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Ephedrine Remains the Vasopressor of Choice for Treatment of Hypotension during Ritodrine Infusion and Epidural Anesthesia

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Background: **Historically, ephedrine has been the vasopressor of choice for treatment of most cases of hypotension in obstetric patients. However, the choice of vasopressor in the parturient receiving a β-adrenergic agent for tocolysis has not been evaluated extensively. The current study evaluated whether ephedrine or phenylephrine better restores uterine blood flow and fetal oxygenation during ritodrine infusion and epidural anesthesia–induced hypotension in gravid ewes.**

Methods: **Fourteen chronically instrumented gravid ewes between 0.8 and 0.9 timed gestational age were used. On separate days, each animal underwent the experimental protocol with one of three agents: ephedrine, phenylephrine, and normal saline–control. The experimental protocol was as follows: (1) at time zero, intravenous infusion of ritodrine was begun; (2) at 120 min, 2% lidocaine was given epidurally to achieve a sensory level of at least T6; and (3) at 135 min, an intravenous bolus of either ephedrine, phenylephrine, or normal saline–control was given, followed by a continuous intravenous infusion of the same agent for 30 min. In the ephedrine and phenylephrine experiments, the rate of infusion was adjusted to maintain maternal mean arterial pressure close to baseline.**

Results: **Ritodrine infusion alone significantly increased maternal heart rate and cardiac output in all three groups. Epidural anesthesia during ritodrine infusion significantly decreased maternal mean arterial pressure, heart rate, cardiac output, uterine blood flow, and fetal arterial oxygen tension for each of the three groups. Both ephedrine and phenylephrine restored maternal mean arterial pressure to baseline, as designed. Ephedrine significantly increased uterine blood flow and fetal arterial oxygen tension when compared with normal saline–control, but phenylephrine did not. Phenylephrine significantly increased uterine vascular resistance when compared with normal saline–control, but ephedrine did not.**

Conclusions: **Although ephedrine and phenylephrine provided similar restoration of maternal mean arterial pressure, ephedrine was superior to phenylephrine in restoring uterine blood flow during ritodrine infusion and epidural anesthesia–induced hypotension in gravid ewes. Also, ephedrine, but not phenylephrine, significantly improved fetal oxygenation when compared to normal saline–control. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Anesthetics, local: lidocaine. Pregnancy: preterm labor. Sympathetic nervous system, α-adrenergic agonists: phenylephrine. Sympathomimetic agents: ephedrine. Tocolytic agents: ritodrine.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 28A.

PRETERM labor and delivery is the leading cause of perinatal mortality and morbidity in the United States.[1,2] Ritodrine, a β-sympathomimetic agent, is the only drug specifically approved by the United States Food and Drug Administration for tocolysis (*i.e.*, the treatment of preterm labor by inhibition of uterine muscle contractions). Although ritodrine is relatively selective for the β_2 receptor, β_1 receptor stimulation also occurs,[3] resulting in an increase in maternal heart rate (HR) and systolic arterial pressure, a decrease in diastolic pressure, and no change or a decrease in mean arterial pressure (MAP).[1,3–6]

Women in whom preterm labor continues despite ritodrine tocolysis often want or need anesthesia. Typically they require induction of anesthesia on an emergency basis. There is one other circumstance when anesthesiologists encounter women who have recently received a β-adrenergic drug. Obstetricians often give

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a β-adrenergic agonist to facilitate resuscitation of distressed fetuses *in utero.*[7,8] The β-adrenergic agonists do not directly increase uteroplacental perfusion. Rather they indirectly improve placental perfusion by relaxing the uterus. (Uteroplacental perfusion occurs between uterine contractions.) Unfortunately, this therapy often fails, and the anesthesiologist must then provide anesthesia to a mother with a distressed fetus, and who just received a bolus injection of a β-adrenergic tocolytic agent.

