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Bupivacaine Toxicity in Pregnant and Nonpregnant Ewes

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The relative central nervous system and cardiovascular toxicity of bupivacaine was compared in pregnant and nonpregnant ewes during continuous infusion of bupivacaine into the jugular vein at the rate of 0.5 mg · kg^{-1} · min^{-1}. In all animals, identical symptoms of toxicity occurred in the following order: convulsions, hypotension, respiratory arrest, and circulatory collapse. The dose of bupivacaine required to produce central nervous system (CNS) toxicity in the pregnant ewe tended to be lower than in the nonpregnant animal, although the difference was not statistically significant ($P < 0.1$). However, the mean dose of bupivacaine resulting in cardiovascular collapse was significantly lower in pregnant ewes (5.1 ± 0.7 mg/kg) than in nonpregnant animals (8.9 ± 0.9 mg/kg). Similarly, bupivacaine blood concentrations at the onset of respiratory arrest and circulatory collapse were lower in the pregnant group, being 5.2 ± 0.7 μg/ml and 5.5 ± 0.8 μg/ml, respectively, *versus* 7.5 ± 1.0 μg/ml and 8.0 ± 0.9 μg/ml, respectively, in the nonpregnant group ($P < 0.05$). The concentration of bupivacaine in the brain of pregnant ewes at the time of cardiovascular collapse was significantly lower ($P < 0.01$) than in the nonpregnant group (7.5 ± 1.5 *vs.* 16.3 ± 1.7 μg/g). The myocardial tissue concentration of bupivacaine also tended to be lower in the pregnant group, although the differences were not statistically significant ($P < 0.1$). Comparisons of bupivacaine doses and blood concentrations associated with the onset of convulsions and circulatory collapse (CC/CNS ratio) with those of lidocaine, reported previously, indicate that a narrower margin of safety exists following administration of bupivacaine in nonpregnant sheep. These ratios were 3.7 ±0.5 and 1.6 ±0.1, respectively, for bupivacaine and 7.1 ± 1.1 and 3.6 ± 0.3, respectively, for lidocaine. In addition, the data indicate that the pregnant sheep may be more sensitive to the cardiotoxic effects of bupivacaine than the nonpregnant animal. (Key words: Anesthesia: obstetric. Anesthetics, local: bupivacaine. Toxicity: bupivacaine.)

THE RELATIVE CARDIOTOXICITY of potent local anesthetics such as bupivacaine and etidocaine and the less potent agents such as lidocaine has been the subject of considerable interest and controversy.[1–10] In general, studies in nonanesthetized cats, dogs, and sheep indicate that the ratio of the dose resulting in cardiovascular collapse to the convulsive dose (CC/CNS ratio) is lower for bupivacaine and etidocaine as compared with lidocaine.[3,10,11]

Many of the cases in which cardiovascular collapse has been reported following the accidental intravenous administration of bupivacaine occurred in parturients. It is not known whether the pregnant patient may be more sensitive to the cardiotoxic effects of local anesthetics or if the widespread use of bupivacaine for obstetric analgesia is responsible for the number of cases reported in pregnant women. The current study was instituted in an effort to evaluate the relative cardiotoxicity of bupivacaine in pregnant and nonpregnant sheep. In addition, the bupivacaine results obtained in this study are being compared with previous data obtained in nonpregnant sheep with lidocaine and etidocaine, since the protocol for all of the studies was identical.

Materials and Methods

Nine nonpregnant adult ewes with a mean (±SE) weight of 41.2 ± 3.1 kg, and eight pregnant sheep weighing 53.6 ± 3.9 kg, carrying fetuses of 130 ± 2 days gestation (term 148 days) were used. The details of the surgical procedure have been described elsewhere.[12] Briefly, in the nonpregnant ewe, polyethylene catheters were placed into a carotid artery and a jugular vein under local infiltration with 2-chloroprocaine. Pregnant ewes were given spinal anesthesia with tetracaine, and catheters were inserted into the carotid artery and jugular vein of the mother and fetus, the fetal catheterization being performed through a small hysterotomy. In addition, ECG electrodes were attached over the ewes' extremities on the day of the study. Experiments were performed at least 3 days after surgery.

