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# *Effect of Intravenous Epinephrine on Uterine Artery Blood Flow Velocity in the Pregnant Guinea Pig*

*David H. Chestnut, M.D.,* Carl P. Weiner, M.D.,† Joseph G. Martin, B.S.,‡ James E. Herrig, B.S.,§ Jin Ping Wang§*

**The purpose of the present study was to determine the effect of intravenously administered epinephrine on the maternal cardiovascular response and uterine artery blood flow velocity (UBFV) in the pregnant guinea pig. Epinephrine (0.2, 0.5, and 1.0 μg/kg) and lidocaine (0.4 mg/kg, with and without 0.2 μg/kg of epinephrine) were administered intravenously to seven chronically instrumented pregnant guinea pigs near term. Lidocaine without epinephrine did not significantly alter maternal heart rate (MHR), maternal mean arterial pressure (MMAP), or UBFV. Epinephrine, with and without lidocaine, resulted in a transient decrease in MHR. Further, epinephrine, with and without lidocaine, resulted in significant elevations in MMAP and significant, dose-related reductions in UBFV. Mean (±SEM) UBFV was 72 ± 4%, 56 ± 4%, and 40 ± 5% of baseline at 30 s after administration of epinephrine, 0.2, 0.5, and 1.0 μg/kg, respectively. It is concluded that these small intravenous boluses of epinephrine result in significant, although transient, reductions in UBFV in the pregnant guinea pig. (Key words: Anesthesia: obstetric. Anesthetics, local: lidocaine. Measurement techniques: Doppler flow probe. Sympathetic nervous system, catecholamines: epinephrine. Uterus: blood flow velocity.)**

DURING INDUCTION OF epidural anesthesia, a test dose of local anesthetic is administered to detect inadvertent intravenous or subarachnoid injection. The potential for local anesthetic toxicity has prompted discussion regarding the ideal composition of the epidural test dose. Moore and Batra[1] administered epinephrine intravenously to nonpregnant volunteers and medicated surgical patients. They concluded that the epidural test dose should include 15 μg of epinephrine. A transient increase in heart rate would indicate that the test dose had been injected intravenously, and that the needle or catheter should be repositioned prior to additional injection of local anesthetic. Recently Abraham *et al.*[2] recommended 2 ml of 1.5% lidocaine in 7.5% dextrose, with 15 μg of epinephrine, as an ideal obstetric test dose.

* Assistant Professor of Anesthesia and Obstetrics and Gynecology.
† Assistant Professor of Obstetrics and Gynecology.
‡ Medical Student.
§ Research Assistant.

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Address reprint requests to Dr. Chestnut.

To our knowledge, there are no published data regarding the effect of 15 μg of intravenously administered epinephrine on uteroplacental blood flow in the human. Ethical constraints limit the potential for performing such a study. The purpose of the present study was to determine the effect of intravenously administered epinephrine on the maternal cardiovascular response and uterine artery blood flow velocity (UBFV) in the chronically instrumented pregnant guinea pig. The advantages of the guinea pig include a hemomonochorial placenta (labyrinth type), cyclic changes in serum estrogen and progesterone concentrations qualitatively similar to those observed in women, and cardiovascular/respiratory alterations during pregnancy analogous to those in women.[3–7]

## Materials and Methods

We used pulsed Doppler ultrasound to monitor continuously UBFV in the pregnant guinea pig. We measured the magnitude of change in the Doppler shift, and we have reported all measurements as per cent change from baseline. Validation of this model was recently reported in detail; the measured flow velocity was both directly proportional and linear to actual uterine artery blood flow (R = 0.984).[8]

The protocol was approved by the University of Iowa Animal Care Committee. Briefly, mixed breed guinea pigs of known mating were obtained from a commercial breeder and allowed to acclimatize to the laboratory environment for 3 days. Using sterile technique and general anesthesia (intramuscular zylazine 0.8 mg/kg and intraperitoneal ketamine 80 mg/kg, supplemented by local infiltration of 1.0% lidocaine), a ventral, midline neck incision was performed, and catheters (polyethylene 50, inside diameter 0.58 mm, outside diameter 0.96 mm) were inserted into the external jugular vein and carotid artery. The arterial catheter was advanced into the descending aorta below the origin of the renal arteries but above the origin of the uterine vessels. Through a midline abdominal incision, a 5–10 mm segment of uterine artery between two pups was dissected free from the mesometrium using microsurgical techniques, and a miniaturized Doppler flow probe (20 mHz crystal, 0.75 mm in diameter, 100 mg in weight) was fixed to the underside of the vessel using a cyanoacrylic glue. A probe shield was constructed *in situ* using a medical-grade silicone polymer. Probe wires and catheters were exteriorized *via* a stab wound in the

