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Which Vasopressor Should Be Used To Treat Hypotension during Magnesium Sulfate Infusion and Epidural Anesthesia?

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Ephedrine restores and/or protects uterine blood flow and fetal well-being in laboratory animals. In contrast, α_1-adrenergic agonists worsen uterine blood flow and fetal condition. We previously demonstrated that magnesium sulfate ($MgSO_4$) attenuates the detrimental effects of phenylephrine on uterine vascular resistance in gravid ewes. Therefore, we performed this study to determine whether ephedrine or phenylephrine better restores and protects uterine blood flow and fetal oxygenation during epidural anesthesia–induced hypotension in hypermagnesemic gravid ewes. Twelve chronically instrumented gravid ewes were each used for three experiments: 1) ephedrine, 2) phenylephrine, and 3) normal saline (NS)-control. For each experiment the protocol was as follows: 1) at time zero, intravenous infusion of $MgSO_4$ was begun; 2) at 150 min a thoracic level of epidural anesthesia was achieved with 2% lidocaine; and 3) at 165 min, an intravenous infusion of ephedrine, phenylephrine, or NS was begun and continued through 195 min. Epidural anesthesia uniformly decreased maternal mean arterial blood pressure (MAP), heart rate, cardiac output, uterine blood flow, and fetal P_{O_2} in each of the three groups. Both ephedrine and phenylephrine restored maternal MAP to baseline, as expected from the experimental design. Ephedrine significantly increased cardiac output and uterine blood flow when compared with NS-control, but phenylephrine did not. Phenylephrine significantly increased uterine vascular resistance when compared with NS-control, but ephedrine did not. As a result, fetal *p*H and P_{O_2} were significantly greater during ephedrine infusion than during infusion of NS-control. Fetal *p*H was stable during ephedrine infusion, but it continued to decrease during phenylephrine infusion. Ephedrine, but not phenylephrine, significantly increased fetal P_{O_2} during treatment of hypotension. We conclude that, although ephedrine and phenylephrine provided similar restoration of maternal MAP, ephedrine was superior to phenylephrine in restoring uterine blood flow during epidural anesthesia–induced hypotension in hypermagnesemic gravid ewes. Furthermore, only ephedrine was clearly superior to NS-control in maintaining fetal *p*H and restoring fetal P_{O_2} during treatment of hypotension. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Anesthetics, local: lidocaine. Ions: magnesium. Pharmacology, tocolytic agents: magnesium sulfate. Pregnancy: hypertension; preterm labor. Sympathetic nervous system, α-adrenergic agonists: phenylephrine. Sympathomimetic agents: ephedrine.)

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EPIDURAL ANESTHESIA–INDUCED hypotension in the parturient results in decreased placental perfusion, which, if sustained, may cause fetal hypoxia and lactic acidosis.[1–4] Intravenous hydration, left uterine displacement, and vasopressor administration are recommended to avoid or treat the maternal hypotension associated with sympathetic blockade. Ephedrine, a mixed α- and β-adrenergic agonist, has been the vasopressor of choice because of its protective effect on uterine blood flow (UBF) in laboratory animals and its record of efficacy and safety in clinical practice.[5–10]

In contrast, α_1-adrenergic agonists such as phenylephrine and methoxamine worsen UBF and fetal condition in pregnant animals.[8,11,12] However, Ramanathan and Grant[13] reported no significant differences in maternal hemodynamic measurements or neonatal blood gas and acid–base measurements in parturients whose epidural anesthesia–induced hypotension was corrected by either intravenous ephedrine or phenylephrine. As a result, some have suggested that it may be safe to give small doses of phenylephrine just sufficient to restore maternal blood pressure to baseline.

In an earlier study, we demonstrated that magnesium sulfate ($MgSO_4$) infusion attenuated the detrimental effects of phenylephrine on uterine vascular resistance (UVR) in gravid ewes.[14] We hypothesized that $MgSO_4$ infusion might blunt the usual increase in UVR during phenylephrine infusion for the treatment of epidural anesthesia–induced hypotension and make phenylephrine's effects on UBF more similar to the effects of ephedrine. The purpose of the present study was to determine whether ephedrine or phenylephrine infusion better restores and protects UBF and fetal oxygenation during epidural anesthesia–induced hypotension in hypermagnesemic gravid ewes.