During the study, the animals were restrained in a cart. Arterial blood pressure and heart rate were mon-

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TABLE 1. Mean (±SE) Preinfusion Values for Heart Rate, Arterial Pressure, pH_a, Pa_{CO_2}, and P_{O_2} in Adult Nonpregnant Ewes, Pregnant Ewes, and Their Fetuses

	Nonpregnant Adult	Mother	Fetus
Heart rate (beats/min)	128 ± 11	109 ± 9	178 ± 13
Mean arterial pressure (mmHg)	90 ± 9	84 ± 3	46 ± 3
pH_a	7.42 ± 0.02	7.48 ± 0.01	7.38 ± 0.01
Pa_{CO_2} (mmHg)	33 ± 1	30 ± 2	44 ± 3
Pa_{O_2} (mmHg)	92 ± 5	99 ± 10	25 ± 1

itored and recorded continuously, while ECG and respiratory rate were recorded intermittently. At no time was any attempt made to support respiration and circulation.

Bupivacaine hydrochloride, 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ was infused continuously into the jugular vein of all the ewes, and arterial blood samples were withdrawn for acid base and drug analyses at the onset of each toxic manifestation, which occurred in sequence as previously described, *viz.* convulsions, hypotension, respiratory arrest, and circulatory collapse. In the pregnant animals, arterial blood samples also were drawn simultaneously from the fetus for determination of bupivacaine concentrations as well as for *p*H, P_{CO_2}, and P_{O_2}. In addition, plasma potassium concentrations were measured (in five pregnant and five nonpregnant ewes). At circulatory collapse, samples of the following organs were obtained from nonpregnant and pregnant sheep, as well as from fetal lambs: brain, lungs, heart, liver, kidneys, and adrenals. These samples were blotted, weighed, and frozen until assayed. Arterial plasma and tissue concentrations of bupivacaine were determined by means of gas chromatography. Using one-way analysis of variance, dosages and plasma concentrations of bupivacaine associated with each toxic manifestation were compared with those for etidocaine and lidocaine, determined in previous experiments. Tissue concentrations at cardiovascular collapse were similarly compared. Student's *t* tests were performed to determine differences between mean doses and concentrations of bupivacaine associated with each toxic manifestation in nonpregnant and pregnant animals ($P < 0.05$ was considered significant).

Results

Mean arterial blood pressure, heart rate, arterial *p*H, Pa_{CO_2}, and Pa_{O_2} prior to infusion of bupivacaine in all animals were normal for our laboratory (table 1). During the infusion, toxic manifestations appeared in all animals in the same sequence previously described for etidocaine and lidocaine. Convulsive activity was the first sign of local anesthetic toxicity, followed by hypotension, respiratory arrest, and cardiovascular collapse. Approximately 3.5 min following the start of bupivacaine infusion, heart rate decreased from 128 ± 11 to 108 ± 24 (mean ± SE) beats/min in the nonpregnant group and from 109 ± 9 to 90 ± 18 beats/min in the pregnant ewes. This mild bradycardia was not associated with any significant change in arterial blood pressure. Tonic-clonic convulsions began approximately 6 min following the start of the bupivacaine infusion. During convulsions the heart rate increased to 189 ± 24 beats/min and 132 ± 8 beats/min ($P < 0.05$) in the nonpregnant and pregnant animal, respectively. Mean arterial pressure increased from 90 ± 9 to 146 ± 9 mmHg in the nonpregnant ewes and from 84 ± 3 to 135 ± 7 mmHg in the pregnant ewes ($P < 0.01$). Most animals hyperventilated spontaneously during convulsions such that no significant changes in arterial blood *p*H, P_{O_2}, or P_{CO_2}, were observed until the late stages of toxicity (table 2). As the infusion continued, hypotension accompanied by bradycardia appeared at approximately 15 min following the start of the infusion in the nonpregnant and at 8 min in the pregnant animals. Respiratory arrest was then observed, preceded by a short period of shallow tachypnea, to be rapidly followed by circulatory collapse, which was the terminal event. Circulatory collapse occurred at 19.4 ± 3.1 min after the start of the drug

TABLE 2. Mean (±SE) Values for pH_a, Pa_{CO_2}, and Pa_{O_2} in Nonpregnant and Pregnant Ewes during Bupivacaine Infusion

