced hypotension and the treatment of hypotension with ephedrine or phenylephrine on fetal and placental haemodynamics and fetal acid-base status in fetuses with either normal placental function or increased placental vascular resistance (R_{UA}).

2 Review of the literature

2.1 Physiology of fetal and placental haemodynamics

The fetal circulation (Fig. 1) is markedly different from the adult circulation. Deoxygenated blood arrives at the placenta via two umbilical arteries. After gas exchange, blood is returned to the fetal circulation via the umbilical vein. The ductus venosus (DV) and the foramen ovale (FO) allow the blood with the highest oxygen content to enter the left side of the fetal heart to supply the myocardium and the brain. The ductus arteriosus (DA) enables most of the blood ejected by the fetal right ventricle to bypass the lungs and to feed the systemic circulation into the descending aorta (DAo) and the placenta. The aortic isthmus (AoI) combines these two parallel circulatory systems.

2.1.1 Cardiac function

The fetal heart provides the driving force to deliver blood throughout the cardiovascular system to supply oxygen and nutrients and to remove metabolic waste. The systolic performance of the heart, or the ability of the ventricles to eject, is dependent on loading conditions, contractility and heart rate. Diastolic performance, which reflects the ability of the heart to fill, may be affected by several factors, including loading conditions and ventricular compliance.

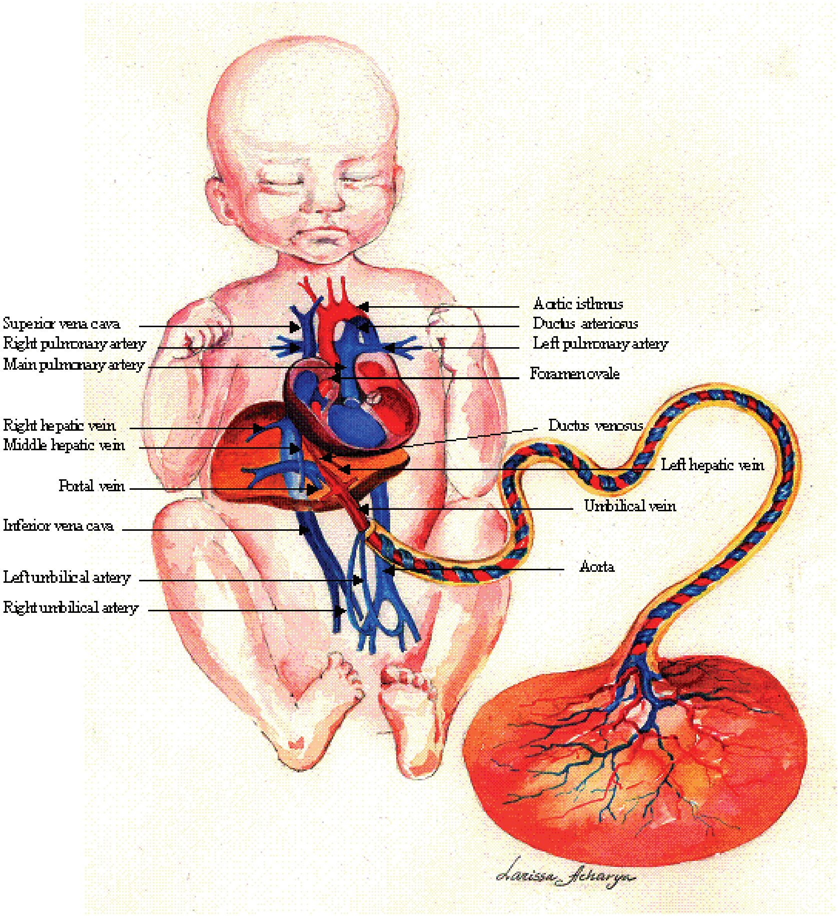


Fig. 1. Overview of fetal circulation. Adopted by permission from Acharya G: The umbilical circulation. A Doppler ultrasonographic study. PhD Thesis 2005, University of Tromsø, Norway.

2.1.1.1 Preload and afterload

Preload and afterload are two interdependent extracardiac factors regulating cardiac performance. Preload is the stress imposed on the ventricular wall at the end of diastole, and afterload is the ventricular wall stress during systole. This wall stress can be quantified by the law of Laplace: Wall stress = PR/2h, where P is pressure, R is the radius of the curvature, and h is the thickness of the ventricular wall. Because the anteroposterior ventricular diameter is greater and the ventricular wall is slightly thinner in the right than the left side of the fetal heart, the resting right ventricular radius-to-wall thickness ratio is larger than that of the left ventricle (Pinson *et al.* 1987). This indicates that, at any given arterial pressure, the right ventricular afterload is higher than the left.

Preload is defined as the sarcomere length immediately before contraction. According to Frank-Starling´s law, a positive correlation exists between sarcomere length and myocardial force. As sarcomere length cannot be determined *in vivo*, preload is estimated by means of surrogate measures, such as ventricular end-diastolic volume or filling pressures. Although the Frank-Starling mechanism is functional in the fetal heart (Kirkpatrick *et al.* 1976), increases in mean atrial pressure above 5−7 mmHg result only in minor increases in the left (Thornburg and Morton 1986), right (Thornburg and Morton 1983) or biventricular (Gilbert 1980; Gilbert 1982) cardiac output. This suggests that, under physiological conditions, the fetal heart operates near the plateau of its Frank-Starling curve. However, it has been shown that if mean arterial pressure (MAP) is held constant, left ventricular stroke volume may continue to rise even above mean left atrial pressure of 10 mmHg (Hawkins *et al.* 1989). Moreover, it has been suggested that the constraining effect on ventricular filling of the pericardium, the solid lungs and the chest wall is the major limitation of fetal left ventricular function (Grant *et al.* 2001).

Afterload can be defined as the arterial impedance opposing ventricular ejection. In the fetal circulation, the right ventricular afterload is regulated by the pulmonary, fetal lower body and placental circulations, while the left ventricular afterload is mainly determined by the brachiocephalic circulation. The fetal heart, especially the right ventricle, is quite sensitive to acute increases in afterload (Gilbert 1982; Reller *et al.* 1986; Thornburg and Morton 1986; Reller *et al.* 1987; Hawkins *et al.* 1989). However, the parallel fetal circulation has some capacity to respond to severely increased right ventricular afterload, induced by occlusion of the DA (Tulzer *et al.* 1991) or banding of the pulmonary artery (Sonesson *et al.* 2004), by immediately shifting cardiac output towards the left ventricle. In addition, during mild and chronic pulmonary hypertension achieved by partially occluding the fetal pulmonary artery, the right ventricular wall thickness was found to increase, which improved the tolerance of increased afterload by decreasing the resting radius-to-wall thickness ratio (Pinson *et al.* 1991).

2.1.1.2 Contractility and heart rate

Contractility is an intrinsic property of the myocyte, which defines the amount of pressure the heart can generate at a given load. It is primarily dependent on the concentration of free cytosolic calcium. During the cardiac action potential, a small amount of calcium enters the cell through depolarization-activated calcium channels, activating further calcium release from the sarcoplasmic reticulum. Calcium binds to troponin C, whereupon troponin I is displaced from its binding site on actin, leading to conformational changes in tropomyosin, which enable the cross-bridging of actin and myosin. (Bers 2002). The sarcoplasmic reticulum of immature myocytes differs structurally from that of adult myocytes (Nassar *et al.* 1987). In addition, fetal myocardium contains a greater proportion of noncontractile elements compared with the adult (Friedman 1972). In accordance with these observations, the contraction velocity and the maximal contractile force of isolated fetal cardiac muscle fibres are significantly lower than those in the neonate or adult, although they increase towards the term of gestation (Anderson *et al.* 1984; Nakanishi and Jarmakani 1984).

Fetal heart rate (HR) is relatively high compared with that of the adult, but decreases towards term (Anderson *et al.* 1984; Tulzer *et al.* 1994; Veille *et al.* 1999; Park *et al.* 2001), while short-term variability increases (Park *et al.* 2001). Spontaneous variations in fetal HR usually correlate positively with cardiac output, although the effect may vary because of concomitant changes in preload, afterload and contractility. However, rapid pacing of the fetal heart decreases stroke volume, as the filling time shortens. (Anderson *et al.* 1986; Anderson *et al.* 1987).

In sheep fetuses, the cardiac sympathetic innervation appears to develop after mid-gestation, but it is not totally complete at birth (Lebowitz *et al.* 1972). The presence of myocardial α-adrenoceptors has been demonstrated in fetal lambs, and phenylephrine can induce a contractile response in fetal ventricular muscle strips *in vitro*. However, the concentration of α-adrenoceptors decreases towards term. (Cheng *et al.* 1980). Ovine myocardial β-adrenoceptors seem to reach maturity in terms of concentration as well as affinity for adrenergic agonists and antagonists near term (Cheng *et al.* 1981), and a mature β-receptor-mediated cardiac response has been verified by 0.64 gestation (Rawashdeh *et al.* 1988). Thus, circulating catecholamines as well as the placental transfer of sympathomimetic drugs may increase fetal HR (Wright *et al.* 1981; Eisler *et al.* 1999) and cardiac contractility (Räsänen *et al.* 1991).

2.1.1.3 Cardiac output and blood pressure

The weight-indexed combined cardiac output (CCO) of the two fetal ventricles, or biventricular output, is significantly higher than that in the adult. Under physiologic conditions, the mean CCO of near-term sheep fetuses is 460−590 ml/min/kg (Rudolph and Heymann 1970; Gilbert 1980; Anderson *et al.* 1981; Itskovitz *et al.* 1987; Block *et al.* 1990; Jensen *et al.* 1991), 60−65% of which is ejected by the right ventricle (Anderson *et al.* 1981; Rudolph 1985). In human fetuses at 23−40 weeks of gestation, the median weight-indexed CCO was 425 ml/min/kg irrespective of gestational age, and the proportions of right (RVCO) and left (LVCO) ventricular cardiac outputs of CCO were 59% and 41%, respectively (Mielke and Benda 2001). In another study on human fetuses, CCO increased over tenfold from 20 gestational weeks to term. The proportion of RVCO of CCO also increased towards term, when RVCO and LVCO constituted 60% and 40% of CCO, respectively. (Räsänen *et al.* 1996b).

There are important differences between the two fetal ventricles associated with the right ventricular dominance. The working myocytes of the fetal right ventricle are larger than those of the left (Smolich *et al.* 1989). The right ventricle has a larger chamber volume (Pinson *et al.* 1987), and the right ventricular function curve is elevated compared with the left (Thornburg and Morton 1983; Thornburg and Morton 1986; Reller *et al.* 1987), demonstrating that, at any physiological atrial filling pressure, the right ventricular stroke volume is greater than that of the left.

As both sides of the fetal heart pump in parallel to the systemic circulation, there is no difference between the left and right ventricular pressures (Johnson *et al.* 2000).

Similarly, the pressure difference between the right and left atria is minimal (Anderson *et al.* 1981; Thornburg and Morton 1986; Reller *et al.* 1987; Johnson *et al.* 2000). With advancing gestation, the left and right ventricular systolic and end-diastolic pressures increase, whereas the atrial pressures remain constant (Johnson *et al.* 2000). In exteriorized human fetuses at 10−20 weeks of gestation, mean carotid arterial pressures varied between 28−35 mmHg (Rudolph *et al.* 1971). In near-term fetal sheep, MAP values of 43−51 mmHg have been reported (Thornburg and Morton 1983; Bocking *et al.* 1988; Block *et al.* 1990; Sipes *et al.* 1992; McGrath *et al.* 1994).

2.1.1.4 Diastolic function and myocardial blood flow

Relaxation of the myocardium is an active process dependent on the ability of myocytes to reduce the concentration of cytosolic calcium (Bers 2002). Ventricular relaxation occurs in four distinct phases: 1) isovolumetric relaxation, 2) early rapid filling, 3) late slow filling and 4) final filling during atrial systole. The isovolumetric relaxation phase does not contribute to ventricular filling, most of which occurs during the rapid filling phase in the adult heart. However, echocardiographic data suggest that atrial systole is more important for ventricular filling in the fetus than it is in the adult (Tulzer *et al.* 1994; Veille *et al.* 1999). Intact fetal lamb hearts seem to be much less compliant than those of adult sheep (Romero *et al.* 1972). Human fetuses seem to have stiffer ventricles than neonates, and their diastolic filling patterns resemble those of a diseased adult heart, although ventricular stiffness progressively decreases with advancing gestation (Veille *et al.* 1999).

The coronary arteries arise from the aortic sinuses to supply the myocardium with oxygenated blood from the left ventricle. Most of the myocardial blood flow is known to occur during diastole. The fetal heart compensates for its relatively hypoxaemic environment by more abundant resting myocardial blood flow compared with the adult, and oxygen delivery is hence comparable to or exceeds that of the adult heart (Fisher *et al.* 1980). Resting myocardial blood flow comprises 2−4% of CCO (Rudolph and Heymann 1970; Itskovitz *et al.* 1987; Block *et al.* 1990; Jensen *et al.* 1991) and is greater to the right than to the left ventricular wall (Fisher *et al.* 1982; Reller *et al.* 1992b; Lohr *et al.* 1994; Reller *et al.* 1995). Fetal atrial myocardial blood flow at rest is less than 50% of ventricular myocardial blood flow (Lohr *et al.* 1994). Upon severe right ventricular pressure loading, the fetal right and left ventricular myocardial blood flows double, with no significant changes in the endocardial-to-epicardial flow ratio (Reller *et al.* 1992b), while the atrial myocardial blood flows increase even more (Lohr *et al.* 1994). Even greater increases in myocardial blood flow may be triggered by adenosine infusion (Reller *et al.* 1992b; Lohr *et al.* 1994) or fetal hypoxaemia (Reller *et al.* 1995). These observations suggest a large myocardial blood flow reserve, which presumably does not limit fetal cardiac performance.

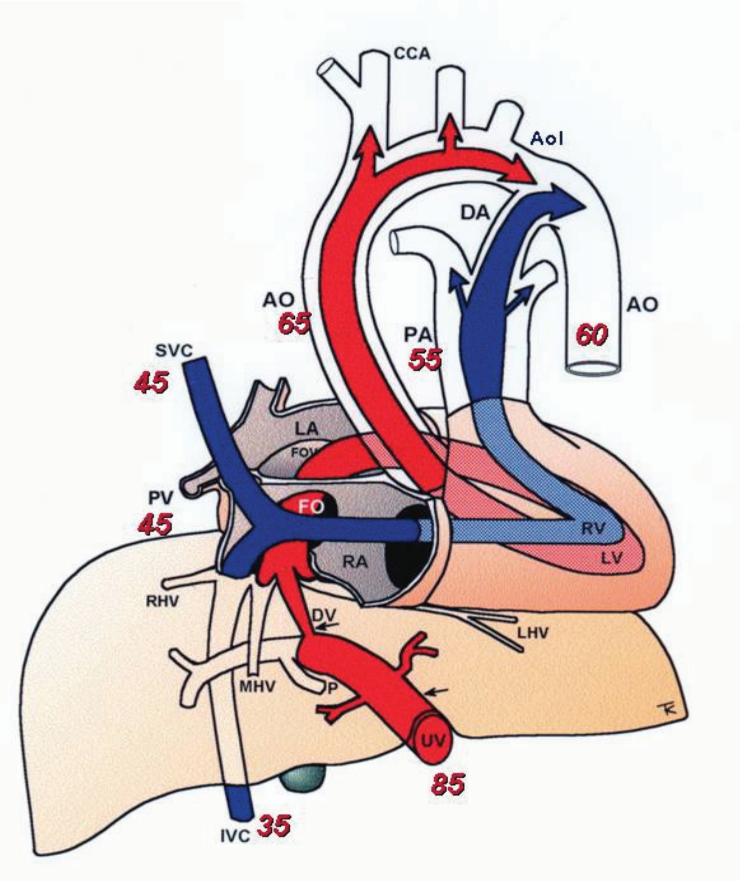


Fig. 2. Central pathways of fetal circulation with oxygen saturation values. Adopted and modified from Kiserud T *et al.* Am J Obstet Gynecol 2000;182:147-153.

2.1.2 Special characteristics of fetal arterial and venous circulation

2.1.2.1 Ductus venosus and foramen ovale

The DV (Fig. 2) is a slender trumpet-like shunt, which connects the intra-abdominal umbilical vein to the inferior vena cava (IVC) via the portal sinus, allowing a large amount of oxygenated umbilical venous blood to bypass the hepatic circulation. During normoxaemia in near-term fetal sheep, 44−55% of umbilical venous blood is shunted through the DV (Edelstone *et al.* 1978; Edelstone and Rudolph 1979; Itskovitz *et al.* 1987; Jensen *et al.* 1991), although later ultrasonographic studies have suggested this proportion to be significantly lower, i.e. 17−36% (Tchirikov *et al.* 1998a; Kiserud *et al.*

2000a). In a study on human fetuses, 39% of the umbilical venous volume blood flow was directed to the DV at 39−41 weeks of gestation (Tchirikov *et al.* 1998b), but another study suggested that this proportion is reduced to a minimum of 18% by 31 weeks of pregnancy (Kiserud *et al.* 2000b). The DV inlet has been shown to contain functional adrenergic nerves and to demonstrate a contractile response via α-adrenoceptors and relaxation via β-receptors (Coceani *et al.* 1984). In acute experiments in fetal sheep *in vivo*, the tonically constricted DV inlet was dilated by nitric oxide, after which phenylephrine did not induce any contraction (Kiserud *et al.* 2000a). In chronically instrumented fetal lambs, noradrenaline and adrenaline seem to increase hepatic vascular resistance, resulting in an increase in the DV blood flow (Paulick *et al.* 1991). This is in accordance with the *in vitro* observations showing a greater α-adrenergic receptor density as well as more pronounced contractile reactivity in the vascular segments of the intrahepatic veins compared with those of the DV (Tchirikov *et al.* 2003).

The FO (Fig. 2) can be described as an opening in the posterior lower part of the atrial septum of the fetal heart. It supplies the fetal left atrium with 17−33% of CCO during the third trimester of human gestation (Sutton *et al.* 1994; Räsänen *et al.* 1996b; Mielke and Benda 2001), which constitutes 50−76% of LVCO (Räsänen *et al.* 1996b; Mielke and Benda 2001). In near-term fetal sheep, the FO flow accounts for 34% of CCO and almost 85% of LVCO (Anderson *et al.* 1981). Under normal conditions, the kinetic energy of blood in the IVC is a more important determinant of the FO blood flow than the minimal pressure gradient between the two atria or that between the IVC and the left atrium (Anderson *et al.* 1981; Anderson *et al.* 1985). However, increased pressure on the left side is thought to be reflected in enhanced diversion of blood into the right atrium (Kiserud 2005).

Animal experiments using the labelled microsphere technique have suggested preferential distribution of the oxygen-rich DV blood through the FO, whereas blood originating from the caudal IVC is mainly directed through the tricuspid valve (Edelstone and Rudolph 1979; Reuss *et al.* 1981). In accordance with this, recent Doppler ultrasonographic studies on human (Kiserud *et al.* 1992) and sheep fetuses (Schmidt *et al.* 1996) have identified two separate blood flow streams within the intrathoracic portion of the IVC. The DV stream, which has a higher velocity, follows the posterior and left aspect of the vena cava and predominantly flows through the FO, whereas the caudal IVC stream with lower velocity passes anteriorly and to the right and is preferentially distributed into the right atrium (Kiserud *et al.* 1992; Schmidt *et al.* 1996). In addition, the right atrium receives most of the venous return from the superior vena cava (Rudolph and Heymann 1967; Schmidt *et al.* 1996).