Materials and Methods

MATERNAL/FETAL INSTRUMENTATION AND POSTSURGICAL CARE

The protocol was approved by the University of Iowa Animal Care Committee. Mixed-breed ewes were ob-

tained 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. All catheters were tunneled subcutaneously and exteriorized through a small incision in the left flank. Finally, an 8.5-Fr introducer (AK09800, Arrow, Reading, PA) was placed percutaneously into the right jugular vein.

A single-orifice, 19-G epidural catheter (Portex, Wilmington, MA) was inserted percutaneously into the epidural space at the lumbosacral junction, and the catheter was secured to the back. Eight milliliters 2% lidocaine was injected through the 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 or procaine penicillin G 300,000 U and dihydrostreptomycin 375 mg (Distrycillin® A.S., Solray Veterinary, Princeton, NJ) were given to the mother intramuscularly before surgery and daily for 3 days after surgery. Gentamicin 80 mg was given to the mother intravenously during surgery and on the day of each experiment, and gentamicin 40 mg was given *via* the amniotic catheter during 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. Mean arterial blood pressure (MAP) was computed arithmetically. The maternal and fetal heart rates (HR) were computed from the arterial waveforms. UBF was measured continuously with a quantitative electromagnetic flowmeter (RF-2500, Dienco). Arterial and venous pressures, HR, and UBF were recorded at 10-s intervals using a computer-based system and customized data acquisition software (Alternatives Unlimited, Des Moines, IA).

Cardiac output measurements were made in triplicate with 10 ml iced saline and a thermodilution cardiac output computer (9520A, Edwards Laboratories). Maternal and fetal arterial blood gas and *p*H values were determined using an Instrumentation Laboratory (1302, Leighton, MA) blood gas analyzer. All values were corrected for temperature (39.5° C). Serum magnesium concentrations were measured using a spectrophotometric technique (Lancer Magnesium Rapid State Diagnostic Kit, Sherwood Medical, St. Louis, MO).

Experimental Protocol

Two vasopressors were chosen for these experiments: phenylephrine (primarily 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 were allowed for the sheep to acclimate to the laboratory environment. Normal saline (NS) 250 ml was infused intravenously during the first 20 min of this time period.
2. Twenty minutes were allowed for baseline measurements. The total volume of crystalloid given was 50 ml.
3. At time zero, each animal received $MgSO_4$ 4 g intravenously over 5 min. The total volume of crystalloid given was 50 ml.
4. At 5 minutes, an intravenous infusion of $MgSO_4$ was begun. Each animal received $MgSO_4$ 4 g/h intravenously for the duration of the experiment. The total rate of crystalloid infusion was 100 ml/h.

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

	Ephedrine (n = 12)	Phenylephrine (n = 12)	Saline (Control) (n = 12)
Maternal			
Heart rate (beats/min)	124 ± 4	120 ± 4	124 ± 4
Mean arterial pressure (mmHg)	95 ± 3	93 ± 3	95 ± 3
Cardiac output (l/min)	11.3 ± 0.5	11.2 ± 0.5	12.1 ± 0.8
Systemic vascular resistance (dyne · s^{-1} · cm^{-5})	650 ± 40	639 ± 38	599 ± 42
Uterine blood flow (ml/min)	737 ± 154	873 ± 141	865 ± 139
Uterine vascular resistance (dyne · s^{-1} · cm^{-5})	13,856 ± 3,115	9,732 ± 1,700	9,828 ± 1,762
*p*H	7.46 ± 0.01	7.46 ± 0.01	7.47 ± 0.01
P_{O_2} (mmHg)	109 ± 3	112 ± 3	111 ± 3
P_{CO_2} (mmHg)	38 ± 1	38 ± 1	36 ± 1
Fetal			
Heart rate (beats/min)	177 ± 5	170 ± 4	173 ± 3
Mean arterial pressure (mmHg)	45 ± 2	45 ± 2	46 ± 2
*p*H	7.32 ± 0.02	7.32 ± 0.02	7.32 ± 0.01
P_{O_2} (mmHg)	18 ± 1	18 ± 1	19 ± 1
P_{CO_2} (mmHg)	51 ± 1	53 ± 1	52 ± 1

Values are reported as mean ± SEM.