	Control	Convulsions	Hypotension	Apnea	Circulatory Collapse
Nonpregnant					
pH_a	7.42 ± 0.02	7.46 ± 0.02	7.30 ± 0.04*	7.21 ± 0.02*	7.20 ± 0.01*
Pa_{CO_2} (mmHg)	33 ± 1	30 ± 1	49 ± 6*	52 ± 4*	61 ± 5*
Pa_{O_2} (mmHg)	92 ± 5	90 ± 5	49 ± 10*	38 ± 4*	26 ± 4*
Pregnant					
pH_a	7.48 ± 0.01	7.48 ± 0.01	7.36 ± 0.04*	7.27 ± 0.07*	7.25 ± 0.08*
Pa_{CO_2} (mmHg)	30 ± 2	32 ± 2	45 ± 6*	48 ± 12	54 ± 10*
Pa_{O_2} (mmHg)	99 ± 10	94 ± 9	62 ± 10*	43 ± 12*	39 ± 12*

*Significantly different from control.

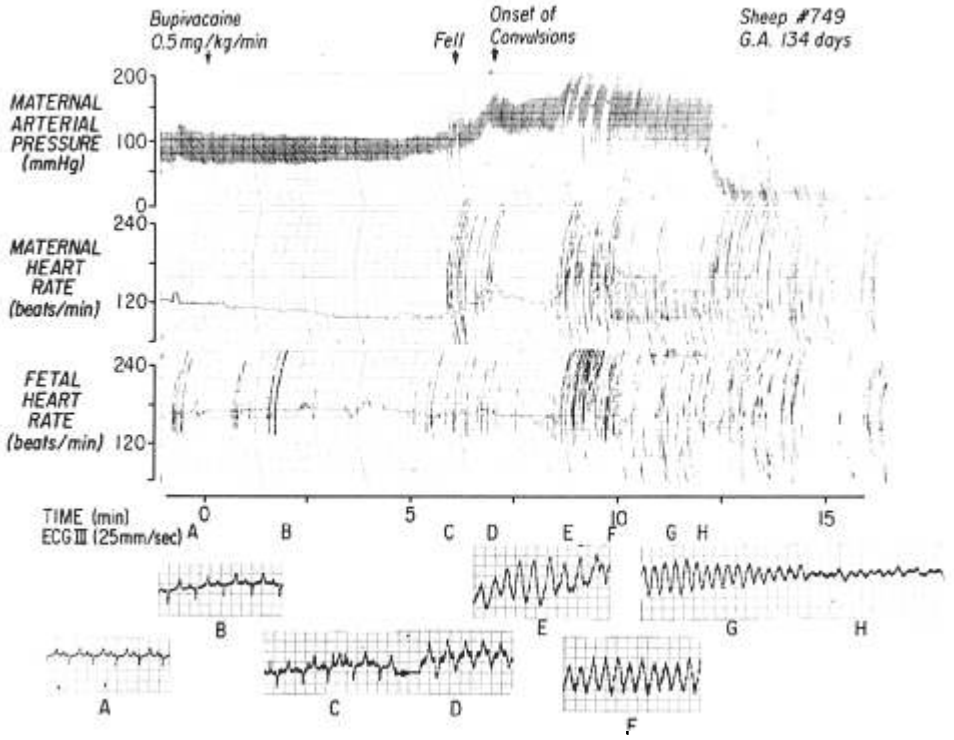

FIG. 1. A typical recording of maternal arterial pressure, heart rate, and ECG, as well as fetal heart rate, in a pregnant sheep during bupivacaine infusion. Frames A to H, representing maternal ECG recordings, show changes from normal sinus rhythm in A, to sinus bradycardia in B, to progressive heart block in C and D, and, finally, to ventricular tachycardia and fibrillation in E through H.

