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Maternal and Fetal Effects of Epinephrine in Gravid Ewes

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Intravenous cannulation by an epidural catheter may complicate epidural anesthesia. Local anesthetic solutions containing epinephrine produce tachycardia and hypertension when given intravenously and may identify intravenous placement. The authors studied the maternal and fetal effects of intravenous epinephrine-containing solutions in ten chronically instrumented gravid ewes. While continuously monitoring maternal and fetal effects, epinephrine 5, 10, or 20 μg iv bolus was injected. Solutions of bupivacaine 5 mg and bupivacaine 5 mg combined with epinephrine 10 μg given iv were also examined. All epinephrine-containing solutions produced a significant increase ($P < 0.001$) in maternal mean arterial pressure, which returned to baseline after 1 min. Maternal heart rates decreased transiently and returned to baseline after 1 min. All epinephrine-containing solutions decreased uterine blood flow (UBF) ($P < 0.001$), and, for doses of 10 to 20 μg, this decrease lasted more than 3 min. Fetal heart rate and mean arterial blood pressure did not change following any test solution, nor did maternal or fetal arterial blood gas values. The authors conclude that small intravenous boluses of epinephrine decreased UBF in these animals. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Sympathetic nervous system: catecholamines; epinephrine. Uterus: blood flow.)

UNINTENTIONAL INTRAVENOUS cannulation by an epidural catheter may complicate epidural anesthesia. If unrecognized, subsequent injections of intravenous local anesthetics may cause seizures, myocardial depression, and cardiac arrest.[1,2] Local-anesthetic solutions containing epinephrine usually produce tachycardia and hypertension when given intravenously and may identify intravenous placement.[3] The effects of these solutions on uterine blood flow (UBF) and the fetus are unknown. In this study we investigated the maternal and fetal effects of intravenous epinephrine-containing solutions in gravid ewes.

Materials and Methods

The Animal Practices Committee approved the protocol. We studied ten gravid ewes, having a mean weight of 56 kg, and of 110 to 125 days gestation (term 145 days). The animals were prepared in the following manner. After fasting the animal for 48 h, we sedated the ewe with pentobarbital 6 mg/kg intravenously and placed her in the right lateral decubitus position. We then induced anesthesia with ketamine 4 mg/kg and maintained anesthesia with ketamine $3 mg \cdot kg^{-1} \cdot h^{-1}$ intravenously. The animal breathed oxygen-enriched room air (nasal cannula 5 l/min) throughout the procedure. Through a left inguinal incision, we cannulated a mammary artery for measurement of maternal mean arterial pressure (MAP) and a mammary vein for infusion of epinephrine solutions or epinephrine solutions containing local anesthetic. We subsequently positioned a square wave electromagnetic flow probe§ around the left uterine artery for UBF measurement and zero-occlusion loops[4] around the descending aorta. We next performed a hysterotomy and cannulated both fetal femoral arteries and one femoral vein. Finally, we introduced a pressure balloon between the chorion and uterine wall for direct intrauterine pressure IUP measurements.

All animals rested 3–5 days following surgery for stabilization of UBF. On the day of the study, we placed the ewes in a quiet, dark room and connected the pressure and flow transducers to separate channels of a dynograph.¶ Following a 15-min period of stable baseline measurements, we injected the test drug and continuously monitored MAP, fetal arterial pressure (FAP), UBF, maternal heart rate (MHR), amniotic fluid pressure (AFP), and fetal heart rate (FHR) for at least 5 min following each test drug. The test solution consisted of either 5, 10, or 20 μg of epinephrine in saline or bupivacaine 5 mg, with or without 10 μg of epinephrine. Before the experiment was repeated with a different concentration of epinephrine in saline, each animal was rested at least 30 min, and we documented at least 15 min of stable baseline measurement. Each animal received only one bupivacaine solution per day, and each animal received all drug solutions. We analyzed maternal and fetal arterial blood gases obtained during the control period, 1, and 5 min following the injection of the test solutions and replaced fetal arterial blood samples with an equal volume of normal saline. We analyzed all continuous data using a multivariate analysis of variance with repeated measures and all paired data with a paired Student's t test where appropriate. A P value of ≤ 0.05 was considered statistically significant.

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¶ Offner®, Type R: Offner Division, Beckman Instruments, Inc., Schiller Park, IL.

TABLE 1. Uterine Blood Flow Following Intravenous Injections of Test Solutions

Test Solution	n	Time							
		0 (control)	15 s	30 s	60 s	90 s	2 min	3 min	5 min
Bup 5 mg	6	100	98 + 3	98 ± 3	98 + 1	99 + 1	102 + 1	98 + 2	98 + 2
Epi 5 μg	8	100	78 + 6*	71 ± 2*	80 + 3*	86 + 2*	95 + 2*	98 + 1	106 + 4
Epi 10 μg	10	100	79 + 7*	64 ± 4*	63 + 3*	69 + 3*	73 + 3*	85 + 2*	96 + 2
Epi 10 μg + Bup 5 mg	8	100	76 + 7*	56 ± 4*	56 + 4*	66 + 6*	75 + 6*	84 + 5*	93 + 5
Epi 20 μg	9	100	77 + 6*	57 ± 4*	55 + 4*	63 + 5*	72 + 4*	86 + 3*	98 + 4

Values expressed as per cent of control and recorded as mean ± SEM.