5. At 150 min, each animal received 10–16 ml 2% lidocaine, injected through the epidural catheter in two equal divided doses 1 min apart. The dose was determined according to the response to the lidocaine given on the day of surgery.
6. Beginning at 155 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 manner similar to the way one would use a needle to assess the sensory level.[15,16]) Additional epidural lidocaine was injected as needed to achieve both a sensory level of T4–T6 and 25%–30% decrease in maternal MAP.
7. At 165 min, an intravenous bolus of either phenylephrine 0.05 mg, ephedrine 2.5 mg, or NS-control solution 2.5 ml was given over 5 s, and a continuous intravenous infusion of ephedrine, phenylephrine 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.
8. At 195 min, the vasopressor or NS infusion was discontinued.
9. At 212 min, the $MgSO_4$ infusion was discontinued.

We used 12 animals for 36 experiments, which were divided into three groups: 1) ephedrine (n = 12); 2) phenylephrine (n = 12); and 3) NS-control (n = 12). Each animal underwent all three experiments in random order. Only one experiment was performed per day, and each animal rested at least overnight before undergoing the next experiment.

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 145, 164, 180, 192, and 207 min. Maternal serum magnesium concentrations were obtained at baseline and at 145 and 207 min.

Baseline hemodynamic, blood gas and acid–base measurements are reported as mean ± SEM. Hemodynamic changes are presented as mean (± SEM) percent 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 64 ± 2 kg. Baseline maternal and fetal hemodynamic, blood gas, and acid–base measurements were similar for the three groups: ephedrine, phenylephrine, and NS-control (table 1). Measurements remained similar among the three groups until 165 min, when the vasopressor or NS infusion was begun. Mean (± SEM) serum magnesium concentrations before $MgSO_4$ infusion and at 145 and 207 min are

TABLE 2. Serum Magnesium Concentrations (mg/dl)

	Baseline	145 min	207 min
Ephedrine	2.4 ± 0.1	6.1 ± 0.2	6.1 ± 0.2
Phenylephrine	2.3 ± 0.1	6.0 ± 0.2	6.3 ± 0.2
Saline (control)	2.3 ± 0.1	5.9 ± 0.2	5.8 ± 0.6

Values are reported as mean ± SEM.

TABLE 3. Median Sensory Level and Total Lidocaine and Vasopressor Doses Given

	Median Sensory Level		Total Dose of 2% Lidocaine (ml)	Total Dose of Vasopressor (mg)
	165 min	180 min		
Ephedrine	T5	T6	21 ± 2	47 ± 7
Phenylephrine	T5	T4	23 ± 3	2.2 ± 0.3
Saline (control)	T5	T4	21 ± 3	—

Lidocaine and vasopressor doses are expressed as mean ± SEM.

listed in table 2. (These concentrations were within the therapeutic range for tocolysis and seizure prophylaxis in pregnant women.[17,18]) 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 3.

Epidural anesthesia uniformly decreased maternal MAP, HR, cardiac output, UBF, and fetal P_{O_2} for each of the three groups (figs. 1–4). Epidural anesthesia significantly decreased systemic vascular resistance (SVR) in the phenylephrine and NS-control groups but not in the ephedrine group at 165 min. The differences between the three groups at 165 min were not significant. UVR did not change during epidural anesthesia alone in any group.

After 165 min, when the infusion of vasopressor or NS was begun, there were differences between the three