The cardiovascular effects of ritodrine persist after discontinuation of a ritodrine infusion.[4,5] There is concern that previously administered ritodrine might increase the likelihood or severity of hypotension during administration of spinal or epidural anesthesia. Shin and Kim‖ observed that maternal hypotension was more common when induction of epidural anesthesia occurred within 30 min of discontinuation of ritodrine when compared with a delay of greater than 30 min. However, we observed that prior administration of ritodrine did not worsen maternal hypotension during administration of epidural lidocaine anesthesia in gravid ewes.[9]

Historically, ephedrine, a mixed α- and β-adrenergic agonist, has been the vasopressor of choice for obstetric patients because it has a more protective effect on uterine blood flow (UBF) than other vasopressors in gravid ewes.[10,11] Hollmen *et al.*[12] observed that prophylactic ephedrine either improved or maintained intervillous blood flow in women undergoing cesarean section during epidural anesthesia. Conventional wisdom has held that ephedrine's β receptor activity increases cardiac output (CO) and thus compensates for its α receptor–mediated uterine vasoconstriction.[13] In contrast, α_1-adrenergic agonists (*i.e.,* phenylephrine and methoxamine) worsen UBF and fetal condition in gravid ewes.[14,15]

Initially, we hypothesized that in a patient or animal already receiving a β agonist (*i.e.,* ritodrine or terbutaline), any vasopressor effect from ephedrine would result from α receptor stimulation. The accompanying uterine vasoconstriction might further decrease UBF. We observed, however, that ephedrine restored UBF velocity during terbutaline infusion and hemorrhagic hypotension in gravid guinea pigs.[16] In addition, ephedrine, but not phenylephrine, preserved UBF velocity during ritodrine infusion in normovolemic gravid guinea pigs.[17] Neither study, however, evaluated fetal oxygenation, and neither study evaluated ephedrine in circumstances when it is more likely to be given clinically (*i.e.*, treatment of epidural or spinal anesthesia–induced hypotension during or after ritodrine infusion). The purpose of the current study was to determine whether ephedrine or phenylephrine infusion better restores and protects UBF and fetal oxygenation during ritodrine infusion and epidural anesthesia–induced hypotension in gravid ewes.

‖ Shin YK, Kim YD: Anesthetic considerations in patients receiving ritodrine therapy for preterm labor (abstract). Anesth Analg 65:S140, 1986.

Materials and Methods

Maternal and Fetal Instrumentation and Postsurgical Care

The protocol was approved by the University of Iowa Animal Care Committee. Briefly, mixed breed ewes were obtained from a commercial breeder at approximately 118 days of timed gestation (term = 145 days). Each animal fasted for 36 h before surgery. At 120 days of gestation, induction of general anesthesia was accomplished with sodium thiopental (8–12 mg/kg). After tracheal intubation, anesthesia was maintained with 1–1.5% halothane in oxygen. Mechanical ventilation was maintained throughout surgery. Using sterile technique, a laparotomy and hysterotomy were performed, and catheters (polyethylene-90) were inserted into the fetal descending aorta *via* each femoral artery. Fenestrated high pressure tubing (MX 566, Medex, Hilliard, OH) was secured to the fetal hind limb to monitor intraamniotic pressure.

After the hysterotomy and laparotomy incisions were closed, a left paramedian incision was made. The left uterine artery was isolated *via* a retroperitoneal approach, and an electromagnetic flow probe (Dienco, Los Angeles, CA) was placed around the artery. Catheters (polyethylene-240) were then inserted into the maternal descending aorta and inferior vena cava *via* the left mammary artery and vein, respectively. Another catheter (polyethylene-240) was inserted into the maternal femoral artery. All catheters were tunneled subcutaneously and exteriorized through a small incision in the left flank. Finally, an 8.5-French introducer (AK09800, Arrow, Reading, PA) was placed percutaneously into the right jugular vein.

Two single-orifice, 19-G epidural catheters (Portex, Wilmington, MA) were percutaneously inserted (approximately 5 cm) into the epidural space, *via* a loss-

of-resistance technique, at two different interspaces at or near the lumbosacral junction, and the catheters were secured to the back. Eight milliliters of 2% lidocaine were injected through the more cephalad epidural catheter before the completion of surgery. After surgery the sensory level of anesthesia was determined.

