British Journal of Anaesthesia **93** (**6**): 825–32 (2004)
doi:10.1093/bja/aeh273 Advance Access publication October 1, 2004

BJA

Effects of ephedrine and phenylephrine on uterine and placental circulations and fetal outcome following fetal hypoxaemia and epidural-induced hypotension in a sheep model†

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Background. Recent studies support the use of α-agonists during regional anaesthesia in uncomplicated term pregnancies. We hypothesized that ephedrine and phenylephrine, administered for maternal hypotension following fetal hypoxaemia, are equal in respect of fetal outcome.

Methods. At 117–132 days gestation, chronically instrumented, anaesthetized and mechanically ventilated ewes were randomized to receive boluses of ephedrine (n=9) or phenylephrine (n=8) for maternal epidural-induced hypotension after a period of fetal hypoxaemia. Uterine (Q_{UtA}) and placental (Q_{UA}) volume blood flows were measured with perivascular transit-time ultrasonic flow probes, and uterine (R_{UtA}) and placental (R_{UA}) vascular resistances were computed from volume blood flows and maternal and fetal mean arterial pressures. Uterine (PI_{UtA}) and umbilical artery (PI_{UA}) pulsatility indices were obtained by Doppler ultrasonography.

Results. Ephedrine increased Q_{UtA} and decreased R_{UtA} and PI_{UtA} from a hypotensive to baseline level and had no significant effect on umbilical circulation. With phenylephrine, Q_{UtA} remained lower (P=0.011) and R_{UtA} higher (P=0.043) than at baseline, although PI_{UtA} decreased to baseline level. PI_{UA} increased from baseline with phenylephrine (P=0.007), whereas Q_{UA} decreased (P=0.050). Maternal volume expansion with hydroxyethyl starch decreased R_{UtA} significantly irrespective of the vasopressor used. There were no significant differences in fetal blood gas values or lactate concentrations between the ephedrine and phenylephrine groups.

Conclusions. Despite the more favourable effects on uterine and placental circulations of ephedrine over phenylephrine, no significant differences in fetal acid–base status or lactate concentrations were observed.

Br J Anaesth 2004; **93**: 825–32

Keywords: anaesthesia, obstetric; anaesthetic techniques, epidural; sympathetic nervous system, pharmacology, ephedrine; sympathetic nervous system, pharmacology, phenylephrine

Accepted for publication: July 14, 2004

Ephedrine is the most commonly used vasopressor in clinical obstetric practice[1] because of its sparing effect on uteroplacental perfusion found in animal experiments.[2–7] This effect has been explained by its partial β-agonism that increases cardiac output (CO)[2 3] and by its decreased tendency to constrict uterine arteries during pregnancy.[4 7] Vasopressors possessing more α-adrenergic activity have generally been avoided in obstetrics because experimental data suggest that they cause more uterine artery vasoconstriction than ephedrine and thus may compromise uterine blood flow.[2–7] As regards fetal outcome, studies in humans suggest that α-agonists, such as phenylephrine, are safe during regional anaesthesia for elective Caesarean section in uncomplicated term pregnancies.[8–13] However, α-agonists have not been studied during fetal compromise.

In this randomized study in a chronic sheep model we tested the hypothesis that ephedrine and phenylephrine, administered for epidural-induced hypotension in anaesthetized and mechanically ventilated ewes after a period of maternal and fetal hypoxaemia, are equal in respect of fetal outcome despite their divergent effects on maternal haemodynamics. The specific aims were to investigate the two vasopressors as regards (i) uterine and placental volume blood flows, vascular resistances, and uterine and umbilical

†Presented in part at the 10th Anniversary Meeting of the European Society of Anaesthesiologists, Nice, France, 6–9 April, 2002.

artery pulsatility indices, (ii) the effects of maternal volume expansion on these parameters, and (iii) fetal acid–base status and lactate concentrations.

Methods

Animal preparation

After approval by the Animal Care and Use Committee, University of Oulu, we used 20 ewes at 112–127 days of gestation (term 145 days). Eleven ewes were carrying one fetus and six ewes had two fetuses, one in each uterine horn. After pre-medication with i.m. ketamine 2 mg kg^{-1} and midazolam 0.2 mg kg^{-1}, anaesthesia was induced with i.v. propofol 4–7 mg kg^{-1} and, after tracheal intubation, maintained with isoflurane 1–2.5% in an oxygen/air mixture. Mechanical ventilation was maintained with a Siemens 730 ventilator (Siemens-Elema AB, Solna, Sweden). 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 for elevations of arterial pressure or heart rate during painful stimuli. 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, hysterotomy was performed and the fetal lower body was exposed. 18-G polyurethane catheters were placed into the fetal inferior vena cava and descending aorta via the femoral vein and artery, respectively. An incision was made in the fetal abdomen 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 both umbilical arteries and secured to the fetal abdomen. The fetus was then returned to the uterine cavity, the lost amniotic fluid was replaced with saline, and the hysterotomy and laparotomy incisions were closed. In the case of twin gestation, only one fetus was instrumented. All catheters and probes were tunnelled subcutaneously, exteriorized through a small incision in the ewe's flank, and flushed daily with heparinized saline. Postoperative analgesia was provided with buprenorphine 0.01 mg kg^{-1} i.m.. The ewes were given ampicillin 1 g and the fetuses 1 000 000 U of benzyl penicillin intravenously daily. All animals received humane care in compliance with the 'European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes' (Council of Europe 1986) and the European Union directive ETS 123 (1997).

