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Effect of Epinephrine on Central Nervous System and Cardiovascular System Toxicity of Bupivacaine in Pigs

Christopher M. Bernards, M.D., Randall L. Carpenter, M.D.,† Mark E. Kenter, M.D.,‡ David L. Brown, M.D.,† Stephen M. Rupp, M.D.,† Gale E. Thompson, M.D.§*

To determine what effect the addition of epinephrine has on bupivacaine toxicity, toxic doses of bupivacaine were administered to awake spontaneously breathing pigs. Twenty animals were randomized to one of two groups. One group received an infusion of bupivacaine with epinephrine (5 μg/ml) at a rate of 2 mg · kg^{-1} · min^{-1}; the other received an infusion of plain bupivacaine at the same rate. Bupivacaine infusion was continued until cardiovascular collapse. Following cardiovascular collapse we attempted to resuscitate the animals *via* open chest cardiac massage and a standardized resuscitation protocol. The addition of epinephrine to bupivacaine significantly increased blood pressure and systemic vascular resistance but not heart rate or cardiac output early in the bupivacaine infusion. Epinephrine had no effect on the dose of bupivacaine that caused cardiovascular collapse (P = 0.1), on the plasma concentration of bupivacaine at collapse (P = 0.9), or on the ability to resuscitate animals following cardiovascular collapse. The addition of epinephrine decreased the dose of bupivacaine required to initiate cardiac dysrhythmias (P = 0.003). The first dysrhythmia experienced by the epinephrine group was second degree heart block, which contrasts with the premature ventricular and atrial dysrhythmias experienced by the plain group. The dose of bupivacaine that produced seizures was also reduced by the addition of epinephrine (P = 0.006). The addition of epinephrine to bupivacaine did not alter the dose of bupivacaine that caused cardiovascular collapse in awake spontaneously breathing pigs but did decrease the dose of bupivacaine that caused seizures and dysrhythmias. (Key words: Anesthetics, local: bupivacaine. Sympathetic nervous system, catecholamines: epinephrine. Toxicity.)

THE ADDITION of epinephrine to local anesthetics has been shown to have several potentially beneficial effects. Epinephrine decreases peak plasma concentration of local anesthetic,[1–3] serves as a marker of intravascular injection,[4] increases the duration of local anesthetic block,[5] and improves the quality of major conduction block.[6] However, it is not known what effect epinephrine has on the primary manifestations of local anesthetic toxicity (*i.e.*, cardiac dysrhythmias, seizures, and cardiovascular collapse) in the event of accidental intravascular injection. Nor is it known what effect the presence of epinephrine has on the ability to resuscitate animals experiencing cardiovascular collapse following a toxic dose of local anesthetic. To determine if the addition of epinephrine to local anesthetics is beneficial or harmful in the event of accidental intravascular injection of a toxic dose of local anesthetic, we employed an awake porcine model of bupivacaine toxicity and compared the toxicity of plain bupivacaine with that of bupivacaine and epinephrine (1: 200,000).

Materials and Methods

The study was approved by our institutional review committee and follows guidelines of the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

After overnight fast, 20 farm bred pigs weighing 17.0–29.9 kg were anesthetized with halothane and nitrous oxide in oxygen for insertion of invasive monitors. Both femoral arteries were cannulated with 20-G 12.5 cm catheters (Arrow model AK-04150). One cannula was used for continuous blood pressure monitoring (Spectramed transducer model T4812AD-R), the other for sampling arterial blood. The right internal jugular vein was cannulated with an 8-Fr central venous introducer with sideport (Arrow model AK 09801). A pulmonary artery catheter (American Edwards) was inserted through the central venous introducer and the distal tip positioned in the pulmonary outflow tract. Pulmonary artery, central venous, and arterial pressures were recorded on a strip chart recorder as was the electrocardiogram. The catheter insertion sites were infiltrated with a total of 10 ml of 0.1% (10 mg) bupivacaine. The anesthetic was discontinued and the animals were suspended in a sling. The animals awakened within 15 min and were allowed to recover for 1 h prior to each experiment.