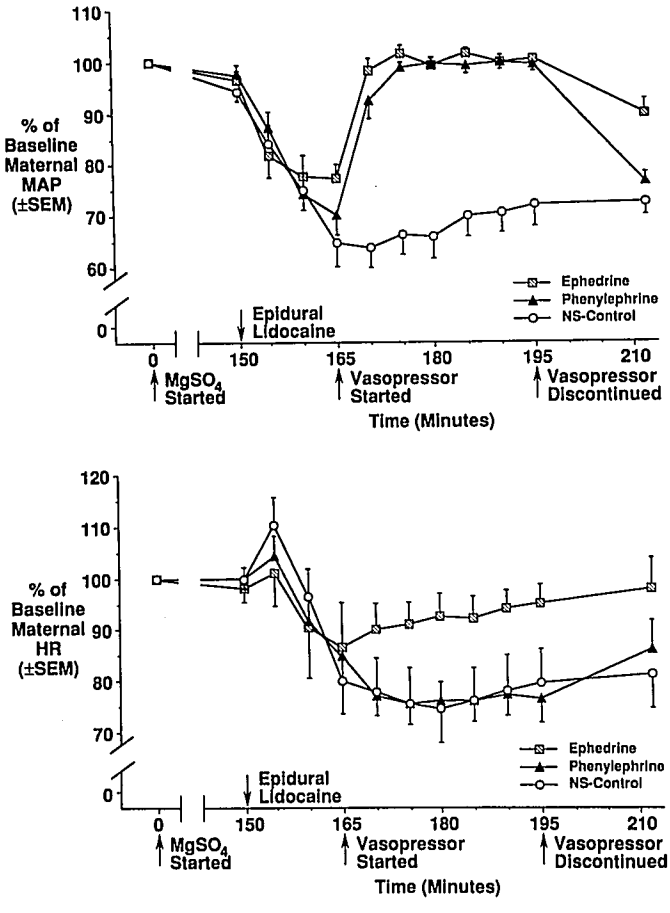

FIG. 1. *Top:* Maternal mean arterial pressure (MAP) over time for the ephedrine, phenylephrine, and normal saline (NS)–control groups. *Bottom:* Maternal heart rate (HR) over time for the ephedrine, phenylephrine, and NS-control groups. Each response is expressed as mean (±SEM) percent of the baseline. Standard error bars, if not shown, are included within the height of the symbols for each data point. Neither ephedrine nor phenylephrine significantly increased maternal HR when compared with NS-control.

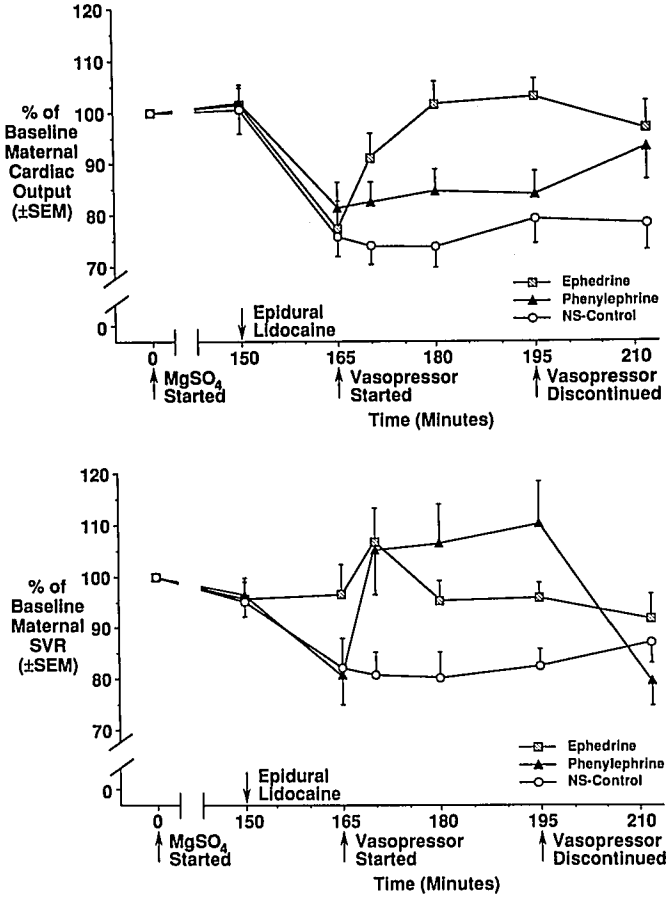

FIG. 2. *Top:* Maternal cardiac output over time for the ephedrine, phenylephrine, and normal saline (NS)–control groups. *Bottom:* Maternal systemic vascular resistance (SVR) over time for the ephedrine, phenylephrine, and NS-control groups. Each response is expressed as mean (±SEM) percent of the baseline. Standard error bars, if not shown, are included within the height of the symbols for each data point. Ephedrine significantly increased maternal cardiac output when compared with NS-control, but phenylephrine did not. Phenylephrine significantly increased SVR when compared with NS-control, but ephedrine did not. Phenylephrine significantly increased SVR when compared with ephedrine.