During the recovery period of 5 days, fetal acid–base status and uterine (Q_{UtA}) and placental (Q_{UA}) volume blood flows were monitored daily. On the day of the experiment (117–132 days gestation), general anaesthesia was induced with propofol 4–7 mg kg^{-1} and maintained throughout the experiment with isoflurane 1–1.5% in an oxygen/air mixture via a tracheal tube and mechanical ventilation. Muscle relaxation was induced with rocuronium 20 mg and monitored with a neurostimulator, with additional boluses given as needed. A thermodilution catheter (Criticath SP5107H, Becton Dickinson, Sandy, UT, USA) was introduced through a jugular vein introducer placed during the primary operation. Under local anaesthesia, a 16-G polyurethane catheter was inserted into the descending aorta of the ewe via a femoral artery, and a 19-G epidural catheter was inserted percutaneously using the loss of resistance technique into the epidural space one interspace above or at the lumbosacral junction. The ewe was then placed supine with right lateral tilt and allowed to stabilize for 30 min before baseline measurements. Ringer's solution was infused freely until pulmonary capillary wedge pressure (PCWP) reached a value of 6 mm Hg, and thereafter at a rate of 100 ml h^{-1}.

Experimental protocol

After all the haemodynamic parameters were stabilized, baseline measurements were obtained (phase 1).

At time zero, maternal and fetal hypoxaemia, defined as maternal oxyhaemoglobin saturation of 80–90%, were induced by replacing oxygen by medical air in the rebreathing circuit (phase 2). At 15 min, the maternal inhaled oxygen concentration was returned to baseline, and the ewe and the fetus were allowed to recover from hypoxaemia (phase 3). At 30 min, the ewe was given 5 ml of bupivacaine 0.5% through the epidural catheter as a test dose, followed in 2 min by a 2-min injection of bupivacaine 0.5% to a total dose of 0.3 ml kg^{-1}. The dose was chosen to achieve a high thoracic level of epidural anaesthesia on the basis of the results of previous studies[5,6] and our experience. Hypotension to at least a 30% decrease in maternal systolic arterial pressure (SAP) was allowed to develop (phase 4). At 45 min, the ewes were randomized into the ephedrine or phenylephrine group by picking a sealed envelope and administration of 1 ml boluses of either ephedrine (5 mg ml^{-1}) or phenylephrine (0.1 mg ml^{-1}) was started to achieve a maternal SAP of at least 90% of the baseline (phase 5). At 75 min, administration of the vasopressor was discontinued. At 80 min, the crystalloid infusion (Ringer's solution 100 ml h^{-1}) was discontinued and 500 ml of hydroxyethyl starch solution (HES) was infused over a period of 10 min, after which the crystalloid infusion was restarted. At 90 min, the vasopressor boluses were restarted, aiming at a maternal SAP of at least 90% of baseline (phase 8). At 120 min, the administration of vasopressor was discontinued. At 165 min, the ewe and the fetus were killed by an i.v. overdose of pentobarbital.

Monitoring protocol

Maternal arterial pressures, central venous pressure (CVP), and pulmonary arterial pressure were measured via disposable pressure transducers (DT-XX, Ohmeda, Hatfield, UK).

The transducers used for fetal arterial and venous blood pressure measurements were reusable (Biopac Systems Inc., Santa Barbara, CA, USA). Maternal and fetal mean arterial pressures (MAPs) were computed arithmetically, and the heart rates (HRs) were computed from the arterial waveforms. Q_{UtA} and Q_{UA} were measured with the perivascular flow probes attached to a flow meter (T206, Transonic Systems Inc., Ithaca, NY, USA). Uterine (R_{UtA}) and placental (R_{UA}) vascular resistances were computed by dividing maternal and fetal MAPs by Q_{UtA} and Q_{UA}, respectively. All those variables were recorded continuously at a sampling rate of 100-Hz 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). The recordings were later analysed at 1-min periods and the median value of the 6000 measurements per variable was chosen to represent a particular minute.

CO was measured in triplicate at the end of each phase with the thermodilution catheter and Datex A/S3 monitor (Datex Inc., Espoo, Finland). PCWP and systemic vascular resistance (SVR) were obtained with the CO measurements. The surface area of the ewe was calculated[14] and cardiac index (CIND) and systemic vascular resistance index (SVRI) were derived from CO and SVR. Maternal and fetal arterial blood samples drawn at the end of each phase were immediately analysed for acid–base values (39°C). Maternal and fetal lactate concentrations were determined in blood samples drawn at the end of phases 1, 4, and 8.