2.1.2.2 Ductus arteriosus and pulmonary circulation

The DA (Fig. 2) is a wide muscular vessel, which connects the pulmonary arterial trunk to the DAo. It allows RVCO to bypass the pulmonary circulation. Its prenatal patency is an active state sustained by prostaglandin E2 (Coceani and Olley 1988). In fetal sheep, 90% of blood ejected by the right ventricle, or 54% of CCO, is normally directed to the DA (Anderson *et al.* 1981). In human fetuses, 78% of RVCO, or 46% of CCO, flows through the DA (Mielke and Benda 2001). This proportion does not change significantly during the second half of gestation (Räsänen *et al.* 1996b). The pulmonary blood flow in near-term sheep fetuses is 6−8% of CCO (Rudolph and Heymann 1970; Anderson *et al.* 1981; Itskovitz *et al.* 1987), although a proportion of almost 12% has also been reported (Jensen *et al.* 1991). The latter is in accordance with a study on human fetuses where pulmonary blood flow was estimated to be approximately 11% of CCO irrespective of gestational age (Mielke and Benda 2001). However, other studies on human fetuses (Sutton *et al.* 1994; Räsänen *et al.* 1996b) have suggested that the proportion of pulmonary blood flow of CCO is clearly larger than that observed in fetal sheep. As human pregnancy advanced from 20 to 30 weeks, fetal pulmonary blood flow increased from 13% to 25% of CCO, after which it remained unchanged until term (Räsänen *et al.* 1996b).

The distribution of RVCO between the pulmonary circulation and the DA is dependent on pulmonary vascular resistance. During the third trimester, the fetal pulmonary arterial bed seems to be under acquired vasoconstriction but highly reactive to changes in fetal oxygen tension. An increase in Po_2 decreases pulmonary vascular resistance or impedance and increases pulmonary blood flow in both human and ovine fetuses (Morin and Egan 1992; Räsänen *et al.* 1998). The effects of fetal hypoxaemia on the pulmonary haemodynamics of fetal sheep are opposite to this (Lewis *et al.* 1976). However, these pulmonary haemodynamic responses to changes in Po_2 are not present during the second trimester (Lewis *et al.* 1976; Morin and Egan 1992; Räsänen *et al.* 1998). The increasing pulmonary vasomotor reactivity with advancing gestation has been explained by the increasing amount of smooth muscle in small pulmonary arteries (Levin *et al.* 1976).

Although fetal vascular reactivity to adrenergic agonists increases towards term, the haemodynamic response to α-adrenergic stimulation remains less pronounced in the pulmonary than the systemic circulation (Nuwayhid *et al.* 1975). This is in accordance with the lower density of α1-adrenoceptors in the intrapulmonary compared with the systemic vascular smooth muscle of late gestation fetal sheep (Shaul *et al.* 1990). However, catecholamines and sympathomimetic drugs may alter fetal pulmonary vascular resistance. In a study on newborn calves, phenylephrine increased and the β-adrenergic agonist isoproterenol decreased both pulmonary arterial and venous vascular resistance (Greenlees *et al.* 1986). In near-term fetal lambs, noradrenaline has been shown to induce nitric oxide dependent pulmonary vasodilation (Jaillard *et al.* 2001; Magnenant *et al.* 2003) involving α2-adrenoceptor activation (Magnenant *et al.* 2003).

2.1.2.3 Aortic isthmus

The AoI (Fig. 2) has a unique position in the fetal circulation as it combines the two parallel circulatory systems. Under normal conditions, the direction of blood flow in the AoI is antegrade or, in other words, towards the DAo (Fouron *et al.* 1994). However, a gradual rise in placental vascular resistance increases the retrograde blood flow component in the AoI, especially during diastole (Bonnin *et al.* 1993; Sonesson and Fouron 1997; Fouron *et al.* 1999). Acute experimental studies on fetal sheep have suggested that if the net blood flow through the AoI becomes retrograde, the delivery of oxygen to the fetal brain is diminished (Fouron *et al.* 1999).

2.1.3 Placental circulation

2.1.3.1 Uteroplacental haemodynamics

Uteroplacental perfusion mainly originates from the uterine arteries, with a minor contribution from the ovarian arteries. The uterine arteries branch into the arcuate and, thereafter, radial arteries, reaching the placenta by the spiral arteries. Uterine volume blood flow (Q_{UtA}) increases dramatically during pregnancy, reaching values up to 800−1000 ml/min at 38 weeks of normal gestation (Konje *et al.* 2001; Konje *et al.* 2003), when it constitutes approximately 12% of maternal cardiac output (Thaler *et al.* 1990). In the uterus, 79−96% of blood flow is distributed into the intervillous space, while the rest supplies the myometrium (Anderson *et al.* 1977).

Q_{UtA} is directly proportional to perfusion pressure and inversely related to uterine vascular resistance (R_{UtA}), with no autoregulatory reserve (Greiss 1966; Berman *et al.* 1976). The ovine uterine vascular bed seems to be more responsive to α-adrenergic vasoconstriction than is the systemic vasculature (Anderson *et al.* 1977; Magness and Rosenfeld 1986). It has been shown in human (Stjernquist and Owman 1990) and ovine (Isla and Dyer 1990) uterine arteries *in vitro* that the vasoconstrictive response is mediated by α1-adrenoceptors. Both α2- and β-adrenergic activation are associated with vasorelaxation in isolated uterine arterioles of pregnant rat (Wang *et al.* 2002). In accordance, isoproterenol has been shown to increase Q_{UtA} at the term of human gestation (Marcus *et al.* 1997). In a similar setting in near-term pregnant sheep, isoproterenol slightly decreased Q_{UtA} (Marcus *et al.* 1996), but this occurred during a simultaneous decrease in maternal MAP.

The uterine vascular responses to sympathomimetic stimulation seem to be modulated by pregnancy. In isolated uterine arterioles of rat, both α1-adrenergic vasoconstriction and α2-adrenergic relaxation are enhanced during pregnancy, while β-adrenoceptor-mediated relaxation seems to be blunted compared with the nonpregnant state (Wang *et al.* 2002). In contrast, both *in vitro* and *in vivo* studies have suggested that the α-adrenergic vasoconstrictive response of the uterine vascular bed is attenuated during normal ovine pregnancy (Magness and Rosenfeld 1986; Tong and Eisenach 1992) as a result of increased nitric oxide activity (Li *et al.* 1996; White *et al.* 1998).

2.1.3.2 Umbilicoplacental haemodynamics

In near-term fetal sheep, up to 45% of CCO, or approximately 200 ml/min/kg, is directed to the umbilical arteries and the placenta (Rudolph and Heymann 1970; Itskovitz *et al.* 1987; Jensen *et al.* 1991). Umbilicoplacental volume blood flow (Q_{UA}) is considerably lower in human fetuses. It increases linearly with CCO and comprises roughly 30% of

CCO throughout the second and third trimesters (Sutton *et al.* 1991b). It has been believed that, in normal human pregnancies, the weight-indexed umbilical venous volume blood flow remains essentially constant at 110−120 ml/min/kg for most of the pregnancy (Gill *et al.* 1981; Sutton *et al.* 1990; Sutton *et al.* 1991b; Barbera *et al.* 1999). However, other ultrasonographic studies have suggested that umbilical venous volume blood flow normalized to estimated fetal weight begins to decrease after the 20th gestational week (Kiserud *et al.* 2000b; Boito *et al.* 2002). Recent longitudinal observations on low-risk pregnancies have shown that maximal umbilical venous volume blood flow is reached at the end of the second trimester. Thereafter, it decreases throughout the third trimester to approximately 66 ml/min/kg at 40 weeks of gestation. (Acharya *et al.* 2005c).

As the umbilicoplacental circulation lacks significant autoregulation, Q_{UA} is directly proportional to perfusion pressure (Berman *et al.* 1976) and inversely related to R_{UA}. R_{UA} comprises the vascular resistances across the umbilical arteries, cotyledons and the umbilical vein, corresponding at rest to 30%, 55% and 15% of total resistance (Adamson *et al.* 1992). Although the structural organization of the placental microcirculation is the main determinant of R_{UA}, changes in the vasomotor tone of the placental vasculature also play a role. The umbilicoplacental vessels have no autonomic innervation (Reilly and Russell 1977; Fox and Khong 1990). Moreover, the human umbilical vessels lack functional β-adrenoceptors (Clyman *et al.* 1975; Errasti *et al.* 1999). However, *in vitro* studies have shown that the human umbilical vessels can respond to phenylephrine and catecholamines by vasoconstriction (Bodelsson and Stjernquist 1995; Errasti *et al.* 1999). This response seems to be mediated by both α1- and α2-adrenoceptors in the umbilical artery (Bodelsson and Stjernquist 1995) but only by α1-adrenoceptors in the umbilical vein (Errasti *et al.* 1999).

2.2 Ultrasonographic assessment of fetal and placental haemodynamics

2.2.1 Methodological considerations

According to the Doppler principle, the observed frequency of sound waves changes if either the source or the observer is moving. In ultrasonography, the Doppler frequency shift, or the change in the frequency of ultrasound returning from moving red blood cells to the transducer, is converted electronically into a graphic representation of the frequency shift as a function of time called the blood flow velocity waveform. The computation is dependent on the speed and direction of blood flow, the operating frequency of the Doppler transducer, and the angle between the transducer and the blood vessel (Dickey 1997; DeVore 2005).

In a continuous-wave Doppler system, ultrasound waves are continuously transmitted and received with two different transducers. In pulsed Doppler devices, a single transducer transmits and receives the ultrasound waves in pulses. With pulsed Doppler devices, it is possible to select the depth from which the Doppler signals are obtained. This allows blood flow analysis within a single vessel. To shorten the time required to obtain the pulsed Doppler waveform, colour Doppler may first be used to identify the structure of interest, to visualize the direction of blood flow, and to optimize the angle of insonation.

From the blood flow velocity waveforms, the presence or absence of blood flow as well as the shape of the waveform, which differs from one vessel to another, can be analyzed qualitatively. By semiquantitative analysis, indices such as the pulsatility index (PI = (PSV − EDV)/TAMXV; where PSV is the peak systolic velocity, EDV is the end-diastolic velocity, and TAMXV is the time-averaged maximum velocity over the cardiac cycle) can be derived from the relations between the systolic and diastolic blood flow components. The PI represents the downstream vascular impedance, i.e. the resistance to pulsatile flow. It is only an indirect estimation of the actual blood flow (Dickey 1997). Within the physiological range, no correction for HR is required (Kofinas *et al.* 1989). Furthermore, it is virtually independent of the angle of insonation, and an angle of less than 60 degrees is considered insignificant (Gudmundsson *et al.* 1990). On the other hand, when absolute velocities are measured or volume blood flows are calculated, the angle of insonation is of much greater concern and should always be kept at less than 30 degrees (Tessler *et al.* 1990). In addition, volume blood flow calculations are highly dependent on accurate measurement of the vessel diameter (Beeby *et al.* 1991; Brodszki *et al.* 1998). Therefore, semiquantitative indices are preferred in smaller vessels, while volume blood flow analysis is recommended only for larger vessels (Dickey 1997).

2.2.2 Cardiac function

2.2.2.1 Cardiac output

The volume blood flow (Q) can be calculated by multiplying the cross-sectional area (CSA) through which blood is flowing by the mean velocity (V_{mean}) of blood flow. The CSA of a vessel can be computed from vessel diameters (r) using the formula: CSA = $\pi(r/2)^2$. V_{mean} is calculated by multiplying the time-velocity integral (TVI), which is obtained by planimetry of the area underneath the Doppler spectrum, by HR. Accordingly, volume blood flow is calculated with the formula: $Q = \pi(r/2)^2 * TVI * HR$. In the fetal heart, LVCO equals the volume blood flow across the aortic valve, RVCO equals the volume blood flow across the pulmonary valve, and their sum equals the CCO.

2.2.2.2 Systolic function

Ventricular ejection force estimates the energy transferred from ventricular myocardial shortening to the work done by accelerating blood into the circulation (Sutton *et al.* 1991a). The left (LVeFo) and right (RVeFo) ventricular ejection forces are calculated from blood flow velocity waveforms obtained across the respective semilunar valves using the formula: $(1.055*CSA*TVI_{acc})*(PSV/TTP)$, in which TVI_{acc} is the TVI during the acceleration period in systole, PSV is the peak systolic velocity, and TTP is the time to peak velocity interval (Isaaz *et al.* 1989; Sutton *et al.* 1991a). Animal studies have suggested that early systolic flow is less affected by changes in afterload and preload than flow during late systole (Noble 1968). However, chronic volume overload increases and acute pressure overload decreases human fetal RVeFo (Räsänen *et al.* 1997), suggesting that ventricular ejection forces are not totally independent of preload and afterload. In normal pregnancies, LVeFo and RVeFo are equal and increase more than tenfold from 20 weeks to term of gestation (Sutton *et al.* 1991a; Rizzo *et al.* 1995), indicating that ejection forces increase with increasing myocardial mass.

Isovolumetric contraction time (ICT) is the time between the closure of the atrioventricular valve and the opening of the semilunar valve (De Muylder *et al.* 1984), which is needed for the ventricle to increase its pressure from an atrial to a systemic level. It has been shown to be a reliable indicator of fetal ventricular performance (Koga *et al.* 2003b), but has been suggested to be dependent on preload and afterload (Metzger *et al.* 1970; Koga *et al.* 2003a; Koga *et al.* 2003b). It remains constant during the second half of pregnancy and does not seem to be affected by changes in fetal HR (Koga *et al.* 2001).

Left (LVFS) and right (RVFS) ventricular fractional shortenings are calculated with the formula: fractional shortening (%) = [(inner diastolic diameter − inner systolic diameter)/inner diastolic diameter]*100 (DeVore *et al.* 1984). The diameters are obtained using M-mode echocardiography. Fractional shortenings reflect ventricular contractility (DeVore *et al.* 1984) but decrease during a severe increase in cardiac afterload (Tulzer *et al.* 1991). In normal fetuses, LVFS and RVFS are independent of gestational age and demonstrate a constant (1:1) right-to-left ratio throughout gestation (DeVore *et al.* 1984).

2.2.2.3 Diastolic function

Isovolumetric relaxation time (IRT) represents the time interval between the closure of the semilunar valve and the opening of the atrioventricular valve. It is needed for the ventricle to actively decrease its pressure to the atrial level. The proportion of IRT of the total cardiac cycle can be used to describe the early diastolic function of the heart. During the second half of normal gestation, this proportion remains constant. This suggests constant diastolic function of the fetal heart during a period of over tenfold increase of cardiac mass. (Tulzer *et al.* 1994).

The ventricular filling patterns can be assessed by measuring the peak flow velocities and TVI values across the atrioventricular valves during early filling (E-wave) and atrial contraction (A-wave). During fetal life, the E- and A-wave peak velocities are higher at the tricuspid valve than at the mitral valve, with no difference in the E-wave/A-wave velocity ratio between the valves (Tulzer *et al.* 1994). With advancing gestation, the E- and A-wave peak velocities as well as the E-wave/A-wave velocity ratio increase (Tulzer *et al.* 1994; Veille *et al.* 1999), but the peak velocity of the A-wave remains higher than that of the E-wave (Tulzer *et al.* 1994). The A-TVI/total TVI ratio, which reflects the atrial contribution to ventricular filling, is greater at the tricuspid valve than at the mitral valve. It does not change with advancing gestation, suggesting unchanged ventricular compliance (Tulzer *et al.* 1994).

2.2.3 Fetal arterial circulation

The flow in the DA is directed from the pulmonary artery towards the DAo both in systole and in diastole throughout pregnancy, and the DA systolic velocities are usually the highest blood flow velocities in the fetal circulation (Huhta *et al.* 1987). With advancing gestation, the PSV and EDV values increase but the PI remains constant (Mielke and Benda 2000). This is thought to reflect a relative constriction of the DA towards the term of pregnancy (Huhta *et al.* 1987).

The blood flow velocity waveform profile of the fetal right or left proximal pulmonary artery (PPA) is characterized by a needle-like systolic peak followed by a short systolic component and a short reverse flow interval at the beginning of diastole. The PPA PI values decrease until 34−35 weeks of normal gestation, after which they do not decrease further. In accordance, the PSV values increase until the latter part of the third trimester. (Räsänen *et al.* 1996a).

In the AoI, a forward flow towards the DAo is present throughout the cardiac cycle in normal human pregnancy. During the last trimester, however, a short retrograde blood velocity waveform component may be observed in early diastole (Fouron *et al.* 1994). If the ratio of the TVI values of the antegrade and retrograde blood flow velocity components (ante/retro TVI) is ≥1, the net blood flow is considered to be antegrade (Fouron *et al.* 1999).

During the second half of normal gestation, the blood flow velocity waveform pattern in the DAo is usually antegrade throughout the cardiac cycle because of low R_{UA}. The weight-related volume blood flow is stable until 37 weeks, after which it decreases slightly. The DAo PI remains stable during the last trimester of gestation. (Marsal *et al.* 1987). In normal pregnancies, the total blood flow in the DAo has been shown to correlate well with the size of the fetal heart and LVCO (Räsänen *et al.* 1988).

Throughout normal pregnancy, there is a continuous diastolic component in the blood flow velocity waveforms of the cerebral arteries (Kirkinen *et al.* 1987). The middle cerebral artery PI values increase slightly until 30−32 weeks (Konje *et al.* 2005) and then gradually decrease (van den Wijngaard *et al.* 1989; Konje *et al.* 2005), indicating decreasing impedance in the fetal cerebral circulation during the latter part of the third trimester.

2.2.4 Fetal venous circulation

The blood flow velocity waveforms of the DV, IVC and hepatic veins are normally triphasic (Hecher *et al.* 1994; Axt-Fliedner *et al.* 2004). They are thought to reflect systemic venous pressure (CVP) (Gudmundsson *et al.* 1999). In the DV, the direction of blood flow is towards the heart throughout the cardiac cycle. During atrial contraction, the direction of flow in the IVC can be away from the heart, zero or towards the heart, with the likelihood of the latter increasing with gestational age. In the right hepatic vein, flow during atrial contraction is generally away from the heart but can be towards the heart during the late third trimester. Venous blood flow velocities increase during the second and third trimesters of pregnancy, being highest in the DV and lowest in the right hepatic vein. (Hecher *et al.* 1994; Axt-Fliedner *et al.* 2004). The venous blood flow velocity waveforms can be used to calculate the PI values for veins (PIV): PIV = (PSV − velocity during atrial contraction)/TAMXV (Hecher *et al.* 1994). The PIV values of the DV, IVC and right hepatic vein decrease with advancing gestation, being lowest in the DV and highest in the right hepatic vein (Hecher *et al.* 1994; Axt-Fliedner *et al.* 2004). In the fetal pulmonary vein (PV), the blood flow velocity profile as well as the changes during pregnancy in PSV and PIV are similar to those of the DV (Lenz and Chaoui 2002).

2.2.5 Placental circulation

2.2.5.1 Uteroplacental haemodynamics

In the uterine circulation, a high-resistance blood flow pattern is invariably present at the beginning of pregnancy. However, the uterine artery PI (PI_{UtA}) begins to decrease and the absolute velocities begin to increase after the 8th week of gestation (Mäkikallio *et al.* 2004). During the second trimester, the uterine artery Doppler indices decrease sharply, and the incidence of early diastolic notching shows a marked reduction (Schulman *et al.* 1986; Fay *et al.* 1994). This is believed to reflect the decreasing R_{UtA} due to the trophoblastic invasion of the spiral arteries (Pijnenborg *et al.* 1980). By 24 gestational weeks, diastolic notching becomes uncommon (Fay *et al.* 1994). After 26 weeks of normal gestation, little or no change is observed in the uterine artery Doppler indices (Schulman *et al.* 1986).

In a computer model, increased peripheral resistance in the placental vascular bed seems to cause a marked increase in PI_{UtA}, creating a notch in the uterine waveform, while a decrease in the uterine artery radius leads to a smaller increase in the PI_{UtA}, and no dicrotic notch appears (Adamson *et al.* 1989). In an *in vivo* sheep preparation, uterine artery Doppler indices increased after uteroplacental vascular embolization but failed to demonstrate an angiotensin II-induced increase in R_{UtA} (Saunders *et al.* 1998).