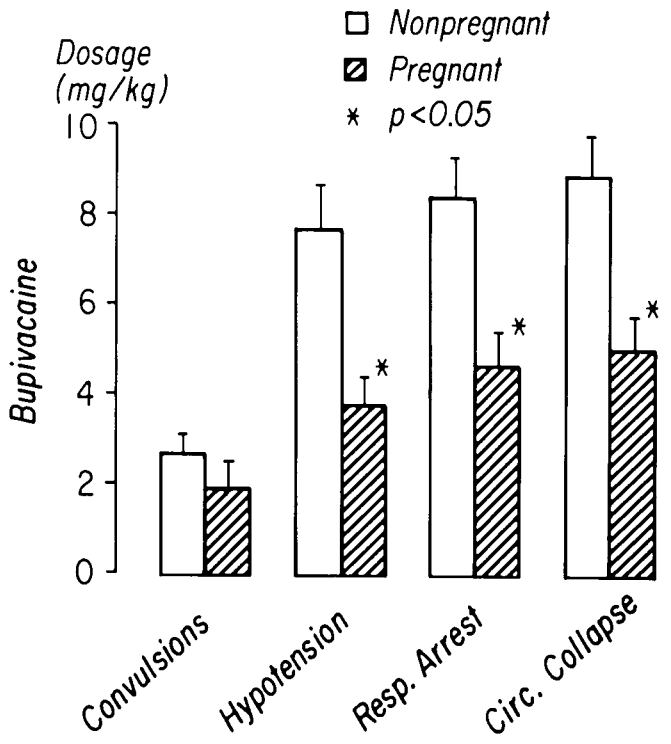

FIG. 2. Mean (±SE) dosages of bupivacaine administered to nonpregnant and pregnant ewes up to the onset of each toxic manifestation. *Significantly different from nonpregnant ewes.

infusion in the nonpregnant group compared with 11.4 ± 1.2 min in the pregnant ewes ($P < 0.05$).

A typical recording of arterial pressure, heart rate, and ECG in a pregnant sheep during bupivacaine infusion is depicted in figure 1. Severe ventricular arrhythmias occurred in all ewes in which terminal ECG patterns were recorded (nine out of the total of 17 animals).

In the fetus, there was a tendency toward an increase in arterial pressure, from 46 ± 3 to 54 ± 4 mmHg ($P < 0.1$), and a decrease in heart rate, from 178 ± 13 to 156 ± 14 beats/min ($P < 0.1$) prior to the onset of maternal convulsions. At the onset of maternal hypotension, fetal arterial pressure had increased to 59 ± 6 mmHg ($P < 0.05$) and heart rate had decreased to 130 ± 20 beats/min ($P < 0.05$). At the time of maternal circulatory collapse, fetal blood pressure and heart rate had decreased markedly to 38 ± 8 mmHg and 100 ± 15 beats/min, respectively ($P < 0.01$). During maternal convulsions, the fetal pH_a did not change significantly, but Pa_{O_2} decreased to 15 ± 0.5 mmHg ($P < 0.01$).

The mean dosages of bupivacaine required for each toxic symptom in nonpregnant and pregnant ewes are depicted in figure 2. Convulsions occurred in nonpregnant animals at a mean dose of 2.7 ± 0.4 mg/kg compared with a dose of 1.9 ± 0.6 mg/kg in pregnant ewes ($P < 0.1$). More serious manifestations of toxicity re-

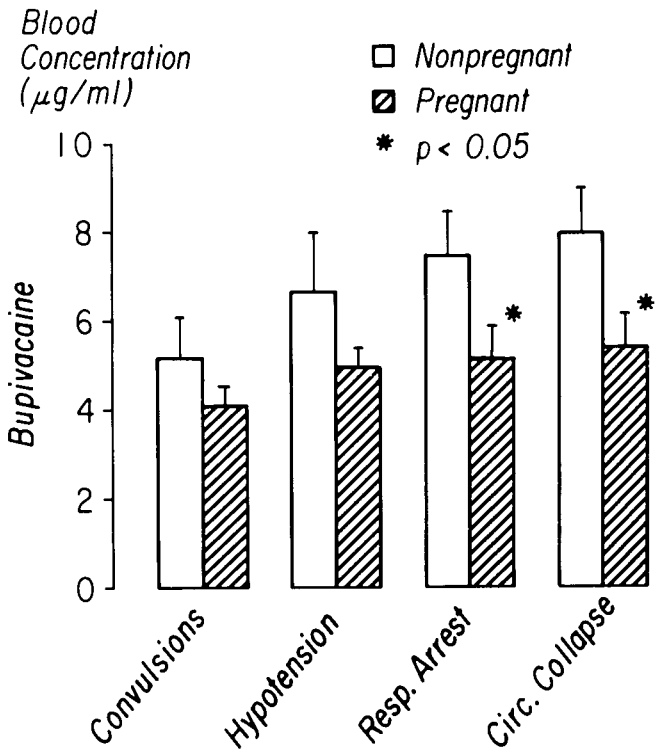

FIG. 3. Mean (±SE) blood concentrations of bupivacaine associated with each toxic manifestation in non-pregnant and pregnant ewes. *Significantly different from nonpregnant ewes.

quired significantly higher doses in nonpregnant sheep. For example, hypotension occurred at a mean dose of 7.7 ± 1 mg/kg in the nonpregnant animals, whereas only 3.8 ± 0.6 mg/kg was required for pregnant animals ($P < 0.05$). Furthermore, the dose necessary to produce circulatory collapse, 8.9 ± 0.9 mg/kg, was almost twice as high as that required by pregnant ewes, 5.1 ± 0.1 mg/kg ($P < 0.05$).

