

## Epidural Anesthesia Worsens Uterine Blood Flow and Fetal Oxygenation during Hemorrhage in Gravid Ewes

Robert D. Vincent, Jr., M.D.,\* David H. Chestnut, M.D.,† Susan L. Sipes, M.D.,‡  
Craig S. DeBruyn,§ Papri Chatterjee, M.S.,§ Christine S. Thompson§

Recent studies suggest that epidural anesthesia initiated before hemorrhage may improve survival and acid-base status in laboratory animals. However, studies of hemorrhagic shock in nonpregnant animals may not be applicable to less severe hemorrhage in pregnant animals. The purpose of this study was to determine whether epidural anesthesia alters maternal and fetal hemodynamic and acid-base responses to hemorrhage in gravid ewes. Twenty-four experiments were performed in twelve chronically instrumented animals between 0.8 and 0.9 of timed gestation. The experimental sequence included: 1) T = 0 min: normal saline 500 ml intravenously; 2) T = 15 min: epidural administration of 0.5% bupivacaine (epidural group) or normal saline (control group); 3) T = 30 min: epidural administration of additional 0.5% bupivacaine (epidural group only) if the sensory level of anesthesia was below T10; 4) T = 45 min: maternal hemorrhage 20 ml/kg over 55 min; and 5) T = 110 min: transfusion of collected maternal blood over 55 min. At 45 min (*i.e.*, 30 min after the epidural injection of bupivacaine), epidural bupivacaine resulted in a median sensory level of T9 in the epidural group. At that time, maternal mean arterial pressure was less ( $P < 0.05$ ) in the epidural group than in the control group ( $14 \pm 2\%$  below baseline *versus*  $4 \pm 1\%$  above baseline, respectively). Maternal mean arterial pressure, heart rate, cardiac output, and uterine blood flow, and fetal  $P_{O_2}$  and  $pH$  all were significantly less during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group. Two fetal deaths occurred during the experiment in the epidural group *versus* none in the control group ( $P$  not significant). Plasma epinephrine concentrations increased similarly during hemorrhage in both groups. Plasma norepinephrine concentrations were significantly less during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group. In summary, epidural anesthesia significantly worsened maternal hypotension, uterine blood flow, and fetal oxygenation during hemorrhage (20 ml/kg) in gravid ewes. If applicable to humans, the present study suggests that epidural anesthesia may adversely affect the compensatory response to *untreated* hemorrhage in pregnant women. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Catecholamines: epinephrine; norepinephrine. Hemorrhage.)

\* Assistant Professor, Department of Anesthesia.

† Professor of Anesthesia and Obstetrics and Gynecology.

‡ Fellow, Department of Obstetrics and Gynecology.

§ Research Assistant.

Received from the University of Iowa College of Medicine, Iowa City, Iowa. Accepted for publication January 6, 1992. Supported in part by National Institutes of Health Biomedical Research Support Grant RR 05372 and National Institutes of Health Grant GM 40917. Presented in part at the Annual Meeting of the Society for Obstetric Anesthesia and Perinatology, Boston, Massachusetts, May 23, 1991, and at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 30, 1991.

Reprints will not be available.

Address correspondence to Dr. Vincent: Department of Anesthesia, the University of Iowa, Iowa City, Iowa 52242.

EPIDURAL ANESTHESIA is contraindicated in pregnant patients who are actively bleeding or are hypovolemic secondary to recent bleeding. However, some normovolemic parturients who are at risk for hemorrhage (*e.g.*, abnormal placentation, partial placental abruption, or intrauterine hemangioma) may request pain relief during labor. There are no published data on the effects of epidural anesthesia on the maternal and fetal responses to hemorrhage *after* induction of epidural anesthesia.

Studies of hemorrhagic shock in nonpregnant animals may not be applicable to pregnant women who bleed during epidural anesthesia. Regional anesthesia-induced hypotension decreases uterine blood flow (UBF).<sup>1</sup> However, epidural anesthesia attenuates the increase in plasma catecholamines<sup>2,3</sup> and the decrease in UBF during certain maternal stress responses.<sup>2</sup> The purpose of this study was to determine whether epidural anesthesia alters the maternal and fetal hemodynamic and acid-base responses to subsequent hemorrhage in gravid ewes.

### Materials and Methods

The protocol was approved by the University of Iowa Animal Care Committee. 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 1.0–2.0% 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 (MX566, Medex, Hilliard, OH) was secured to the fetal hindlimb to monitor amniotic pressures. 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 *via* the left mammary and femoral arteries and into the inferior vena cava vein *via* the left mammary vein. All catheters were tunneled subcutane-

ously and exteriorized through a small incision in the left flank. A single-orifice, 19-G catheter (Portex, Wilmington, MA) was inserted percutaneously into the epidural space at the lumbosacral junction, and the catheter was secured to the back. Finally, an 8.5-Fr introducer (AK-09800, Arrow, Reading, PA) was placed percutaneously into the right jugular vein. Eight milliliters 2% lidocaine was injected through the epidural catheter before the animal was awakened. After surgery, the sensory level of anesthesia was determined using a curved hemostat: specifically, the sheep responds to application of the hemostat with muscular twitching above the level of anesthesia.