Doppler ultrasonographic recordings (Acuson Sequoia 512, Mountain View, CA, USA) from the maternal main uterine artery and the fetal umbilical artery were obtained at the end of each phase. Mean values for the uterine (PI_{UtA}) and umbilical artery (PI_{UA}) pulsatility indices (PI=(peak systolic velocity – end diastolic velocity)/time-averaged maximum velocity over the cardiac cycle) were derived from three consecutive blood velocity waveforms.

Statistical analysis

Data were analysed using SPSS 10.1 for Windows software package (SPSS Inc., Chicago, IL, USA). Comparisons of single parametric variables between the groups were made using Student's *t*-test. For parameters that were continuously or repeatedly monitored, analyses of variance for repeated measurements (ANOVA) were used to evaluate whether there were significant differences between the groups (between-subjects *P*), or significant changes in measurements over time (within-subjects *P*), or significant differences in changes over time between the groups (interaction *P*). Because of skewed distribution, logarithmic transformation of R_{UtA} was used. The means of the last 5 min for phases 1, 2, 3, and 4 and the second to last 5 min for phases 5 and 8 were considered representative for each phase and used in the analyses. Two-tailed *P*-values were used. The data are presented as mean (SD) or mean differences with 95% confidence intervals (95% CI).

Results

Nine ewes in the ephedrine group and eight in the phenylephrine group were included in the analyses. One ewe was excluded because the fetus had not fully recovered from the primary operation and two because of misplacement of the epidural catheter.

The mean weights of ewes and fetuses, gestational age on the day of experiment, degree of fetal hypoxaemia (the percentage of fetal P_{O_2} during hypoxaemia *vs* baseline fetal P_{O_2}), duration of hypotension, and degree of hypotension (the percentage of mean maternal SAP during the last 5 min of hypotension *vs* baseline SAP) were comparable between the groups (Table 1). Mean total volume of vasopressor given was significantly greater (*P*=0.001) in the phenylephrine group (22.4 (8.1) ml) than in the ephedrine group (9.4 (4.5) ml). During the whole experiment, maternal blood gas values and lactate concentrations (Tables 2 and 4) and end-tidal isoflurane concentrations were comparable between the two groups. In 15 ewes and fetuses, mean Q_{UtA} (726 (163) *vs* 760 (287) ml min^{-1}; *P*=0.6) and Q_{UA} (407 (125) *vs* 401 (136) ml min^{-1}; *P*=0.8) measured before the induction of general anaesthesia were comparable with values during phase 1 (baseline).

Pre-randomization comparisons (ANOVA of phases 1, 2, 3, and 4; Tables 2 and 3) confirmed that there were no significant differences between the groups before vasopressor administration, except for CIND (between-subjects *P*=0.025). Because the randomization was performed after phase 4, the changes from baseline during phases 2 (hypoxaemia), 3 (recovery from hypoxaemia), and 4 (hypotension) are reported with the two groups combined. During phase 2 maternal and fetal P_{O_2} decreased significantly from baseline values. At the end of phase 3, Q_{UA} (mean difference 53, 95% CI 26–79 ml min^{-1}; *P*=0.001) and fetal HR (16, 95%

Table 1 Group characteristics. Values are mean (SD) [range]

	Ephedrine group (*n*=9)	Phenylephrine group (*n*=8)	*P*-value
Weight, ewe (kg)	75 (7) [65–84]	69 (6) [58–77]	0.078
Weight, fetus (kg)	2.5 (0.6) [1.65–3.51]	2.7 (0.6) [1.68–3.83]	0.5
Gestational age on the day of experiment (days)	126 (5) [117–132]	125 (4) [119–132]	0.9
Degree of fetal hypoxaemia (% of baseline)	70 (6) [60–77]	71 (7) [62–85]	0.9
Duration of maternal hypotension (min)	9 (3) [3–12]	10 (2) [8–13]	0.4
Degree of maternal hypotension (% of baseline)	59 (11) [43–71]	62 (7) [51–72]	0.5
Total amount of vasopressor given (mg)	46.9 (22.4) [20–85]	2.2 (0.8) [1.2–3.6]	

Table 2 Maternal haemodynamic parameters, blood gas values, lactate concentrations, and inhaled oxygen concentration before vasopressor administration. Values are mean (SD). *Pairwise $P<0.05$ as compared with baseline. †Missing values because of technical difficulties in data collection. ‡Pre-randomization comparisons. PCWP=pulmonary capillary wedge pressure, SVRI=systemic vascular resistance index, R_{UtA}=uterine artery vascular resistance