Blood concentrations of bupivacaine associated with the onset of convulsions were 5.2 ± 0.9 μg/ml in the nonpregnant ewes and 4.2 ± 0.4 μg/ml in the pregnant ones ($P < 0.1$) (fig. 3). Respiratory arrest and circulatory collapse occurred with higher blood concentrations in the nonpregnant ewes (7.5 ± 1.0 μg/ml and 8.0 ± 0.9 μg/ml, respectively) than those found in the pregnant ones, 5.2 ±0.7 μg/ml and 5.5 ±0.8 μg/ml, respectively ($P < 0.05$). At the time of maternal circulatory collapse, the fetal plasma concentration of bupivacaine was 2.0 ± 0.4 μg/ml.

The mean tissue concentrations of bupivacaine obtained at the time of circulatory collapse were similar between the nonpregnant and pregnant groups; the only statistically significant differences observed were in the brain concentrations of the drug (fig. 4). Bupivacaine

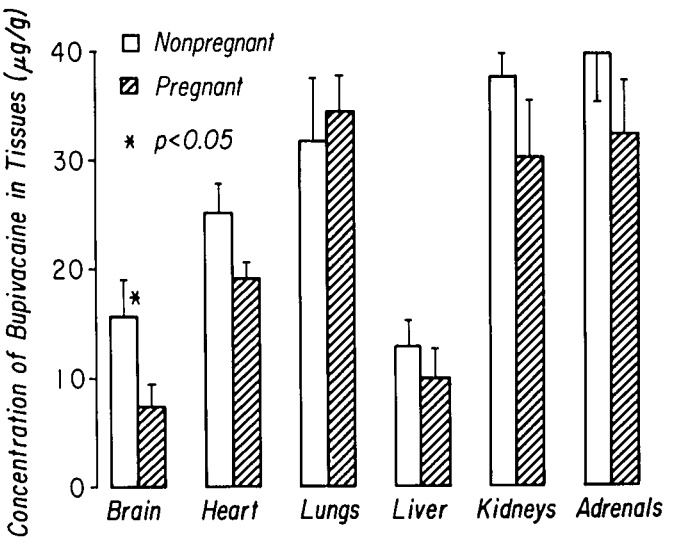

FIG. 4. Mean (±SE) tissue concentrations of bupivacaine obtained at circulatory collapse in nonpregnant and pregnant ewes. *Significantly different from pregnant ewes.

concentrations in the fetal organs, obtained at maternal circulatory collapse, are shown in table 3.

The plasma potassium concentrations prior to and during bupivacaine infusion were similar in nonpregnant and in pregnant animals. Therefore, all potassium values have been combined (table 4). Potassium concentrations tended to increase as intoxication became more severe. Although these changes reached statistical significance ($P < 0.05$) as the respiratory and circulatory arrest developed in the animal, values remained within the normal range for sheep.

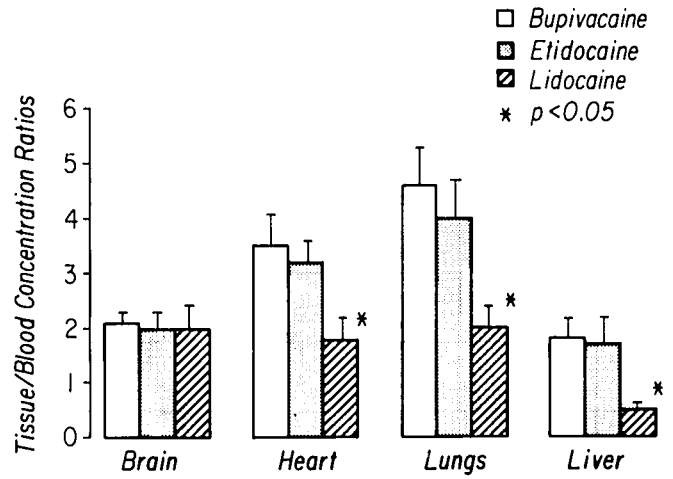

FIG. 5. Comparison of tissue/blood concentration ratios in the main organs of nonpregnant adult sheep between bupivacaine, etidocaine, and lidocaine. *Significantly different from other two drugs.