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 3 days. Procaine penicillin G 500,000 U and dihydrostreptomycin 625 mg (Distrycilin®, Solvay, Princeton, NJ) were given to the mother intramuscularly the day of surgery and daily for 3 days after surgery. Gentamicin 80 mg was given to the mother intravenously 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.

Each experiment was performed with the animal standing, supported by a canvas sling, within an approved transport cart. The canvas sling allowed the animals to remain upright despite fatigue during the experiment, and despite the occurrence of hindlimb weakness during epidural anesthesia.

Before the first experiment, a pulmonary artery catheter (93A-831H-7.5F, American Edwards, Santa Ana, CA) was inserted through the jugular vein introducer. Maternal arterial blood pressure, central venous pressure, pulmonary artery pressure, and fetal arterial blood pressure were measured continuously with disposable strain gauge pressure transducers (46951-02, Abbott Critical Care Systems, North Chicago, IL) *via* Coulbourn transducer couplers (S72-25, 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 heart rate (HR) and fetal HR were computed from the arterial waveforms. Uterine artery blood flow was measured continuously with a quantitative electromagnetic flow meter (RF-2500, Dienco). Arterial and venous pressures, HR, and UBF were recorded at 10-s intervals using a computer-based data acquisition system (Alternatives Unlimited, Des Moines, IA).

Cardiac output measurements were made in triplicate with 10 ml iced saline and a thermodilution cardiac output computer (9520A, American Edwards). Maternal and fetal arterial blood gas and pH measurements were determined using an Instrumentation Laboratory (1302, Leighton, MA) blood gas analyzer. All values were corrected for temperature (39.5° C).

The experimental sequence included the following:

1. Sixty minutes was allowed for the animal to acclimate to the laboratory environment.
2. Ten minutes was required for baseline measurements.
3. At time zero, each animal received a 500-ml intravenous bolus of normal saline over 12 min.
4. At 15 min, each animal received 6–20 ml 0.5% bupivacaine (epidural group) or an identical volume of normal saline (control group) *via* the epidural catheter. The initial dose of bupivacaine was based on the response to epidural lidocaine at surgery.
5. At 30 min, additional 0.5% bupivacaine was injected *via* the epidural catheter (epidural group only) if the sensory level of anesthesia was lower than T10.
6. At 30 min, each animal received heparin 15,000 U intravenously.
7. At 45 min, each animal was bled 20 ml/kg *via* the femoral arterial catheter with a constant rate withdrawal-infusion pump over 55 min.
8. At 110 min, the collected maternal arterial blood was reinfused over 55 min.
9. Hemodynamic measurements were continued until the end of the experiment at 170 min.

Plasma norepinephrine (NE) and epinephrine (EPI) concentrations were determined by <sup>3</sup>H radioenzymatic assay<sup>4</sup> from duplicate samples of maternal arterial blood collected at baseline and at 45, 75, and 100 min. This assay has a sensitivity of 20 pg/ml for both EPI and NE. The median intraassay coefficient of variation for the paired samples was 5.4% for EPI and 9.6% for NE.

Twenty-four experiments were performed in 12 animals. Both experiments were performed in each animal in random order, but only one experiment was done each day.

All data are reported as mean  $\pm$  SEM unless noted otherwise. Statistical analysis of hemodynamic, acid-base, and arterial blood gas measurements was by repeated measures analysis of variance. Fisher's exact test (two-tail) was used to compare survival data between the two groups. Stepwise linear regression analysis was used to compare the UBF/MAP responses during hemorrhage between groups.  $P < 0.05$  was considered significant.

## Results

The mean weight of the animals was  $64 \pm 3$  kg. The two groups were similar with regard to baseline maternal and fetal hemodynamic, blood gas, and acid-base measurements (table 1). Two fetal deaths occurred during the experiment (at 93 and 104 min) in the epidural group *versus* none in the control group ( $P$  not significant).

At 45 min (30 min after epidural bupivacaine *or* normal

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

	Epidural Group (n = 12)	Control Group (n = 12)
<b>Maternal</b>		
Heart rate (beats/min)	126 ± 4	128 ± 3
(mmHg)	97 ± 3	100 ± 3
Stroke volume (ml)	89 ± 3	89 ± 4
Cardiac output (l/min)	11.2 ± 0.5	11.4 ± 0.6
Uterine blood flow	853 ± 101	836 ± 94
Pulmonary capillary wedge pressure	9.3 ± 1.1	9.8 ± 1.3
Systemic vascular resistance (dyne · cm <sup>-5</sup> · s <sup>-1</sup> )	681 ± 47	696 ± 56
Uterine vascular resistance (dyne · cm <sup>-5</sup> · s <sup>-1</sup> )	11,120 ± 2,950	12,320 ± 3,740
pH	7.45 ± 0.01	7.46 ± 0.01
P <sub>O<sub>2</sub></sub> (mmHg)	105 ± 3	108 ± 2
P <sub>CO<sub>2</sub></sub> (mmHg)	38 ± 1	38 ± 1
<b>Fetal</b>		
Heart rate (beats/min)	171 ± 5	164 ± 4
Mean arterial (mmHg)	44 ± 2	45 ± 1
pH	7.34 ± 0.01	7.32 ± 0.02
P <sub>O<sub>2</sub></sub> (mmHg)	21 ± 1	21 ± 1
P <sub>CO<sub>2</sub></sub> (mmHg)	52 ± 1	52 ± 1

All values are expressed as mean ± SEM.