After surgery, each animal was kept in an approved cage in a restricted area, fed a balanced diet, and allowed a recovery period of at least 4 days. Procaine and benzathine penicillin G (Dual-Pen®, Tech America, Kansas City, MO) 600,000 U was given to the mother intramuscularly 3 days before surgery, on the day of surgery and on the 1st day after surgery. Gentamycin 80 mg was given to the mother intravenously during surgery, on the 2nd day after surgery, and on the day of each experiment. Gentamycin 40 mg was given *via* the amniotic catheter during surgery, on the 2nd day after surgery, and on the day of each experiment. Postoperative analgesia was provided by administration of nalbuphine hydrochloride as needed.

Experimental Measurements and Data Acquisition

Each experiment was performed with the animal standing, supported by a canvas sling, within an approved transport cart. The canvas sling allowed the animal to remain upright at all times.

Before the first experiment in each animal, a pulmonary artery catheter (93A-131H-7F or 93A-831H-7.5F, American Edwards Laboratories, Santa Ana, CA) was inserted through the jugular vein introducer. Sterility was maintained with an 80-cm sheath. Maternal arterial blood pressure, central venous pressure, pulmonary artery pressure, and fetal arterial blood pressure were measured continuously *via* disposable strain gauge pressure transducers (46951-02, Abbott Critical Care Systems, North Chicago, IL) and transducer couplers (572-25 Coulbourn Instruments, Lehigh Valley, PA). Fetal pressures were corrected by subtraction of simultaneous intraamniotic pressure. MAP was computed arithmetically. The maternal and fetal HRs were computed from the arterial waveforms. Uterine artery blood flow (UBF) was measured continuously with a quantitative electromagnetic flowmeter (RF-2500, Dienco, Los Angeles, CA). Arterial and venous pressures, HRs, and UBF were recorded at 10-s intervals using a computer-based system and customized data acquisition software (Alternatives Unlimited, Des Moines, IA).

CO measurements were made in triplicate with 10 ml of iced saline and a thermodilution CO computer (9520A, Edwards Laboratories). Maternal and fetal arterial blood gas and *p*H measurements were determined using an Instrumentation Laboratory (1302, Leighton, MA) blood gas analyzer. All values were corrected for temperature (39.5°C).

Experimental Protocol

Fourteen animals were used. On 3 separate days, each animal underwent the experimental protocol with one of three therapeutic modalities, in random order, for a total of 42 studies. The animals were allowed to rest at least overnight between experimental days. The experimental protocol evaluated maternal and fetal responses to epidural anesthesia–induced hypotension during ritodrine infusion, followed by treatment with one of two different vasopressors or normal saline (NS)–control. The two vasopressors chosen were phenylephrine (an α_1-adrenergic agonist) and ephedrine (a mixed α- and β-adrenergic agonist). The phenylephrine solution was prepared as 0.02 mg/ml. The ephedrine solution was prepared as 1 mg/ml.

The experimental sequence included the following:

1. Forty minutes was allowed for the sheep to acclimate to the laboratory environment. NS 250 ml was infused intravenously during the first 20 min of this time period.
2. Twenty minutes was allowed for baseline measurements.
3. At time zero, an intravenous infusion of ritodrine 0.002 mg·kg·min was begun. The total rate of crystalloid infusion was 100 ml/h.
4. At 120 min, each animal received 10–16 ml of 2% lidocaine, injected through one of the two epidural catheters in two equal divided doses 1 min apart. The dose was determined according to the response to the epidural lidocaine given on the day of surgery.
5. Beginning at 125 min, the sensory level of anesthesia was determined with a curved hemostat at 5-min intervals. (We did not pinch the skin of the sheep. Rather, we used the hemostat in a gentle manner, similar to the way one would use a needle to assess the sensory level.) Additional epidural lidocaine was injected as needed in order to achieve a sensory level of T4–T6.
6. At 135 min, an intravenous bolus of either phenylephrine 0.05 mg, ephedrine 2.5 mg, or NS-control

Table 1. Baseline Maternal and Fetal Hemodynamic, Blood Gas, and Acid–Base Measurements