Bup = bupivacaine; Epi = epinephrine.
$P \leq 0.05$–0.001.

Results

Epinephrine-containing solutions significantly decreased UBF. For doses of 10 or 20 μg, these decreases lasted longer than 3 min ($P < 0.001$), and for all doses the UBF decreases were maximal between 30 and 60 s following injection (table 1). Bupivacaine 5 mg did not decrease UBF. The addition of bupivacaine 5 mg to epinephrine 10 μg did not alter epinephrine's effect. The decreases in UBF following epinephrine 10 μg, epinephrine 20 μg, and the combination of epinephrine 10 μg and bupivacaine 5 mg were not statistically different. Maternal and fetal arterial blood gases did not change following any injection (tables 2 and 3).

FHRs and MAPs did not change throughout each 5-min experiment, and significant fetal cardiovascular responses were not associated with any test solution.

MHR and MAP did not change following bupivacaine 5 mg. All epinephrine-containing solutions produced a significant increase ($P < 0.001$) in MAP, which returned to the baseline after 1 min (fig. 1). MHRs decreased transiently and returned to the baseline after 1 min (fig. 2).

Discussion

The epinephrine doses used in this study approximate the amounts recommended clinically for epidural test doses. Moore and Batra[3] recommend a minimum test dose of 15 μg of epinephrine. They administered 15 μg of epinephrine intravenously to a series of nonpregnant patients and heart rate increased within 23 ± 6 s and returned to baseline within 32 ± 33 s while systolic blood pressure increased maximally 22 ± 14 mmHg. In our animals maternal arterial blood pressure changes were similar in onset and duration. However, UBF remained decreased more than 2 min following the return of maternal cardiovascular changes to baseline. Surprisingly, we found that 10–20 μg of epinephrine produced a transient slowing of heart rate rather than a tachycardia. However, 19% of Moore and Batra's patients also responded to the epinephrine test dose with initial slowing of the heart rate, and 50% of their patients demonstrated abnormal heart rate rhythms with approximately 5% developing either junctional or sinus slowing. Since our epinephrine-induced hypertension was of a similar magnitude and duration to that in their patients, perhaps our pregnant ewes had a more-sensitive baroreceptor response to epinephrine-induced hypertension than did the human subjects in Moore and Batra's study.

The cardiovascular changes observed in this study and in Moore and Batra's study in nonpregnant humans are brief and minor. Moore and Batra recommend continuously monitoring either the radial pulse or using an elec-

TABLE 2. Maternal Arterial Blood Gases Following Intravenous Injection of Test Solutions

Solution	n	Control	1 min	5 min
Maternal pH				
Bup 5 mg	6	7.51 ± 0.01	7.52 ± 0.01	7.52 ± 0.01
Epi 10 μg	11	7.49 ± 0.02	7.52 ± 0.01	7.52 ± 0.01
Bup 5 mg + Epi 10 μg	8	7.54 ± 0.02	7.54 ± 0.01	7.54 ± 0.01
Maternal Pa_{CO_2} (mmHg)				
Bup 5 mg	6	24 ± 2	24 ± 2	26 ± 2
Epi 10 μg	11	26 ± 1	26 ± 1	25 ± 1
Bup 5 mg + Epi 10 μg	8	25 ± 1	26 ± 1	25 ± 2
Maternal Pa_{O_2} (mmHg)				
Bup 5 mg	6	95 ± 3	98 ± 3	94 ± 4
Epi 10 μg	11	103 ± 3	103 ± 3	101 ± 3
Bup 5 mg + Epi 10 μg	8	99 ± 3	100 ± 5	100 ± 4

See table 1 for abbreviations.

Values expressed as per cent of control and recorded as mean ± SEM.

TABLE 3. Fetal Arterial Blood Gases Following Intravenous Injection of Test Solutions

Solution	n	Control	1 min	5 min
Fetal pH				
Bup 5 mg	6	7.39 ± 0.03	7.38 ± 0.02	7.38 ± 0.02
Epi 10 μg	11	7.38 ± 0.01	7.39 ± 0.01	7.39 ± 0.01
Bup 5 mg + Epi 10 μg	8	7.38 ± 0.02	7.37 ± 0.02	7.36 ± 0.03
Fetal Pa_{CO_2} (mmHg)				
Bup 5 mg	6	36 ± 2	37 ± 1	36 ± 1
Epi 10 μg	11	35 ± 2	37 ± 1	37 ± 1
Bup 5 mg + Epi 10 μg	8	37 ± 1	38 ± 1	37 ± 1
Fetal Pa_{O_2} (mmHg)				
Bup 5 mg	6	20 ± 1	21 ± 1	20 ± 1
Epi 10 μg	11	23 ± 2	21 ± 2	21 ± 1
Bup 5 mg + Epi 10 μg	8	20 ± 2	20 ± 1	20 ± 2

See table 1 for abbreviations.

