Anesthesiology
66:508-512, 1987

The Effect of Ephedrine upon Uterine Artery Blood Flow Velocity in the Pregnant Guinea Pig Subjected to Terbutaline Infusion and Acute Hemorrhage

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The purpose of the present study was to determine the effect of intravenously administered ephedrine upon uterine artery blood flow velocity (UBFV) in the gravid guinea pig subjected to terbutaline infusion and acute hemorrhage. Ephedrine, 1.0 mg/kg, was administered intravenously to ten chronically instrumented pregnant guinea pigs near term, before and after intravenous infusion of terbutaline and acute hemorrhage. Before terbutaline and hemorrhage, ephedrine increased maternal mean arterial pressure (MMAP) by 30 ± 1% (P = .0001) and 17 ± 1% (P = .0001) at 30 s and at 1 min after injection, respectively; UBFV was decreased by 10 ± 4% (P < .01) and 14 ± 4% (P < .01) at 1 min and at 90 s after injection, respectively. Infusion of terbutaline (1.5–6.0 ug·kg^{-1}·min^{-1}) increased maternal heart rate (MHR) by 22 ± 1% (P = .0001), decreased MMAP by 13 ± 2% (P = .0001), and decreased UBFV by 24 ± 3% (P = .0001). During hypotension resulting from acute hemorrhage, ephedrine, 1.0 mg/kg, was superior to placebo in restoring MMAP and UBFV toward the prebleed values. The authors concluded that ephedrine, 1.0 mg/kg, results in a small, transient decrease in UBFV in the normotensive gravid guinea pig. However, ephedrine aids restoration of UBFV in the gravid guinea pig rendered hypotensive by acute hemorrhage during terbutaline infusion. (Key words: Hemorrhage. Measurement techniques: Doppler flow probe. Sympathetic nervous system, sympathomimetic agents: ephedrine. Tocolytic agents: terbutaline. Uterus: blood flow velocity.)

PREMATURITY REMAINS the leading cause of perinatal morbidity and mortality in the United States.[1-3] Beta-sympathomimetic agents (*e.g.*, terbutaline, ritodrine) are frequently administered for tocolysis (the treatment of premature labor by inhibition of uterine muscle contractions). While these agents are relatively selective for the beta-2-receptor (*e.g.*, uterine smooth muscle), beta-1-receptor stimulation also occurs, resulting in an increase in maternal heart rate and systolic arterial pressure, a decrease in diastolic arterial pressure, and no change or a decrease in mean arterial pressure.[2,4-6] Beta-mimetic tocolytic agents are generally avoided in patients who have vaginal bleeding, for fear that severe hypotension will occur. However, we have administered these agents to bleeding women (*e.g.*, placenta previa) when the fetus was of borderline viability.

Ephedrine, a mixed alpha and beta agonist,[7] has a more favorable influence on uterine blood flow in gravid ewes than other vasopressors.[8,9] Conventional teaching has been that the increase in cardiac output secondary to beta-receptor stimulation compensates for alpha-receptor mediated uterine vasoconstriction.[7-9] Ephedrine is thus considered the preferred vasopressor in obstetric practice. There are no published data regarding the effect of ephedrine on uterine blood flow in the pregnant patient or animal experiencing acute hemorrhage while receiving a beta-mimetic tocolytic agent. Our hypothesis was that, in a hypotensive patient or animal with preexisting beta-receptor stimulation, any vasopressor effect from ephedrine would result from alpha-receptor stimulation. The accompanying uterine vasoconstriction might further decrease uterine blood flow. The purpose of the present study was to determine the effect of intravenously administered ephedrine upon uterine artery blood flow velocity (UBFV) in the gravid guinea pig subjected to terbutaline infusion and acute hemorrhage.

Methods and Materials

We utilized pulsed Doppler ultrasound to continuously monitor uterine artery blood flow velocity (UBFV) in the pregnant guinea pig.[10] We measured the magnitude of change in the Doppler shift, and we report all measurements as the percent change from baseline. We recently reported the validation of this model; the measured flow velocity was both directly proportional and linear to actual uterine artery blood flow (R = 0.984).[10] The advantages of the guinea pig as a model include a hemomonochorial placenta (labyrinth type), cyclic changes in serum estrogen

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Received from the Departments of Anesthesia and Obstetrics and Gynecology, University of Iowa College of Medicine, Iowa City, Iowa. Accepted for publication November 25, 1986. Supported in part by Biomedical Research Support Grant PR05372 from the Biomedical Research Support Branch, Division of Research Facilities and Resources, National Institutes of Health, and by Basil O'Connor Starter Research Grant 5-482 from the March of Dimes Birth Defects Foundation. Presented in part at the annual meeting of the Society for Gynecologic Investigation, Toronto, Ontario, Canada, March 20, 1986; and at the annual meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 21, 1986.