There were no significant differences between the two groups.

saline), epidural bupivacaine (total dose 17 ± 2 ml) resulted in a median sensory level of T9 in the epidural group (table 2).

Maternal HR was lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group (fig. 1). During transfusion, maternal HR was slightly higher ( $P < 0.05$ ) in the epidural group than in the control group.

At 45 min (*i.e.*, 30 after the induction of epidural anesthesia and just before hemorrhage), maternal MAP was lower ( $P < 0.05$ ) in the epidural group than in the control group (fig. 1). Also, maternal MAP was lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group. However, during transfusion there was no significant difference between the two groups.

At 45 min, maternal cardiac output was lower ( $P < 0.05$ ) in the epidural group than in the control group (fig. 2). During hemorrhage, maternal cardiac output was lower ( $P < 0.05$ ) in the epidural group than in the control group.

Maternal stroke volume decreased during hemorrhage ( $P < 0.05$ ) and increased during transfusion ( $P < 0.05$ ) in both groups (data not shown). However, there was no significant difference between the two groups at any time.

TABLE 2. Median Sensory Level of Anesthesia over Time in the Epidural Group

Time (min)	Level of Anesthesia
45	T9
75	T8
105	T9
135	T12
165	T13

Maternal pulmonary capillary wedge pressure did not differ significantly between the two groups at any time (fig. 2).

Maternal systemic vascular resistance increased significantly during hemorrhage only in the epidural group ( $P < 0.05$ ) (fig. 2).

UBF was significantly lower ( $P < 0.05$ ) and uterine vascular resistance (UVR) tended to be higher ( $P = 0.060$ , not significant) during hemorrhage in the epidural group than in the control group (fig. 3). Regression analysis of UBF on maternal MAP during hemorrhage (*i.e.*, 45–105 min) indicates that the UBF response to hypotension was similar in the two groups (fig. 4).

Fetal HR measurements did not differ over time either within or between groups (data not shown). Fetal MAP increased during hemorrhage ( $P < 0.05$ ) in both groups (data not shown).

Maternal pH measurements were not significantly different between the two groups during hemorrhage (fig. 5). However, maternal pH was slightly lower during transfusion ( $P < 0.05$ ) in the epidural group than in the control group.

Fetal P<sub>O<sub>2</sub></sub> and pH were lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group (fig. 6). Fetal pH decreased significantly during hemorrhage ( $P < 0.05$ ) in the epidural group, but not in the control group (fig. 6).

Plasma EPI concentrations increased during hemorrhage ( $P < 0.05$ ) in both groups (fig. 7). However, there was no significant difference in plasma EPI concentrations between groups at any time. At 45 min, plasma NE concentrations were decreased below baseline measurements ( $P < 0.05$ ) in the epidural group but not in the control

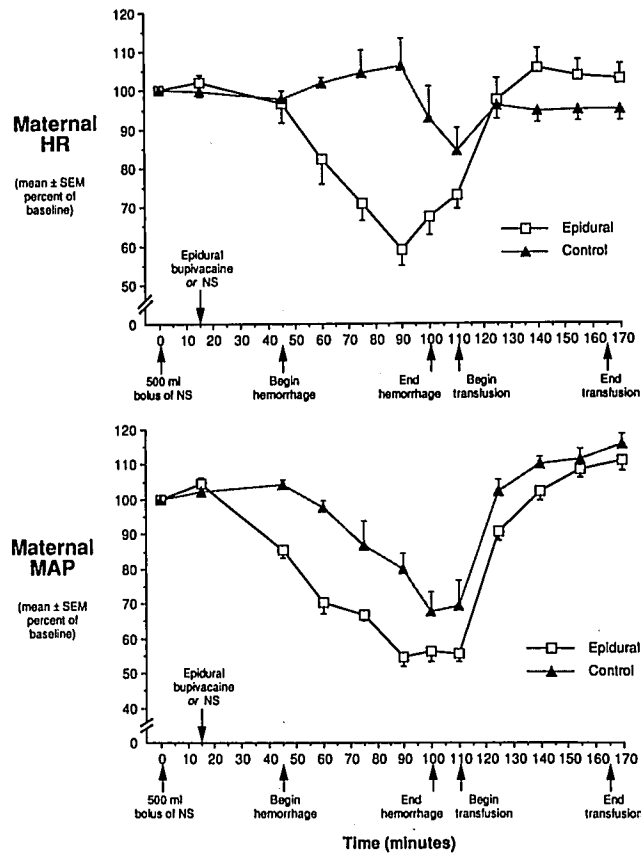


FIG. 1. Maternal heart rate (HR) and mean arterial pressure (MAP) responses over time. Maternal HR was lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group. During transfusion, maternal HR was slightly higher ( $P < 0.05$ ) in the epidural group than in the control group. Maternal MAP was lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group.

group (fig. 7). Also, plasma NE concentrations were lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group.