2.2.5.2 Umbilicoplacental haemodynamics

In the umbilical artery, the diastolic blood flow velocity component increases with advancing gestation. It usually emerges after 12 gestational weeks and should always be visible after 16 weeks of normal gestation (Wladimiroff *et al.* 1991). Recent longitudinal observations at 19−42 weeks of normal human gestation have shown that the umbilical artery PSV, EDV and TAMXV progressively increase with gestational age and show a positive correlation with umbilical venous volume blood flow (Acharya *et al.* 2005a).

Throughout the second half of uncomplicated pregnancy, the umbilical artery PI (PI_{UA}) shows a continuous reduction (Acharya *et al.* 2005b) but does not seem to correlate significantly with umbilical venous volume blood flow (Acharya *et al.* 2005a).

The PI_{UA} is determined by the ratio of total R_{UA} to umbilical artery resistance (Thompson and Trudinger 1990). In fetal sheep, the PI_{UA} does not reveal changes in vascular resistance mediated by umbilical arterial vasoconstriction due to angiotensin II infusion, but reflects an increase in the resistance of cotyledons caused by placental embolization (Adamson *et al.* 1990). An exponential increase in PI_{UA} is obtained only after more than 60% of the terminal vascular branches have been obliterated (Thompson and Trudinger 1990). Therefore, the PI_{UA} seems to reflect the haemodynamic and morphological events taking place at the level of placental villi (Giles *et al.* 1985; Morrow *et al.* 1989; Macara *et al.* 1996) and should not be considered an accurate indicator of changes in Q_{UA} or R_{UA} (Adamson *et al.* 1990).

2.3 Fetal and placental haemodynamics in placental insufficiency

Placental insufficiency is a process that leads to progressive deterioration in placental function, with a decrease in the transplacental transfer of oxygen and nutrients to the fetus, resulting in chronic fetal hypoxaemia and growth restriction (Gagnon 2003). The fetal circulatory responses to placental insufficiency can be divided into early and late, corresponding to the degree of fetal compromise. The early responses result from the effects of increased R_{UA} on the distribution of CCO as well as from active organ autoregulation (Hecher *et al.* 1995; Hecher *et al.* 2001; Ferrazzi *et al.* 2002). After the establishment of fetal arterial redistribution, significant changes in venous Doppler waveforms develop due to increased cardiac afterload (Hecher *et al.* 1995; Hecher *et al.* 2001; Ferrazzi *et al.* 2002) and possible myocardial failure (Mäkikallio *et al.* 2002b). Reverse EDV in the umbilical artery, decreased PSV values at the level of the pulmonary and aortic valves (Ferrazzi *et al.* 2002) and decreased short-term variation of fetal HR (Hecher *et al.* 2001) are also late findings. These late responses are closely related to increased perinatal mortality (Hecher *et al.* 2001; Ferrazzi *et al.* 2002).

2.3.1 Placental circulation

2.3.1.1 Uteroplacental haemodynamics

During the third trimester, only 36% of pre-eclamptic patients show signs of increased uterine artery vascular impedance (Li *et al.* 2005), but if present, such signs are powerful predictors of an adverse pregnancy outcome (Aardema *et al.* 2001; Li *et al.* 2005). Abnormal uterine artery blood flow velocity profiles have been associated with impaired physiologic adaptation of the spiral arteries (Aardema *et al.* 2001; Kuzmina *et al.* 2005). In normal pregnancies, the trophoblast invasion of the spiral arteries has been shown to begin at least by the 8th week of gestation (Pijnenborg *et al.* 1980). In a low-risk population, elevated uterine artery Doppler indices at 11−14 gestational weeks may be related to later intrauterine growth restriction (Martin *et al.* 2001; Dugoff *et al.* 2005). However, abnormal uterine blood flow velocity waveforms at 23 weeks of gestation may be more sensitive predictors of severe placental insufficiency (Papageorghiou *et al.* 2001). The absence of diastolic notches in the uterine artery blood flow velocity waveform at 11−14 weeks of gestation seems to be associated with higher birth weight, whereas the presence of bilateral diastolic notches at 18−23 weeks predicts lower birth weight (Prefumo *et al.* 2004). A significant relation between the elevation of the PI_{UtA} along with the depth of the uterine notch at 20−23 weeks of low-risk gestation and the frequency of later adverse pregnancy outcomes has been demonstrated (Becker *et al.* 2002).

2.3.1.2 Umbilicoplacental haemodynamics

In the umbilical circulation, reduced umbilical venous volume blood flow may be the first sign of disturbed villous perfusion (Ferrazzi *et al.* 2000). This reduction is associated with a lower blood flow velocity, with no change in the diameter of the umbilical vein (Rigano *et al.* 2001). Absence and reversal of the umbilical artery EDV are related to extremely elevated R_{UA}, since they do not occur before 60−70% of the villous vasculature is damaged (Morrow *et al.* 1989). In preterm growth-restricted fetuses, absent or reverse umbilical artery EDV is associated with high perinatal morbidity and mortality (Rochelson *et al.* 1987; Kurkinen-Raty *et al.* 1997; Soregaroli *et al.* 2002; Spinillo *et al.* 2005).

2.3.2 Fetal cardiac function

As elevated R_{UA} increases the right ventricular afterload, it may impair the right ventricular function. In the fetal parallel circulation, this leads to a redistribution of CCO towards the left ventricle (al-Ghazali *et al.* 1989). Because of this shift in CCO in favour of the left ventricle, even fetuses who suffer from severe placental insufficiency, with increased afterload, increased pulsatility in the systemic venous blood flow velocity profiles and biochemical evidence of myocardial cell damage, are able to maintain their CCO (Mäkikallio *et al.* 2002b). In very preterm pregnancies complicated by placental insufficiency, a decrease in CCO observed within 24 hours before delivery has been related to suboptimal neurodevelopmental outcome at 1 year of corrected age (Kaukola *et al.* 2005).

It has been demonstrated that, in severe placental insufficiency, RVFS decreases whereas LVFS is not significantly affected (Räsänen *et al.* 1989; Mäkikallio *et al.* 2002b). Other indicators of increased right ventricular afterload have also been observed, such as increased cardiac size (Mäkikallio *et al.* 2002b) and ventricular inner diameters, especially those of the right ventricle (Räsänen *et al.* 1988; Räsänen *et al.* 1989), and frequent visualization of tricuspid valve regurgitation (Mäkikallio *et al.* 2002b).

In fetuses with growth restriction secondary to placental insufficiency, ventricular ejection forces have been shown to decrease symmetrically in both ventricles, and this finding is associated with a poorer perinatal outcome (Rizzo *et al.* 1995). In another study on fetuses with signs of myocardial cell damage, however, ejection forces were not affected (Mäkikallio *et al.* 2002b). The controversy might be explained by the normal umbilical artery pH values of the fetuses in the latter study (Mäkikallio *et al.* 2002b), since the ventricular ejection forces correlated directly with the severity of fetal acidosis in the first study (Rizzo *et al.* 1995).

A prolonged ICT may sometimes be observed in placental insufficiency and, if present, it is related to an adverse neonatal outcome (Koga *et al.* 2001). Fetal acidaemia has also been shown to be related to prolonged ICT (Yumoto *et al.* 2005).

Placental insufficiency can impair the diastolic performance of the fetal heart, and IRT may be prolonged in fetuses with growth restriction (Tsyvian *et al.* 1995; Mäkikallio *et al.* 2003). In addition, the E-wave/A-wave velocity ratio of the mitral valve may decrease, suggesting a larger contribution of atrial contraction to ventricular filling in growth-restricted fetuses (Tsyvian *et al.* 1998). However, these findings were not observed in fetuses with placental insufficiency and signs of myocardial cell damage (Mäkikallio *et al.* 2002b).

In an ovine model of intrauterine growth restriction, increased umbilical artery Doppler indices correlated positively with fetal blood pressure, suggesting that increased placental vascular resistance leads to systemic hypertension (Galan *et al.* 2005).

2.3.3 Fetal arterial circulation

Experimental studies have demonstrated that increased R_{UA} causes changes in the AoI blood flow profile before any significant changes in the umbilical artery blood flow velocity waveforms are observed (Bonnin *et al.* 1993). Similarly, in human fetuses with placental insufficiency, retrograde AoI net blood flow may be detected in the presence of a normal umbilical artery blood flow velocity waveform profile (Sonesson and Fouron 1997; Mäkikallio *et al.* 2002a). In human fetuses with abnormal umbilical artery PI values, absence or reversal of EDV is frequently observed in the AoI (Sonesson and Fouron 1997).

In placental insufficiency, fetuses with antegrade net blood flow in the AoI show a shift in RVCO to the systemic circulation, and blood flow across the FO comprises the majority of LVCO, while fetuses with retrograde AoI net blood flow fail to demonstrate these changes and show signs of increased left atrial pressure (Mäkikallio *et al.* 2003). In a study on fetuses with equally impaired placental function (Mäkikallio *et al.* 2002a), arterial redistribution was similar regardless of the direction of the AoI net blood flow, except that the coronary blood flow was more often visualized if the AoI net blood flow was retrograde. Right ventricular afterload was higher in fetuses with retrograde net blood flow. This was attributable to increased PPA PI, as there were no differences in the DA and DAo PI values. Furthermore, fetuses with retrograde net blood flow in the AoI demonstrated increased pulsatility in the DV blood flow velocity waveforms. (Mäkikallio *et al.* 2002a). These findings suggest that the oxygen content of the blood entering the left ventricle is diminished in fetuses with retrograde net blood flow in the AoI, as previously suggested on the basis of animal experiments (Fouron *et al.* 1999). Retrograde net blood flow in the AoI of human fetuses has also been associated with nonoptimal neurodevelopmental outcome at 2−4 years of age (Fouron *et al.* 2005).

In ovine fetuses, fetal hypoxaemia caused by placental embolization increases cerebral blood flow and decreases cerebral vascular resistance (Gagnon *et al.* 1997). Doppler studies of growth-restricted human fetuses have demonstrated reduced vascular impedance and increased blood flow velocities in the cerebral arteries (Wladimiroff *et al.* 1986; van den Wijngaard *et al.* 1989; Hecher *et al.* 2001; Ferrazzi *et al.* 2002; Mäkikallio *et al.* 2002a) and opposite changes in the DAo (Jouppila and Kirkinen 1986; Wladimiroff *et al.* 1986; Räsänen *et al.* 1988; Hecher *et al.* 2001; Mäkikallio *et al.* 2002a).

Coronary artery blood flow may be visualized under favourable imaging conditions in normal fetuses from 31 weeks of gestation onwards (Baschat *et al.* 1997). In growth-restricted fetuses with abnormal arterial and venous Doppler findings, it may be visualized at an earlier gestational age (Baschat *et al.* 1997) and is associated with fetal hypoxaemia, acidaemia and a poor perinatal outcome (Baschat *et al.* 1997; Baschat *et al.* 2000). This end-stage phenomenon coincides with deteriorating venous blood flow velocity waveform patterns (Baschat *et al.* 2000).

2.3.4 Fetal venous circulation

Elevated right ventricular afterload may cause the right ventricular end-diastolic pressure to increase, leading to an increase in the reversal of flow into the venous system upon atrial contraction. Thus, the abnormalities in fetal venous Doppler waveforms are observed during atrial contraction and include atrial pulsations in the umbilical vein, increased reversed A-wave component in the fetal IVC and hepatic veins and a decreased or reversed A-wave component in the DV (Hecher *et al.* 1995). They are believed to reflect increased CVP (Gudmundsson *et al.* 1999). Atrial pulsations in the umbilical vein originate in the fetal venous system, being transmitted towards the placenta (Reed and Anderson 2000). The abnormal venous Doppler waveforms are late findings of severe placental insufficiency, which are associated with fetal acidaemia (Baschat *et al.* 2004), myocardial cell damage (Mäkikallio *et al.* 2000; Mäkikallio *et al.* 2002b) and high morbidity and mortality (Hecher *et al.* 1995; Hecher *et al.* 2001; Ferrazzi *et al.* 2002; Kaukola *et al.* 2005; Schwarze *et al.* 2005).

2.4 Fetal and placental responses to hypoxaemia

The fetal oxidative metabolism is totally dependent on the ongoing transplacental transfer of oxygen from the mother to the fetus, which may be impaired if either uteroplacental or umbilicoplacental perfusion is significantly reduced, or if the oxygen content of maternal arterial blood decreases. Under these circumstances, the fetal haemodynamic responses are directed towards the preservation of oxygen transport to the heart, brain and adrenal glands (Itskovitz *et al.* 1987; Jensen *et al.* 1991; Reid *et al.* 1991). The responses are modified by the duration (Bocking *et al.* 1988) and severity (Block *et al.* 1990) of fetal hypoxaemia.

2.4.1 Oxygen delivery and consumption

The partial pressure of oxygen (Po_2) in fetal arterial blood is much lower than that during postnatal life. However, under normal conditions, the fetal arterial oxygen content is not much lower than that of the adult. Fetal red blood cells have a higher affinity for oxygen than maternal red blood cells because of the relatively high concentration of haemoglobin F. (Harris 1999). Under hypoxaemic stress, this high haemoglobin-oxygen affinity is essential for maintaining oxidative metabolism (Edelstone *et al.* 1989).

As the placenta is metabolically active, placental oxygen consumption accounts for approximately 40% of the total uterine oxygen uptake at the term of ovine gestation (Meschia *et al.* 1980). During elective Caesarean delivery under epidural anaesthesia in humans, the mean placental oxygen consumption was estimated to be 37 ml/min/kg, while that of the fetus was 6.8 ml/min/kg (Bonds *et al.* 1986). Factors that influence fetal oxygen consumption include growth, activity, organ metabolism, hormonal status and substrate availability (Harris 1999).

During maternal hypoxaemia and upon a 43% decrease in fetal sheep arterial Po_2, fetal oxygen delivery decreased by 23%. Overall oxygen consumption initially increased by 30% and was later maintained at the control level for several hours, until severe acidaemia developed. (Rurak *et al.* 1990).

When Q_{UtA} was reduced, resulting in a 45% decrease in fetal arterial Po_2 and a 40% decrease in oxygen delivery, without progressive fetal acidaemia despite increased fetal lactate concentrations, fetal lambs were able to maintain oxidative metabolism up to 24 hours. The unchanged overall fetal oxygen consumption was initially achieved by increasing Q_{UA}, followed by an increase in oxygen extraction. (Bocking *et al.* 1992). In another study, a short-term 50% reduction in fetal oxygen delivery, achieved by decreasing Q_{UtA}, decreased fetal arterial Po_2, oxygen delivery and oxygen consumption by 32%, 50% and 44%, respectively. Oxygen delivery to the myocardium and brain was maintained, whereas that to the adrenal glands increased dramatically. (Jensen *et al.* 1991).

A 50% reduction of Q_{UA} lasting for 4−5 minutes resulted in a 24% decrease in fetal arterial Po_2 and a 54% decrease in oxygen delivery. Despite increased oxygen extraction, overall oxygen consumption decreased. Cerebral and myocardial oxygen supply was maintained with only a moderate reduction in peripheral, gastrointestinal and renal oxygen delivery. However, pulmonary oxygen delivery decreased by 70%. (Itskovitz *et al.* 1987).

2.4.2 Haemodynamic responses

2.4.2.1 Umbilicoplacental circulation

In response to acute hypoxaemia in fetal sheep, Q_{UA} has been shown to remain unchanged (Cohn *et al.* 1974; Block *et al.* 1990) or to increase (Bocking *et al.* 1988; Reid *et al.* 1991; van Huisseling *et al.* 1991; Bocking *et al.* 1992), and the proportion of CCO distributed to the placenta may increase (Jensen *et al.* 1991). If hypoxaemia is prolonged, the initially increased Q_{UA} returns to the control level with a tendency to decrease further (Bocking *et al.* 1988; Bocking *et al.* 1992). Concurrent with the development of acidaemia, Q_{UA} decreases significantly (Block *et al.* 1990).

2.4.2.2 Heart rate, blood pressure and cardiac output

During late gestation, acute hypoxaemia usually causes vagally mediated bradycardia in fetal sheep (Cohn *et al.* 1974; Itskovitz *et al.* 1987; Block *et al.* 1990; Jensen *et al.* 1991; Reid *et al.* 1991; Gardner *et al.* 2002b) with an increase (Cohn *et al.* 1974; Itskovitz *et al.* 1987; Jensen *et al.* 1991; Reid *et al.* 1991; Gardner *et al.* 2002b) or no significant change (Bocking *et al.* 1988; Block *et al.* 1990; van Huisseling *et al.* 1991) in fetal blood pressure. However, some investigators have reported that, after an initial decrease, fetal HR may later return to the control level (van Huisseling *et al.* 1991) or even increase (Bocking *et al.* 1988). With severe acidaemia, fetal HR decreases further, but blood pressure remains relatively stable (Block *et al.* 1990).

If acute fetal hypoxaemia is due to umbilical cord compression, CCO decreases (Itskovitz *et al.* 1987). Otherwise, CCO does not seem to be significantly affected (Cohn *et al.* 1974; Jensen *et al.* 1991; Reid *et al.* 1991) or may even show a tendency to increase (Block *et al.* 1990). It has been shown that ventricular function is well preserved in the normotensive fetus. However, if hypoxaemia is accompanied by an increase in arterial blood pressure, the right ventricular function curve is shifted downward, leading to a decrease in CCO. (Reller *et al.* 1989). In addition, CCO decreases when the fetus becomes acidaemic (Block *et al.* 1990).

2.4.2.3 Fetal arterial circulation

The increased cerebral, coronary and adrenal volume blood flows in response to acute fetal hypoxaemia are well established (Cohn *et al.* 1974; Itskovitz *et al.* 1987; Bocking *et al.* 1988; Block *et al.* 1990; Jensen *et al.* 1991; Reid *et al.* 1991). The increased volume blood flow is associated with decreased vascular resistance in the vital organs (Jensen *et al.* 1991; Reid *et al.* 1991). This circulatory compensation is present in sheep fetuses despite severe acidaemia until cardiovascular collapse is evident (Block *et al.* 1990). In the absence of progressive acidaemia, the sheep fetus is able to maintain the circulatory adjustments protecting the vital organs for at least 48 hours (Bocking *et al.* 1988).

During hypoxaemia in near-term fetal sheep, pulmonary vascular resistance is known to increase dramatically (Lewis *et al.* 1976), and pulmonary volume blood flow decreases (Lewis *et al.* 1976; Itskovitz *et al.* 1987; Jensen *et al.* 1991). Volume blood flows to most other peripheral organs also tend to decrease in response to acute hypoxaemia. Reid *et al.* induced a 38% decrease in fetal sheep arterial Po_2 by decreasing Q_{UtA} and reported increased vascular resistance values in the gut, kidneys, skeletal muscle, bone and skin, while those in the liver and spleen showed no significant change (Reid *et al.* 1991). Jensen *et al.* also reduced Q_{UtA} and induced fetal hypoxaemia of comparable degree and duration and reported decreased blood flows to the skin as well as the upper and lower trunk, whereas volume blood flows to the gut, kidneys, spleen and liver did not change significantly (Jensen *et al.* 1991). However, Itskovitz *et al.* induced a 23% decrease in fetal arterial Po_2 by short-term umbilical cord compression and reported that greater proportions of CCO were distributed to the kidneys, gut, bone, skin and muscles (Itskovitz *et al.* 1987). Hypoxaemia with severe acidaemia is characterized by markedly decreased volume blood flows to most peripheral organs (Block *et al.* 1990).