	Baseline (phase 1)	Hypoxaemia (phase 2)	Recovery from hypoxaemia (phase 3)	Hypotension (phase 4)	n†	Within-subjects P-value‡	Between-subjects P-value‡	Interaction (phase · group) P-value‡
Mean arterial pressure (mm Hg)	94 (8)	96 (9)	94 (8)	51 (7)*	17	<0.001	>0.9	0.8
Heart rate (min^{-1})	124 (13)	130 (15)	126 (16)	72 (9)*	17	<0.001	0.4	0.8
Cardiac index (litre min^{-1} m^{-2})	6.3 (0.7)	6.4 (0.8)	6.1 (0.7)	3.7 (0.6)*	14	<0.001	0.025	>0.9
Central venous pressure (mm Hg)	5 (2)	5 (2)	5 (2)	5 (2)	17	0.2	0.7	0.7
PCWP (mm Hg)	7 (2)	7 (2)	7 (3)	7 (3)	14	0.8	0.9	0.3
SVRI (dyne s m^2 cm^{-5})	1253 (143)	1199 (143)	1301 (184)	1056 (210)*	13	0.001	0.15	0.6
Uterine blood flow (ml min^{-1})	776 (299)	806 (314)	820 (296)	244 (120)*	16	<0.001	0.3	0.5
R_{UtA} (mm Hg ml^{-1} min^{-1})	0.138 (0.050)	0.137 (0.050)	0.131 (0.048)	0.261 (0.147)*	16	0.001	0.4	>0.9
Uterine artery pulsatility index	0.70 (0.12)	0.77 (0.17)	0.69 (0.15)	2.47 (0.89)*	10	<0.001	0.7	0.8
pH	7.33 (0.05)	7.34 (0.04)	7.32 (0.04)	7.34 (0.06)	16	0.10	0.2	0.8
Arterial P_{O_2} (kPa)	15.5 (4.4)	7.9 (1.5)*	15.1 (4.1)	14.0 (4.2)*	16	<0.001	0.4	0.6
Arterial P_{CO_2} (kPa)	5.1 (0.4)	4.8 (0.4)*	4.9 (0.4)*	4.7 (0.4)*	16	0.002	0.093	0.5
Lactate concentration (mmol $litre^{-1}$)	0.6 (0.3)			0.6 (0.3)	17	0.13	0.5	0.6
Inhaled oxygen concentration (%)	44 (8)	18 (2)*		45 (13)	16	<0.001	0.9	0.8

Table 3 Fetal haemodynamic parameters, blood gas values, and lactate concentrations before vasopressor administration. Values are mean (SD). *Pairwise $P<0.05$ as compared with baseline. †Missing values because of technical difficulties in data collection. ‡Pre-randomization comparisons. R_{UA}=placental vascular resistance

	Baseline (phase 1)	Hypoxaemia (phase 2)	Recovery from hypoxaemia (phase 3)	Hypotension (phase 4)	n†	Within-subjects P-value‡	Between-subjects P-value‡	Interaction (phase · group) P-value‡
Mean arterial pressure (mm Hg)	51 (6)	54 (7)	50 (6)	59 (7)*	17	< 0.001	0.7	>0.9
Heart rate (min^{-1})	171 (29)	183 (27)	155 (22)*	163 (36)	17	0.037	0.16	0.8
Umbilical blood flow (ml min^{-1})	390 (112)	399 (141)	337 (115)*	396 (124)	17	0.001	0.7	0.6
R_{UA} (mmHg ml^{-1} min^{-1})	0.143 (0.047)	0.150 (0.044)	0.166 (0.056)*	0.162 (0.047)*	17	0.002	0.5	0.5
Umbilical artery pulsatility index	0.81 (0.22)	0.73 (0.20)	0.78 (0.19)	0.91 (0.26)	14	0.01	0.11	0.2
pH	7.32 (0.04)	7.33 (0.04)	7.33 (0.04)	7.31 (0.06)	13	0.11	0.5	0.6
P_{O_2} (kPa)	3.1 (0.5)	2.2 (0.4)*	3.0 (0.5)	2.0 (0.4)*	13	< 0.001	0.7	0.5
P_{CO_2} (kPa)	6.6 (0.7)	6.2 (1.0)	6.3 (0.8)	6.8 (0.9)	13	0.071	>0.9	0.13
Base excess (mmol $litre^{-1}$)	0.5 (2.7)	−1.3 (5.1)	−1.3 (3.2)	−2.0 (5.4)	14	0.2	0.13	0.3
Lactate concentration (mmol $litre^{-1}$)	1.9 (0.7)			2.2 (0.8)*	17	0.015	0.5	>0.9

CI 3–29 min^{-1}; P=0.017) were significantly lower and R_{UA} higher (0.022, 95% CI 0.008–0.037 mm Hg ml^{-1} min^{-1}; P=0.004) than at baseline. During phase 4 maternal MAP, HR, CIND, SVRI, Q_{UtA}, P_{O_2}, and fetal P_{O_2} decreased, and R_{UtA}, PI_{UtA}, fetal MAP, and fetal lactate concentrations increased from baseline values. R_{UA} remained elevated (Tables 2 and 3).

Following vasopressor administration, when compared with baseline (ANOVA of phases 1, 5, and 8), there were significant differences in changes over time between the two groups (interaction P) in maternal MAP, HR, CIND, CVP, PCWP, SVRI, Q_{UtA}, R_{UtA}, and fetal PI_{UA} (Figs 1 and 2 and Tables 4 and 5).