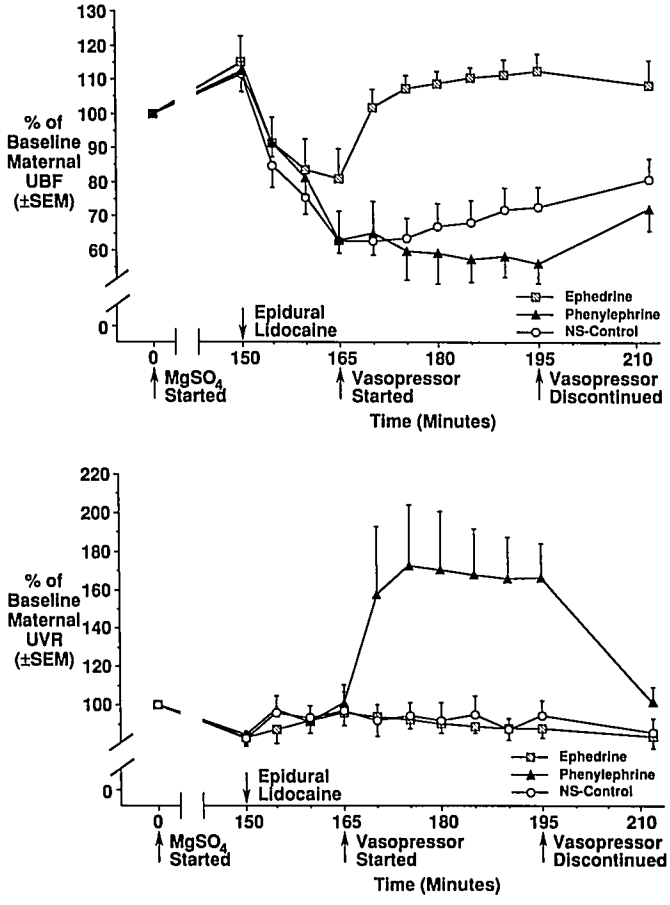

FIG. 3. *Top:* Maternal uterine blood flow (UBF) over time for the ephedrine, phenylephrine, and normal saline (NS)–control groups. *Bottom:* Maternal uterine vascular resistance over time for the ephedrine, phenylephrine, and NS-control groups. Each response is expressed as mean (±SEM) percent of the 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.

groups. The presentation of the results will focus on the differences between 165 and 210 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 increased maternal HR (fig. 1) when compared with NS-control.

Ephedrine significantly increased maternal cardiac output when compared with NS-control ($P < 0.05$), but phenylephrine did not (fig. 2). Phenylephrine significantly increased SVR when compared with NS-control ($P < 0.05$), but ephedrine did not (fig. 2). Phenylephrine