	Ephedrine (n = 14)	Phenylephrine (n = 14)	Saline (Control) (n = 14)
Maternal			
Heart rate (beats/min)	120 ± 4	117 ± 3	118 ± 2
Mean arterial pressure (mmHg)	101 ± 2	102 ± 3	105 ± 1
Cardiac output (L/min)	9.7 ± 0.4	10.3 ± 0.4	10.1 ± 0.4
Systemic vascular resistance (dyne · s^{-1} · cm^{-5})	770 ± 33	738 ± 33	782 ± 28
Left uterine blood flow (ml/min)	610 ± 79	625 ± 97	618 ± 87
Uterine vascular resistance (dyne · s^{-1} · cm^{-5})	16,800 ± 3,900	17,400 ± 4,000	18,400 ± 5,000
*p*H	7.47 ± 0.01	7.47 ± 0.01	7.47 ± 0.01
Pa_{O_2} (mmHg)	103 ± 4	103 ± 4	103 ± 3
Pa_{CO_2} (mmHg)	36 ± 1	37 ± 1	37 ± 1
Hematocrit (%)	31 ± 1	30 ± 1	30 ± 1
Fetal			
Heart rate (beats/min)	172 ± 4	170 ± 2	174 ± 4
Mean arterial pressure (mmHg)	45 ± 1	44 ± 1	46 ± 1
*p*H	7.32 ± 0.01	7.33 ± 0.01	7.32 ± 0.01
Pa_{O_2} (mmHg)	21 ± 1	19 ± 1	21 ± 1
Pa_{CO_2} (mmHg)	52 ± 1	52 ± 1	51 ± 1
Hematocrit (%)	42 ± 1	40 ± 1	39 ± 1

Values are mean ± SEM.

solution 2.5 ml was given over 5 s, and a continuous intravenous infusion of phenylephrine, ephedrine, or NS was begun at 0.05 mg/min, 2.5 mg/min, or 2.5 ml/min respectively. The ephedrine or phenylephrine infusion rate was adjusted to maintain maternal MAP at the baseline level. We did not make any adjustments in the rate of infusion of NS.

7. At 165 min, the vasopressor or NS infusion was discontinued.
8. At 180 min, the ritodrine infusion was discontinued.
9. At the end of the last experimental day, the ewe and her fetus were painlessly killed with an intravenous injection of sodium pentobarbital (Beuthanasia-D Special®, Steris Laboratories, Phoenix, AZ).

Hemodynamic measurements were obtained over time throughout each experiment. Baseline measurements were obtained over 20 min as an average of 120 observations. Other recorded measurements represent the mean of 12–18 observations made at 10-s intervals over a 2–3-min observation period. Maternal and fetal blood gas and acid–base measurements were obtained at baseline and at 115, 134, 150, 162, and 177 min.

Baseline hemodynamic, blood gas and acid–base measurements are reported as mean (± SEM). Hemodynamic changes are presented as mean (± SEM) percentage of baseline. Statistical analysis was performed by repeated measures analysis of variance for overall differences between the experiment groups. *Post hoc* testing was performed using the Bonferroni correction where appropriate. $P < 0.05$ was considered significant.

Results

The mean (± SEM) weight of the animals was 61 ± 2 kg. Baseline maternal and fetal hemodynamic, blood gas and acid–base measurements were similar for the three groups (table 1). Measurements remained similar among the three groups until 135 min, when the vasopressor or NS infusion was begun. The median sensory levels achieved, the mean volumes of lidocaine administered, and the mean total doses of vasopressor given to each group are listed in table 2.

Ritodrine infusion significantly increased both maternal HR and CO to approximately 136% and 132% of baseline, respectively, for each of the three groups ($P < 0.0001$) (data not shown). Ritodrine infusion significantly decreased maternal systemic vascular resistance for each of the three groups ($P < 0.0001$) (fig. 1). Ritodrine infusion also slightly decreased maternal MAP ($P < 0.01$) and UBF ($P < 0.05$), but did not significantly affect fetal arterial oxygen tension (Pa_{O_2}) or

Table 2. Median Sensory Level and Total Lidocaine and Vasopressor Doses Given

	Median Sensory Level		Total Dose of 2% Lidocaine* (ml)	Total Dose of Vasopressor* (mg)
	135 min	151 min		
Ephedrine	T5	T5	22 ± 2	33 ± 3
Phenylephrine	T4	T4	19 ± 2	2.0 ± 0.2
Saline (control)	T4	T5	20 ± 2	—

* Values are mean ± SEM.

maternal uterine vascular resistance (figs. 1 and 2 and table 3) for each of the three groups.