TABLE 3. Mean (±SE) Values for Concentrations of Bupivacaine in Fetal Tissues

	Brain	Heart	Lungs	Liver	Kidneys	Adrenals
Concentrations (μg/g)	6.2 ± 0.9	4.2 ± 0.7	2.4 ± 0.4	7.5 ± 0.6	3.2 ± 0.5	6.7 ± 1.2

Discussion

Previous *in vivo* and *in vitro* animal studies have indicated that bupivacaine may be more cardiotoxic than lidocaine.[3,5-8] This hypothesis is based on the observation that lower doses of bupivacaine are required to produce cardiovascular collapse relative to lidocaine, even when the difference in anesthetic potency of the two agents is considered, and that lethal cardiac arrhythmias frequently are associated with the rapid intravenous administration of bupivacaine but not lidocaine.

A comparison of results obtained in this study in nonpregnant animals with bupivacaine, and previous studies from our laboratory with lidocaine and etidocaine, also indicates that differences in the CC/CNS ratio exist between the more potent agents, *i.e.,* bupivacaine and etidocaine, and the less potent drug, lidocaine (table 5). For example, the CC/CNS dosage ratio was 7.1 ± 1.1 for lidocaine, compared with a value of 4.4 ± 0.9 for etidocaine and 3.7 ± 0.5 for bupivacaine. Similar differences in the CC/CNS blood level ratios existed between the three agents. In addition, cardiac arrhythmias were observed in the bupivacaine-treated animals in the current study, whereas no arrhythmias were noted in the previous lidocaine study.

A comparison of the tissue/blood concentration ratios of bupivacaine in nonpregnant adult sheep obtained in this study, with the ratios for etidocaine and lidocaine derived from previous studies, is shown in figure 5. With the exception of the brain, this ratio was higher for bupivacaine and etidocaine than for lidocaine. The relatively greater uptake of bupivacaine and etidocaine by the heart may be responsible for the enhanced cardiotoxicity of these agents. The reason for this greater uptake by cardiac tissue as compared with the brain is not known at this time.

The present study not only compared the effects of equipotent doses of local anesthetics in nonpregnant sheep but examined also the differences between pregnant and nonpregnant animals, since many of the adverse cardiac effects ascribed to bupivacaine have occurred in parturients. Significantly lower doses of bupivacaine were required to produce cardiovascular collapse in the pregnant ewe, as compared with the nonpregnant animal. Although the doses associated with the onset of convulsions were not significantly different, they did tend to be lower in pregnant animals. Ravindran *et al.* demonstrated in mice that the threshold to local anesthetic-induced convulsions was reduced in pregnancy.[13] The enhanced cardiac toxicity in pregnant animals apparently is not due to a greater uptake of drug by the myocardium. The cardiac tissue/blood concentration ratio of bupivacaine was approximately 3.5 in nonpregnant ewes compared with a value of approximately 3.3 in pregnant animals. This suggests that the enhanced cardiotoxicity may be related to a greater sensitivity of the myocardium during, at least, the late stages of pregnancy to the potential cardiodepressant effect of bupivacaine. In this regard, it has been shown that isolated nerves from pregnant rabbits are more sensitive to conduction blockade by bupivacaine than those from nonpregnant rabbits.[14] The possible role of the hormones of pregnancy on the physiologic function of nerves and cardiac membranes remains to be investigated.

Although the results of this study clearly indicate that pregnant ewes are more vulnerable in terms of cardiovascular collapse when bupivacaine is administered intravenously, it is not known whether this observation is unique to bupivacaine or whether the cardiotoxicity of all local anesthetics may be enhanced in pregnant animals. Additional studies with other local anesthetics in pregnant and nonpregnant animals obviously are warranted.