### Discussion

We observed that epidural anesthesia administered *before* hemorrhage worsened maternal hypotension, UBF, and fetal oxygenation and pH during hemorrhage in gravid ewes. However, Shibata *et al.*<sup>5</sup> observed that thoracic epidural anesthesia initiated *before* hemorrhage increased survival and decreased metabolic acidosis during hemorrhagic shock in nonpregnant dogs. Differences in methodology may partially explain the apparent contrast of the findings of the present study to those of Shibata *et al.*<sup>5</sup> First, we studied pregnant animals because we were also interested in the effects of epidural anesthesia and hemorrhage on maternal UBF and on fetal oxygenation and acid-base status. Second, we bled our animals less extensively because the more severe hypotension achieved

in their study would have caused death in all fetuses. Third, we bled each animal identically (20 ml/kg), irrespective of the decrease in maternal MAP during hemorrhage. Thus, maternal MAP was lower in the ewes bled during epidural anesthesia. In contrast, Shibata *et al.*<sup>5</sup> bled anesthetized dogs (both with and without epidural anesthesia) to a uniform MAP (*i.e.*, 40 mmHg) that was maintained until the end of the experiment.

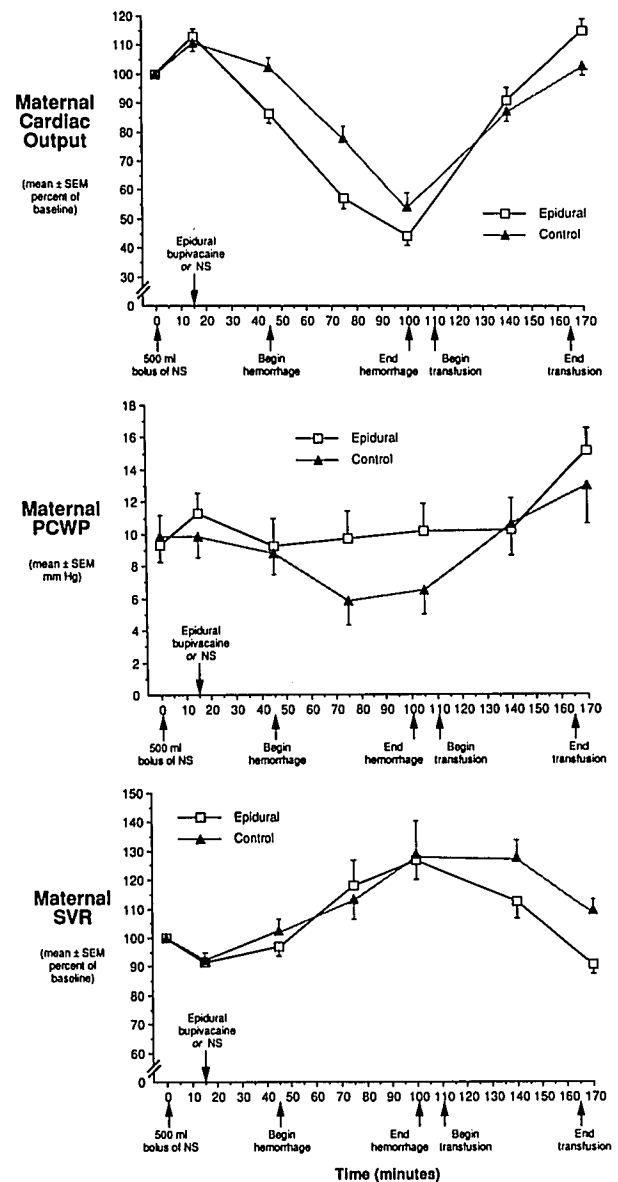


FIG. 2. Maternal cardiac output, pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR) responses over time. Maternal cardiac output was lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group. Maternal PCWP did not differ significantly between the two groups at any time. SVR increased during hemorrhage ( $P < 0.05$ ) in the epidural group but not in the control group.

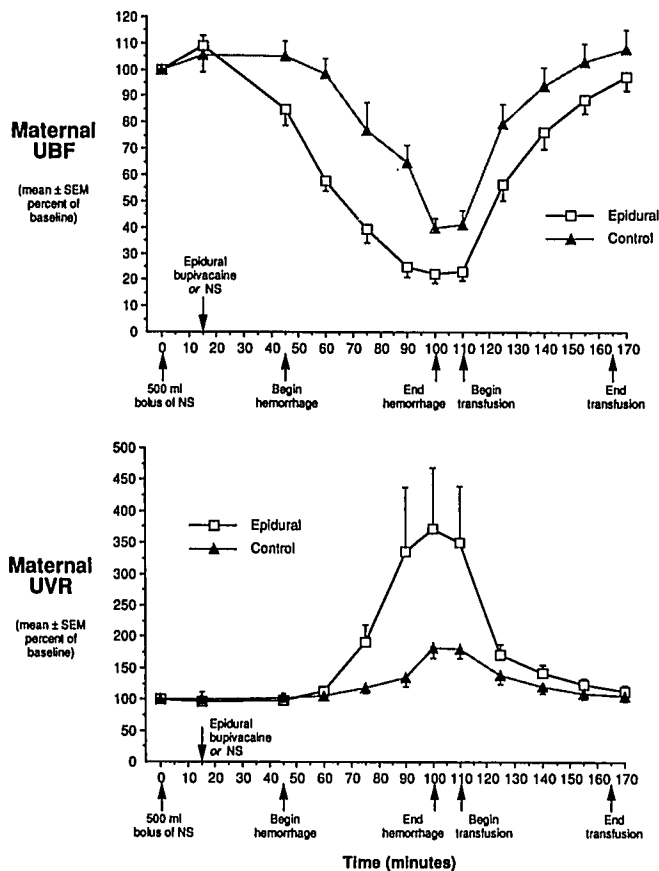


FIG. 3. Uterine blood flow (UBF) and uterine vascular resistance (UVR) responses over time. UBF was lower ( $P < 0.05$ ) and UVR tended to be higher ( $P = 0.060$ , not significant) during hemorrhage in the epidural group than in the control group.