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and progesterone levels qualitatively similar to those observed in women, and cardiovascular/respiratory alterations during pregnancy analogous to those occurring in pregnant women.[11-15]

The protocol was approved by the University of Iowa Animal Care Committee. Mixed breed guinea pigs of known mating were obtained from a commercial breeder at 0.6 of timed gestation (term = 65 days) and allowed to acclimate to the laboratory environment for 2 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. 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. Through a midline abdominal incision, a 5–10 mm segment of uterine artery 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. Care was taken to confine the glue to the underside and prevent encasement of the artery. (Proper probe attachment does not result in maternal hypertension or fetal growth retardation, and UBFV increases progressively as expected during the remainder of the gestation.[10]) 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 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, fresh vegetables, and water were supplied *ad libitum*. The room lights were cycled (12 h on, 12 h off). No experiments were undertaken until normal weight gain and activity had resumed, and in no case before the 8th postoperative day. All experiments were performed with the animal in familiar surroundings, with unimpaired mobility.

Experiments were performed between 50 and 60 days gestation. Animal weights on experiment days varied between 747 and 1210 gm (mean ± S.D. = 965 ± 131 gm). Maternal heart rate (MHR) and maternal mean arterial pressure (MMAP) were obtained through the arterial catheter. Maternal heart rate, MMAP, and mean UBFV were recorded continuously on a biomedical strip chart recorder.

Twenty experiments were performed in ten animals (two experiments per animal). Each experiment was preceded by a control period of at least 1 h. Each animal then received ephedrine, 1.0 mg/kg, intravenously. Fifteen minutes later, each animal received a continuous intravenous infusion of terbutaline, 1.5–6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, for at least 1 h, with the dose titrated to result in a 20% increase in MHR. Each animal was then subjected to an acute blood loss of 12 ml/kg over 5 min *via* the arterial catheter. The terbutaline infusion was discontinued, and the intravenous catheter was flushed with saline, midway during the blood loss. One minute after hemorrhage, each animal again received ephedrine, 1.0 mg/kg.

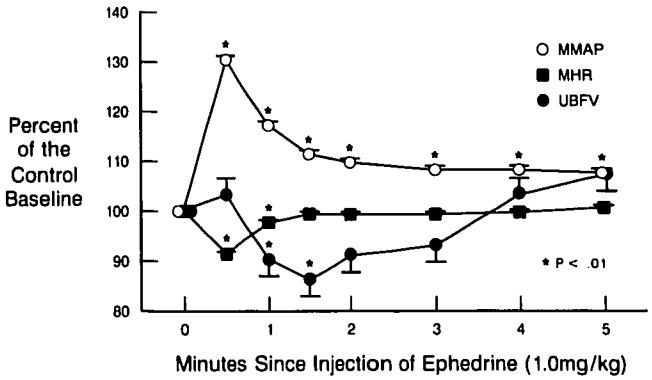

FIG. 1. Control response over time of maternal mean arterial pressure (MMAP), maternal heart rate (MHR), and uterine artery blood flow velocity (UBFV) after intravenous administration of ephedrine, 1.0 mg/kg. All values are expressed as mean (±SEM) % of the control baseline. The asterisk indicates $P < .01$, when compared with the control baseline.

In a separate experiment on an alternate day, the experimental sequence was repeated, except that each animal received placebo (saline, 0.2 ml) after hemorrhage. The order of the two experiments was altered between the ten animals.

Changes in MHR, MMAP, and UBFV during the 5 min after drug administration were compared with the preceding baseline values and are expressed as mean (±SEM) percent of baseline. Statistical analysis was by analysis of variance, with Bonferroni adjustment, and paired *t* test, as appropriate.

Results

Before terbutaline and hemorrhage, ephedrine increased MMAP by 30 ± 1% and 17 ± 1% at 30 s and at 1 min after injection, respectively ($P = .0001$) (fig. 1). The increase in MMAP remained significant through 5 min ($P = .0001$). There was a transient but significant decrease in MHR ($P = .0001$). Uterine blood flow velocity was decreased by 10 ± 4% ($P < .01$) and 14 ± 4% ($P < .01$) at 1 min and at 90 s after injection, respectively.