With ephedrine (phase 5) maternal MAP, HR, CI, SVRI, Q_{UtA}, R_{UtA}, and PI_{UtA} as well as R_{UA}, fetal MAP, and P_{O_2} returned from hypotensive to baseline levels. After maternal volume expansion (phase 8) CVP, PCWP, CIND, and PI_{UtA} increased and SVRI, R_{UtA}, and PI_{UA} decreased significantly from baseline values (ANOVA of phases 1, 5, and 8 for the ephedrine group; Figs 1 and 2 and Tables 4 and 5).

With phenylephrine (phase 5) maternal MAP, HR, and CIND remained significantly lower than at baseline. SVRI increased to baseline levels, and CVP and PCWP increased significantly from baseline values. Q_{UtA} increased significantly but remained lower than at baseline. PI_{UtA} decreased to baseline levels. R_{UtA} decreased but returned to baseline only after maternal volume expansion (phase 8). Phenylephrine corrected fetal hypoxaemia, restored fetal MAP to baseline level, and had no effect on fetal HR. PI_{UA} increased (phase 5) and, after prolonged phenylephrine administration (phase 8), Q_{UA} decreased significantly, but there were no significant changes in R_{UA}, fetal blood gases, or lactate concentrations (ANOVA of phases 1, 5, and 8 for the phenylephrine group; Figs 1 and 2 and Tables 4 and 5).

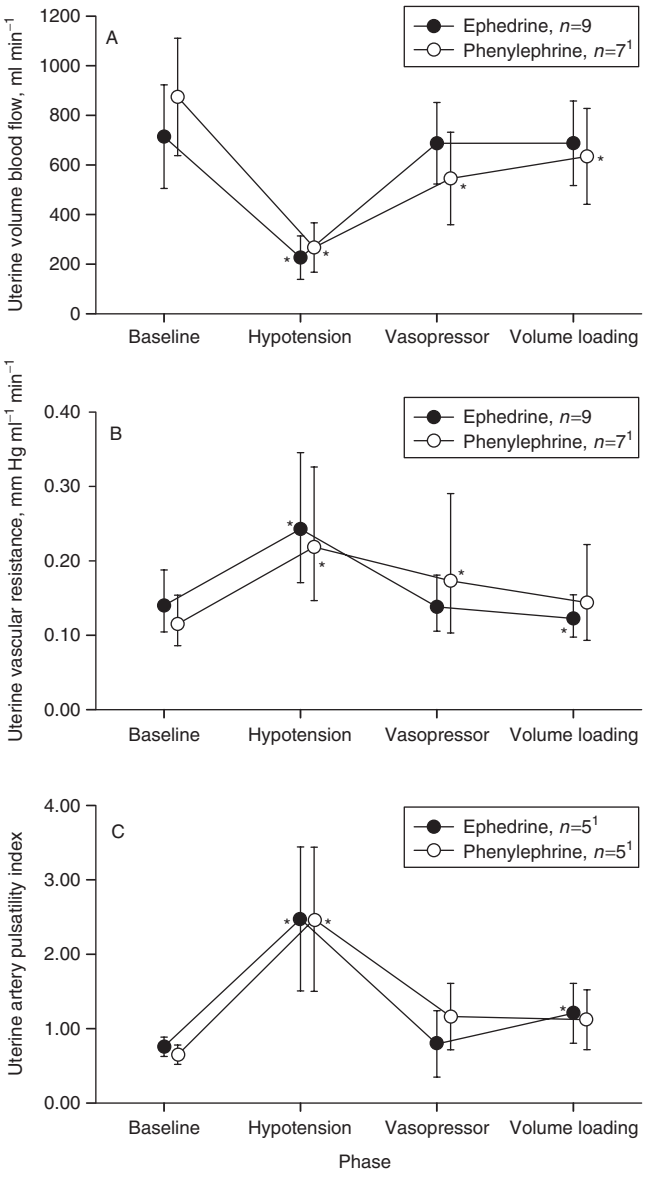

Fig 1 Uterine artery volume blood flows (A), uterine artery vascular resistances (B), and uterine artery pulsatility indices (C) at baseline and during hypotension, vasopressor treatment, and vasopressor treatment after maternal volume loading. The values are mean±95% CI. There were significant differences in changes over time between the ephedrine and phenylephrine groups in uterine artery volume blood flow (interaction P=0.004) and uterine artery vascular resistance (interaction P=0.004). *Pairwise P<0.05 as compared with baseline. [1]Missing values because of technical difficulties in data collection.