Possible benefits of epidural anesthesia during hemorrhagic hypotension may be related to sympathetic blockade. Previous investigators<sup>6-8</sup> have demonstrated that  $\alpha$ -adrenergic antagonists increase organ blood flow and decrease mortality during hemorrhagic shock in animals. In these studies, animals were bled to a predetermined MAP (e.g., 40 mmHg) that was maintained for a specified period of time. Thus, the blood volume removed during hemorrhage may have been less in the treated than in the control animals. (Of course, in clinical practice control of blood pressure during massive hemorrhage is less precise.) In contrast to these studies in which a predetermined MAP was achieved and maintained during hemorrhagic shock, Block *et al.*<sup>9</sup> observed that  $\alpha_1$  blockade with prazosin worsened the hemodynamic response to hemorrhage (20% blood volume loss) in nonpregnant ewes. Also, Da Luz *et al.*<sup>11</sup> found that the  $\alpha$  antagonist

phenolamine was not effective for treating hypovolemic shock in patients.

In the present study, we found that maternal HR decreased significantly during hemorrhage in the epidural group but not in the control group. Similarly, Shibata *et al.*<sup>5</sup> also found that HR decreased during hemorrhage after "upper level" (C6 to T10) epidural anesthesia. Also, Bonica *et al.*<sup>10</sup> observed that HR decreased 30% in male volunteers given epidural anesthesia after hemorrhage (10 ml/kg). They noted that two of these patients experienced periods of "vagal arrest" necessitating intravenous ephedrine. Together, these observations suggest that epidural anesthesia may predispose to bradycardia during hemorrhagic hypotension.

Others have observed decreased HR during hemorrhage in unanesthetized humans and in animals.<sup>11,12</sup> During hemorrhagic hypotension, increased vagal afferent nerve activity mediated *via* intracardiac volume receptors initiates a sympathoinhibitory phase of hemorrhage that includes decreased HR.<sup>12,13</sup> However, it is unclear whether the bradycardia observed during hemorrhage and hypotension is detrimental.<sup>12</sup> Oberg and Thoren<sup>14</sup> speculated that decreased HR during hemorrhage may be a protective mechanism that allows for improved ventricular filling during periods of hypovolemia. Indeed, atropine increases HR but not MAP during lower body negative-pressure-induced hypotension in humans.<sup>15</sup> In the present study, it is unclear whether the bradycardia observed during hemorrhage in the epidural group represents a compensatory response to optimize cardiac preload. However, we note that pulmonary capillary wedge pressure measurements were similar in the two groups during hemorrhage.

In the present study, lower maternal MAP and greater UVR were responsible for the substantially lower UBF in the epidural group. At least two different mechanisms may be responsible for the increase in UVR during hemorrhagic hypotension. First, generalized sympathetic nervous system stimulation occurs during hemorrhage.<sup>16,17</sup> NE release from postganglionic sympathetic nerve terminals and elevated secretion of EPI and NE from the adrenal medulla result in increased UVR.<sup>18-21</sup> Second, the maternal stress hormones arginine vasopressin and angiotensin II also increase during hemorrhagic hypotension.<sup>22-26</sup> These hormones increase UVR in gravid ewes.<sup>27,28</sup> In the present study, UVR tended to be higher during hemorrhage in the epidural group than in the control group. Thus, greater hypotension in the epidural group was associated with increased uterine arterial vasoconstriction. This occurred despite epidural anesthesia-induced blockade of the sympathetic nerves to the uterus and lower plasma NE concentrations.

Although we did not attempt to correct for the difference in maternal MAP caused by epidural anesthesia

11 Da Luz PL, Shubin H, Weil MH: Effectiveness of phenolamine for reversal of circulatory failure (shock). *Crit Care Med* 1:135-140, 1973.

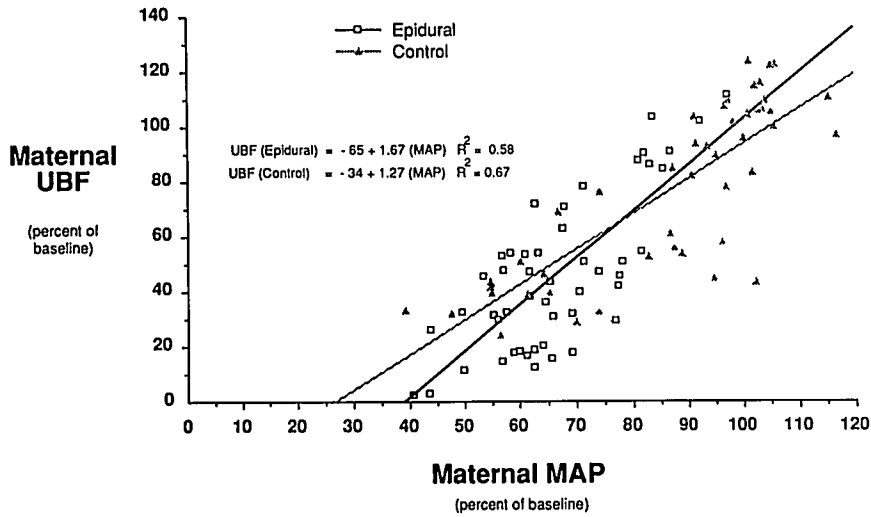


FIG. 4. Maternal uterine blood flow (UBF) versus maternal mean arterial pressure (MAP) during hemorrhage (*i.e.*, 45–105 min). UBF for a given maternal MAP was similar during hemorrhage in the two groups. Regression analysis of UBF on maternal MAP during hemorrhage indicates that the UBF response to hypotension was similar in the two groups.