TABLE 1. Maximal Change in Maternal Heart Rate

| Drug | Dosage | N* | Mean, ± SEM, % of Baseline |
|---|---|---|---|
| Epinephrine | 0.2 μg/kg | 7/15 | 92 ± 2† |
| Epinephrine | 0.5 μg/kg | 7/15 | 92 ± 2† |
| Epinephrine | 1.0 μg/kg | 6/11 | 86 ± 2† |
| Lidocaine | 0.4 mg/kg | | |
| Without epinephrine | | 7/15 | 97 ± 2 |
| With epinephrine | 0.2 μg/kg | 7/15 | 92 ± 2† |

* Animals/experiments.
† $P < 0.05$, when compared with baseline.

nape of the neck. Catheter patency was maintained by a daily 1-ml bolus of a heparin–saline solution (300 u/ml).

After surgery the animals remained in individual cages. Guinea pig chow and water were supplied *ad libitum* and supplemented with fresh vegetables. The room lights were cycled (12 hours on, 12 hours off). No experiments were undertaken until normal weight gain and activity had resumed, and in no case before the fourth postoperative day. All experiments were performed with the animal in familiar surroundings, with unimpaired mobility.

Experiments were performed between 45 and 60 days gestation (term = 65 days). Animal weights on experiment days varied between 710 and 1100 g (mean ± SD = 913 ± 119 g). Maternal heart rate (MHR) and maternal mean arterial pressure (MMAP) were obtained through the arterial catheter (Electromedics transducer, model #MS20-BA07ADS). MHR, MMAP, and mean UBFV were recorded continuously on a biomedical strip chart recorder. Fifteen experiments were performed in seven animals. Each experiment was preceded by a control period of at least 1 h. In each experiment, each animal received, in random order, epinephrine 0.2 and 0.5 μg/kg; and 0.4 mg/kg of lidocaine (Xylocaine® 1.5% with dextrose 7.5%, Astra Pharmaceutical Products, Westborough, MA), with and without 0.2 μg/kg of epinephrine. During 11 of these 15 experiments, six animals also received 1.0 μg/kg of epinephrine. Each drug was mixed with saline (total volume = 0.2 ml) and administered intravenously over 15 s. MHR, MMAP, and UBFV were allowed to return to within 10% of control before administration of the subsequent drug solution. The minimum interval between doses was 15 min. Changes in MHR, MMAP, and UBFV during the 5 min after drug administration were compared with the baseline observed before drug administration. All results are reported as mean (±SEM) per cent of baseline.

Maximal changes in MHR were assessed by analysis of co-variance. Changes in MMAP and UBFV over time were analyzed by analysis of variance with repeated measures, with Bonferroni adjustment. The mean differences among the drug–dose categories were examined by the Tukey Studentized-range multiple comparison technique. $P < 0.05$ was considered significant.

## Results

Each dose of epinephrine, with and without lidocaine, resulted in a transient decrease in MHR (table 1). Maternal heart rate usually returned to baseline within 30 s of administration of epinephrine, and always returned to baseline within 60 s. Only the lidocaine without epinephrine did not significantly alter MHR.

Tables 2 and 3 include the changes over time in MMAP and UBFV. Epinephrine, 0.2 μg/kg, produced a modest elevation in MMAP, which was significantly different from baseline only at 30 s after injection. UBFV was 72 ± 4% of baseline at 30 s and remained significantly below baseline through 90 s.

Epinephrine, 0.5 μg/kg, resulted in a significant increase in MMAP through 1 min after injection. UBFV was 56 ± 4% of baseline at 30 s and remained significantly below baseline through 4 min.

Epinephrine, 1.0 μg/kg, resulted in a significant increase in MMAP through 90 s after injection. UBFV was 40 ± 5% of baseline at 30 s and remained significantly below baseline through 4 min.

Lidocaine without epinephrine did not significantly al-

TABLE 2. Change in Maternal Mean Arterial Pressure (% of baseline)

| Drug | N* | Seconds Following Injection of Test Solution | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 30 | 60 | 90 | 120 | 180 | 240 | 300 |
| Epinephrine, 0.2 μg/kg | 7/15 | 100 | 113 ± 3† | 106 ± 3 | 102 ± 3 | 99 ± 3 | 98 ± 3 | 97 ± 3 | 98 ± 3 |
| Epinephrine, 0.5 μg/kg | 7/15 | 100 | 121 ± 3† | 114 ± 3† | 103 ± 3 | 102 ± 3 | 100 ± 3 | 95 ± 3 | 101 ± 3 |
| Epinephrne, 1.0 μg/kg | 6/11 | 100 | 135 ± 4† | 117 ± 4† | 108 ± 4† | 106 ± 4 | 104 ± 4 | 104 ± 4 | 104 ± 4 |
| Lidocaine, 0.4 mg/kg | 7/15 | 100 | 107 ± 4 | 103 ± 4 | 104 ± 4 | 102 ± 4 | 104 ± 4 | 103 ± 4 | 104 ± 4 |
| Lidocaine, 0.4 mg/kg, with epinephrine, 0.2 μg/kg | 7/15 | 100 | 111 ± 3† | 105 ± 3 | 101 ± 3 | 99 ± 3 | 98 ± 3 | 99 ± 3 | 100 ± 3 |