Epidural anesthesia during ritodrine infusion significantly decreased maternal MAP ($P < 0.0001$), UBF ($P < 0.01$), and fetal Pa_{O_2} ($P < 0.0001$) for each of the three groups (figs. 1 and 2 and table 3). Following administration of epidural anesthesia, maternal HR and CO declined to approximately 112% ($P < 0.001$) and 105% ($P < 0.0001$) of baseline, respectively, in each of the three groups (data not shown). Epidural anesthesia during ritodrine infusion did not significantly affect maternal systemic vascular resistance or uterine vascular resistance.

After 135 min, when the infusion of vasopressor or saline was begun, there were several differences between the three groups. The presentation of the results will focus on those differences between 135 and 180 min.

Ephedrine and phenylephrine both returned maternal MAP to baseline (fig. 1), as would be expected from the experimental design. Neither ephedrine nor phenylephrine significantly altered maternal HR when compared with NS-control. There was no significant difference between the ephedrine and phenylephrine groups in maternal HR (data not shown).

Neither ephedrine nor phenylephrine significantly increased maternal CO when compared with NS-control (data not shown). Both ephedrine and phenylephrine significantly increased maternal systemic vascular resistance when compared with NS-control (fig. 1) ($P < 0.001$). However, there was no significant difference between the ephedrine and phenylephrine groups in maternal systemic vascular resistance.

Ephedrine significantly increased UBF when compared with NS-control ($P < 0.001$), but phenylephrine did not (fig. 2). The difference in UBF between the ephedrine and phenylephrine groups was also statistically significant ($P < 0.001$). Phenylephrine increased uterine vascular resistance when compared with NS-control ($P < 0.001$), but ephedrine did not (fig. 2).

Neither ephedrine nor phenylephrine significantly altered fetal *p*H or arterial carbon dioxide tension (Pa_{CO_2}), when compared to NS-control (table 3). Ephedrine, but not phenylephrine, significantly increased fetal Pa_{O_2} when compared to NS-control (table 3) ($P < 0.001$). However, there was no significant difference between the ephedrine and phenylephrine groups in fetal Pa_{O_2}.

Fetal HR and MAP responses did not differ significantly either within or between groups (data not shown).

Discussion

In the current study, the effects of two vasopressors, ephedrine and phenylephrine, were evaluated in the treatment of epidural anesthesia–induced hypotension in gravid ewes subjected to ritodrine infusion. Ritodrine was given at a constant dosage of 0.002 mg · kg · min, which increased maternal HR and CO approximately 36% and 32%, respectively. This dose of ritodrine is similar to the dose given to pregnant women for tocolysis. The cardiovascular response was also similar to that which is observed clinically. Most obstetricians avoid giving a dose of ritodrine that causes the maternal HR to increase by more than 20–30%. As expected, the onset of a high thoracic level of epidural anesthesia was associated with a decrease in maternal MAP, HR, CO, UBF, and fetal Pa_{O_2} in all three groups. Despite the restoration of maternal MAP to baseline with each of the two vasopressor infusions, ephedrine was superior to phenylephrine in restoring UBF. In contrast, only phenylephrine significantly increased uterine vascular resistance. Also, ephedrine, but not phenylephrine was superior to NS-control in restoring fetal Pa_{O_2}.

The results of the current study augment earlier animal studies in which ephedrine, used to treat ma-