2.4.2.4 Fetal venous circulation

In fetal sheep, hypoxaemia causes a marked dilatation of the entire DV (Kiserud *et al.* 2000a). The proportion of umbilical venous blood shunted through the DV increases, and a greater proportion of the DV blood is distributed through the foramen ovale to the heart and brain (Itskovitz *et al.* 1987; Jensen *et al.* 1991).

When fetal hypoxaemia was caused by reducing Q_{UtA}, the abdominal IVC volume blood flow and its contribution to the CCO decreased (Jensen *et al.* 1991), while during umbilical cord compression, the abdominal IVC volume blood flow increased and constituted a greater proportion of CCO (Itskovitz *et al.* 1987). In either case, superior vena caval volume blood flow did not change significantly, but its contribution to CCO increased (Itskovitz *et al.* 1987; Jensen *et al.* 1991).

2.5 Fetal and placental responses to maternal vasopressor therapy

2.5.1 Pharmacologic characteristics of vasopressors

Sympathomimetic drugs are derivatives of β-phenylethylamine. They are used for the treatment of hypotension because of their α- and β-adrenergic effects. Direct-acting sympathomimetic drugs act directly on the adrenergic receptors. These agents may exhibit considerable selectivity for a specific receptor subtype or may act on several receptors. Indirect-acting drugs increase the availability of noradrenaline to stimulate adrenergic receptors. Agents that indirectly release noradrenaline from the adrenergic nerve terminals and also directly activate receptors are referred to as mixed-acting sympathomimetic drugs.

2.5.1.1 Ephedrine

Ephedrine is a mixed-acting α- and β-adrenoceptor agonist (Westfall and Westfall 2006). Because of two asymmetrical carbon atoms, four stereoisomers of ephedrine exist. Among these, *l*-ephedrine is used as a vasopressor (Kobayashi *et al.* 2003). It increases HR and cardiac output and variably affects SVR, resulting in a rise in blood pressure (Westfall and Westfall 2006). A study that measured maternal cardiovascular parameters noninvasively using impedance cardiography during epidural anaesthesia for Caesarean delivery has shown that the increase in cardiac output is mainly associated with an increased preload, suggesting vasoconstriction in the venous capacitance bed (Ramanathan and Grant 1988). The vasoconstrictor response may be entirely due to indirect actions (Kobayashi *et al.* 2003), and tachyphylaxis may therefore occur upon repetitive dosage (Westfall and Westfall 2006). In male rats, the systemic vascular response to ephedrine seems to be partly counteracted by ephedrine-induced endothelial nitric oxide production secondary to β2-receptor stimulation (Dabisch *et al.* 2003). *In vitro* studies have suggested that the nitric oxide release in the uterine arteries in response to ephedrine is enhanced during ovine pregnancy, which reduces the uterine vasoconstrictive response to ephedrine compared with nonpregnant sheep (Li *et al.* 1996).

As ephedrine lacks a hydroxyl group on the benzene ring, it is a highly lipophilic drug (Westfall and Westfall 2006). Consequently, it readily crosses the placenta with neonatal blood concentrations close to maternal blood levels (Hughes *et al.* 1985). It also crosses the blood-brain barrier and acts as a stimulant in the central nervous system (Westfall and Westfall 2006). Interestingly, when small doses of ephedrine were given to parturients to prevent hypotension during spinal anaesthesia for Caesarean delivery, neonatal spectral electroencephalography showed significant changes compared with controls during the first few hours after delivery (Kangas-Saarela *et al.* 1990).

2.5.1.2 Phenylephrine

Phenylephrine is a direct-acting α1-selective adrenoceptor agonist. Chemically, it differs from adrenaline only in that it lacks a hydroxyl group at position 4 on the benzene ring, which makes it less potent than adrenaline at both α- and β-receptors. (Westfall and Westfall 2006). In the prevention of hypotension during spinal anaesthesia for Caesarean delivery, the potency ratio of phenylephrine to ephedrine has recently been shown to be approximately 80:1 (Saravanan *et al.* 2006). With a hydroxyl group at position 3, phenylephrine is less lipophilic than ephedrine (Westfall and Westfall 2006). The placental transfer of phenylephrine has not been verified.

The cardiovascular effects of phenylephrine are mainly due to the activation of α1-adrenergic receptors in the vascular smooth muscle. As a result, SVR increases and blood pressure is maintained or elevated. (Westfall and Westfall 2006). Phenylephrine also constricts the capacitance bed, resulting in a rise in preload and cardiac output (Ramanathan and Grant 1988). However, another study that assessed maternal haemodynamics using suprasternal Doppler ultrasonography suggested that, during prophylactic infusion of phenylephrine, cardiac output decreases if maternal HR decreases (Ashpole *et al.* 2005). Importantly, parturients treated with phenylephrine are more likely to develop bradycardia than those treated with ephedrine (Lee *et al.* 2002a). In rats, nitric oxide does not appear to play a role in the systemic vascular response to phenylephrine as it does with ephedrine (Dabisch *et al.* 2003). However, the contractile response to phenylephrine in the isolated uterine artery rings of pregnant guinea pigs has been shown to diminish as a result of increased basal nitric oxide activity (White *et al.* 1998).

2.5.1.3 Other vasopressors

Other sympathomimetic drugs have also been investigated in the obstetric setting. Mephentermine is a mixed-acting sympathomimetic drug with α1-selective direct effects. Since it releases noradrenaline, the effects have many similarities to those of ephedrine (Westfall and Westfall 2006). Etilefrine is a direct-acting synthetic derivative of noradrenaline, which acts on both α- and β-receptors (Strumper *et al.* 2005). Metaraminol has prominent direct effects on α-adrenergic receptors but also indirectly stimulates the release of noradrenaline (Westfall and Westfall 2006). Methoxamine is a pure direct-acting α-agonist (Wright *et al.* 1992).

2.5.2 Uteroplacental haemodynamics

2.5.2.1 Sheep experiments

Both *in vivo* (James *et al.* 1970; Ralston *et al.* 1974; Sipes *et al.* 1992; McGrath *et al.* 1994) and *in vitro* (Tong and Eisenach 1992; Li *et al.* 1996) studies on near-term gravid ewes have consistently suggested that ephedrine has a sparing effect on Q_{UtA} compared with sympathomimetic drugs possessing more α-adrenergic activity. In acute experiments under nitrous oxide-oxygen analgesia, ephedrine and mephentermine restored Q_{UtA} more completely than metaraminol after 10−15 minutes of hypotension due to spinal anaesthesia (James *et al.* 1970). When maternal blood pressure was increased by 50% in chronically instrumented, normotensive ewes, Q_{UtA} remained unchanged with ephedrine, but was reduced with mephentermine, metaraminol and methoxamine by 20%, 45% and 62%, respectively (Ralston *et al.* 1974). In a chronic sheep preparation with hypermagnesaemia, the administration of ephedrine for maternal epidural-induced hypotension increased Q_{UtA} compared with the hypotensive values and had no effect on R_{UtA}, whereas phenylephrine increased R_{UtA} with no significant effect on Q_{UtA} (Sipes *et al.* 1992). Similar results were obtained when ephedrine and phenylephrine were compared in the treatment of hypotension while infusing the β-adrenoceptor agonist ritodrine during epidural anaesthesia in chronically instrumented ewes (McGrath *et al.* 1994). Yet, etilefrine and ephedrine were found to be comparable in restoring Q_{UtA} during epidural-induced hypotension in chronically instrumented ewes (Strumper *et al.* 2005).

2.5.2.2 Clinical studies

Clinical studies also suggest that ephedrine does not compromise Q_{UtA}. During epidural anaesthesia for elective Caesarean delivery, a prophylactic 15 mg bolus of ephedrine tended to increase intervillous blood flow, which was assessed using an intravenous (i.v.) radioisotope technique (Hollmen *et al.* 1984). During prophylactic ephedrine infusion without volume preloading, no difference was found between the uterine artery PI values before and after the induction of spinal anaesthesia for elective Caesarean delivery (Chan *et al.* 1997). When normotensive parturients received ephedrine during labour to increase MAP up to 20% above baseline, the reduction in uterine artery blood flow velocities and the increase in the resistance index caused by uterine contractions was almost completely reversed (Ducros *et al.* 2002).

Some studies have compared the effects of ephedrine on uterine artery PI values to those of other sympathomimetic agents during elective Caesarean delivery. Alahuhta *et al.* administered ephedrine or phenylephrine as prophylactic infusion to prevent hypotension during spinal anaesthesia. The uterine and arcuate artery PI values remained stable in the ephedrine group but increased significantly in the phenylephrine group. (Alahuhta *et al.* 1992). Prophylactic infusion of neither ephedrine nor metaraminol was found to cause significant increases in uterine artery PI values during spinal anaesthesia (Ngan Kee *et al.* 2001b). When hypotension due to epidural anaesthesia was treated with a bolus of ephedrine or methoxamine, followed by infusion, the uterine artery PI remained stable with ephedrine but markedly increased with methoxamine (Wright *et al.* 1992). However, when boluses of ephedrine or etilefrine were administered for maternal hypotension during spinal anaesthesia, the uterine artery PI increased significantly in both groups (Räsänen *et al.* 1991).

2.5.3 Umbilicoplacental haemodynamics

Our knowledge of umbilicoplacental haemodynamics during maternal administration of sympathomimetic drugs is limited to measurements of umbilical artery PI values during regional anaesthesia for elective Caesarean delivery. No significant changes in umbilical artery PI values after ephedrine (Räsänen *et al.* 1991; Alahuhta *et al.* 1992; Wright *et al.* 1992; Thomas *et al.* 1996), phenylephrine (Alahuhta *et al.* 1992; Thomas *et al.* 1996; Blythell *et al.* 2005), etilefrine (Räsänen *et al.* 1991) or methoxamine (Wright *et al.* 1992) have been observed.

2.5.4 Fetal haemodynamics

Several studies on human and ovine pregnancies have failed to reveal any significant changes in fetal HR after maternal administration of ephedrine (Ralston *et al.* 1974; Räsänen *et al.* 1991; Sipes *et al.* 1992; Wright *et al.* 1992; Alahuhta *et al.* 1994; McGrath *et al.* 1994; Thomas *et al.* 1996; Strumper *et al.* 2005), phenylephrine (Sipes *et al.* 1992;

Alahuhta *et al.* 1994; McGrath *et al.* 1994), etilefrine (Räsänen *et al.* 1991; Strumper *et al.* 2005), mephentermine (Ralston *et al.* 1974), metaraminol (Ralston *et al.* 1974) or methoxamine (Ralston *et al.* 1974). However, phenylephrine (Thomas *et al.* 1996) and methoxamine (Wright *et al.* 1992) may decrease and ephedrine (Wright *et al.* 1981; Ngan Kee *et al.* 2000) may increase human fetal HR. Prophylactic ephedrine infusion after the initiation of epidural analgesia for labour has been shown to reduce the frequency of adverse fetal HR changes commonly observed immediately afterwards (Kreiser *et al.* 2004). Similarly, 25 mg of prophylactic intramuscular (i.m.) ephedrine decreased late decelerations in fetal HR tracings during the first hour of combined spinal epidural analgesia. However, this was associated with an increased incidence of fetal tachycardia. (Cleary-Goldman *et al.* 2005).

In sheep experiments, fetal MAP has not been shown to be significantly affected by ephedrine (Ralston *et al.* 1974; Sipes *et al.* 1992; McGrath *et al.* 1994; Strumper *et al.* 2005), phenylephrine (Sipes *et al.* 1992; McGrath *et al.* 1994), etilefrine (Strumper *et al.* 2005), mephentermine (Ralston *et al.* 1974) or methoxamine (Ralston *et al.* 1974). However, when metaraminol was administered to chronically instrumented, normotensive ewes, transient elevations in fetal MAP were observed (Ralston *et al.* 1974).

Few studies on vasopressors have used Doppler ultrasonography to assess human fetal haemodynamics. Alahuhta *et al.* demonstrated that fetal renal artery PI values decreased after prophylactic phenylephrine infusion, while no changes in ventricular fractional shortenings of the fetal heart were observed. Ephedrine infusion seemed to have no significant effects on fetal haemodynamics. (Alahuhta *et al.* 1992). However, Räsänen *et al.* reported increased RVFS and decreased PI values in fetal renal and middle cerebral arteries after bolus administration of ephedrine for maternal hypotension, whereas no significant changes were observed following etilefrine administration (Räsänen *et al.* 1991).

2.5.5 Fetal acid-base status

2.5.5.1 Sheep experiments

When ephedrine, mephentermine, metaraminol and methoxamine were administered to chronically instrumented, normotensive ewes, no significant changes in fetal acid-base status were observed (Ralston *et al.* 1974). However, sheep experiments have suggested ephedrine to be superior to metaraminol and methoxamine in reversing fetal hypoxaemia and acidaemia after 45 minutes of hypotension associated with spinal anaesthesia (Shnider *et al.* 1968; Shnider *et al.* 1970a; Shnider *et al.* 1970b). Ephedrine has also turned out to be more effective than phenylephrine in correcting fetal hypoxaemia due to epidural-induced hypotension in hypermagnesaemic ewes (Sipes *et al.* 1992) or during ritodrine infusion (McGrath *et al.* 1994). Yet, when short-term hypotension induced by epidural anaesthesia was treated with ephedrine or etilefrine, no significant changes in acid-base status were observed with either medication (Strumper *et al.* 2005).

2.5.5.2 Clinical studies

In human pregnancies, prophylactic ephedrine does not necessarily increase (Ngan Kee *et al.* 2000; Loughrey *et al.* 2002; Lee *et al.* 2002b) and may even decrease umbilical artery pH values (Hughes *et al.* 1985; Lee *et al.* 2004) when compared with controls without vasopressor prophylaxis during regional anaesthesia for elective Caesarean delivery. Furthermore, the use of prophylactic ephedrine may be associated with an increased incidence of fetal acidosis, defined as an umbilical artery pH < 7.2, at least if hypotension still is present (Shearer *et al.* 1996). Yet, a meta-analysis failed to demonstrate an increased risk of fetal acidosis with increasing doses of ephedrine (Lee *et al.* 2004). Furthermore, some studies have suggested that prophylactic ephedrine might still improve neonatal acid-base status (Datta *et al.* 1982; Chan *et al.* 1997). When prophylactic infusion of ephedrine was compared with boluses as required, with no significant differences in the total doses of ephedrine used, maternal blood pressure was more stable in the infusion group, resulting in higher umbilical artery pH values (Turkoz *et al.* 2002).

When mephentermine (Kansal *et al.* 2005) and etilefrine (Räsänen *et al.* 1991) were compared to ephedrine in the treatment of hypotension due to spinal anaesthesia for elective Caesarean delivery, neonatal acid-base profiles were found to be comparable. Some studies comparing ephedrine to phenylephrine in the prevention and treatment of maternal hypotension have also failed to observe any difference in neonatal acid-base profiles (Ramanathan and Grant 1988; Alahuhta *et al.* 1992; Hall *et al.* 1994; Pierce *et al.* 1994; Ayorinde *et al.* 2001). However, others have suggested higher umbilical artery pH values with phenylephrine than with ephedrine (Moran *et al.* 1991; LaPorta *et al.* 1995; Thomas *et al.* 1996; Cooper *et al.* 2002). A meta-analysis showed that umbilical artery pH values are higher after phenylephrine, but could not demonstrate a difference in the incidence of a fetal umbilical artery pH < 7.2 (Lee *et al.* 2002a). Yet, later studies have suggested that fetal acidosis is less frequent after metaraminol (Ngan Kee *et al.* 2001b), phenylephrine combined with ephedrine (Mercier *et al.* 2001; Cooper *et al.* 2002) and phenylephrine alone (Cooper *et al.* 2002) compared with ephedrine alone. In a retrospective multivariate analysis of 337 cases, ephedrine was found to be the major predictor of umbilical artery pH and BE. The model suggested that the use of ephedrine, compared with that of phenylephrine, was associated with an average decrease in pH by 0.042 units and a further decrease of 0.014 units for each minute of hypotension. (Ngan Kee and Lee 2003). Yet, none of the vasopressor studies has demonstrated any difference in neonatal Apgar scores.

3 Hypothesis and aims of the thesis

Knowledge of the effects of maternally administered ephedrine and phenylephrine on human fetal and placental haemodynamics is sparse and limited to elective Caesarean deliveries in uncomplicated pregnancies. We hypothesized that, after short-term fetal hypoxaemia, which activates fetal cardiovascular compensatory mechanisms, the treatment of maternal hypotension with ephedrine or phenylephrine results in divergent responses in fetal and placental haemodynamics. This hypothesis was tested in chronically instrumented near-term sheep fetuses with either normal placental function or increased R_{UA} induced by placental embolization with microspheres. The specific aims of the thesis were:

1. To evaluate the physiologic basis of umbilical artery Doppler velocimetry in the assessment of umbilicoplacental circulation under varying conditions of blood flow and resistance and to examine the relationships between umbilicoplacental haemodynamics and ultrasonographic parameters reflecting fetal cardiac function (I).
2. To establish Doppler ultrasonographic parameters of fetal cardiovascular haemodynamics related to diminished fetal oxygenation (II).
3. To determine the effects of maternal hypotension and its treatment with ephedrine or phenylephrine on utero- and umbilicoplacental haemodynamics and fetal blood gas values and lactate concentrations after exposure to short-term hypoxaemia in fetuses with normal placental function (III).
4. To determine the effects of maternal hypotension and its treatment with ephedrine or phenylephrine on utero- and umbilicoplacental haemodynamics and fetal blood gas values and lactate concentrations after exposure to a further decrease in oxygenation in chronically hypoxaemic fetuses with increased R_{UA} (IV).
5. To examine fetal cardiovascular haemodynamic responses to maternally administered ephedrine or phenylephrine in fetuses exposed to short-term hypoxaemia and maternal hypotension and to investigate whether these responses are altered in fetuses with increased R_{UA} (V).

4 Material and methods

4.1 Fetal sheep model

Healthy ewes of Finnish breed with time-dated pregnancies were obtained from a local breeder and transferred to the Laboratory Animal Centre of the University of Oulu. Before surgery, the sheep were kept in pens in groups and allowed to acclimatize for at least 4 days to the new environment with controlled temperature (20 ºC), air humidity (50%) and ventilation (12 times per hour) and a 12-hour daylight-darkness cycle. The animals were fed 100–200 g of barley, 100 g of turnip rape molasses (Farmarin Rypsi, Suomen Rehu, Seinäjoki, Finland), 25–30 g of minerals (Lammas Hertta-Minera, Suomen Rehu, Vaasa, Finland) and 20 g of sea salt daily. In addition, they had unlimited access to tap water and hay. All animals received humane care in compliance with the `European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes´ (ETS 123, Council of Europe 1986) and the European Union Directive 86/609/ETY (European Community 1986). The State Provincial Office of Oulu approved the research protocol on the basis of ethical assessment by the Animal Care and Use Committee, University of Oulu.

4.1.1 Surgical procedures

The ewes and their fetuses were instrumented at 110−131 days of gestation (0.76−0.90 of term). The surgical procedures were similar in all animals. After overnight fasting, the animals were premedicated with i.m. ketamine 2 mg/kg and midazolam 0.2 mg/kg. General anaesthesia was induced with i.v. propofol 4−7 mg/kg and, after tracheal intubation, maintained with isoflurane at an end-tidal concentration of 1−2.5% in an oxygen/air mixture. Mechanical ventilation was begun with an inhaled oxygen concentration of 40% and a tidal volume of 8–10 ml/kg delivered 17 times per minute by a Siemens 730 ventilator (Siemens-Elema AB, Solna, Sweden) and adjusted individually to maintain arterial Po_2 above 11.0 kPa and Pco_2 between 4.5 and 5.4 kPa. Muscle relaxants were not used during the operation. I.v. fentanyl 0.1−0.15 mg was administered routinely before the surgical incision, and additional 0.05−0.1 mg boluses were given as required for elevations of arterial pressure or HR during painful stimuli. An auricular artery was cannulated for invasive monitoring of arterial pressure during the operation. In addition, a pulmonary artery introducer catheter was inserted into a jugular vein to serve as a permanent i.v. line.