All values are expressed as per cent of control and recorded as mean ± SEM.

* Animals/experiments.
† $P < 0.05$, when compared with baseline.

TABLE 3. Change in Uterine Blood Flow Velocity (% of baseline)

| Drug | N* | Seconds Following Injection of Test Solution | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 30 | 60 | 90 | 120 | 180 | 240 | 300 |
| Epinephrine, 0.2 μg/kg | 7/15 | 100 | 72 ± 4† | 83 ± 4† | 90 ± 4† | 98 ± 4 | 98 ± 4 | 98 ± 4 | 99 ± 4 |
| Epinephrine, 0.5 μg/kg | 7/15 | 100 | 56 ± 4† | 75 ± 4† | 78 ± 4† | 86 ± 4† | 91 ± 4† | 91 ± 4† | 94 ± 4 |
| Epinephrine, 1.0 μg/kg | 6/11 | 100 | 40 ± 5† | 62 ± 5† | 70 ± 5† | 78 ± 5† | 81 ± 5† | 86 ± 5† | 92 ± 5 |
| Lidocaine, 0.4 mg/kg | 7/15 | 100 | 92 ± 4 | 98 ± 4 | 101 ± 4 | 106 ± 4 | 105 ± 4 | 103 ± 4 | 104 ± 4 |
| Lidocaine, 0.4 mg/kg, with epinephrine, 0.2 μg/kg | 7/15 | 100 | 71 ± 4† | 82 ± 4† | 90 ± 4† | 93 ± 4 | 95 ± 4 | 101 ± 4 | 100 ± 4 |

All values are expressed as per cent of control and recorded as mean ± SEM.

* Animals/experiments.
† $P < 0.05$, when compared with baseline.

ter MMAP or UBFV. Lidocaine with epinephrine, 0.2 μg/kg, resulted in changes similar to epinephrine, 0.2 μg/kg, without lidocaine. UBFV was 71 ± 4% of baseline at 30 s and remained significantly below baseline through 90 s after injection.

When mean differences among the drug–dose categories were examined, the mean response in MMAP associated with epinephrine, 1.0 μg/kg, was significantly greater than all other responses, except that with epinephrine, 0.5 μg/kg (fig. 1). Each mean response in UBFV was significantly different from all other mean responses, except that there was no significant difference between the mean responses after epinephrine, 0.2 μg/kg, with and without lidocaine (fig. 2).

## Discussion

Wallis *et al.*[9] reported a 14% decrease in uterine blood flow during the first 15 min after induction of epidural anesthesia in normotensive pregnant sheep with 2-chloroprocaine and 60–80 μg of epinephrine. Three subsequent investigations examined the effects of 20–100 μg of epidurally administered epinephrine on human intervillous blood flow measured by intravenous injection of radioactive xenon.[10–12] No significant decrease in intervillous blood flow was demonstrated.

The epinephrine was administered epidurally in the aforementioned four studies. However, inadvertent cannulation of an engorged epidural vein occurs commonly in obstetric patients.[2,13] Greiss[14] reported dose-related reductions in uterine blood flow after continuous intravenous administration of 0.1–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine in gravid ewes. Further, Greiss reported that "changes in uterine conductance persisted long after blood pressure had returned to preinfusion levels."[14] Similarly, Rosenfeld *et al.*[15] administered to gravid ewes a continuous intravenous infusion of 0.2 to 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of epinephrine. They demonstrated a 39% reduction in uterine artery blood flow, which is midway between the 28% and 44% reductions in UBFV that we have observed after bolus intravenous epinephrine injections of 0.2 and 0.5 μg/kg, respectively. Using microspheres, Rosenfeld *et al.*[15] also found that the vasculature of all three uterine tissues (endometrium, myometrium, and placenta) was sensitive to the vasoconstrictive effects of epinephrine. Recently Hood *et al.*[16] reported dose-related reductions in uterine blood flow for 3 min after bolus intravenous injection of 5, 10, and 20 μg of epinephrine in gravid ewes.