The animals were blindly randomized into two groups of ten animals each. One group (plain group) received an iv infusion of plain bupivacaine (7.5 mg/ml) at a rate of 2 mg · kg^{-1} · min^{-1}, and the second group (epinephrine group) received bupivacaine with epinephrine (5 μg/ml) at a rate of 2 mg · kg^{-1} · min^{-1}. This was equal to an epinephrine infusion rate of 1.3 μg · kg^{-1} · min^{-1}. The infusions were administered by a positive pressure infusion pump *via* the venous infusion port of the pulmonary artery catheter and were continued until cardiovascular collapse (defined as a mean arterial pressure of 30 mmHg). During bupivacaine infusion the animals were continuously observed for tonic/clonic convulsions.

* Fellow.
† Staff Anesthesiologist.
‡ Resident.
§ Chairman.

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Address reprint requests to Dr. Bernards: Department of Anesthesiology, RN-10, University of Washington, Seattle, Washington, 98195.

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At cardiovascular collapse the trachea was intubated, the animals were placed on a table, and a right thoracotomy was performed. To ensure that resuscitation began at the same time in all animals, we allowed 3 min to elapse between cardiovascular collapse and beginning open chest cardiac massage and ventilation with 100% oxygen. Resuscitation continued until successful (defined as stable cardiac rhythm and systolic blood pressure greater than 80 mmHg for 2 min) or until 20 min elapsed. Resuscitation followed Advanced Cardiac Life Support (ACLS) protocol[7] except that bretylium (5 mg/kg repeated at 10 min if necessary) replaced lidocaine in treatment of ventricular fibrillation. Bretylium was used because it is superior to lidocaine in treatment of bupivacaine-induced ventricular fibrillation.[8] In addition, epinephrine was administered in doses of 0.5–1.0 mg to maintain adequate systolic blood pressure during cardiac compressions (defined as greater than 90 mmHg) not at 5-min intervals as per ACLS protocol. Energies of 20–40 watt · seconds were used for internal defibrillation.

Arterial blood samples were drawn just prior to beginning bupivacaine infusion for determination of baseline Na^+, K^+, Cl^-, HCO_3^{2-}, hematocrit, epinephrine, norepinephrine, *p*H, Pa_{CO_2}, and Pa_{O_2} values. Blood was drawn for determination of plasma bupivacaine concentrations at the onset of seizures, at cardiovascular collapse, and 5 min after cardiovascular collapse. Epinephrine and norepinephrine measurements were repeated 2.5 min after beginning drug infusion and at cardiovascular collapse. Arterial blood gas measurements were repeated at cardiovascular collapse and 5 min after collapse to determine adequacy of ventilation and circulation. Blood samples totaled less than 40 ml in each animal.

A "resuscitatable dose 50," *i.e.*, the dose of bupivacaine at which 50% of the animals could not be resuscitated, was studied by a modification of Dickson's method for sequential sampling of quantal response data.[9] This method uses the results of each trial to determine the treatment for the subsequent trial. For this study if an animal was successfully resuscitated, the next animal in its same group received a bolus of bupivacaine at cardiovascular collapse equal to 20% of the dose required to produce cardiovascular collapse in that animal. If an animal was resuscitated following a 20% bolus, the next animal received a 40% bolus, and so on. If an animal was not successfully resuscitated, the subsequent animal received a bolus that was reduced by 20%. [We used a 10% dose adjustment for the first four animals and a 20% adjustment for the remaining 16 animals.] All boluses were from the same solution used to produce cardiovascular collapse. Using this method, we hoped to define a "resuscitatable dose 50" in much the same way that MAC is defined.

The investigators remained blinded as to the presence or absence of epinephrine by having a technician not involved in the conduct of the experiment prepare the solutions. In addition, the technician, not the investigators, followed the cardiovascular response to bupivacaine infusion and determined the point of cardiovascular collapse from a digital display of mean arterial pressure. The investigators were not blinded to the size of the additional bupivacaine bolus at cardiovascular collapse but were blinded to the animal's group.

Bupivacaine Analysis

Plasma samples were assayed for total bupivacaine by the method of Mather and Tucker.[10] This involved extraction of the drug from plasma and assay by gas chromatography using a flame ionization detector. The bupivacaine assay had a coefficient of variation of 4.2% and a sensitivity limit of 0.03 μg/ml base.