Laparotomy was performed and a 6-mm transit-time ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY, USA) was secured around a proximal part of the uterine artery supplying the pregnant uterine horn. Thereafter, the fetal hind limbs and abdomen were exteriorized via a hysterotomy, and 18-G polyurethane catheters were placed into the fetal IVC and DAo via the femoral vein and artery, respectively. An incision was made in the fetal abdomen immediately below the umbilical cord insertion, and the umbilical arteries were identified. A 4-mm transit-time ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY, USA) was placed around the umbilical arteries and secured to the fetal abdomen. In the case of twin gestation, only one fetus was instrumented. The fetus was then returned to the uterine cavity, the lost amniotic fluid was replaced with 0.9% saline (39˚C), and the hysterotomy and laparotomy incisions were closed. All catheters and cables were tunnelled subcutaneously and exteriorized through a small incision in the ewe's flank and placed in a pouch attached to the flank. The laparotomy incision was infiltrated with 20 ml of 0.5% bupivacaine to relieve pain during the first few postoperative hours.

4.1.2 Postoperative care

After surgery, the sheep were kept in individual pens. Throughout the 5-day period between the instrumentation and the experiment, i.m. buprenorphine 0.01 mg/kg was administered twice daily. The ewes were given ampicillin 1 g i.v., and the fetuses received 1,000,000 U of benzyl penicillin i.v. daily, and the catheters were flushed with heparinized saline. Fetal acid-base values and Q_{UtA} and Q_{UA} were monitored daily. The animals were withdrawn from the study and killed in the case of progressive fetal deterioration or intrauterine death, and if signs of active labour or poor maternal health were observed.

4.1.3 Placental embolization

To increase placental vascular resistance, the placenta was embolized on the fourth postoperative day with 45−150 µm microspheres (Contour Emboli, Target Therapeutics, Fremont, CA, USA). A dry volume of 0.25 ml microspheres was suspended in 0.5 ml of albumin 20% and diluted with 10 ml of saline. This solution was injected into the fetal descending aorta via the femoral artery catheter in 1 ml increments every 15 minutes until fetal arterial oxygen saturation decreased by 30% from the preembolization values (Gagnon *et al.* 1996).

4.2 Experimental protocol

4.2.1 Animal preparation

The experiments on 34 ewes and fetuses were performed on the fifth postoperative day at 115−136 days of gestation. General anaesthesia was induced using i.v. propofol 4−7 mg/kg and maintained throughout the experiment with isoflurane 1−1.5% in an oxygen/air mixture via a tracheal tube. Muscle relaxation was induced with rocuronium 20 mg to facilitate mechanical ventilation. The 14 ewes with placental embolization received 500 ml of hydroxyethyl starch solution as rapid infusion before the induction of general anaesthesia. Thereafter, Ringer's solution was infused at a rate of 200 ml/h. To the 20 ewes with normal placental function, Ringer's solution was freely infused after the induction of anaesthesia until pulmonary capillary wedge pressure (PCWP) reached a value of 6 mmHg and thereafter at a rate of 100 ml/h.

A thermodilution catheter (Criticath SP5107H, Becton Dickinson, Sandy, UT, USA) was introduced through the jugular vein introducer placed during the primary operation, and a 16-G polyurethane catheter was placed into the descending aorta of the ewe via a femoral artery. A 19-G epidural catheter was inserted into the epidural space at the lumbosacral junction or, if this approach failed, at the lowest lumbar interspace. The ewe was then placed supine with a right lateral tilt. A 30-minute stabilization period was allowed to all animals to adjust the mechanical ventilation to maintain maternal arterial Po_2 above 11.0 kPa and Pco_2 between 4.5 and 5.4 kPa.

4.2.2 Study phases

The experimental protocol was divided into eight phases (Fig. 3). During phase 1, the baseline measurements were obtained. At time zero, acute maternal hypoxaemia was induced by replacing oxygen with medical air in the rebreathing circuit (phase 2). At 15 minutes, the maternal inhaled oxygen concentration was returned to the baseline, and the ewe and the fetus were allowed to recover from hypoxaemia (phase 3). At 30 minutes, the ewe was given 5 ml of 0.5% bupivacaine through the epidural catheter as a test dose. Thereafter, bupivacaine 0.5% was administered to a total dose of 0.3 mg/kg over a 2-minute period. Hypotension to at least a 30% decrease of maternal systolic arterial pressure was allowed to develop (phase 4). At 45 minutes, the ewes were randomized into the ephedrine or phenylephrine groups by picking a sealed envelope. During the next 30 minutes, 5 mg boluses of ephedrine or 0.1 mg boluses of phenylephrine were administered to maintain a maternal systolic arterial pressure of at least 90% of the baseline (phase 5). After phase 5, the embolized ewes and their fetuses were killed with an intravenous overdose of pentobarbital. For the nonembolized animals, the administration of the vasopressor was discontinued at 75 minutes to determine the degree of hypotension (phase 6). At 80 minutes, the crystalloid infusion (Ringer's solution 100 ml/min) was discontinued, and 500 ml of hydroxyethyl starch solution was infused over a period of 10 minutes (phase 7), after which the crystalloid infusion was restarted. At 90 minutes, the vasopressor boluses were restarted for the next 30 minutes, aiming at a maternal systolic arterial pressure of at least 90% of the baseline (phase 8). Thereafter, the administration of the vasopressor was again discontinued, and the animals were euthanized. For postmortem examination, the fetuses were removed from the uterus and weighed.

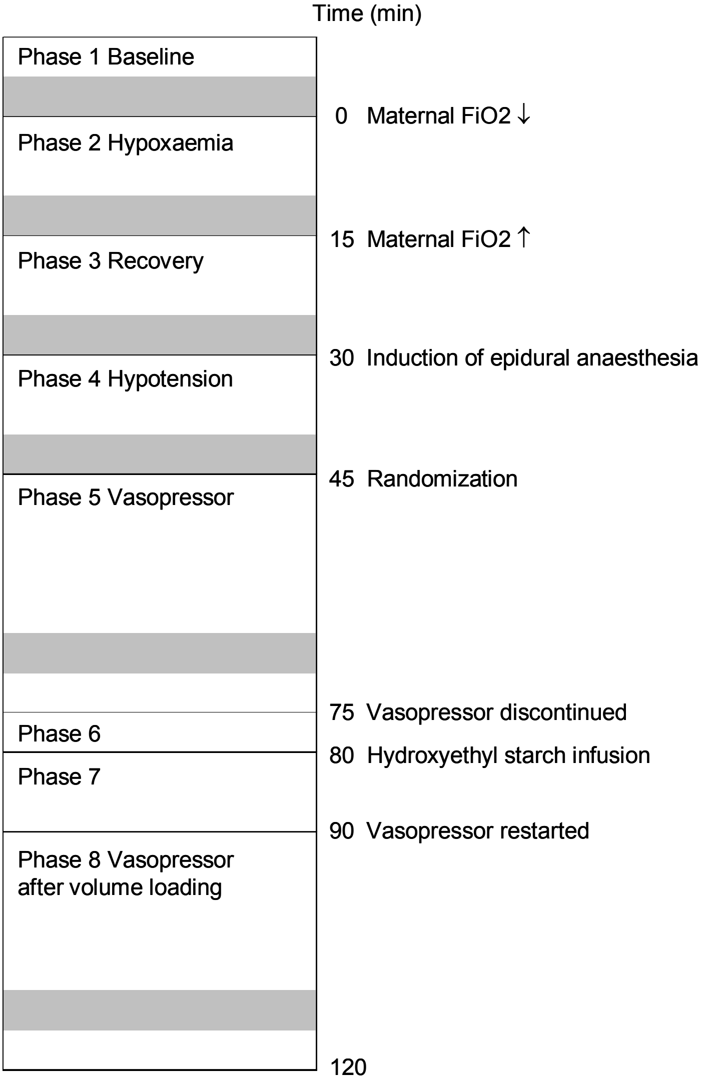


Fig. 3. Flow chart of the experimental protocol. Grey columns indicate the measurement periods for each phase.

Table 1. Total number of animals at each phase and their distribution in studies I−V

Phase	R_{UA}	Total	Study I	Study II	Study III	Study IV	Study V
Baseline (1)	Control	20	16	12	17		12
	Embolized	14	5			13	12
Hypoxaemia (2)	Control	20		12	17*		
	Embolized	14				13*	
Recovery (3)	Control	20		12	17*		
	Embolized	14				13*	
Hypotension (4)[1]	Control	20[2]			17*		12
	Embolized	14[3]				13*	12
Vasopressor (5)	Control	17	5 P		9 E/8 P		6 E/6 P
	Embolized	13				7 E/6 P	6 E/6 P
Vasopressor + volume load (8)	Control	17			9 E/8 P		
	Embolized	13					

[1] Randomization into the ephedrine (E) or phenylephrine (P) group was performed at the end of phase 4. [2] One ewe was excluded before randomization because of severe fetal acidosis and two because of epidural misplacement. [3] One ewe was excluded before randomization because of severe fetal acidosis. *Pre-randomization comparisons.

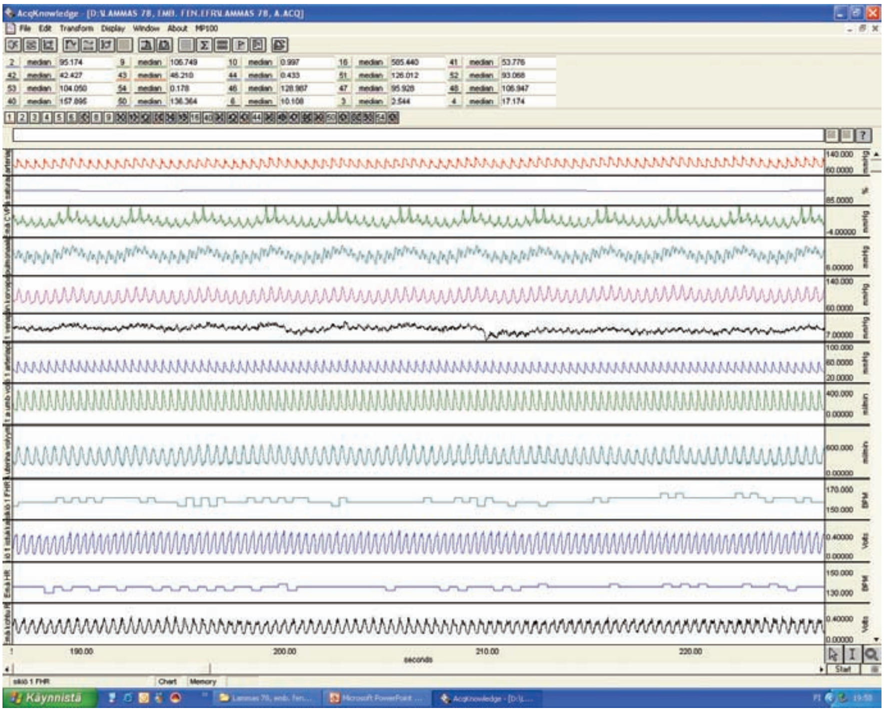
4.3 Monitoring protocol

4.3.1 Invasive measurements

The maternal arterial catheter and the pulmonary artery catheter were attached to disposable pressure transducers (DT-XX, Ohmeda, Hatfield, UK) to measure systemic and pulmonary arterial pressures and CVP. The fetal arterial and venous catheters were connected to reusable transducers (Biopac Systems Inc., Santa Barbara, CA, USA) for pressure measurement. The fetal pressure transducers were zeroed to the atmospheric pressure at the level of the maternal groin and calibrated against the pressure of 114 mmHg by using a 150-cm water hose. As significant changes in intra-amniotic pressure were unlikely to occur in our nonlabouring, anaesthetized and paralyzed ewes, fetal pressures were not corrected for intra-amniotic pressure. Maternal and fetal MAP values were computed arithmetically, and the HR readings were computed from the arterial waveforms. The perivascular transit-time ultrasonic flow probes were attached to a flow meter (T206, Transonic Systems Inc., Ithaca, NY, USA) to measure Q_{UA} and Q_{UtA} (D'Almeida *et al.* 1996; Koenig *et al.* 1996; Sokol *et al.* 1996). R_{UtA} and R_{UA} were computed by dividing maternal and fetal MAPs by Q_{UtA} and Q_{UA}, respectively.

All these variables were recorded continuously at a 100-Hz sampling rate using a polygraph (UIM100A, Biopac Systems Inc., Santa Barbara, CA, USA) and computerized data acquisition software (Acqknowledge v. 3.5.7 for Windows, Biopac Systems Inc., Santa Barbara, CA, USA) (Fig. 4). The recordings were later analyzed in one-minute periods, and the median value of the 6000 measurements per variable was chosen to represent a particular minute. The means of the last five minutes of phases 1, 2, 3 and 4 and the second to last five minutes of phases 5 and 8 were considered representative for each phase and used in the analyses (Fig. 3). Studies III and IV report both maternal and fetal parameters, whereas studies I, II and V concentrate on the fetal parameters.

For studies III and IV, maternal cardiac output was measured in triplicate at the end of each phase with the thermodilution catheter and a Datex A/S3 monitor (Datex Inc., Espoo, Finland). Pulmonary capillary wedge pressure (PCWP) and SVR were obtained with cardiac output measurements. The surface area of the ewe was calculated (Bennett 1973), and cardiac index (CI) and systemic vascular resistance index (SVRI) were derived from cardiac output and SVR.



2	median	95.174	9	median	106.749	10	median	0.997	16	median	505.440	41	median	53.776
42	median	42.427	43	median	46.210	44	median	0.433	51	median	126.012	52	median	93.068
53	median	104.050	54	median	0.178	46	median	128.987	47	median	95.928	48	median	106.947
40	median	157.896	50	median	136.364	6	median	10.108	3	median	2.544	4	median	17.174

Fig. 4. Polygraph tracings of maternal and fetal haemodynamic measurements over a time period of 40 s at baseline.

4.3.2 Ultrasonographic measurements

Doppler ultrasonography was performed at the end of each phase by using image-directed colour and pulsed Doppler equipment (Acuson Sequoia 512, Mountain View, CA, USA) with a 4-8 MHz convex or a 5 MHz sector probe. The high-pass filter was set at the minimum, and the angle of insonation was kept below 15 degrees. The ultrasonographic examinations were performed by a single investigator. They were videotaped and analyzed later by using the cardiovascular measurement package included in the ultrasound equipment. Three consecutive cardiac cycles were measured for each parameter and the mean values were used for analyses.

4.3.2.1 Placental haemodynamics

Uteroplacental circulation was assessed by determining the PI values from the blood flow velocity waveforms of the main uterine artery on the placental side (III, IV).

Blood flow velocity waveforms of the umbilical artery were obtained from the free loops of the umbilical cord, and PSV, EDV and TAMXV were measured (I). In addition, the umbilical artery V_{mean} was calculated as TVI*HR (I). Furthermore, umbilical artery PI values were determined (I, II, III, IV).

4.3.2.2 Fetal cardiac function

The diameters of the aortic and pulmonary valves were measured in frozen real-time images during systole by using the leading-edge-to-leading-edge method. The mean value of three separate valve diameter measurements was used to calculate the CSA of the valve. Volume blood flows across the aortic (LVCO) and pulmonary (RVCO) valves were determined using the formula: CSA*TVI*HR. Weight-indexed LVCO, RVCO and CCO (I, II, V) and the proportions (%) of LVCO and RVCO of CCO (I, V) were calculated. In addition, LVeFo and RVeFo were determined by the formula: $(1.055 \cdot CSA \cdot TVI_{acc}) \cdot (PSV/TTP)$, where TVI_{acc} is the TVI during the acceleration period in systole and TTP is the time-to-peak velocity interval (Isaaz *et al.* 1989; Sutton *et al.* 1991a). Weight-indexed ventricular ejection forces were used in the analyses (I, II, V).

Left ventricular time intervals were acquired by placing the Doppler gate into the left ventricle and obtaining simultaneously blood flow velocity waveforms of the mitral and aortic valves. The ICT was measured as the time period between the closure of the mitral valve and the opening of the aortic valve (De Muylder *et al.* 1984), while the IRT was measured as the time period between the closure of the aortic valve and the opening of the mitral valve (Tulzer *et al.* 1994). The proportions (%) of ICT (II, V) and IRT (I, II, V) of the total cardiac cycle were calculated.

At the level of the tricuspid and mitral valves, inflow velocity waveforms were recorded. The E-wave/A-wave TVI ratio as well as the A-wave TVI/total TVI ratio were calculated for both valves (Tulzer *et al.* 1994) (II).

Right and left ventricular inner diameters were measured from the M-mode recordings by placing the M-mode cursor perpendicularly towards the interventricular septum at the level of atrioventricular valves in a four-chamber view of the heart. LVFS and RVFS were calculated using the formula: ventricular fractional shortening (%) = [(inner diastolic diameter ─ inner systolic diameter)/inner diastolic diameter] x 100 (DeVore *et al.* 1984) (II, V).

4.3.2.3 Fetal arterial and venous circulation

Blood flow velocity waveforms in the DAo were assessed at the level of the diaphragm. The blood flow velocity waveforms of the left or right PPA were recorded immediately after the bifurcation of the main pulmonary artery before its first branching. The PI values for DAo, DA and PPA (II, V) were determined. AoI blood flow velocity waveforms were recorded and the AoI ante/retro TVI ratio was calculated (Fouron *et al.* 1999) (II, V).

To assess fetal venous circulation, PIV values were calculated from the IVC, DV, LHV (II, V) and PV (V) blood flow velocity waveforms.

4.3.2.4 Intraobserver variability

The intraobserver variability in ultrasonographic measurements was assessed in five fetuses using two sets of measurements performed consecutively in the same examination setting during phases 1, 2 and 3 (I, II).

4.3.3 Laboratory analyses

At the end of the measurement period of each phase, blood samples were drawn from the catheters placed in the maternal and fetal descending aortas. They were immediately analyzed for blood gas values (Ciba Corning 288, Corning Inc., Acton, MA, USA). Maternal and fetal pH, Po_2 and Pco_2 were corrected to the temperature of 39°C (I, II, III, IV).

Maternal and fetal lactate concentrations were determined (RapidLab 865, Chiron Diagnostics, Essex, UK) in heparinized blood samples drawn at the end of phases 1, 4 (III, IV), 5 (IV) and 8 (III).

4.4 Statistical analysis

The data were analyzed using either the SPSS for Windows (versions 10.1, 11.0, 11.5, and 12.0.1; SPSS Inc., Chigaco, IL, USA) (I, III, IV, V) or the StatView for Macintosh (version 5.0; SAS Institute Inc., Cary, NC, USA) software package (II). Between the two groups, comparisons were made using Student´s t-test if the data were normally distributed or, otherwise, the Mann-Whitney U-test was chosen (III, IV, V). When comparisons were made between more than two groups, and the data were normally distributed, one-way analysis of variance (ANOVA) was used (I). For parameters that were continuously or repeatedly monitored, ANOVA for repeated measurements was chosen (II, III, IV, V). If ANOVA showed statistical significance, the Scheffe F-test (I, II), the least significant difference adjustment for multiple comparisons (III, V) or the Bonferroni adjustment (IV) was used for *post hoc* analysis. In the case of two groups (III, IV, V), the differences between the groups (between-subjects P), the changes in measurements over time (within-subjects P) and the differences in changes over time between the groups (interaction P) were evaluated. In addition, linear regression analysis was used to show the relationships between the measured parameters (I, II). A two-tailed P-value of 0.05 or less was selected as the level of statistical significance (I−V).