The results of the present study complement previous studies that used different methodology (electromagnetic flow probe[14,16] and microspheres[15]) in a different species. Further, in both the present study and the study of Hood *et al.*,[16] a bolus of epinephrine, comparable to that included in the epidural test dose, was administered. When calculated on a mg/kg basis, the smallest dose of epinephrine (0.2 μg/kg) administered in the present study approximates the recommended epidural test dose of epinephrine[1,2] administered to a patient weighing 75 kg.

Hood *et al.*[16] and we observed hypertension similar in magnitude and duration to that observed by Moore and Batra[1] after intravenous administration of 15 μg of epi-

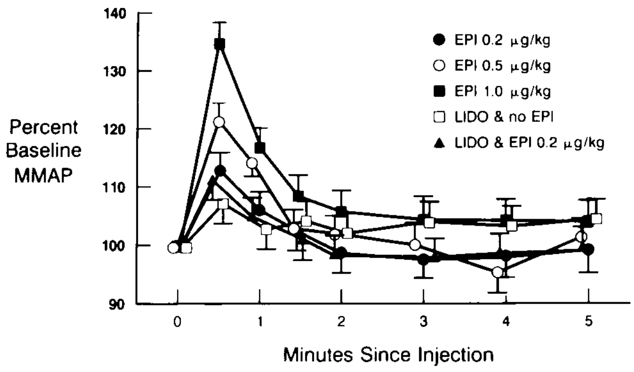


FIG. 1. Response over time of maternal mean arterial pressure (MMAP). All values are expressed as mean (±SEM) % of baseline. EPI = epinephrine; LIDO = lidocaine. The mean response in MMAP to 1.0 μg/kg epinephrine was significantly greater than all other responses except that with epinephrine, 0.5 μg/kg.

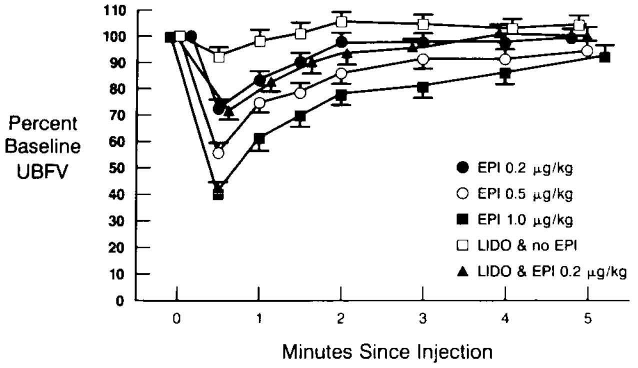


FIG. 2. Response over time of uterine artery blood flow velocity (UBFV) after intravenous administration of the five drug–dose categories. All values are expressed as mean (±SEM) % of baseline. EPI = epinephrine; LIDO = lidocaine. Each mean response in UBFV was significantly different from all other mean responses except that there was no significant difference between the mean responses after epinephrine, 0.2 μg/kg, with and without lidocaine.

nephrine to nonpregnant volunteers. However, both Hood *et al.*[16] and we observed that intravenous epinephrine consistently resulted in a transient decrease in heart rate rather than a tachycardia. In contrast, Moore and Batra[1] observed an initial decrease in heart rate in only 19% of their patients. Hood *et al.* speculated that their pregnant ewes may have had "a more sensitive baroreceptor response to epinephrine-induced hypertension than did the human subjects in Moore and Batra's study."[16] While the difference in heart rate response may reflect species difference, a difference in the ratio of alpha/beta receptor occupation cannot be excluded. It is significant that Greiss,[14] Hood *et al.*,[16] and we observed that the decrease in uterine blood flow[14,16]/UBFV was consistently of greater duration than the duration of the maternal cardiovascular response.

The dose of lidocaine (0.4 mg/kg) administered in the present study approximates the epidural test dose of lidocaine recommended by Abraham *et al.*[2] To our knowledge, there is no previously published study of the effect of intravenously administered lidocaine *with* epinephrine on uterine blood flow or UBFV. In contrast, the lack of significant change in UBFV after a bolus intravenous injection of lidocaine *without* epinephrine is consistent with the study reported by Biehl *et al.*[17] They observed no significant change in uterine blood flow in gravid ewes subjected to continuous intravenous infusion of 0.15–0.25 $mg \cdot kg^{-1} \cdot min^{-1}$ of lidocaine.[17]

We conclude that small intravenous boluses of epinephrine result in significant, although transient, reductions in UBFV in the pregnant guinea pig. While we acknowledge that these results were obtained in the guinea pig rather than in the human, the similar results obtained in both pregnant sheep and guinea pigs suggest that this effect is not limited to one species.

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