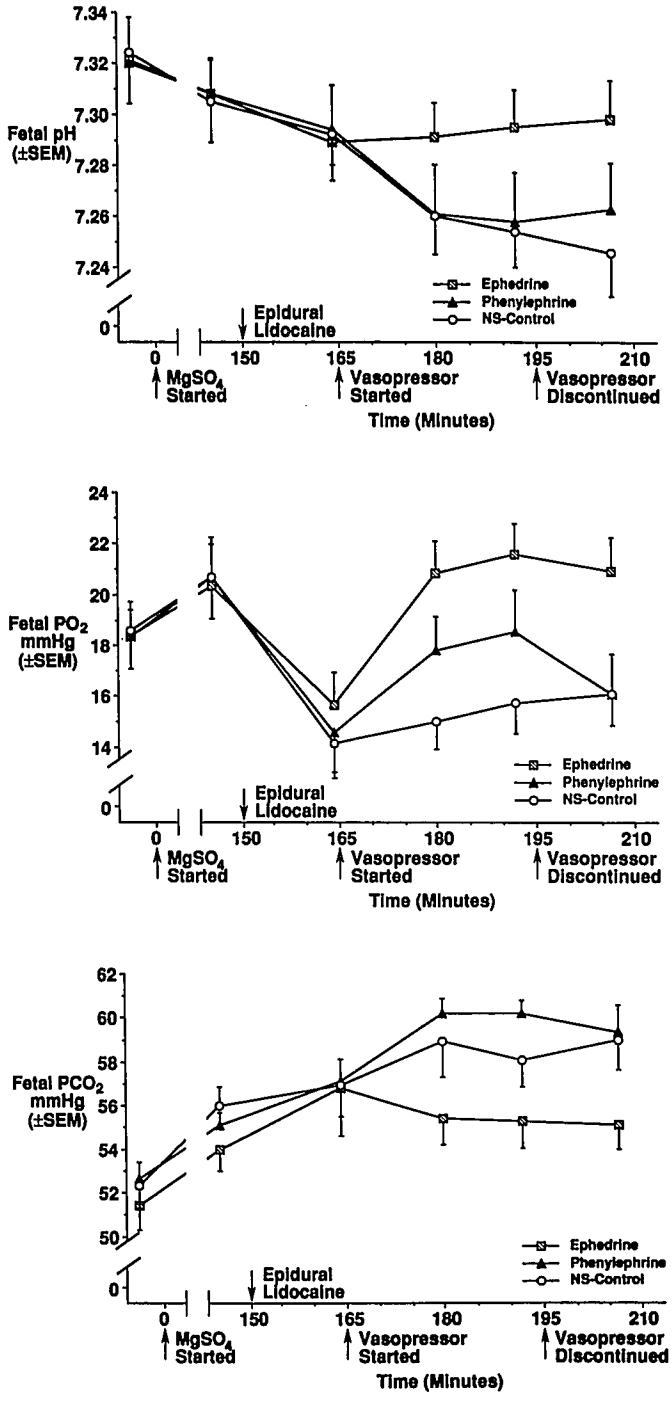

FIG. 4. *Top:* Fetal *p*H over time for the ephedrine, phenylephrine, and normal saline (NS)–control groups. *Middle:* Fetal P_{O_2} over time for the ephedrine, phenylephrine, and NS-control groups. *Bottom:* Fetal P_{CO_2} over time for the ephedrine, phenylephrine, and NS-control groups. Each response is expressed as mean (±SEM). Standard error bars, if not shown, are included within the height of the symbols for each data point. Fetal *p*H and P_{O_2} were significantly greater during ephedrine infusion than during infusion of NS-control. Fetal P_{CO_2} was significantly lower during infusion of ephedrine than during infusion of phenylephrine.

also significantly increased SVR when compared with ephedrine ($P < 0.05$).

Ephedrine significantly increased UBF when compared with NS-control ($P < 0.05$), but phenylephrine did not (fig. 3). The difference in UBF between the ephedrine and phenylephrine groups was also statistically significant ($P < 0.05$). Phenylephrine increased UVR when compared with NS-control ($P < 0.05$), but ephedrine did not (fig. 3).

Fetal *p*H and P_{O_2} were significantly greater during ephedrine infusion than during infusion of NS-control (fig. 4). Fetal *p*H was stable during ephedrine infusion, but it continued to decrease during phenylephrine infusion. Ephedrine, but not phenylephrine, significantly increased fetal P_{O_2} during treatment of hypotension. However, there was no significant difference between the ephedrine and phenylephrine groups in fetal *p*H and P_{O_2}. Fetal P_{CO_2} was significantly lower during infusion of ephedrine than during infusion of phenylephrine (fig. 4).

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

Discussion

The primary focus of the present study was to evaluate the effects of two vasopressors: ephedrine and phenylephrine, in the treatment of epidural anesthesia–induced hypotension in hypermagnesemic gravid ewes. As expected, the onset of a high thoracic level of epidural anesthesia produced a marked decrease in maternal MAP, HR, cardiac output, UBF, and fetal P_{O_2} in all groups, whereas UVR was unchanged. Ephedrine and phenylephrine were then administered at rates just sufficient to restore maternal MAP to baseline. Despite similar restoration of maternal MAP, there were differences between the ephedrine and phenylephrine groups in UBF and UVR responses during vasopressor infusion. Furthermore, only ephedrine significantly increased fetal P_{O_2} and maintained fetal *p*H.