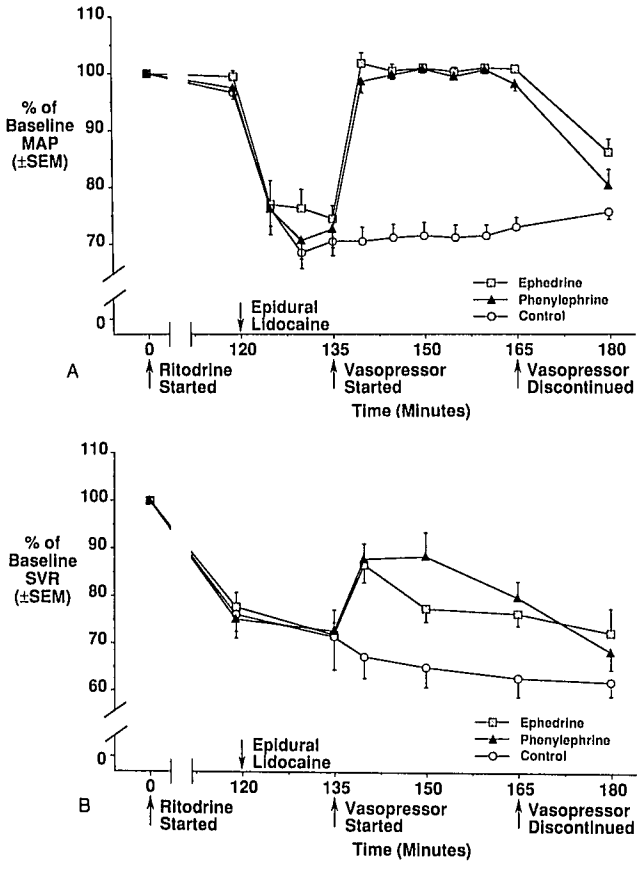

Fig. 1. (*A*) Maternal mean arterial pressure (MAP) over time for the ephedrine, phenylephrine, and NS-control groups. (*B*) Maternal systemic vascular resistance (SVR) over time for the ephedrine, phenylephrine, and NS-control groups. Each response is expressed as mean (± SEM) percentage of baseline. Standard error bars, if not shown, are included within the height of the symbols for each data point. Both ephedrine and phenylephrine significantly increased maternal MAP when compared with NS-control. Both ephedrine and phenylephrine significantly increased maternal systemic vascular resistance when compared to NS-control.

ternal hypotension, improved maternal UBF and fetal blood gas and acid–base measurements. James *et al.*[10] showed that ephedrine restored UBF during spinal anesthesia–induced hypotension in gravid ewes. Shnider *et al.*[18] observed that ephedrine improved fetal acidosis during spinal anesthesia in gravid ewes. Hollmen *et al.*[12] reported that ephedrine preserved intervillous blood flow during epidural anesthesia in pregnant women. James *et al.*,[10] Shnider *et al.*,[18] and others[15] also observed that, in contrast, α-adrenergic agonists had a deleterious effect on UBF in gravid ewes.

Conventional wisdom has held that ephedrine's β receptor activity increases CO, thus compensating for its α receptor–mediated uterine vasoconstriction. Thus, some anesthesiologists have contended that ephedrine might not protect UBF in patients recently subjected to β sympathomimetic infusion.# The current study augments our earlier observations regarding the efficacy of ephedrine in restoring or protecting UBF velocity in