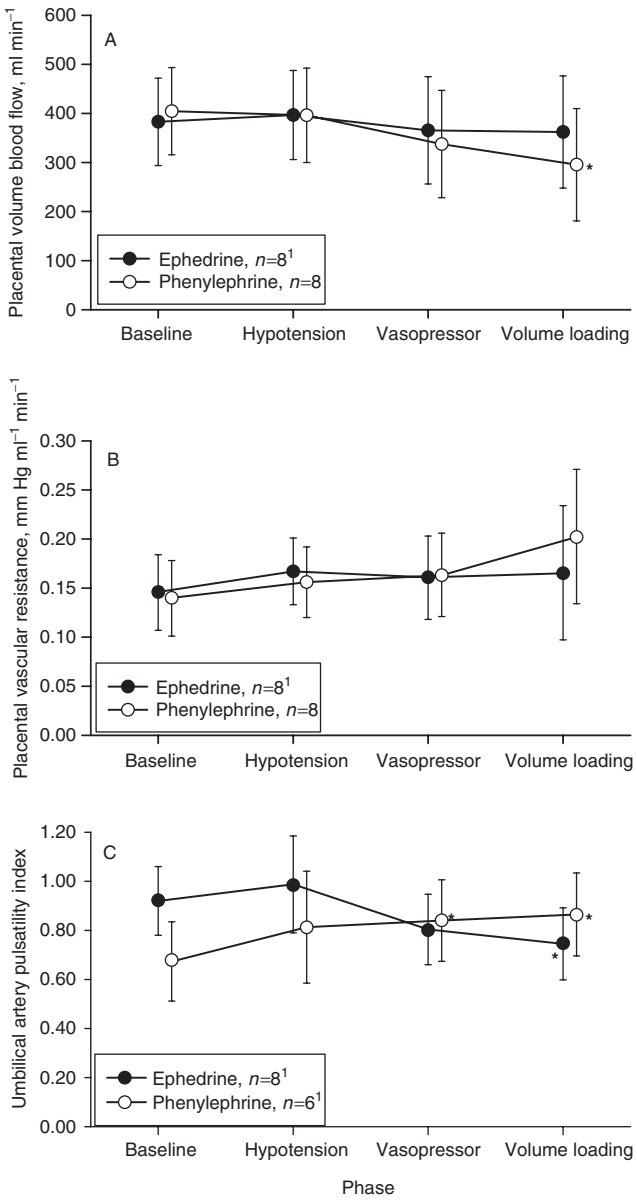

Fig 2 Placental volume blood flows (A), placental vascular resistances (B), and umbilical artery pulsatility indices (C) at baseline and during hypotension, vasopressor treatment, and vasopressor treatment after maternal volume loading. The values are mean±95% CI. There was a significant difference in changes over time between the ephedrine and phenylephrine groups in umbilical artery pulsatility index (interaction P<0.001). *Pairwise $P \leq 0.05$ as compared with baseline. [1]Missing values because of technical difficulties in data collection.

Discussion

The effects of different vasopressors on human fetal outcome have been studied only in healthy term fetuses undergoing elective Caesarean section. However, it has been shown earlier that during the first stage of normal vaginal labour after uncomplicated pregnancy, fetal s.c. mean P_{O_2} values decrease by about 25%.[15] Similarly, significant decreases in fetal oxygen saturation have been described even in healthy fetuses during uncomplicated labour.[16] A hypoxaemic stimulus triggers compensatory mechanisms in the fetus, including the redistribution of fetal circulation in favour of the brain, heart, and the adrenals. Because hypoxaemia may change vascular reactivity of the fetal circulation, responses to maternal hypotension and vasopressor therapy may become unpredictable. The present study on chronically instrumented, anaesthetized and mechanically ventilated ewes was designed to investigate the effects of maternal epidural-induced

Table 4 Maternal haemodynamic parameters, blood gas values and lactate concentrations during vasopressor treatment. Values are mean (SD). *Pairwise $P<0.05$ as compared with baseline. †Missing values because of technical difficulties in data collection. E=ephedrine, P=phenylephrine, MAP=mean arterial pressure, CVP=central venous pressure, PCWP=pulmonary capillary wedge pressure, SVRI=systemic vascular resistance index