The pressor effects of ephedrine and phenylephrine result from two different mechanisms. Ephedrine stimulates both α- and β-adrenergic receptors.[19] Its pressor effects are due primarily to cardiac stimulation, with a smaller contribution from arterial vasoconstriction.[19] In addition, β-adrenergic agonists such as ephedrine may increase cardiac output by decreasing venous capacitance and increasing venous return to the heart.[20,21] Earlier animal studies using intravenous ephedrine to treat hypotension during pregnancy demonstrated that it both restored maternal MAP and improved maternal UBF and fetal blood gas and acid–base measurements. James *et al.*[5] observed that ephedrine restored UBF during spinal anesthesia-induced hypotension in gravid ewes. Further, Eng *et al.*[6] demonstrated that ephedrine resulted in either stabilization or improvement of fetal P_{O_2} toward control values during spinal anesthesia–induced hypotension in pregnant monkeys. Shnider *et al.*[7] noted that ephedrine caused improvement of fetal acidosis during spinal anesthesia in gravid ewes. In contrast, these and other animal studies noted that α-adrenergic agonists had a deleterious effect on UBF.[12,22,23] Thus, ephedrine has been the vasopressor of choice in obstetric anesthesia practice.

Phenylephrine is primarily an α_1-adrenergic receptor agonist with minimal β-adrenergic receptor effects.[19] Its pressor effects are due to vasoconstriction and increased peripheral vascular resistance. The pressor response to phenylephrine is accompanied by a reflex bradycardia, which results in decreased cardiac output. Magness and Rosenfeld[22] showed that phenylephrine caused a dose-dependent increase in maternal MAP, SVR, and UVR with concomitant decreases in maternal HR, cardiac output, and UBF in gravid ewes. The increase in UVR exceeded that of SVR.[22] The pressor response to phenylephrine was attenuated during pregnancy.[22] The same authors[23] later demonstrated that the SVR response to phenylephrine was not changed during pregnancy, but the decrease in maternal HR and cardiac output was greater in pregnant animals than in nonpregnant animals.[23] Greiss and Crandell[12] showed that phenylephrine restored maternal MAP during spinal anesthesia without causing any significant improvement in UBF in gravid ewes. In some cases, phenylephrine administration had to be discontinued because of the risk of fetal demise secondary to worsened UBF.[12] Thus, animal studies have consistently demonstrated decreased UBF following phenylephrine administration during pregnancy.

Earlier studies[14,16,24] from this laboratory demonstrated that $MgSO_4$ infusion can change both maternal and fetal responses to hypotension and vasopressor administration. Chestnut *et al.*[24] observed that $MgSO_4$ worsened maternal hypotension during hemorrhage in gravid ewes. Vincent *et al.*[16] reported that $MgSO_4$ decreased maternal MAP but not UBF or fetal P_{O_2} during epidural anesthesia in gravid ewes. Sipes *et al.*[14] later observed that $MgSO_4$ did not affect the action of phenylephrine on SVR but, rather, attenuated the increase in UVR and the decrease in UBF in response to phenylephrine infusion. These results suggested that hypermagnesemia might alter the uterine vascular response to ephedrine or phenylephrine during epidural anesthesia–induced hypotension.

The present study augments previous studies of vasopressor administration in pregnant animals by observing responses to ephedrine or phenylephrine during epidural anesthesia–induced hypotension in *hypermagnesemic* gravid ewes. Under these conditions, ephedrine restored UBF and did not alter UVR, whereas phenylephrine did not

improve UBF and markedly increased UVR. Thus, our results are similar to those of previous studies that did not administer $MgSO_4$.[5-7,12,22,23] One potential explanation for this finding may be that $MgSO_4$ affected all three groups similarly. It is also possible that the effect of $MgSO_4$ on the uterine vascular response to phenylephrine was small, so that relative differences between ephedrine and phenylephrine were preserved. It is important to note that even in the presence of hypermagnesemia, which may have provided partial protection of UBF during phenylephrine infusion, phenylephrine increased UVR and did not maintain fetal *p*H during epidural anesthesia–induced hypotension.