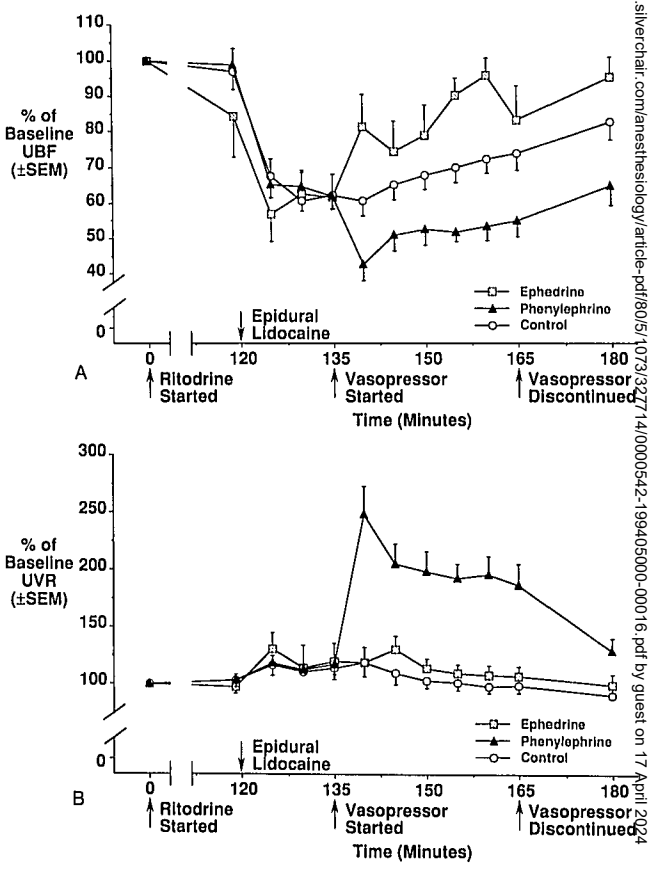

Fig. 2. (*A*) Uterine blood flow (UBF) over time for the ephedrine, phenylephrine, and NS-control groups. (*B*) Uterine vascular resistance (UVR) over time for the ephedrine, phenylephrine, and NS-control groups. Each response is expressed as mean (± SEM) percentage of baseline. Standard error bars, if not shown, are included within the height of the symbols for each data point. Ephedrine significantly increased UBF when compared with NS-control, but phenylephrine did not. In addition, ephedrine significantly increased UBF when compared with phenylephrine. Phenylephrine increased UVR when compared with NS-control, but ephedrine did not.

Weeks S: Hazards of beta mimetic tocolysis, McGill University Review Course in Anesthesia (syllabus). Montreal, McGill University, 1985, pp 1–13.

Table 3. Fetal Blood Gas and Acid–Base Measurements

	Ritodrine Started (0 min)	Epidural Lidocaine Injected (120 min)	Vasopressor Started (135 min)	Vasopressor Discontinued		
				150 min	165 min	180 min
Fetal *p*H						
Control	7.32 ± .01	7.34 ± .01	7.32 ± .01	7.31 ± .01	7.31 ± .01	7.31 ± .01
Ephedrine	7.32 ± .01	7.34 ± .01	7.32 ± .01	7.32 ± .01	7.32 ± .01	7.33 ± .01
Phenylephrine	7.33 ± .01	7.35 ± .02	7.32 ± .01	7.30 ± .01	7.31 ± .01	7.31 ± .01
Fetal Pa_{O_2} (mmHg)						
Control	21.0 ± .6	21.6 ± .5	16.6 ± .9	16.6 ± .9	16.6 ± .9	17.8 ± .9
Ephedrine	20.6 ± .6	20.3 ± .7	16.5 ± .9	21.0 ± .9	21.2 ± .8	19.1 ± .9
Phenylephrine	19.2 ± 1.0	20.2 ± .6	15.1 ± 1.0	18.1 ± .9	17.8 ± .8	17.3 ± .9
Fetal Pa_{CO_2} (mmHg)						
Control	51.3 ± 1.0	49.0 ± 1.2	50.9 ± 1.3	53.4 ± 1.7	52.9 ± 1.6	51.7 ± 1.7
Ephedrine	51.6 ± 1.1	49.3 ± 1.1	51.3 ± 1.3	50.2 ± 1.3	49.9 ± 1.1	50.0 ± 1.0
Phenylephrine	51.8 ± 1.1	48.9 ± 1.7	51.9 ± 1.2	52.2 ± 1.3	53.9 ± 1.8	53.8 ± 1.9

Values are mean ± SEM (n = 14). Neither ephedrine nor phenylephrine significantly altered fetal *p*H and Pa_{CO_2} over time compared with NS control. Ephedrine, but not phenylephrine, significantly increased fetal Pa_{O_2} over time compared with NS control ($P < 0.001$).

gravid guinea pigs subjected to terbutaline or ritodrine infusion.[16,17] Ramanathan *et al.*** observed that ephedrine increases cardiac preload in pregnant women to a greater degree than it increases afterload. This suggests that ephedrine does not depend solely on β-adrenergic stimulation to increase CO.

Tong and Eisenach[19] recently evaluated the effects of ephedrine and metaraminol in the uterine and femoral vessels of gravid and nongravid ewes *in vitro*. They noted that ephedrine had a more selective constrictive effect at the femoral *versus* the uterine vessels compared to metaraminol, and that this selectivity was even more pronounced during pregnancy. Constriction to both agents was abolished by phentolamine. They suggested that "both ephedrine and metaraminol constrict uterine and systemic vessels by actions on α adrenoceptors, and that ephedrine may spare uterine perfusion during pregnancy due to more selective constriction of systemic vessels than that caused by metaraminol." Tong and Eisenach's study also suggests that ephedrine's protective effects on UBF does not depend solely on β-adrenergic stimulation.