5 Results

5.1 Effects of placental embolization

At baseline, the embolized fetuses (IV) had 52% lower Q_{UA}, 110% higher R_{UA}, 48% higher PI_{UA}, 35% lower Po_2, 11% higher Pco_2 and 36% higher lactate concentrations compared with the nonembolized fetuses (III) (Table 2). With the exception of increased PI_{UA} values, the Doppler ultrasonographic parameters of fetal cardiovascular haemodynamics were not statistically significantly different between the embolized and nonembolized fetuses (V) (Table 3).

Table 2. Fetal MAP, HR, CVP, Q_{UA}, R_{UA}, PI_{UA}, and blood gas values at baseline

Variable	Nonembolized fetuses (III)	n	Embolized fetuses (IV)	n
MAP (mmHg)	51 (6)	17	49 (6)	13
HR (beats/min)	171 (29)	17	176 (23)	13
CVP (mmHg)	11 (3)	12	10 (2)	13
Q_{UA} (ml/min)	390 (112)	17	189 (85)*	13
R_{UA} (mmHg/ml/min)	0.143 (0.047)	17	0.301 (0.110)*	13
PI_{UA}	0.81 (0.22)	14	1.20 (0.33)*	12
pH	7.32 (0.04)	13	7.32 (0.05)	13
Po_2 (kPa)	3.1 (0.5)	13	2.0 (0.6)*	13
Pco_2 (kPa)	6.6 (0.7)	13	7.3 (0.6)*	13
Base excess (mmol/l)	0.5 (2.7)	14	1.5 (2.7)	13
Lactate concentration (mmol/l)	1.9 (0.7)	17	2.6 (0.7)*	13

Values are mean (SD). * $p < 0.05$ compared with nonembolized fetuses.

5.2 Umbilical artery Doppler velocimetry (I)

The correlations of the umbilical artery absolute blood flow velocities and PI_{UA} with invasively measured Q_{UA} and R_{UA} as well as with Doppler-derived parameters of fetal cardiac function were determined under baseline conditions, after placental embolization and during maternal administration of phenylephrine.

The umbilical artery EDV ($R = 0.68$, $p < 0.001$), TAMXV ($R = 0.52$, $p = 0.006$) and V_{mean} ($R = 0.64$, $p < 0.001$) correlated positively with Q_{UA} and showed negative correlations with R_{UA}, whereas the PSV did not demonstrate significant correlations with either Q_{UA} or R_{UA}. The PI_{UA} correlated negatively with Q_{UA} ($R = 0.55$, $p = 0.003$) and positively with R_{UA} ($R = 0.46$, $p = 0.018$).

The umbilical artery PSV, EDV and TAMXV and the PI_{UA} did not correlate with weight-indexed LVCO or RVCO, LVeFo or RVeFo or IRT%. Nor did Q_{UA} or R_{UA} show any correlation with ventricular outputs, ejection forces or IRT%.

5.3 Responses to maternal hypoxaemia

Maternal hypoxaemia was induced by replacing oxygen with medical air in a rebreathing circuit. As the mean (SD) maternal inhaled oxygen concentration decreased from 44 (8) to 18 (2) %, a concomitant decrease in the mean maternal arterial Po_2 from 15.5 (4.4) to 7.9 (1.5) kPa was observed (III). Maternal haemodynamic parameters, including Q_{UtA} and R_{UtA}, remained stable (III, IV).

5.3.1 Nonembolized fetuses (II)

During maternal hypoxaemia, fetal arterial Po_2 decreased by approximately 30% ($p < 0.001$). Fetal pH, Pco_2 or base excess (BE) were not affected by a short-term decrease in fetal oxygenation.

Fetal HR did not change significantly. MAP and systolic arterial pressure increased ($p < 0.05$), whereas CVP, Q_{UA}, R_{UA} and PI_{UA} were stable.

The PPA PI increased significantly, while the AoI ante/retro TVI ratio decreased (Fig. 5). The DAo PI and DA PI as well as the DV, IVC and LHV PIV values were unaffected.

The mean (SD) RVCO increased from 416 (106) to 487 (179) ml/min/kg ($p < 0.05$), while CCO increased from 681 (156) to 772 (256) ml/min/kg ($p < 0.05$). The proportions of ICT and IRT of the total cardiac cycle were significantly greater ($p < 0.05$) during hypoxaemia than at baseline. However, ventricular ejection forces were unaffected and the E-wave/A-wave TVI ratio as well as the A-wave TVI/total TVI ratio for mitral and tricuspid valves were stable.

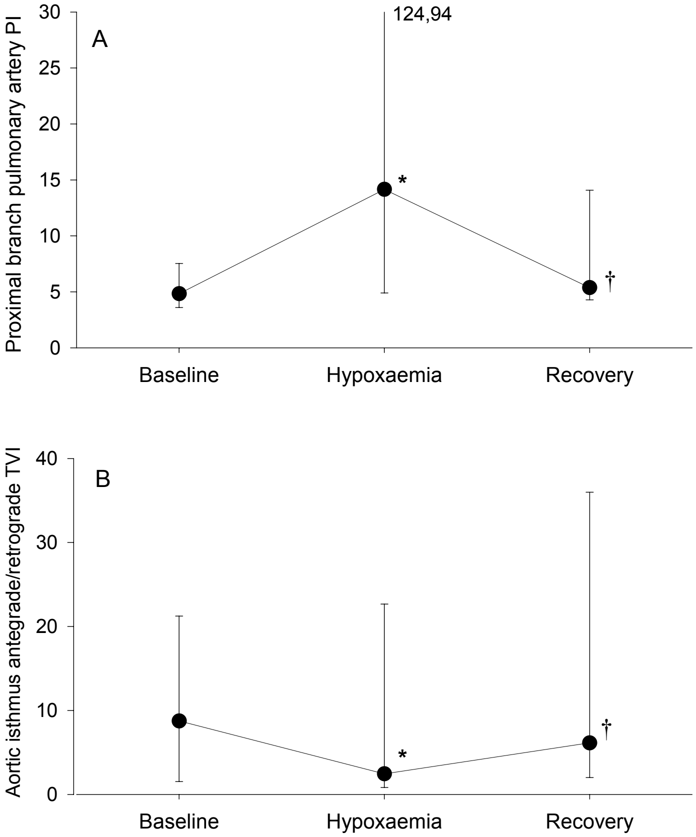


Fig. 5. Proximal branch pulmonary artery pulsatility index (PI) (A) and ratio of the time-velocity integrals (TVI) of the antegrade and retrograde blood flow velocity components of the aortic isthmus (B) in nonembolized sheep fetuses at baseline, during hypoxaemia and at the recovery phase. Values are median ± range. $^*p < 0.05$ compared with baseline. $^\dagger p < 0.05$ compared with hypoxaemia.

5.3.2 Embolized fetuses (IV)

In response to maternal hypoxaemia, fetal arterial Po_2 decreased further by approximately 40% ($p < 0.001$). However, fetal pH, Pco_2 and BE were not affected.

Fetal HR, MAP and CVP did not change significantly. The mean (SD) Q_{UA} decreased from 189 (85) to 164 (90) ml/min ($p = 0.004$), and the mean R_{UA} increased by approximately 40%. Yet, the increase in R_{UA} did not reach statistical significance ($p = 0.069$). The PI_{UA} remained stable.

5.4 Responses to maternal hypotension

After the induction of epidural anaesthesia, the mean maternal MAP, HR and CI all decreased by approximately 40% (III, IV). Concomitantly, a nearly 70% reduction in Q_{UtA} was observed (Fig. 6) (III, IV). In accordance with the invasive observations on R_{UtA}, the PI_{UtA} increased during hypotension (Fig. 6) (III, IV).

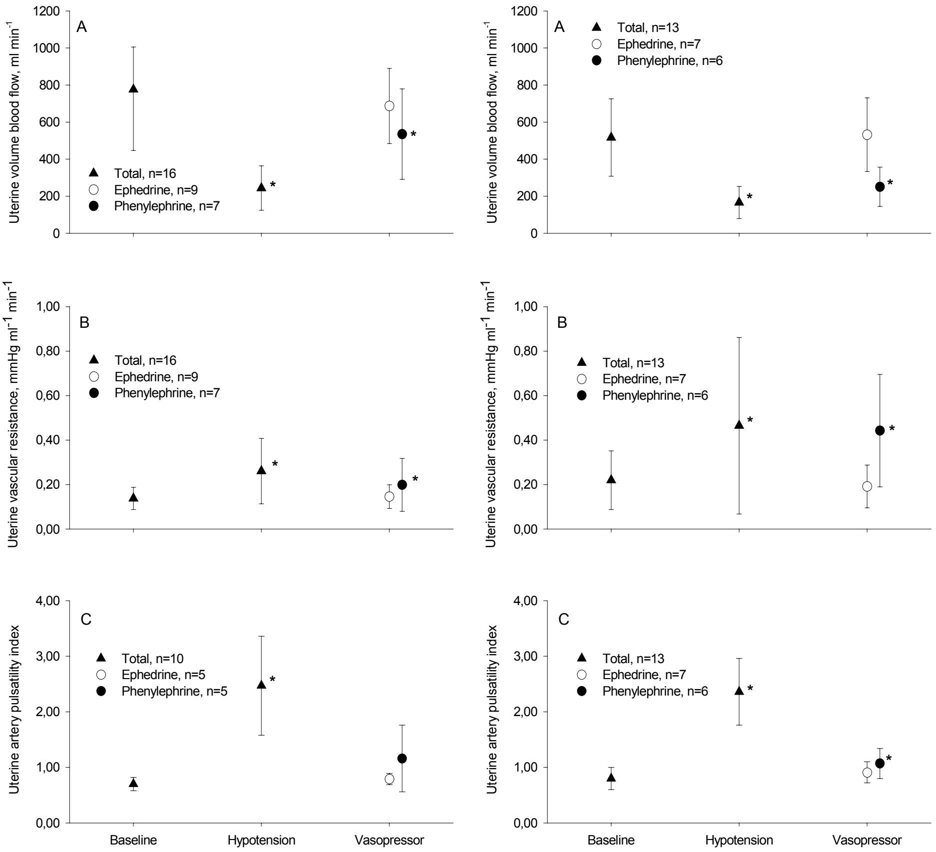


Fig. 6. Uteroplacental volume blood flows (A) and vascular resistances (B) and uterine artery pulsatility index values (C) in nonembolized (left panel) and embolized (right panel) ewes at baseline, during maternal hypotension and during vasopressor therapy. *p < 0.05 compared with baseline.

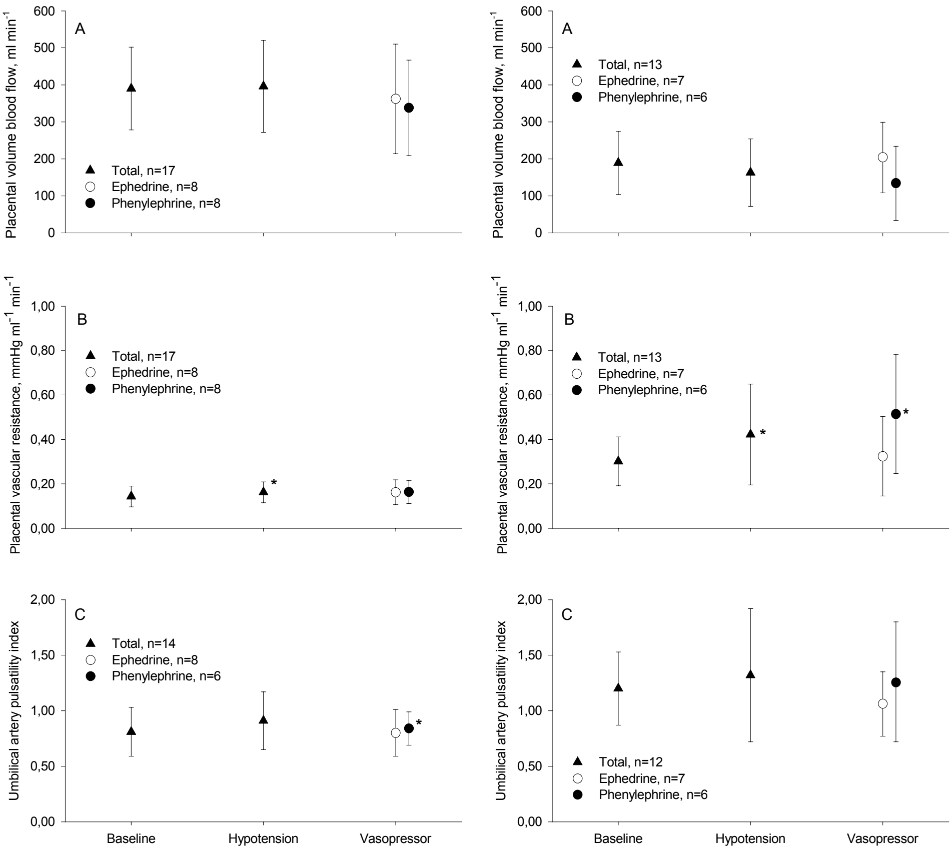


Fig. 7. Umbilicoplacental volume blood flows (A) and vascular resistances (B) and umbilical artery pulsatility index values (C) in nonembolized (left panel) and embolized (right panel) fetuses at baseline, during maternal hypotension and during vasopressor therapy. *p < 0.05 compared with baseline.

5.4.1 Nonembolized fetuses

During maternal hypotension, fetal arterial Po_2 decreased by 35% ($p < 0.001$), and the mean (SD) fetal lactate concentration increased from 1.9 (0.7) to 2.2 (0.8) mmol/l ($p = 0.015$). However, fetal pH, Pco_2 and BE did not change significantly. (III).

Fetal MAP increased ($p < 0.001$), while HR and CVP did not change. Although Q_{UA} did not change significantly, R_{UA} increased ($p = 0.031$) (Fig. 7). However, PI_{UA} values remained stable (Fig. 7). (III).

In contrast to the first episode of short-term hypoxaemia, the latter hypoxaemic insult caused no significant changes in the fetal cardiac outputs or Doppler-derived parameters reflecting systolic or diastolic cardiac function (Table 3). Furthermore, the AoI ante/retro TVI ratio did not change (Table 3). However, PPA PI and PV PIV increased (Table 3). (V).

5.4.2 Embolized fetuses

In response to maternal hypotension, fetal arterial Po_2 decreased further by 35% ($p = 0.001$), while fetal Pco_2 did not change. The mean (SD) fetal pH decreased from 7.32 (0.05) to 7.27 (0.08) ($p = 0.030$) and BE from 1.5 (2.7) to -1.6 (4.0) mmol/l ($p = 0.021$). In addition, the mean (SD) fetal lactate concentration increased from 2.59 (0.69) to 4.5 (1.7) mmol/l ($p < 0.001$). (IV).

Fetal MAP, HR and CVP did not change significantly. R_{UA} increased by almost 50% ($p = 0.038$), while Q_{UA} or PI_{UA} were not significantly affected (Fig. 7). (IV).

In chronically hypoxaemic fetuses, maternal hypotension caused no significant changes in fetal cardiac outputs (Table 3). PPA PI and PV PIV increased, and the AoI ante/retro TVI ratio decreased (Table 3). DA PI as well as the PIV values for IVC, DV and LHV remained unchanged. (V).

Table 3. Fetal cardiac outputs, ventricular ejection forces, ICT%, PPA PI, PV PIV and AoI ante/retro (a/r) TVI at baseline, during hypotension and after vasopressor treatment

	Drug	Nonembolized fetuses^{1}			Embolized fetuses^{1}		
		Baseline	Hypotension	Vasopressor	Baseline	Hypotension	Vasopressor
LVCO	E	262 (63)	236 (70)	265 (38)	253 (65)^{2}	253 (65)^{2}	242 (70)^{2}
	P	260 (53)^{2}	256 (81)^{2}	207 (52)$^{2*\#}$	307 (211)	271 (141)	241 (105)
RVCO	E	390 (115)^{2}	359 (78)^{2}	413 (71)^{2}	447 (163)^{2}	499 (194)^{2}	413 (129)^{2}
	P	448 (113)^{2}	509 (203)^{2}	436 (161)^{2}	513 (293)	499 (168)	460 (153)
CCO	E	641 (179)^{2}	580 (133)^{2}	682 (80)^{2}	700 (202)^{2}	752 (251)^{2}	654 (191)^{2}
	P	708 (165)^{2}	765 (245)^{2}	643 (202)^{2}	821 (502)	770 (296)	701 (239)
LVeFO	E	5.8 (2.1)	5.9 (1.5)	6.2 (1.4)	5.2 (1.8)	5.0 (1.0)	4.7 (1.6)
	P	6.6 (1.1)^{2}	5.0 (1.5)^{2}	4.5 (1.4)^{2}*	7.2 (6.1)	6.6 (4.1)	5.4 (2.7)
RVeFo	E	6.3 (2.5)^{2}	7.6 (1.6)^{2}	6.8 (2.3)^{2}	8.0 (4.8)	8.4 (3.5)	7.0 (3.0)
	P	7.0 (1.9)^{2}	8.3 (3.1)^{2}	7.0 (3.2)^{2}	9.5 (6.7)	9.6 (3.8)	8.5 (6.2)
ICT%	E	5.0 (1.8)	5.6 (1.9)	4.6 (1.1)	5.3 (1.9)	5.9 (1.2)	6.4 (3.8)
	P	4.4 (0.8)	5.1 (1.2)	5.2 (1.0)	4.8 (0.9)	6.7 (0.8)*	6.2 (1.0)*
PPA PI	E	5.3 (1.5)	16.5 (10.5)*	7.7 (3.3)$^{\#}$	14.3 (19.9)	37.3 (15.4)*	7.9 (4.6)$^{\#}$
	P	5.1 (1.0)	18.8 (16.1)*	16.0 (16.2)*	6.4 (4.5)	24.7 (9.7)*	13.7 (8.2)$^{*\#}$
PV PIV	E	4.3 (1.9)^{3}	31.2 (40.4)^{3}	6.7 (1.6)^{3}	7.6 (7.7)	36.0 (41.3)*	5.9 (5.1)$^{\#}$
	P	4.8 (2.0)^{2}	13.0 (27.6)^{2*}	10.5 (8.3)^{2}	5.8 (4.1)	18.2 (14.2)*	16.1 (15.1)*
AoI a/r TVI	E	5.5 (3.2)	13.8 (27.6)	9.2 (9.9)	15.6 (14.8)	3.6 (6.1)*	24.4 (14.2)$^{\#}$
	P	9.9 (5.2)	8.9 (11.9)	10.5 (14.3)	27.4 (27.9)	2.9 (2.5)*	6.4 (8.0)

Values are mean (SD). ^{1} n = 6 unless stated otherwise, ^{2} n = 5, ^{3} n = 3. * $p < 0.05$ compared with baseline.
# $p < 0.05$ between hypotension and vasopressor treatment. E = ephedrine, P = phenylephrine.

5.5 Responses to maternal vasopressor therapy

5.5.1 Ephedrine

The median [range] total dose of ephedrine given by the end of phase 5 was 25.0 [15.0−55.0] mg in the nonembolized ewes (III) and 30.0 [20.0−50.0] mg in the embolized ewes (IV). By the end of phase 8, the median [range] total dose of ephedrine administered to the nonembolized ewes was 47.5 [20.0−85.0] mg (III).

With ephedrine, maternal MAP and CI returned to the baseline level (III, IV), while HR was either restored (III) or increased above (IV) the baseline values. Concomitantly, Q_{UtA}, R_{UtA} and PI_{UtA} were normalized to the baseline values (III, IV) (Fig. 6).

Ephedrine corrected the decrease in fetal Po_2 secondary to maternal hypotension (III, IV). Fetal pH, BE and lactate concentrations remained at the baseline level in the nonembolized fetuses (III) and did not further deteriorate from the hypotensive values in the embolized fetuses (IV).