alone, UBF during hemorrhage was closely related to maternal MAP in both groups. This suggests that UVR increases as MAP decreases, independent of the cause (*i.e.*, sympathectomy and hemorrhage *vs.* hemorrhage alone) of maternal hypotension. We speculate that increased concentrations of arginine vasopressin and (possibly) plasma renin activity may have counterbalanced reduced sympathetic activity in the epidural group. Indeed, Peters *et al.*<sup>29</sup> found that epidural anesthesia-induced hypotension increased plasma arginine vasopressin concentrations in dogs. However, results of studies of the response of plasma renin activity to hypotension during epidural anesthesia are conflicting. Ecoffey *et al.*<sup>30</sup> and Stanek *et al.*<sup>31</sup> found that plasma renin activity increased during epidural anesthesia-induced hypotension. However, Pe-

ters *et al.*<sup>29</sup> and Zayas *et al.*<sup>32</sup> found that the response of plasma renin activity to hypovolemia was attenuated during high thoracic epidural anesthesia.

Because both experiments were performed in each ewe, some animals underwent hemorrhage 1–2 days after an initial hemorrhage. The adrenergic and humoral responses to hemorrhage may be altered when bleeding is repeated at short intervals.<sup>33,34</sup> Thus, the inability of epidural anesthesia to alter the UBF/MAP relationship to hemorrhagic hypotension in the present study might have been different if each animal had been bled only once. However, altered neurohumoral responses should not have caused the differences observed *between* groups since the order of experiments was randomized.

In the present study, the animals remained upright but

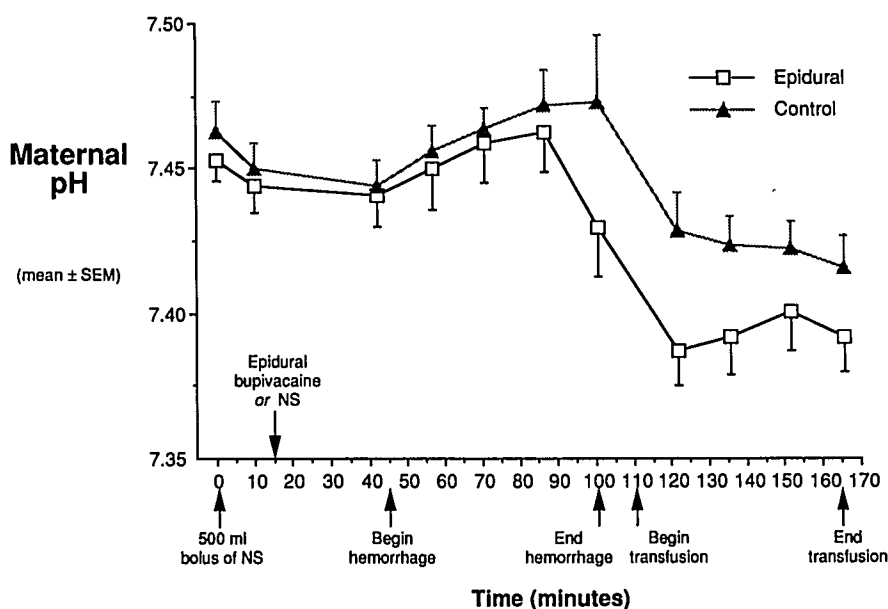


FIG. 5. Maternal pH response over time. Maternal pH was slightly lower during transfusion ( $P < 0.05$ ) in the epidural group than in the control group.

were supported by a canvas sling. This increases amniotic pressure slightly in some animals, indicating uterine (and possibly) vena caval compression (unpublished observation). Thus, aortocaval compression may have contributed to the hemodynamic changes observed during hemorrhage. However, we do not believe that this was responsible for the differences observed between groups during hemorrhage. First, amniotic pressure measurements were not significantly different during hemorrhage in the two groups (data not shown). Also, many animals in the control group became fatigued and also were supported by the canvas sling during hemorrhage.