Recently, several studies of healthy, term parturients undergoing elective cesarean section with regional anesthesia have suggested that small doses of phenylephrine appear to be as safe and efficacious as ephedrine in the treatment of hypotension.[20–22] Ramanathan and Grant[20] demonstrated no significant differences in maternal blood pressure, stroke volume, end-diastolic volume, neonatal Apgar scores, or neonatal blood gas and acid–base measurements in parturients whose epidural anesthesia–induced hypotension during cesarean section was corrected by bolus doses of either ephedrine or phenylephrine. Moran *et al.*[21] compared the use of phenylephrine and ephedrine in the prevention of maternal hypotension in parturient women undergoing repeat cesarean section during spinal anesthesia. Although the authors noted significant differences between the groups in mean umbilical artery *p*H, arterial carbon dioxide tension, and base deficit, all of the mean values were within normal limits and the differences were thought to be of minimal clinical significance. They reported no significant differences between groups in the remaining maternal and neonatal acid–base measurements, Apgar scores or Early Neonatal Neurobehavior Scale scores. Alahuhta *et al.*[22] gave a bolus of either ephedrine or phenylephrine after administration of spinal anesthesia, followed by an infusion of the same vasopressor until cesarean delivery of the infant. They gave an additional bolus of vasopressor and increased the infusion rate if a decrease in maternal systolic blood pressure of more than 10 mmHg occurred. Using Doppler velocimetry recordings, they noted no significant differences in uterine or placental arcuate artery blood flow velocity waveform indices after administration of ephedrine. In contrast, phen-

** Ramanathan S, Grant G, Turndorf H: Cardiac preload changes with ephedrine therapy for hypotension in obstetric patients (abstract). Anesth Analg 65:S125, 1986.

ylephrine significantly increased the uterine and placental arcuate artery blood flow velocity waveform indices, and significantly decreased the fetal renal artery vascular resistance. However, there were no significant differences between the groups in Apgar scores or umbilical cord blood gas and acid–base measurements, all of which were within normal range. All of these studies included healthy women with term fetuses, who probably have a large margin of safety. None of these studies evaluated the effects of ephedrine or phenylephrine in laboring women with a compromised fetus, or in women with a preterm fetus.

Some anesthesiologists avoid the use of ephedrine for women in whom tachycardia persists after administration of a β-adrenergic tocolytic drug. In the current study, maternal HR had decreased during the 15 min between epidural administration of lidocaine and the administration of ephedrine or phenylephrine. Ephedrine did not increase maternal HR. Two groups of investigators have reported that ephedrine decreased maternal HR when used to treat epidural or spinal anesthesia–induced hypotension during cesarean section in healthy, term parturients.[20,22] Ramanathan and Grant[20] opined that the decrease in HR seen after vasopressor treatment with either ephedrine or phenylephrine was probably due to the baroceptor reflex initiated by improved perfusion pressure. The current study is consistent with our clinical observation that ephedrine does not worsen maternal tachycardia when used to treat hypotension in women who recently received a β-adrenergic drug.

There are several limitations in the clinical application of the current study. First, there are known α- and β-adrenergic receptor distribution differences among species. These differences may alter vascular responses to α- and β-adrenergic agonists. Second, in clinical practice these vasopressors are typically given as intermittent boluses, whereas in the current study they were given as a bolus, followed by constant infusion for 30 min to restore maternal MAP to baseline. Third, in clinical practice, anesthesiologists give a bolus of crystalloid in addition to giving a vasopressor to treat maternal hypotension. In the current study, we relied on vasopressor alone. Had we given a bolus of crystalloid, the sheep may have required smaller doses of vasopressor to restore maternal MAP. However, the doses of ephedrine and phenylephrine did not appear excessive when examined in terms of milligrams per kilogram per minute, and we speculate that bolus administration of drug might have exaggerated the difference between drugs in uterine vascular response.

We conclude that although ephedrine and phenylephrine provided similar restoration of maternal MAP, ephedrine was superior to phenylephrine in protecting UBF during ritodrine infusion and epidural anesthesia–induced hypotension in gravid ewes. Also, ephedrine, but not phenylephrine, significantly improved fetal oxygenation, when compared to NS-control. If applicable to humans, the current study suggests that ephedrine is the vasopressor of choice for the treatment of maternal hypotension in women recently subjected to β-adrenergic tocolytic therapy.

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