	Group	Baseline (phase 1)	Vasopressor (phase 5)	Vasopressor and volume loading (phase 8)	$n^{\dagger}$	Within-subjects *P*-value	Between-subjects *P*-value	Interaction (phase · group) *P*-value
MAP (mm Hg)	E	94 (9)	91 (9)	81 (7)*	9	<0.001	0.5	0.015
	P	94 (9)	82 (9)*	82 (7)*	8			
Heart rate (min^{-1})	E	125 (15)	138 (14)	130 (18)	9	<0.001	<0.001	<0.001
	P	123 (12)	75 (11)*	81 (9)*	8			
Cardiac index (litre min^{-1} kg^{-1})	E	6.4 (0.7)	6.8 (0.8)	8.2 (1.1)*	8	<0.001	<0.001	<0.001
	P	6.1 (0.6)	4.6 (0.6)*	5.4 (0.4)*	8			
CVP (mm Hg)	E	5 (2)	5 (2)	6 (2)*	9	<0.001	0.017	<0.001
	P	5 (1)	8 (2)*	10 (3)*	8			
PCWP (mm Hg)	E	6 (1)	6 (2)	8 (2)*	7	<0.001	0.032	0.001
	P	7 (2)	9 (3)*	12 (3)*	8			
SVRI (dyne s m^2 cm^{-5})	E	1188 (161)	1076 (130)	843 (109)*	8	<0.001	<0.001	0.021
	P	1314 (99)	1374 (171)	1225 (205)	7			
pH	E	7.32 (0.04)	7.30 (0.04)*	7.28 (0.06)*	9	<0.001	0.6	0.2
	P	7.35 (0.06)	7.31 (0.08)*	7.28 (0.08)*	8			
P_{O_2} (kPa)	E	15.9 (5.2)	15.3 (4.9)	15.8 (5.5)	9	0.7	0.7	0.2
	P	15.7 (3.8)	17.2 (5.2)	16.4 (4.9)	8			
P_{CO_2} (kPa)	E	5.2 (0.4)	5.0 (0.4)	5.0 (0.5)	9	0.2	0.2	0.7
	P	4.9 (0.4)	4.8 (0.4)	4.9 (0.5)	8			
Lactate (mmol $litre^{-1}$)	E	0.6 (0.3)		0.6 (0.2)	9	0.4	0.4	0.3
	P	0.5 (0.3)		0.4 (0.3)	8			

Table 5 Fetal haemodynamic parameters, blood gas values and lactate concentrations during vasopressor treatment. Values are mean (SD). †Missing values because of technical difficulties in data collection. E, ephedrine; P, phenylephrine; MAP, mean arterial pressure; BE, base excess

	Group	Baseline (phase 1)	Vasopressor (phase 5)	Vasopressor and volume loading (phase 8)	$n^{\dagger}$	Within-subjects *P*-value	Between-subjects *P*-value	Interaction (phase · group) *P*-value
MAP (mm Hg)	E	51 (7)	52 (6)	51 (6)	9	0.6	0.6	0.6
	P	51 (5)	50 (6)	49 (7)	8			
Heart rate (min^{-1})	E	163 (24)	162 (29)	165 (30)	9	0.2	0.6	0.2
	P	181 (33)	162 (21)	166 (39)	8			
pH	E	7.31 (0.05)	7.29 (0.07)	7.32 (0.06)	8	0.091	0.7	0.14
	P	7.33 (0.04)	7.29 (0.06)	7.28 (0.08)	8			
P_{O_2} (kPa)	E	3.1 (0.4)	3.1 (0.5)	2.8 (0.5)	8	0.008	0.7	0.5
	P	3.1 (0.6)	2.9 (0.4)	2.7 (0.5)	8			
P_{CO_2} (kPa)	E	6.5 (0.7)	5.8 (1.3)	6.4 (1.2)	8	0.2	0.12	0.6
	P	6.7 (0.5)	6.7 (1.2)	7.3 (1.2)	8			
BE (mmol $litre^{-1}$)	E	−1.2 (3.1)	−4.5 (5.2)	−1.1 (1.8)	8	0.018	0.3	0.5
	P	1.1 (2.7)	−2.5 (3.8)	−1.3 (4.5)	8			
Lactate (mmol $litre^{-1}$)	E	1.7 (0.6)		2.1 (1.3)	9	0.033	0.19	0.2
	P	2.0 (0.8)		3.2 (2.1)	8			

hypotension and its treatment with ephedrine or phenylephrine on uterine and placental circulations and fetal outcome after a period of fetal hypoxaemia. In our protocol, fetal hypoxaemia was induced by maternal hypoxaemia, but the percentage decrease in fetal P_{O_2} was comparable with that seen in human fetuses during the course of normal vaginal labour.[15] After a short hypoxaemic period, maternal and fetal P_{O_2} were restored as we did not aim to induce fetal acidaemia. However, the reduced fetal HR and Q_{UA} and the increased R_{UA} before the induction of epidural anaesthesia indicate that the degree and duration of the hypoxaemic insult were sufficient to activate compensatory mechanisms in the fetoplacental unit. Before vasopressor administration a short but profound period of maternal hypotension was allowed to develop to induce further fetal stress, manifested by decreased fetal P_{O_2} and increased MAP and lactate concentrations.

There are several limitations in our study to consider before extrapolating our results to humans. First, both the macrostructure of the ovine placenta with the arrangement of fetal and maternal blood compartments and the structure of the maternal cell layers differ from those of the human placenta. Accordingly, differences in the placental transfer of vasopressors may exist. In addition, human and ovine

responses to vasopressors may vary because there are species differences in α- and β-adrenergic receptor distribution. Secondly, for ethical reasons and to allow a supine position, the experiments were performed under general anaesthesia. Although Q_{UtA} and Q_{UA} before the induction of general anaesthesia were comparable with values measured during general anaesthesia at baseline, the combination of general and regional anaesthesia may have modified maternal haemodynamics more extensively than epidural anaesthesia alone. Thirdly, because of a relatively complex and long-lasting study protocol the fetuses were exposed to vasopressors for a longer period than is clinically relevant. Fourthly, although the number of animals was comparable with that of previous experimental studies, the sample size was limited, which may reduce the power of this study. However, previous studies on fetal sheep have shown that physiologic changes in the umbilicoplacental circulation can be applied to human pregnancies.[15 17]