Although hypoxia, hypercarbia, acidosis, and hyperkalemia have been reported to accentuate the cardiac toxicity of bupivacaine,[11,15,16] these factors were not responsible for the differences observed between the

TABLE 4. Mean (±SE) Plasma Potassium Concentrations Measured at Each Toxic Manifestation in 10 Adult Sheep

	Preinfusion	Convulsions	Hypotension	Apnea	Circulatory Collapse
Potassium concentration (mEq/l)	3.57 ± 0.13	3.83 ± 0.18	4.09 ± 0.20	4.46 ± 0.26*	4.20 ± 0.21*

* Significantly different from the preinfusion value.

TABLE 5. Mean (±SE) Ratios of Circulatory Collapse (CC) and Convulsive (CNS) Dosages and Blood Concentrations of Bupivacaine, Etidocaine, and Lidocaine in Adult Sheep

	Bupivacaine		Etidocaine*	Lidocaine*
	Pregnant	Nonpregnant	Nonpregnant	Nonpregnant
Dosage ratios (CC/CNS)	2.7 ± 0.4	3.7 ± 0.5†	4.4 ± 0.9	7.1 ± 1.1
Blood level ratios (CC/CNS)	1.4 ± 0.1	1.6 ± 0.1†	1.7 ± 0.2†	3.6 ± 0.3

* Calculated from previously published data.
† Significantly different from lidocaine.

pregnant and nonpregnant animals. Minimal changes in any of these variables were observed in either group prior to the advent of cardiovascular collapse.

In summary, the data from this and previous studies from our laboratories suggest that in the nonpregnant sheep the margin of safety with regard to cardiac toxicity is less for agents such as bupivacaine and etidocaine as compared with lidocaine. In addition, the safety margin for bupivacaine is further reduced in pregnant animals. The differences between agents in the nonpregnant animals appear to be related to differences in myocardial drug uptake, whereas the difference between pregnant and nonpregnant animals is suggestive of a greater myocardial sensitivity in the former.

References

1. Ryan DW: Accidental intravenous injection of bupivacaine: A complication of obstetrical epidural anaesthesia. Br J Anaesth 45:907–908, 1973
2. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine (Editorial). ANESTHESIOLOGY 51: 285–287, 1979
3. deJong RH, Ronfeld RA, DeRosa RA: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 61:3–9, 1982
4. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 61:317–322, 1982
5. Sage DJ, Feldman HS, Arthur GR, Datta S, Ferretti AM, Norway SB, Covino BG: Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. Anesth Analg 63:1–7, 1984
6. Clarkson CW, Hondeghem MD, Matsubara T, Levinson G: Possible mechanism of bupivacaine toxicity: Fast inactivation block with slow diastolic recovery (abstract). Anesth Analg 63:199, 1984
7. Tanz RD, Heskett T, Loehning RW, Fairfax CA: Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 63:549–556, 1984
8. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA: Bupivacaine-induced cardiac arrhythmias in sheep. ANESTHESIOLOGY 60:10–18, 1984
9. Marx, GF: Cardiotoxicity of local anesthetics—the plot thickens (editorial). ANESTHESIOLOGY 60:3–5, 1984
10. Morishima HO, Pedersen, H, Finster M, Feldman HS, Covino BG: Etidocaine toxicity in the adult, newborn and fetal sheep. ANESTHESIOLOGY 58:342–346, 1983
11. Avery T, Redon D, Schaenzer G, Rusy BF: The influence of serum potassium on cerebral and cardiac toxicity of bupivacaine and lidocaine. ANESTHESIOLOGY 61:133–138, 1984
12. Morishima HO, Pedersen H, Finster M, Sakuma K, Bruce SL, Gutsche BB, Stark I, Covino BG: Toxicity of lidocaine in adult, newborn, and fetal sheep. ANESTHESIOLOGY 55:57–61, 1981
13. Ravindran RS, Kim KC, Baldwin SJ: The effect of pregnancy on the threshold to local anesthetic induced convulsions in mice (abstract). ANESTHESIOLOGY 57:A400, 1982
14. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG: Differential sensitivities of mammalian nerve fibers during pregnancy. Anesth Analg 62:1070–1072, 1983
15. Morishima HO, Covino, BG: Toxicity and distribution of lidocaine in nonasphyxiated and asphyxiated baboon fetuses. ANESTHESIOLOGY 54:182–186, 1981
16. Komai H, Rusy BF: Hyperkalemia and bupivacaine block of AV conduction. ANESTHESIOLOGY 53:S210, 1980