Infusion of terbutaline increased MHR by 22 ± 1% ($P = .0001$), decreased MMAP by 13 ± 2% ($P = .0001$), and

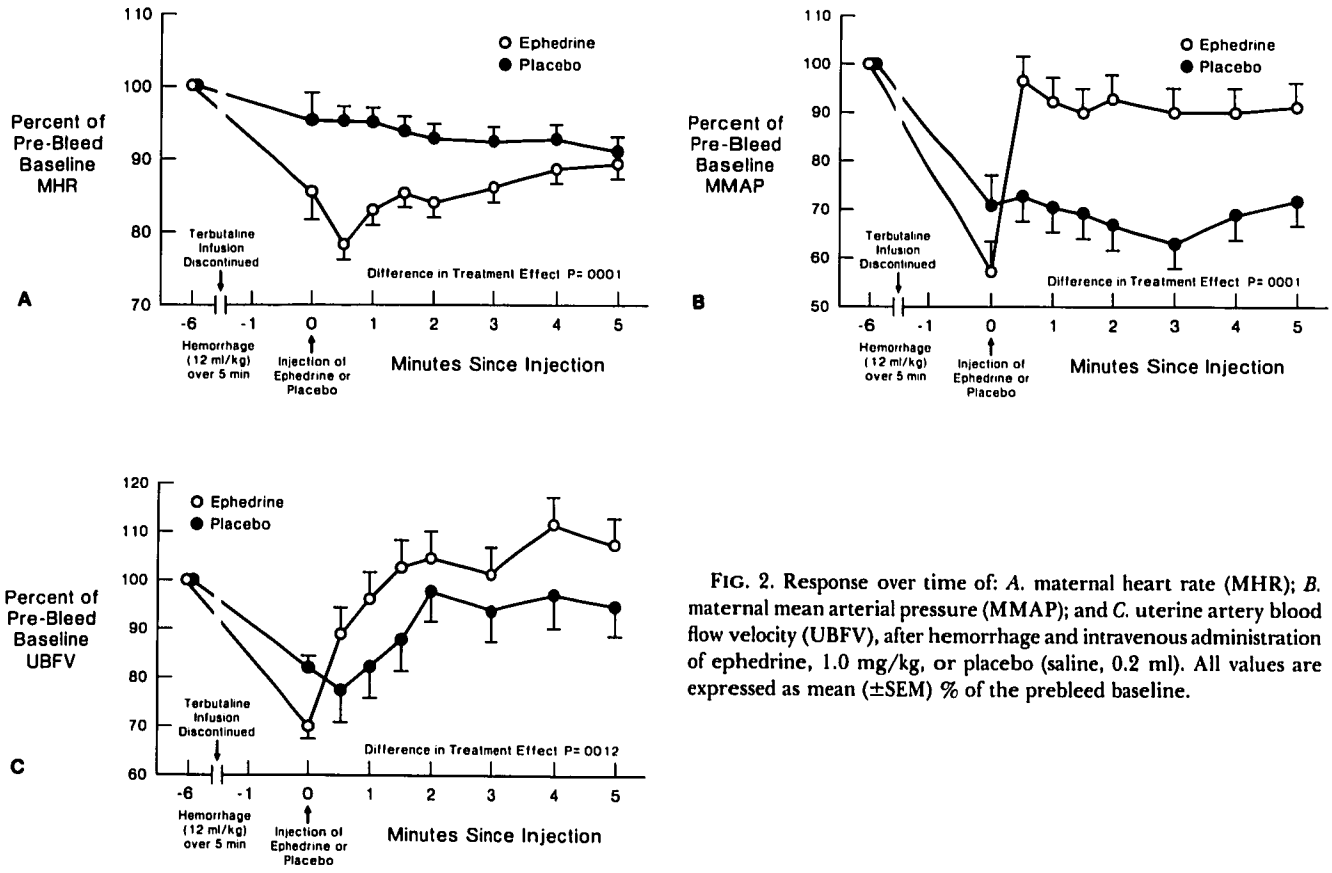

FIG. 2. Response over time of: *A.* maternal heart rate (MHR); *B.* maternal mean arterial pressure (MMAP); and *C.* uterine artery blood flow velocity (UBFV), after hemorrhage and intravenous administration of ephedrine, 1.0 mg/kg, or placebo (saline, 0.2 ml). All values are expressed as mean (±SEM) % of the prebleed baseline.

decreased UBFV by 24 ± 3% (P = .0001). There were no significant differences in the mean responses to ephedrine or terbutaline on the days that the animals received ephedrine after hemorrhage, when compared with the mean responses on the days that they received placebo after hemorrhage.