As shown in earlier animal studies,[5 6] we observed that Q_{UtA} decreased significantly during hypotension and was restored to baseline level by ephedrine. Phenylephrine increased Q_{UtA} but this remained lower than at baseline. The concomitant increase in R_{UtA} during hypotension was normalized by ephedrine but not phenylephrine. This indicates that the lower Q_{UtA} with phenylephrine did not merely result from the lower maternal MAP during phenylephrine treatment than at baseline, but was caused by increased vascular resistance and vasoconstriction of the uterine arterial bed. To our knowledge, placental circulation has not been monitored directly in any previous studies of vasopressors. In the present study, ephedrine had no significant effect on placental circulation whereas Q_{UA} decreased after prolonged administration of phenylephrine. This may reflect the passage of phenylephrine through the placenta and its direct effect on the umbilicoplacental circulation. Previously, phenylephrine has been shown to induce concentration-dependent contractions in human umbilical artery *in vitro*.[17]

Placental vascular resistance comprises the vascular resistances across the umbilical arteries, umbilical veins and the cotyledons, corresponding at rest to 30, 15, and 55% of the total resistance.[18] PI_{UA} is determined by the ratio of total placental resistance to umbilical artery resistance.[19] It has been shown in fetal sheep that PI_{UA} does not reveal changes in vascular resistance mediated by umbilical arterial vasoconstriction caused by angiotensin II infusion but reflects increases in resistance of the cotyledons caused by placental embolization.[20] An exponential increase in PI_{UA} is obtained only after more than 60% of the terminal vascular branches are obliterated.[19] Likewise, increasing the peripheral resistance of the uterine vascular bed in a computer model caused a marked increase in PI_{UtA}, and although a decrease in uterine artery radius also increased PI_{UtA}, the effect was accentuated when the resistance of the distal vascular bed was high.[21] In the present study, PI_{UtA} and PI_{UA} were compared with continuously monitored volume blood flows and vascular resistances. Our results suggest that PI_{UtA} and PI_{UA} may not directly reflect changes in vascular resistance caused by vasopressors or volume expansion, as discussed earlier.[20 22]

I.V. volume loading is used in human pregnancies to reduce the incidence and severity of maternal hypotension caused by regional anaesthesia.[1] Recent clinical studies on humans showed no beneficial effect of a crystalloid bolus on the incidence of hypotension or total requirements of ephedrine[23] or metaraminol.[24] However, uteroplacental perfusion was not monitored in these studies. In a chronic sheep preparation, 500 ml of HES increased CO and Q_{UtA} significantly.[25] In the present study, 500 ml of HES was infused after 30 min of vasopressor therapy. We observed a significant decrease in R_{UtA} in each vasopressor group. Thus, volume expansion with 500 ml of HES had a similar favourable effect on uteroplacental perfusion irrespective of the vasopressor used.

We found no significant differences in fetal blood gases or lactate concentrations between the groups. This contradicts the findings of clinical studies on Caesarean delivery under spinal anaesthesia suggesting higher umbilical cord pH values with α-agonists than with ephedrine.[10–12] Furthermore, Cooper and co-workers showed that the incidence of fetal acidosis, defined as umbilical artery pH less than 7.20, was significantly higher with ephedrine than with phenylephrine after elective Caesarean section at term gestation.[13] Combination of both drugs allowed a marked reduction in the dose of ephedrine, resulting in lower incidence of acidosis.[13] In the present study, the amount of ephedrine given over 75 min was similar to doses administered in clinical studies[10 11 13] within 30 min. Thus, the dose of ephedrine per minute was relatively low compared with that used in humans. In addition, the concentrations of vasopressor solutions we chose on the basis of clinical experience[8 26] were not equipotent in sheep under combined general and epidural anaesthesia. The mean total volume of ephedrine given was significantly lower than that of phenylephrine. However, the dose of phenylephrine per minute was comparable with that used clinically.[13] These divergencies in vasopressor requirement may partly explain why no pH differences were observed even after prolonged exposure to vasopressors. Furthermore, the present study was performed in near term fetuses. Cooper and colleagues proposed that increased fetal metabolic rate secondary to β-adrenergic stimulation is the mechanism for lower pH values with ephedrine.[13] A progressive increase in fetal pressor response to ephedrine has been demonstrated in fetal sheep, suggesting enhanced release of noradrenaline with advancing gestation.[27] Term fetuses may thus be more sensitive to ephedrine as regards the development of fetal acidaemia.

In summary, ephedrine had more favourable effects on uterine and placental circulations than phenylephrine. However, no significant differences in fetal acid–base status or lactate concentrations were observed.

Acknowledgements

This study was supported by grants provided by the Academy of Finland and the University of Oulu. The authors wish to thank Pasi Ohtonen, MSc, for statistical consultation.

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