During the maternal administration of ephedrine, fetal MAP, HR and CVP were comparable to the baseline values (III, IV). Q_{UA} and PI_{UA} were not affected, and R_{UA} returned to the baseline level (Fig. 7) (III, IV). PPA PI and PV PIV as well as the decrease of the AoI ante/retro TVI ratio observed in the embolized fetuses were restored to the baseline values (Table 3) (V). All other Doppler-derived parameters reflecting fetal cardiovascular haemodynamics remained unchanged (V).

5.5.2 Phenylephrine

The median [range] total dose of phenylephrine given by the end of phase 5 was 1.1 [0.8−1.8] mg in the nonembolized ewes (III) and 1.6 [0.9−1.8] mg in the embolized ewes (IV). By the end of phase 8, the median [range] total dose of phenylephrine administered to the nonembolized ewes was 2.3 [1.2−3.6] mg (III).

At the end of phase 5, maternal MAP was comparable to baseline values in the embolized ewes (IV). However, MAP was significantly lower than at baseline (82 (9) vs. 94 (9) mmHg, $p = 0.002$) in the nonembolized ewes (III). Maternal HR did not change from hypotensive values, and CI remained significantly lower than at baseline (III, IV). Q_{UtA} increased from the hypotensive level but was lower than at baseline, and R_{UtA} remained elevated (Fig. 6) (III, IV). The PI_{UtA} decreased from the hypotensive level, but remained slightly higher than at baseline in the embolized ewes (Fig. 6) (IV).

Phenylephrine restored fetal Po_2 to the baseline level (III, IV). Fetal pH, BE and lactate concentrations remained at the baseline level in the nonembolized fetuses (III). In the embolized fetuses, pH and BE did not further deteriorate from the hypotensive values. However, the mean (SD) fetal lactate concentration increased ($p = 0.004$) further to 6.7 (2.3) mmol/l. (IV).

Fetal MAP, HR and CVP were comparable to the baseline values (III, IV). In the embolized fetuses, Q_{UA} and PI_{UA} did not differ significantly from the baseline values, while R_{UA} remained elevated ($p = 0.050$) (Fig. 7) (IV). In the nonembolized fetuses, Q_{UA} decreased ($p = 0.050$) after prolonged phenylephrine administration, whereas R_{UA} remained unchanged (III).

In the fetuses of the phenylephrine group as a whole, PPA PI ($p < 0.001$) and PV PIV ($p = 0.029$) remained at the hypotensive level and the AoI ante/retro TVI ratio remained below ($p = 0.031$) the baseline (V). LVCO ($p = 0.004$) and LVeFo ($p = 0.010$) decreased, and ICT% remained elevated ($p = 0.002$) (V). All other Doppler-derived parameters reflecting fetal arterial and venous circulation or fetal cardiac function were comparable to the baseline values (V). Subgroup analysis showed that, despite a similar trend, the changes in LVCO and LVeFo were significant only in the nonembolized fetuses, while the prolongation of ICT was significant in the embolized fetuses (Table 3) (V).

5.6 Intraobserver variability of ultrasonographic measurements

In Doppler parameters reflecting fetal cardiovascular haemodynamics, the mean (SD) intraobserver variabilities were 7.2 (2.6) %, 7.5 (2.2) % and 5.1 (2.0) % for the TVI, PI and PIV calculations, respectively (II). In time interval measurements, the corresponding variability was 6.0 (2.3) % (II). In the umbilical artery, the intraobserver variabilities ranged from 1.7% to 3.2% (95% confidence interval, 0.8 to 5.1%) for absolute flow velocity measurements and from 1.1% to 5.1% (95% confidence interval, 0.2 to 6.8%) for TVI and PI calculations (I).

6 Discussion

The extensive use of ephedrine as the primary vasopressor in obstetric practice (Burns *et al.* 2001) has largely been based on the results of previous experiments on pregnant ewes. These studies have suggested that ephedrine is superior to other vasopressors in restoring Q_{UtA} (James *et al.* 1970; Sipes *et al.* 1992; McGrath *et al.* 1994) and reversing fetal hypoxaemia (Sipes *et al.* 1992; McGrath *et al.* 1994) and acidaemia (Shnider *et al.* 1968; Shnider *et al.* 1970a; Shnider *et al.* 1970b) after maternal hypotension of variable duration. The notion of ephedrine as the vasopressor of choice in human pregnancy was first challenged in 1988 by Ramanathan and Grant. They compared ephedrine and phenylephrine in the treatment of hypotension during elective Caesarean delivery under epidural anaesthesia and were unable to demonstrate any difference in neonatal acid-base profiles or Apgar scores (Ramanathan and Grant 1988). Since then, numerous studies on elective Caesarean deliveries under spinal anaesthesia have shown that umbilical artery pH values are comparable (Alahuhta *et al.* 1992; Hall *et al.* 1994; Pierce *et al.* 1994; Ayorinde *et al.* 2001) or higher (Moran *et al.* 1991; LaPorta *et al.* 1995; Thomas *et al.* 1996; Cooper *et al.* 2002; Lee *et al.* 2002a) if phenylephrine instead of ephedrine is used to prevent or treat maternal hypotension. This suggests that phenylephrine may be a better vasopressor than ephedrine in uncomplicated human pregnancy. However, the two vasopressors have not been compared in pregnancies complicated by short-term or long-term fetal hypoxaemia.

6.1 Validity of the fetal sheep model

The rationale of a sheep model in vasopressor research may be questioned by the controversy between the findings of early vasopressor studies on experimental animals and the recent clinical evidence from human pregnancies. However, the present study involves many improvements compared with the previous studies on vasopressors in pregnant ewes. Whereas James *et al.* (James *et al.* 1970) performed their experiments in less than 60 minutes after surgical procedures, we assessed chronically instrumented ewes and their fetuses. Unlike Ralston *et al.* (Ralston *et al.* 1974), who administered vasopressors to normotensive ewes, or Shnider *et al.* (Shnider *et al.* 1968; Shnider *et al.*

1970a; Shnider *et al.* 1970b), who allowed a 45-minute period of hypotension before vasopressor treatment, we treated short-term hypotension induced by epidural anaesthesia. In addition, our ewes received intravenous volume loading with either hydroxyethyl starch or Ringer´s solution before the induction of epidural anaesthesia. In contrast to the more recent experimental studies of McGrath *et al.* (McGrath *et al.* 1994), Sipes *et al.* (Sipes *et al.* 1992) and Strumper *et al.* (Strumper *et al.* 2005), we assessed our ewes in the supine position, allowing free venous return from the splanchnic region and the extremities. In addition to fetal arterial blood gas values, we also determined lactate concentrations, which have been suggested to be more sensitive than pH in predicting neurological disability in human neonates (Kruger *et al.* 1999; Shah *et al.* 2004). Most importantly, as opposed to all previous work in this field, we included extensive invasive and noninvasive monitoring of fetal and umbilicoplacental haemodynamics in our protocol. However, several aspects of the present study should be carefully considered before extrapolating our results to human fetuses.

6.1.1 Interspecies differences

The duration of pregnancy in sheep is approximately half of that in humans. Compared with the human fetus, the sheep fetus has a higher growth rate, a higher temperature and a lower haemoglobin concentration (Kiserud 2005). In contrast to a single large placenta as in humans, the sheep placenta comprises several small placentomes. Furthermore, both the arrangement of the fetal and maternal blood compartments and the number of cell layers between the maternal and fetal circulations differ from those of the human placenta. The countercurrent blood flow pattern that is partly present in the sheep placenta (Leiser and Kaufmann 1994) may suggest enhanced placental transfer of vasopressors in sheep compared with humans. However, the diffusion barrier is thicker in the synepitheliochorial placenta of sheep compared with the haemomonochorial placenta of humans (Leiser and Kaufmann 1994).

Although the cardiovascular physiology of fetal sheep greatly resembles that of human fetuses, it is not uniform. Importantly, the proportion of Q_{UA} of CCO is considerably larger while that of pulmonary volume blood flow is smaller in sheep compared with human fetuses. Anatomical differences of the cardiovascular system also exist, as the sheep fetus has two umbilical veins and a longer intrathoracic IVC (Kiserud 2005). In addition, the aortic arch only gives rise to one common brachiocephalic trunk in sheep. Although the segment between the origin of this trunk and the implantation of the DA is longer than in humans, it is otherwise equivalent to the AoI in human fetuses (Bonnin *et al.* 1993). Despite these differences in cardiovascular physiology and anatomy, sheep experiments have been extensively used in the research of fetal and umbilicoplacental haemodynamics. Recent Doppler ultrasonographic studies suggest that the phasic flow events associated with the cardiac cycle in fetal sheep (Schmidt *et al.* 1996) can be applied to human fetuses (Kiserud *et al.* 1992).

In addition, there are interspecies differences in adrenergic receptor distribution (Wei and Sulakhe 1979) and affinity (Li and Rouleau 1991), possibly resulting in varying vascular responses to vasopressors. It has recently been suggested that phenylephrine is more potent than ephedrine by a factor of 80 for equivalent maternal arterial pressure control during regional anaesthesia in human pregnancies (Saravanan *et al.* 2006). However, both the present observations (III, IV, V) and the previous studies on pregnant ewes (Sipes *et al.* 1992; McGrath *et al.* 1994) suggest a phenylephrine-to-ephedrine dose ratio of approximately 1:20. Yet, the discrepancy may not be solely related to adrenoceptor function, as in all studies comparing ephedrine to phenylephrine in pregnant ewes, the maternal responses may have been modified by additional factors, such as isoflurane anaesthesia (III, IV, V), ritodrine infusion (McGrath *et al.* 1994) or hypermagnesaemia (Sipes *et al.* 1992). Interestingly, the total doses of both ephedrine (Cooper *et al.* 2002; Cooper *et al.* 2004; Kansal *et al.* 2005) and phenylephrine (Cooper *et al.* 2004; Ngan Kee *et al.* 2004a; Ngan Kee *et al.* 2004b; Ngan Kee *et al.* 2005) given in some recent clinical studies on human pregnancies compare well with those administered within 30 minutes after the initiation of vasopressor therapy in our sheep model.

6.1.2 Fetal instrumentation

The surgical procedures may constitute a major stress for sheep fetuses. It has previously been shown that important metabolic disturbances may last for a few days after surgical manipulation of fetal sheep (Clapp *et al.* 1977), and that three days are required for the proper recovery of fetal myocardial function following invasive cannulation (De Muylder *et al.* 1983). After a recovery period of five days, fetal blood gas values as well as the invasive haemodynamic parameters measured at baseline were comparable to the previous observations on chronically instrumented near-term sheep fetuses (Itskovitz *et al.* 1987; Bocking *et al.* 1988; Block *et al.* 1990; Jensen *et al.* 1991; Bocking *et al.* 1992) and suggest stable fetal sheep preparations.

6.1.3 Placental embolization

Although fetal pH and BE measured at baseline were comparable in the embolized (IV) and the nonembolized fetuses (III), fetal Po_2 values were significantly lower and lactate concentrations higher in the embolized fetuses. Even in severe cases of placental insufficiency in humans, fetal pH values at the time of delivery may not differ from those of fetuses with uncomplicated pregnancies (Mäkikallio *et al.* 2001). However, severe placental insufficiency is often associated with fetal hypoxaemia (Soothill *et al.* 1987; Pardi *et al.* 1993). It has been shown that growth-restricted fetuses with only slightly elevated PI_{UA} may tolerate relatively low Po_2 values, whereas fetuses with markedly increased PI_{UA} develop significant lactataemia at comparable levels of oxygenation (Marconi *et al.* 1990).

Chronic placental embolization of fetal sheep over a period of 21 days leads to systemic hypertension (Murotsuki *et al.* 1997), and human fetuses with severe placental insufficiency are also believed to be hypertensive. Furthermore, severe placental insufficiency may lead to fetal cardiovascular compromise. Doppler ultrasonography may demonstrate a redistribution of CCO in favour of the left ventricle (al-Ghazali *et al.* 1989; Mäkikallio *et al.* 2002b), signs of increased right ventricular afterload (Räsänen *et al.* 1989; Mäkikallio *et al.* 2002b), increased impedance to flow in the pulmonary circulation (Mäkikallio *et al.* 2002a) and retrograde net blood flow in the AoI (Sonesson and Fouron 1997; Mäkikallio *et al.* 2002a; Mäkikallio *et al.* 2003). Eventually, fetal atrial pressures and CVP may increase, as indicated by abnormal venous Doppler waveforms (Hecher *et al.* 1995; Mäkikallio *et al.* 2002b). In the present study (IV), neither fetal MAP nor CVP were affected by placental embolization performed 24 hours before the experiments. Furthermore, the Doppler ultrasonographic parameters of fetal central and peripheral haemodynamics remained within the normal range (V).

Thus, although the increase in R_{UA} induced by placental embolization was sufficient to cause fetal hypoxaemia and lactataemia, it was not associated with circulatory adjustments in fetal sheep. This may be related to the short duration of the insult as well as to the capacity of umbilicoplacental circulation to partially compensate for placental embolization (Gagnon *et al.* 1996). Yet, our findings suggest that the fetal heart has the capability and resources to maintain its function in conditions with increased afterload.

6.1.4 Combined general and epidural anaesthesia

For ethical reasons and to allow the supine position necessary for detailed ultrasonographic examinations, the present experiments were performed while the sheep were under general anaesthesia. This is an important limitation in our study. The combination of general anaesthesia and a high thoracic level epidural block may have caused excessive vasodilation with a concomitant significant reduction in venous return. This could explain the maternal bradycardia observed during hypotension (Kinsella and Tuckey 2001). Additionally, some degree of aortocaval compression may have been present, with parallel effects on maternal haemodynamics. In conscious ewes in a standing position, epidural-induced maternal hypotension as such does not necessarily reduce maternal HR (Strumper *et al.* 2005), whereas a significant reduction in HR occurs during simultaneous magnesium sulphate infusion (Sipes *et al.* 1992), which has additional vasodilatory effects (Euser and Cipolla 2005). Yet, high thoracic level epidural anaesthesia alone can markedly reduce venous return and lead to bradycardia, especially in the obstetric setting (Kinsella and Tuckey 2001).

As isoflurane readily crosses the placenta (Dwyer *et al.* 1995), it may modify fetal cardiovascular regulation. It has been shown in chronically instrumented dogs that isoflurane enhances the pulmonary vasodilator response to the β-adrenoceptor agonist isoproterenol, while it has no effect on the pulmonary vasoconstrictor response to phenylephrine (Greenlees *et al.* 1986). It may therefore be possible that our results exaggerate the divergent effects of ephedrine and phenylephrine on fetal pulmonary haemodynamics (V). In addition, isoflurane has been shown to attenuate compensatory homeostatic mechanisms during hypoxaemia in adult rabbits and rats (Durieux *et al.* 1992; Stekiel *et al.* 1995). Despite isoflurane anaesthesia, however, newborn lambs are able to increase cardiovascular performance during hypoxaemia (Brett *et al.* 1989), as also indicated by our observations on fetal sheep (II).

6.1.5 Ultrasonographic measurements

The technological advances in Doppler ultrasonography permit detailed examination of the fetal central and peripheral circulations. The Doppler ultrasonographic parameters of the present study are commonly used in the assessment of human fetal well-being (Hecher *et al.* 1994; Räsänen *et al.* 1997; Räsänen *et al.* 1998; Mielke and Benda 2000; Mäkikallio *et al.* 2002b). The Doppler methodology has also been increasingly applied to animal research in the field of fetal cardiovascular physiology (Schmidt *et al.* 1996; Tchirikov *et al.* 1998a; Kiserud *et al.* 2000a).

There are several sources of error in these measurements, which may affect their accuracy and reproducibility. Interobserver errors have been shown to be consistently greater than intraobserver errors (Simpson and Cook 2002). In the present study, all ultrasonographic investigations were performed and analyzed by a single investigator. The intraobserver variabilities in the ultrasonographic parameters of fetal cardiovascular (II) and umbilicoplacental (I) haemodynamics were comparable to those reported in human fetal studies during the second half of gestation (Räsänen *et al.* 1996b; Mäkikallio *et al.* 2002b; Acharya *et al.* 2005a). To minimize methodological errors (Tessler *et al.* 1990), the angle of insonation was always kept at less than 15 degrees. As cardiac output calculations are highly dependent on the accurate measurement of the valve diameter (Beeby *et al.* 1991), the mean value of three separate valve diameter measurements was used for CSA calculations.

6.2 Doppler velocimetry of placental circulation

Doppler-derived umbilical artery blood flow velocity waveforms represent temporal changes in the velocity of blood cells during the cardiac cycle and are influenced by upstream (heart), downstream (resistance) and local factors. We determined the correlations of the umbilical artery absolute blood flow velocities and PI_{UA} with Doppler-derived parameters of fetal cardiac function as well as with invasively measured Q_{UA} and R_{UA} (I). The relationships were investigated not only during baseline conditions but also after manipulating placental haemodynamics by placental embolization and by maternal administration of phenylephrine. Importantly, we could not demonstrate any association between the Doppler ultrasonographic parameters of fetal cardiac function and umbilicoplacental haemodynamics, suggesting that umbilical artery blood flow velocity waveforms cannot be used to derive information of fetal cardiac function.

The umbilical artery absolute velocities, with the exception of PSV, correlated positively with Q_{UA} and showed negative correlations with R_{UA} (I), supporting their use in the assessment of umbilicoplacental circulation. A recent longitudinal study in low-risk human pregnancies (Acharya *et al.* 2005a) similarly suggested that the umbilical artery absolute velocities are closely related to umbilical venous volume blood flow. In human fetuses, however, PSV was also found to correlate well with umbilical venous volume blood flow (Acharya *et al.* 2005a). The discrepancy could perhaps be explained by the narrow gestational age range of the present study. Furthermore, a large proportion of our measurements were obtained in fetuses with increased R_{UA}. The results of the present study are in agreement with the earlier findings showing that umbilical artery diastolic blood flow velocities decrease with progressive placental embolization without any significant change in systolic velocities (Morrow *et al.* 1989).

Previous studies have suggested that PI_{UA} reflects the haemodynamic and morphological events taking place at the level of placental villi (Giles *et al.* 1985; Morrow *et al.* 1989; Macara *et al.* 1996). In the present study, PI_{UA} was found to correlate negatively with Q_{UA} and positively with R_{UA} (I). In spite of this, however, PI_{UA} values were unaffected when Q_{UA} or R_{UA} changed significantly during fetal hypoxaemia (IV), maternal hypotension (III, IV) or phenylephrine administration (IV). Thus, our results support the earlier findings suggesting that PI_{UA} cannot be considered an accurate indicator of the changes in Q_{UA} or R_{UA} caused by vasoactive drugs (Adamson *et al.* 1990) or the changes in fetal oxygenation (van Huisseling *et al.* 1991).

Similarly, our observations on uteroplacental haemodynamics during the treatment of maternal hypotension with phenylephrine (III, IV) are in accordance with the earlier studies suggesting that PI_{UtA} may not directly reflect changes in Q_{UtA} and R_{UtA} caused by vasopressors (Saunders *et al.* 1998). Importantly, our results demonstrate that, during phenylephrine administration, a significant impairment in uteroplacental haemodynamics may be present despite totally normal PI_{UtA} values (III).

6.3 Responses to maternal hypoxaemia and hypotension

Fetal cardiovascular responses to acute hypoxaemia include peripheral vasoconstriction with redistribution of CCO towards the brain, heart and adrenal glands (Jensen *et al.* 1991; Reid *et al.* 1991). This circulatory adjustment is present in sheep fetuses despite severe acidaemia until cardiovascular collapse is evident (Block *et al.* 1990). It seems to be maintained by a combination of local vasodilator effects involving nitric oxide activity (Reller *et al.* 1995) and a general vasoconstrictive effect mediated by endocrine factors, including catecholamines (Hooper *et al.* 1990). Previous experiments in fetal sheep have suggested that the balance between vasodilator and vasoconstrictive effects may be modified in fetuses pre-exposed to adverse intrauterine conditions. When near-term sheep fetuses were exposed to transient hypoxaemia caused by umbilical cord compression lasting for three days, fetal vasoconstrictive responses to later periods of acute hypoxaemia were found to be attenuated as a result of increased nitric oxide activity (Gardner *et al.* 2002b). In the case of long-term prevailing hypoxaemia, however, fetal vasoconstrictive responses to further hypoxaemic insults were enhanced due to increased circulating concentrations of noradrenaline and vasopressin (Gardner *et al.* 2002a).