We acknowledge that vasopressor administration may have changed the volume of distribution for magnesium and resulted in acute changes in serum magnesium concentrations.[25] Magnesium concentrations were similar at 145 and 207 min (table 2), but we did not measure serum magnesium concentrations during vasopressor administration. If vasopressor infusion caused acute, transient changes in magnesium concentrations in the present study, one could expect similar changes to occur in clinical practice. Thus, such changes in magnesium concentration, if they do occur, would not change the conclusions or application of the present study.

We also acknowledge the apparent conflict between the present study and our earlier study.[16] In the earlier study,[16] $MgSO_4$ decreased maternal MAP but not UBF or fetal P_{O_2} during epidural anesthesia. Differences in the methods help explain the apparent difference in results. First, in the earlier study, each animal received 500 ml of NS intravenously immediately before epidural anesthesia. The bolus infusion of NS increased maternal cardiac output, and this helped to protect both cardiac output and UBF during epidural anesthesia. In the present study, animals did not receive a bolus of crystalloid immediately before epidural anesthesia. Second, in the earlier study, animals in the $MgSO_4$ group had a median sensory level of T10 and a maximum decrease in maternal MAP of 18 ± 3% below baseline. In the present study, we deliberately sought to achieve a higher sensory level and a greater decrease in maternal MAP during epidural anesthesia. The lack of volume expansion before anesthesia and the more extensive sympathetic blockade during anesthesia likely were responsible for the greater decreases in maternal MAP, cardiac output, and UBF in all three groups in the present study.

The results of the present study have several important limitations when applied to the use of ephedrine and phenylephrine in obstetric practice. First, there are known α- and β-adrenergic receptor distribution differences among species and resultant differences in vascular responses to α- and β-adrenergic agonists. Second, whereas the pregnant woman is nearly supine during labor and operative delivery, the animals were standing. Third, in clinical practice these vasopressors are given as intermittent boluses, whereas in the present study ephedrine and phenylephrine were continuously infused over 30 min in order to just restore maternal MAP to baseline. Fourth, in clinical practice the anesthesiologist gives both vasopressor and crystalloid to restore maternal MAP, whereas in the present study we relied on vasopressor alone. These differences in management could change the magnitude of the systemic and uterine vascular responses observed. However, there is no evidence that we gave excessive doses of either ephedrine or phenylephrine, and we speculate that bolus administration of drug might have exaggerated the difference between drugs in uterine vascular response.

Recently, some have suggested that a small dose of phenylephrine, just sufficient to restore maternal blood pressure to baseline, might be as safe as ephedrine for the treatment of hypotension during regional anesthesia in pregnant women. Ramanathan and Grant[13] reported no significant difference in maternal blood pressure, stroke volume, and end-diastolic volume or neonatal Apgar scores, blood gas measurements, and acid–base measurements in pregnant women whose epidural anesthesia–induced hypotension was corrected by either intravenous ephedrine or phenylephrine. Similarly, Moran *et al.*[26] demonstrated no difference in maternal acid–base or neonatal blood gas and acid–base measurements in women who received phenylephrine for treatment of spinal anesthesia–induced hypotension. Patients enrolled in these studies were healthy women undergoing elective repeat cesarean section. Undoubtedly, most of these women had a large margin of maternal and fetal reserve. Neither the present study nor earlier studies[13,26] evaluated the effects of ephedrine or phenylephrine on the compromised fetus. However, we note that fetuses undergoing labor or compensating for high-risk maternal conditions such as pregnancy-induced hypertension may be unable to tolerate the effects of additional decreases in uteroplacental perfusion. Thus, optimization of uterine perfusion during maternal hypotension and vasopressor administration may be important in such fetuses. Nonetheless, we acknowledge that there are specific situations when maternal conditions may dictate the administration of an α-adrenergic agonist rather than ephedrine for treatment of hypotension.

We conclude that, although ephedrine and phenylephrine provided similar restoration of maternal MAP, ephedrine was superior to phenylephrine in restoring UBF during epidural anesthesia–induced hypotension in hypermagnesemic gravid ewes. Furthermore, only ephedrine was clearly superior to NS-control in maintaining fetal *p*H and increasing fetal P_{O_2} during treatment

of hypotension. If applicable to humans, the present study suggests that ephedrine is preferred to phenylephrine for treatment of hypotension during regional anesthesia in the presence of hypermagnesemia.

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