Values expressed as per cent of control and recorded as mean ± SEM.

trocardioscope. Unfortunately, pain and anxiety frequently accompany labor and delivery and also increase blood pressure and heart rate. These changes may obscure epinephrine's transient minor cardiovascular changes, even during continuous monitoring.

Epinephrine test solutions consistently decreased UBF. The epinephrine test solutions containing 10–20 μg decreased UBF to 55–65% of control, and flow remained significantly decreased more than 3 min following injection. This degree of UBF decrease resembles the decrease that occurs during a normal uterine contraction. Because AFP did not change, this decrease most likely reflects a direct effect on the vessels. Although we found no evidence of fetal compromise with our test solutions, our animals were not in labor; UBF reductions of this magnitude might compromise the fetus if superimposed on a contraction. Impaired placental function might also increase the sensitivity to decreased UBF in much the same manner as contractions produce late decelerations of the FHR when placental function is compromised. Impairment of uteroplacental function occurs commonly in severe preeclampsia and diabetes, and these patients may not tolerate any decrease in UBF. Preeclamptic women have increased pressor responses to angiotension II and norepinephrine.[5] The severe preeclamptic may be excessively sensitive to intravenous epinephrine and become severely hypertensive with correspondingly severe decreases in UBF. Finally, we tested the effects of small doses of epinephrine; the results of accidental intravenous injection of larger doses of epinephrine-containing local anesthetic are unknown.

Previous studies assessed the effects of epidural epinephrine solutions in parturients using a radioisotopic method of quantitating intervillous blood flow (IVBF).[6–8] Our findings may contrast with the findings of the IVBF studies; we did not assess IVBF, and we studied the effects of bolus injection of intravenous epinephrine. IVBF studies require a baseline measurement of IVBF followed by a period of at least 10–15 min before a second measurement can be obtained. In her letter to the editor,[9] Marx questions the contention that epidural epinephrine can be used safely in obstetric practice based on these three studies. She correctly pointed out that in only one of the three studies did IVBF remain unchanged in all cases, and that "decreases in IVBF were demonstrable in at least 18% of cases following addition of epinephrine 50 μg and in 78% following 80–100 μg" epidurally administered.

One patient reported by Albright[10] received an unin-

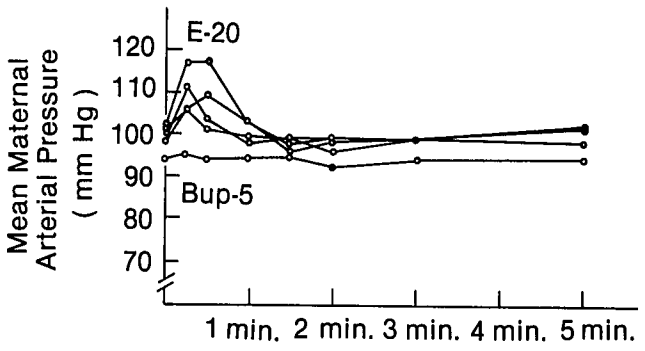

FIG. 1. Mean maternal arterial pressure (mmHg) following the injection of epinephrine-containing solutions.

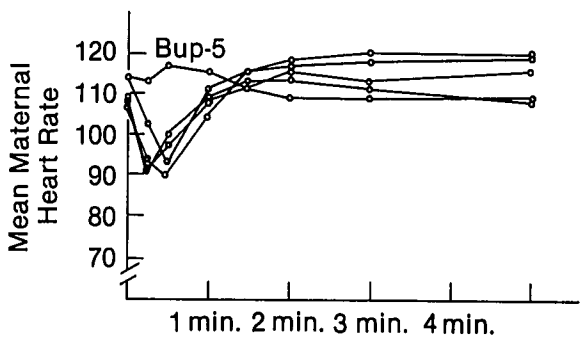

FIG. 2. Mean maternal heart rate (beats/min) following the injection of epinephrine-containing solutions.

tentional intravenous injection of 55 μg of epinephrine mixed in 11 ml of 2% chloroprocaine and demonstrated the expected increase in blood pressure and heart rate. IVBF 10–15 min following injection was still 15% below control. Unfortunately, measurement during the first 10 min after the epinephrine injection was not accomplished, and the extent of IVBF decrease is unknown. The uneventful recovery of both mother and fetus may only demonstrate the reserve available to this healthy parturient.

We conclude that small intravenous boluses of epinephrine decreased UBF in our animals. If applicable to humans, such transient changes might be significant in a patient with compromised placental function.

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