In our protocol, the fetuses were exposed to two subsequent short periods of acute decreases in fetal oxygenation: First, maternal inspiratory oxygen content was decreased. After a short recovery period, Q_{UtA} was significantly reduced by epidural-induced hypotension. Additionally, some of the fetuses were chronically hypoxaemic as a result of placental embolization 24 hours before the experiments. As opposed to the fetuses with normal placental function (III), the fetuses with placental embolization developed a marked increase in fetal lactate concentrations with minor decreases in fetal pH and BE during the latter hypoxaemic episode (IV).

In late gestation sheep fetuses, hypoxaemia typically induces hypertension and vagally mediated bradycardia (Cohn *et al.* 1974; Itskovitz *et al.* 1987; Jensen *et al.* 1991; Gardner *et al.* 2002b). We observed no significant changes in fetal HR during hypoxaemia (III, IV). This is not surprising, however, as a previous study has suggested that HR may return to the control level merely 10−20 minutes after the onset of a hypoxaemic insult (van Huisseling *et al.* 1991). A rise in arterial blood pressure was observed only in the nonembolized fetuses (II, III), indicating that the degree of placental embolization was sufficient to modify the physiologic responses to hypoxaemia. This is further supported by the fact that, in the fetuses with placental embolization, Q_{UA} decreased or R_{UA} increased when fetal oxygenation was further compromised by maternal hypoxaemia or hypotension (IV). In line with the previous observations on sheep fetuses with normal placental function showing either an increase or no change in Q_{UA} in response to acute hypoxaemia (Cohn *et al.* 1974; Reid *et al.* 1991), Q_{UA} remained unchanged in the nonembolized fetuses (III).

At near-term ovine gestation, hypoxaemia decreases fetal pulmonary volume blood flow and increases pulmonary vascular resistance (Lewis *et al.* 1976), while the effects of an increase in fetal Po_2 are the opposite (Morin and Egan 1992). In human pregnancy, maternal hyperoxygenation has been shown to decrease fetal PPA PI and increase pulmonary volume blood flow at 31−36 weeks of gestation (Räsänen *et al.* 1998). Depending on the muscularization of small arteries (Levin *et al.* 1976), this pulmonary vasomotor reactivity to changes in fetal oxygen tension does not develop before the third trimester (Lewis *et al.* 1976; Morin and Egan 1992; Räsänen *et al.* 1998). In the present study on near-term sheep fetuses, irrespective of placental function, a decrease in fetal Po_2 was associated with an increase in PPA PI (II, V). In accordance with the previous observations, this suggests vasoconstriction in the pulmonary arterial bed during fetal hypoxaemia. Furthermore, the increase in PPA PI was shown to correlate positively with the relative decrease in fetal oxygenation (II).

Previous studies have suggested that, if fetal hypoxaemia is due to umbilical cord compression, which leads to increased afterload, CCO decreases (Itskovitz *et al.* 1987). Similarly, if hypoxaemia is accompanied by a marked increase in arterial pressure, the right ventricular function curve is shifted downward (Reller *et al.* 1989). Without a concomitant increase in ventricular afterload, however, CCO is usually not significantly affected by hypoxaemia (Jensen *et al.* 1991; Reid *et al.* 1991). We observed increases in weight-indexed RVCO and CCO in the nonembolized fetuses during maternal hypo-oxygenation, while LVCO remained unchanged (II). This might reflect enhanced myocardial contractility due to catecholamine release (Hooper *et al.* 1990; Gardner *et al.* 2002a; Gardner *et al.* 2002b). However, ICT was prolonged and ventricular ejection forces remained unchanged (II). The increase in CCO could also be associated with increased stroke volume due to vasoconstriction of the capacitance bed. Importantly, our findings demonstrate that the fetal right ventricle is, at least acutely, capable of increasing its output even in the presence of increased MAP. During a recurrent hypoxaemic episode, however, fetal RVCO and CCO did not increase (V). This could be related to the slight increase in R_{UA}, which was likely to further increase right ventricular afterload. In the embolized fetuses, cardiac outputs remained unchanged during fetal hypoxaemia caused by maternal hypotension (V).

In the fetus, the AoI has a dynamic role in combining the two parallel circulatory systems. Acute experiments on fetal sheep have shown that the oxygen content of the blood entering the fetal brain is diminished if the net blood flow through the AoI becomes retrograde (Fouron *et al.* 1999). During the first episode of acute fetal hypoxaemia, we observed a relative increase in the AoI retrograde blood flow component in the nonembolized fetuses (II). This was persumably associated with an increase in the volume blood flow through the DA, resulting from the increase in RVCO and pulmonary vasoconstriction (II), and a simultaneous decrease in the vascular resistance in the cerebral circulation. However, during the decrease in fetal Po_2 caused by maternal hypotension, with no change in RVCO, the AoI ante/retro TVI ratio decreased only in fetuses with placental embolization (V). It has previously been shown in fetal sheep that an acute increase in R_{UA} results in a fall in the net forward flow through the AoI (Bonnin *et al.* 1993). It thus appears that the relative increase in the AoI retrograde blood flow component in the embolized fetuses was associated not only with pulmonary vasoconstriction directing blood from the pulmonary to the systemic circulation but also with markedly elevated R_{UA}.

Taken together, our results demonstrate that fetuses with normal placental function can successfully tolerate transient hypoxaemic episodes. In addition to the well-established redistribution of CCO towards the vital organs in response to hypoxaemia, the fetus redistributes its RVCO from the pulmonary to the systemic circulation and is also able to increase its CCO, with concomitant changes in the AoI blood flow profile. However, fetal haemodynamic responses to subsequent hypoxaemic insults of comparable degree and duration may not be equal, suggesting that pre-exposure to hypoxaemia modifies fetal cardiovascular compensatory mechanisms. Furthermore, the compensatory responses to an acute decrease in fetal oxygenation of chronically hypoxaemic fetuses with increased R_{UA} seem to differ from those of normal fetuses. This is associated with a reduced capacity to cope with even short periods of recurrent hypoxaemia, as indicated by the development of lactataemia in fetuses with placental embolization.

6.4 Responses to maternal vasopressor therapy

Previously, Alahuhta *et al.* compared uteroplacental vascular impedance values during maternal administration of ephedrine or phenylephrine in human pregnancy and reported that PI_{UtA} remained stable in the ephedrine group but increased significantly in the phenylephrine group (Alahuhta *et al.* 1992). In the present study, the decrease in Q_{UtA} and the increase in R_{UtA} associated with maternal hypotension were restored by ephedrine but not fully by phenylephrine (III, IV). Our findings are in accordance with the previous observations on pregnant ewes (Sipes *et al.* 1992; McGrath *et al.* 1994) and presumably partly associated with the divergent effects of the two drugs on maternal CI. Ephedrine restored maternal HR and CI because of its β-adrenergic function. With the pure α-agonist phenylephrine, however, maternal HR remained at the hypotensive level, and CI was only partially restored. It has been suggested that phenylephrine and ephedrine are equally effective in restoring cardiac output in hypotensive human parturients (Ramanathan and Grant 1988). Yet, cardiac output has been shown to decrease with phenylephrine if maternal HR decreases (Ashpole *et al.* 2005), suggesting that phenylephrine is not an ideal vasopressor if maternal hypotension is accompanied by bradycardia.

In addition, both ephedrine and phenylephrine are capable of producing uterine arterial vasoconstriction (Isla and Dyer 1990; Stjernquist and Owman 1990; Tong and Eisenach 1992; Li *et al.* 1996; White *et al.* 1998). The contractile response of the uterine artery to both ephedrine and phenylephrine is attenuated in pregnancy as a result of increased nitric oxide activity (Li *et al.* 1996; White *et al.* 1998). Compared with other vasopressors, however, ephedrine may constrict systemic vessels more selectively than the uterine artery during pregnancy (Tong and Eisenach 1992), which may partly explain its favourable effect on uteroplacental haemodynamics.

Recent *in vitro* observations on human umbilical arteries have shown concentration-dependent contractions with phenylephrine (Bodelsson and Stjernquist 1995) and no contraction with ephedrine at the concentrations capable of producing significant effects on atrial and anococcygeal tissues (Kobayashi *et al.* 2003). Our findings on chronically instrumented sheep fetuses also suggest that ephedrine may have a sparing effect on umbilicoplacental circulation. During ephedrine administration, Q_{UA} and R_{UA} were comparable to the baseline values (III, IV). With phenylephrine, however, R_{UA} remained elevated in the embolized fetuses (IV). Furthermore, Q_{UA} decreased after prolonged phenylephrine administration in the nonembolized fetuses (III). These observations could reflect the transplacental passage of phenylephrine with a direct constrictive effect on umbilicoplacental circulation.

Both ephedrine and phenylephrine corrected the decrease in fetal Po_2 secondary to maternal hypotension (III, IV). Similarly, fetal pH and BE were comparable between the two vasopressor groups (III, IV). In fetuses with increased R_{UA}, however, fetal lactate concentrations increased further from hypotensive values when maternal hypotension was treated with phenylephrine (IV). This could reflect impaired clearance of lactate from the fetus as a result of reduced placental perfusion during phenylephrine administration. Importantly, it has been suggested that neonatal arterial lactate concentrations are more sensitive than pH in predicting neurological disability in the newborn (Shah *et al.* 2004). Similarly, in the retrospective study of Kruger *et al.*, several patients with a hypoxic brain injury showed an increase in fetal scalp blood lactate concentrations although the respective pH value was still normal (Kruger *et al.* 1999). As lactate is the major end-product of anaerobic metabolism, fetal lactate levels might give more specific information about the degree of metabolic acidosis than pH, which also includes the more rapidly changing respiratory component.

Obviously, our results contradict the findings in human pregnancies suggesting higher umbilical artery pH values with phenylephrine than with ephedrine (Moran *et al.* 1991; LaPorta *et al.* 1995; Thomas *et al.* 1996; Cooper *et al.* 2002; Lee *et al.* 2002a). It has recently been suggested that increased fetal metabolic rate secondary to β-adrenergic stimulation is the mechanism for the lower pH with ephedrine (Cooper *et al.* 2002; Ngan Kee and Lee 2003). Indeed, infusion of the β-adrenergic agonist isoproterenol increases fetal oxygen consumption as well as blood glucose and lactate concentrations and decreases pH in fetal sheep (Gournay *et al.* 1999). In addition, human neonatal noradrenaline concentrations are higher after ephedrine than after phenylephrine (LaPorta *et al.* 1995). Noradrenaline is released into the fetal circulation during hypoxaemia

(Hooper *et al.* 1990; Gardner *et al.* 2002a; Gardner *et al.* 2002b). It could be possible that the endogenous noradrenaline concentrations in our fetuses exposed to recurrent hypoxaemic insults were elevated to such an extent that the additional β-adrenergic stimulation caused by ephedrine was not sufficient to further increase fetal metabolism.

However, if the lowering of human fetal pH by ephedrine proves to be related to increased metabolic rate, it may be relevant to question whether it is of any harm. Compared with neonates born by Caesarean delivery, vaginally delivered infants show markedly higher catecholamine concentrations, which have been associated with improved neonatal respiratory (Faxelius *et al.* 1983) and metabolic adaptation (Hagnevik *et al.* 1984). Interestingly, β-adrenergic stimulation with maternal infusion of terbutaline before elective Caesarean delivery seems to promote comparable positive effects on the newborn infant (Eisler *et al.* 1999).

A study on newborn calves has suggested that phenylephrine increases and β-adrenergic stimulation decreases pulmonary arterial and venous vascular resistances (Greenlees *et al.* 1986). Although both ephedrine and phenylephrine corrected fetal hypoxaemia in the present study, fetal PPA PI and PV PIV remained elevated with phenylephrine (V). This suggests an α1-adrenergic vasoconstrictor effect on the pulmonary circulation. The β-adrenergic effects of ephedrine seem to compensate for its α1-adrenergic actions in the pulmonary circulation.

In human fetuses, prophylactic maternal infusion of neither ephedrine, nor phenylephrine seems to have any effect on fetal cardiac function (Alahuhta *et al.* 1992). However, the administration of 10 mg boluses of ephedrine for maternal hypotension has been shown to increase fetal cardiac contractility (Räsänen *et al.* 1991). This could be associated with the fact that bolus dosage may result in higher peak concentrations in maternal blood, with increased placental transfer of vasopressors to the fetal circulation. In the present study on sheep fetuses, in which 5 mg boluses of ephedrine were administered to a mean total dose comparable to that given by Alahuhta *et al.* (Alahuhta *et al.* 1992), ephedrine had no effect on fetal cardiac function (V). However, after bolus dosage of phenylephrine, resulting in a considerably larger mean total dose than in the study of Alahuhta *et al.* (Alahuhta *et al.* 1992), LVCO and LVeFo decreased and ICT was prolonged (V), suggesting impaired cardiac contractility (Rizzo *et al.* 1995; Koga *et al.* 2003b). Yet, phenylephrine has been shown to induce a contractile response in fetal ventricular muscle strips *in vitro* (Cheng *et al.* 1980). Since fetal acidosis can reduce myocardial contractility (Rizzo *et al.* 1995), fetal lactataemia observed in the phenylephrine group, if it reflects tissue hypoxia, could have caused impairment of cardiac performance. Right ventricular function was not affected, however, even though the increased PPA PI and R_{UA} suggest that the right ventricular afterload was elevated. Furthermore, the decrease in LVCO was more pronounced in the nonembolized fetuses, in which the lactate concentrations were comparable between the ephedrine and phenylephrine groups (III). This suggests that left ventricular function was impaired by a mechanism other than, or additive to, fetal acidaemia.

Reduced venous return caused by pulmonary vasoconstriction can lead to a decrease in left ventricular preload, unless blood flow through the FO increases. In fetal sheep, the kinetic energy of blood in the IVC is a more important determinant of the FO blood flow than the pressure gradient between the two atria or that between the IVC and the left atrium (Anderson *et al.* 1981; Anderson *et al.* 1985). In the intrathoracic portion of the

IVC of human (Kiserud *et al.* 1992) and sheep (Schmidt *et al.* 1996) fetuses, two blood streams with different flow velocities can be identified. The blood stream originating from the DV has a higher velocity and is preferentially directed through the FO, whereas the blood stream originating from the caudal IVC has a lower velocity and predominantly flows into the right atrium (Kiserud *et al.* 1992; Schmidt *et al.* 1996). Under normal conditions in near-term fetal sheep, the proportion of the FO flow of the LVCO is approximately 85% (Anderson *et al.* 1981). During hypoxaemia, both the proportion of DV blood shunted through the FO (Itskovitz *et al.* 1987) and that of umbilical blood shunted through the DV increase (Itskovitz *et al.* 1987; Kiserud *et al.* 2000a). These compensatory changes are likely to lead to an increase in the FO blood flow. This could have compensated for the reduced pulmonary venous return with no change in left ventricular preload or LVCO during maternal hypotension. As fetal hypoxaemia was corrected by phenylephrine, shunting through the DV and FO may have returned to the baseline. Therefore, the FO may not have been able to fully compensate for the reduced pulmonary volume blood flow associated with phenylephrine treatment.

The AoI ante/retro TVI ratio, which decreased in the embolized fetuses during fetal hypoxaemia caused by maternal hypotension, was restored to the baseline level by ephedrine but not by phenylephrine (V). This may be associated with the divergent effects of ephedrine and phenylephrine on pulmonary haemodynamics and R_{UA}. Furthermore, the decrease in LVCO during phenylephrine administration was likely to have a parallel effect on the AoI haemodynamics.

To summarize, after exposure to hypoxaemia and maternal hypotension, the effects of ephedrine on uteroplacental and umbilicoplacental circulations were more favourable than those of phenylephrine. In addition, maternal administration of ephedrine restored fetal cardiovascular haemodynamics to the baseline conditions in cases with both normal and elevated R_{UA}. With phenylephrine, however, fetal PPA PI remained elevated, left ventricular function was impaired, and the relative increase in the AoI retrograde blood flow component observed in fetuses with increased R_{UA} was not fully reversed. Although no significant differences in fetal acid-base status or lactate concentrations were observed in the fetuses with normal placental function, phenylephrine administration led to increased lactate concentrations in those with elevated R_{UA}.

6.5 Clinical implications

The current data suggest that phenylephrine may be a better vasopressor than ephedrine during elective Caesarean delivery in uncomplicated human pregnancy (Lee *et al.* 2002a; Cooper *et al.* 2004). However, a large proportion of Caesarean deliveries are performed during some degree of fetal compromise, such as acute relative hypoxaemia following the first stage of uncomplicated labour (Aarnoudse *et al.* 1981; Dildy *et al.* 1994), or chronic hypoxaemia associated with placental insufficiency (Soothill *et al.* 1987; Pardi *et al.* 1993). The present results in fetal sheep demonstrate that hypoxaemia activates fetal cardiovascular compensatory mechanisms. Furthermore, the capacity of fetuses with increased R_{UA} to tolerate acute hypoxaemia, maternal hypotension or vasopressor therapy seems to be reduced. Therefore, we should not extrapolate the findings of vasopressor studies on uncomplicated pregnancies to fetuses compromised by acute or chronic hypoxaemia. The present study supports the use of ephedrine for the treatment of maternal hypotension during fetal compromise. However, our results may not be applicable to human fetuses. Yet, large doses of phenylephrine should perhaps be avoided in placental insufficiency until this question has been addressed in human pregnancy.

7 Conclusions

1. Umbilical artery blood flow velocity waveforms cannot be used to derive information of fetal cardiac function (I). Uterine and umbilical artery PI values should not be considered as accurate indicators of changes in volume blood flows or vascular resistances caused by vasopressor treatment (III, IV).
2. Hypoxaemia modifies fetal cardiovascular haemodynamics. In fetuses with normal placental function, an increase in CCO, a rise in PPA PI and a relative increase in the AoI retrograde blood flow component are Doppler ultrasonographic parameters related to a decrease in fetal oxygenation (II). However, the haemodynamic responses to subsequent hypoxaemic insults may vary (V). Furthermore, the compensatory responses to a further decrease in the oxygenation of fetuses with increased R_{UA} differ from those of healthy fetuses (V). This is associated with a reduced capacity to tolerate even short periods of recurrent acute hypoxaemia (IV).
3. The effects of ephedrine on uteroplacental and umbilicoplacental circulations were more favourable than those of phenylephrine. Yet, no significant differences in fetal pH or BE were observed (III, IV). In fetuses with increased R_{UA}, however, fetal lactate concentrations increased further from hypotensive values when maternal hypotension was treated with phenylephrine (IV).
4. After exposure to hypoxaemia and maternal hypotension, maternal administration of ephedrine restored fetal cardiovascular haemodynamics to baseline conditions in cases with both normal and elevated R_{UA}. With phenylephrine, however, fetal PPA PI remained elevated, left ventricular function was impaired, and the relative increase in the AoI retrograde blood flow component observed in the fetuses with increased R_{UA} was not fully reversed (V).

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I Acharya G, Erkinaro T, Mäkikallio K, Lappalainen T & Räsänen J (2004) Relationships among Doppler-derived umbilical artery absolute velocities, cardiac function, and placental volume blood flow and resistance in fetal sheep. Am J Physiol Heart Circ Physiol 286: H1266-H1272.

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