Figure 2 illustrates the maternal hemodynamic responses after hemorrhage and subsequent injection of ephedrine or placebo. Ephedrine again resulted in a transient decrease in MHR, followed by a gradual rise toward the prebleed baseline (fig. 2A). Placebo was associated with a gradual decline in MHR.

Ephedrine restored MMAP to 97 ± 5% and 92 ± 5% of the prebleed baseline at 30 s and at 1 min after injection, respectively; MMAP remained stable through 5 min (fig. 2B). In contrast, placebo did not restore MMAP.

Ephedrine restored UBFV to 89 ± 7% and 96 ± 7% of the prebleed baseline at 30 s and at 1 min after injection, respectively; UBFV did not differ significantly from the prebleed baseline at any time during the 5 min after injection of ephedrine (fig. 2C). Placebo was associated with a delayed response of significantly less magnitude (P = .0012).

Discussion

Using an electromagnetic flow probe, Ralston *et al.*[9] demonstrated a small, statistically insignificant decrease in uterine blood flow after administration of 1.0 and 2.0 mg/kg of ephedrine in normotensive pregnant ewes. Our results in normotensive guinea pigs are not inconsistent with their study, although the 10–14% decreases in UBFV at 60–90 s in our study were statistically significant.

The effect of terbutaline on uterine blood flow in pregnancy is controversial. Caritis *et al.*[16] and Nuwayhid *et al.*[17] observed no significant change in uterine blood flow after continuous intravenous infusion of 0.12–0.80 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of terbutaline in pregnant ewes. Using radioactive microspheres, Martensson *et al.*[18] reported no significant change in uteroplacental blood flow after continuous intravenous infusion of 1.1–11.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of terbutaline in anesthetized pregnant guinea pigs. In contrast, Ayromlooi *et al.*[19] observed a 26% decrease in uterine blood flow after intravenous infusion of 1500 μg of terbutaline over 30 min in pregnant ewes. Recently, Van de Walle and Martin[20] reported a 10% decrease in absolute placental blood flow

following the continuous intravenous infusion of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of ritodrine in pregnant guinea pigs. They concluded that "in the pregnant guinea pig, beta-adrenergic agents have no demonstrable vasodilator effect on the maternal vessels supplying the placenta . . . , [and] that the effect of these agents on maternal placental blood flow depends on the balance between the increase in cardiac output and vasodilatation in the carcass."[20] We observed a mean 24% decrease in UBFV at a dosage of terbutaline that produced a mean 22% increase in MHR. In the human patient, there is little tocolytic benefit to be gained by administering a dosage of beta-agonist higher than that necessary to achieve this endpoint.[21,22]

Lyrenas *et al.*[23] reported that the mean terminal half-life of terbutaline in plasma of pregnant women is 3.7 h. Further, the cardiovascular effects of beta-mimetic tocolytic agents are known to persist following their discontinuation. Shin and Kim[24] recently observed that maternal hypotension was more common in women in whom induction of epidural anesthesia occurred within 30 min of discontinuation of ritodrine, compared with women in whom there was a delay of greater than 30 min. Ravindran *et al.*[25] and Gerris *et al.*[26] also recommended a delay in induction of general anesthesia after the last injection of the beta-mimetic agent. However, induction of anesthesia for women with failed tocolysis may be required on an emergency basis.

During hypotension resulting from spinal anesthesia in gravid ewes, James *et al.*[8] observed that ephedrine was superior to metaraminol in increasing uterine blood flow toward control values. In the present study, ephedrine was superior to placebo in restoring MMAP and UBFV after hemorrhage. The response to ephedrine was compared with the response to placebo in order to differentiate any effect of ephedrine from the animals' physiologic adaptation to the hemorrhage. The restoration in UBFV was contrary to our original hypothesis, and suggests that ephedrine increased cardiac output despite the presence of preexisting beta-receptor stimulation. Ramanathan *et al.*[27] recently reported that ephedrine increases cardiac preload more effectively than it increases afterload in pregnant women. Lawson and Wallfisch[28] also concluded that ephedrine "produces venoconstriction to a greater degree than arterial constriction . . . [and] causes a redistribution of blood centrally, improves venous return . . . , increases cardiac output, and restores uterine perfusion."[28]

We conclude that ephedrine, 1.0 mg/kg, results in a small, transient decrease in UBFV in the normotensive gravid guinea pig. However, ephedrine aids restoration of UBFV in the gravid guinea pig rendered hypotensive by acute hemorrhage during terbutaline infusion. If applicable to humans, the present study suggests that ephedrine is a rational choice for the initial treatment of hypotension in the pregnant patient who experiences hemorrhage during or following administration of terbutaline.

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