In summary, epidural anesthesia significantly worsened maternal hypotension, UBF, and fetal  $P_{O_2}$  and  $pH$  during hemorrhage (20 ml/kg) in gravid ewes. Intravascular volume replacement promptly eliminated the differences between groups in maternal MAP, cardiac output, and fetal  $P_{O_2}$ . However, fetal  $pH$  remained slightly lower during transfusion in the epidural group. If applicable to humans, the present study suggests that epidural anesthesia may

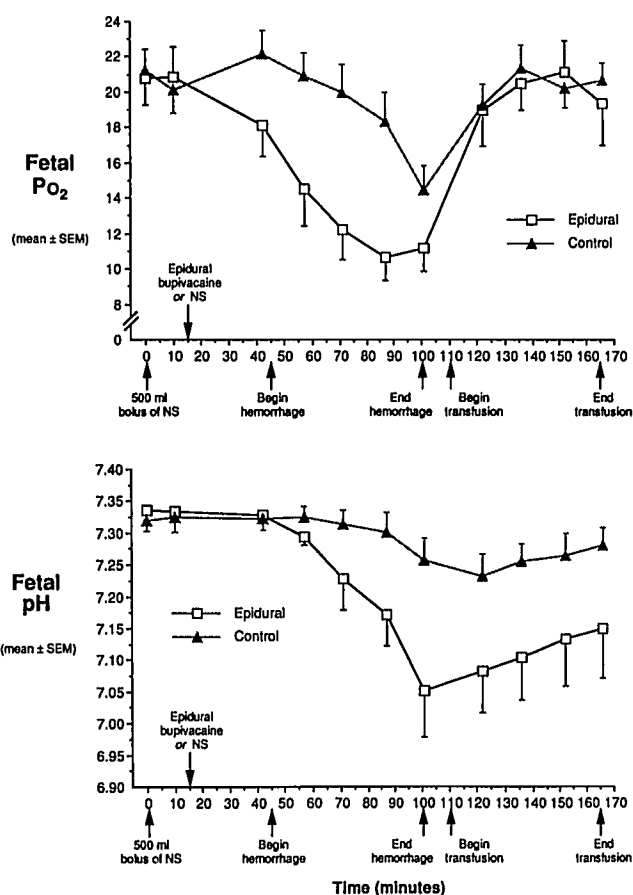


FIG. 6. Fetal  $P_{O_2}$  and  $pH$  responses over time. Fetal  $P_{O_2}$  and  $pH$  were lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group. Fetal  $pH$  decreased during hemorrhage ( $P < 0.05$ ) in the epidural group but not in the control group.

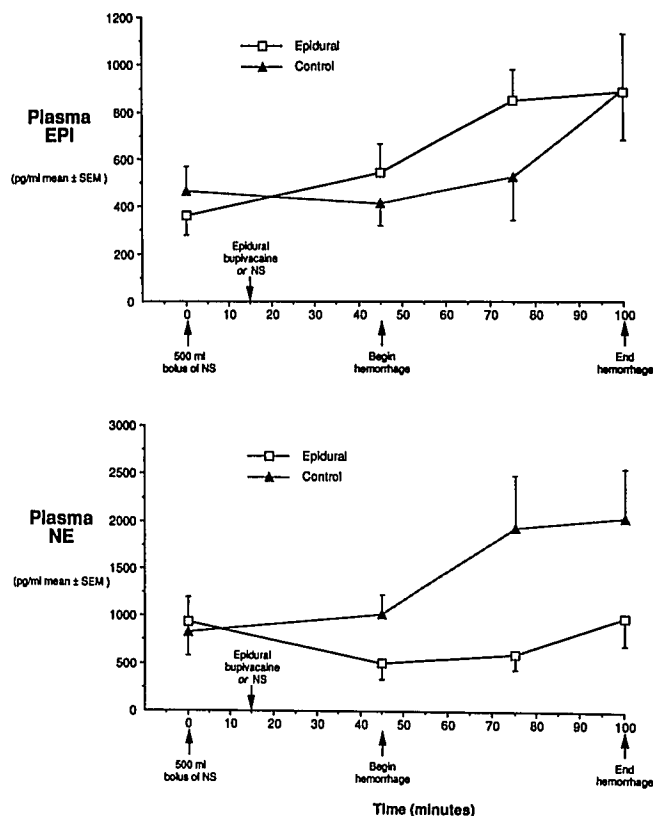


FIG. 7. Plasma epinephrine (EPI) and norepinephrine (NE) concentrations over time. Plasma EPI concentrations increased during hemorrhage ( $P < 0.05$ ) in both groups. At 45 min, plasma NE concentrations were decreased below baseline measurements ( $P < 0.05$ ) in the epidural group but not in the control group. Also, plasma NE concentrations were lower during hemorrhage ( $P < 0.05$ ) in the epidural group than in the control group.

adversely affect the compensatory response to *untreated* hemorrhage in pregnant women.

### References

- Greiss FC, Crandell DL: Therapy for hypotension induced by spinal anesthesia during pregnancy. *JAMA* 191:89-92, 1965
- Shnider SM, Wright RG, Levinson G: Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. *ANESTHESIOLOGY* 50:524-527, 1979
- Shnider SM, Abboud TK, Artal R, Henriksen EH, Stefani SJ, Levinson G: Maternal catecholamines decrease during labor after lumbar epidural anesthesia. *Am J Obstet Gynecol* 147: 13-15, 1983
- Peuler JD, Johnson GA: Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci* 21:625-636, 1977
- Shibata K, Yamamoto Y, Murakami S: Effects of epidural anesthesia on cardiovascular response and survival in experimental hemorrhagic shock in dogs. *ANESTHESIOLOGY* 71:953-959, 1989
- Hershey SG, Zweifach BW, Antopol W: Factors associated with protection against experimental shock. *ANESTHESIOLOGY* 17: 265-276, 1956

7. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG: The nature of irreversible shock: Experimental and clinical observations. *Ann Surg* 160:682-710, 1964
8. Lotz F, Beck L, Stevenson JAF: The influence of adrenergic blocking agents on metabolic events in hemorrhagic shock in the dog. *Can J Biochem* 33:741-752, 1955
9. Block SM, Rose JC, Ernest JM, Flowe K, South S, Zimmerman C: Cardiovascular and endocrine response to hemorrhage after alpha-1 blockade in lambs and ewes. *Am J Physiol* 252:R314-R319, 1987
10. Bonica JJ, Kennedy WF, Akamatsu TJ, Gerbershagen HU: Circulatory effects of peridural block: III. Effects of acute blood loss. *ANESTHESIOLOGY* 36:219-227, 1972
11. Jacobsen J, Sofelt S, Sheikh S, Warberg J: Cardiovascular and endocrine responses to hemorrhage in the pig. *Acta Physiol Scand* 138:167-173, 1990
12. Sander-Jensen K, Secher NH, Bie P, Warberg J, Schwartz TW: Vagal slowing of the heart during haemorrhage: Observations from 20 consecutive hypotensive patients. *Br Med J* 292:364-366, 1986
13. Schadt JC, Ludbrook J: Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *Am J Physiol* 260:H305-H318, 1991
14. Oberg B, Thoren P: Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat: A possible cause of the vasovagal reaction. *Acta Physiol Scand* 85:164-173, 1972
15. Murray RH, Shropshire S: Effect of atropine on circulatory responses to lower body negative pressure and vasodepressor syncope. *Aerospace Med* 41:717-722, 1970
16. Guyton AC: *Textbook of Medical Physiology*. Philadelphia, WB Saunders, 1991, p 264
17. Gann DS, Amaral JF: Endocrine and metabolic responses to injury, *Principles of Surgery*. Edited by Schwartz SI, Shires GT, Spencer FC. New York, McGraw-Hill, 1992, pp 1-68
18. Greiss FC, Gobble FL: Effect of sympathetic nerve stimulation on the uterine vascular bed. *Am J Obstet Gynecol* 97:962-967, 1964
19. Barton MD, Killam AP, Meschia G: Response of ovine uterine blood flow to epinephrine and norepinephrine. *Proc Soc Exp Biol Med* 145:996-1003, 1974
20. Rosenfeld CR, Barton MD, Meschia G: Effects of epinephrine on distribution of blood flow in the pregnant ewe. *Am J Obstet Gynecol* 124:156-163, 1976
21. Greiss FC: Uterine vascular response to hemorrhage during pregnancy: With observations on therapy. *Obstet Gynecol* 27:549-554, 1966
22. Lilly MP, DeMaria EJ, Bruhn TO, Gann DS: Potentiated cortisol response to paired hemorrhage: role of angiotensin and vasopressin. *Am J Physiol* 257:R118-R126, 1989
23. Oliver JR, Korner PI, Woods RL, Zhu JL: Reflex release of vasopressin and renin in hemorrhage is enhanced by autonomic blockade. *Am J Physiol* 258:H221-H228, 1990
24. Wang BC, Sundet WD, Hakumaki MOK, Goetz KL: Vasopressin and renin responses to hemorrhage in conscious, cardiac denervated dogs. *Am J Physiol* 245:H399-H405, 1983
25. Larsson B, Olsson K, Fyhrquist F: Vasopressin release induced by hemorrhage in the goat. *Acta Physiol Scand* 104:309-317, 1978
26. Quail AW, Woods RL, Korner PI: Cardiac and arterial baroreceptor influences in release of vasopressin and renin during hemorrhage. *Am J Physiol* 252:H1120-H1126, 1987
27. Sipes SL, Chestnut DH, Vincent RD, Weiner CP, Thompson CS, Chatterjee P: Does magnesium sulfate alter the maternal cardiovascular response to vasopressor agents in gravid ewes? *ANESTHESIOLOGY* 75:1010-1018, 1991
28. Greiss FC, Van Wilkes D: Effects of sympathomimetic drugs and angiotensin on the uterine vascular bed. *Obstet Gynecol* 23:925-930, 1967
29. Peters J, Schlaghecke R, Thouet H, Arndt JO: Endogenous vasopressin supports blood pressure and prevents severe hypotension during epidural anesthesia in conscious dogs. *ANESTHESIOLOGY* 73:694-702, 1990
30. Ecoffey C, Edouard A, Pruszczyński W, Taly E, Samii K: Effects of epidural anesthesia on catecholamines, renin activity, and vasopressin changes induced by tilt in elderly men. *ANESTHESIOLOGY* 62:294-297, 1985
31. Stanek B, Schwarz M, Zimpfer M, Raberger G: Plasma concentrations of noradrenaline and adrenaline and plasma renin activity during extradural blockade in dogs. *Br J Anaesth* 52:305-311, 1980
32. Zayas VM, Sharrock MB, Blumenfeld J, McDonald M, Sealey J: Hormonal responses during hypotensive epidural anesthesia (abstract). *ANESTHESIOLOGY* 75:A112, 1991
33. Lilly MP, Engeland WC, Gann DS: Adrenal medullary responses to repeated hemorrhage in the conscious dog. *Am J Physiol* R1193-R1199, 1986
34. Lilly MP, DeMaria EJ, Bruhn TO, Gann DS: Potentiated cortisol response to paired hemorrhage: Role of angiotensin and vasopressin. *Am J Physiol* 257:R118-R126, 1989