Catecholamine Analysis

Heparinized blood samples for catecholamine analysis were immediately transferred to tubes containing metabisulfite and disodium ethylenedinitrilotetraacetic acid, thoroughly mixed, and placed on ice. Within 30 min the plasma was collected by centrifugation and stored at −20° C until analysis. Norepinephrine and epinephrine concentrations were determined by high performance liquid chromatography (LCEC Application note no. 14 from Bioanalytical Systems Inc., West Layfayette, Indiana). This procedure involved addition of an internal standard to the plasma followed by adsorption of the catecholamines and internal standard onto alumina. After washing using a Bioanalytical Systems® centrifugal microfilter, the compounds were eluted from the alumina for analysis. The extracted samples were analyzed on a high performance liquid chromatograph using a C18 phase column and electrochemical detector. This procedure measures plasma concentration of catecholamines with a reproducibility of approximately 10% at concentrations of 500 pg/ml and has a limit of detection of 50 pg/ml.

Statistical Analysis

Differences between the groups for categorical and noncategorical variables were analyzed by one-way analysis of variance (ANOVA) (time to first dysrhythmia, time to cardiovascular collapse, time to seizure, ability to resuscitate, and bupivacaine concentration) or ANOVA for repeated measures (blood pressure, heart rate, epinephrine concentrations, norepinephrine concentrations). Fisher's exact test was used to evaluate the relation between development of ventricular fibrillation and ability to successfully resuscitate the animals.

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TABLE 1. Group Characteristics at Baseline

	Weight (kg)	Gender (M/F)	Duration of Anesthesia (min)	Hct (%)	Na^+ (mm/l)	K^+ (mm/l)	Cl^- (mm/l)
Plain	22.5 ± 3.4	5/5	41.3 ± 9	27 ± 3	139 ± 5	4.4 ± 0.3	103 ± 5
Epinephrine	23.8 ± 3.5	5/5	41.7 ± 18	29.8 ± 8	139 ± 6	4.3 ± 0.4	105 ± 13

Values are mean ± SD; n = 10 for each data point.

Results

Animal groups did not differ with respect to weight, gender, duration of anesthesia for catheter placement, or baseline metabolic variables (table 1). Baseline hemodynamic variables (systolic blood pressure, diastolic blood pressure, mean arterial pressure, central venous pressure, cardiac output, and systemic vascular resistance) did not differ between the groups with the exception of heart rate, which was higher in the control group (table 2; figs. 1 and 2).

The hemodynamic data cover the first 3 min of bupivacaine infusion. Although we have data beyond 3 min for some animals, animals began to experience cardiovascular collapse after 3 min resulting in too few complete data sets for meaningful comparisons between the groups.

Blood pressure increased early in the bupivacaine infusion in both groups. The increase occurred earlier and was of greater magnitude in the epinephrine group (fig. 1; table 2). Cardiac output decreased throughout the bupivacaine infusion in the epinephrine group. Cardiac output initially increased in the plain group only to decrease in parallel with the epinephrine group (fig. 2). Cardiac output differed significantly between the two groups only at 1 min. Systemic vascular resistance was significantly greater in the epinephrine group only at 1 min into the bupivacaine infusion (table 2). Central venous pressure increased equally in both groups between baseline and cardiovascular collapse (table 2).

The epinephrine group developed cardiac dysrhythmias at a lower dose of bupivacaine than the plain group (table 3). All animals in the epinephrine group experienced second degree heart block as their first manifestation of cardiac dysrhythmias. Animals in the plain group developed premature atrial and ventricular contractions as the first manifestation of cardiac dysrhythmias.

The dose of bupivacaine that produced cardiovascular collapse and the plasma concentration of bupivacaine at collapse did not differ between the groups ($P = 0.1$) (table 3). The cause of cardiovascular collapse in all animals was profound hypotension progressing to electromechanical dissociation and terminating in sinus arrest. No animal experienced cardiovascular collapse because of ventricular fibrillation. However, eight of 20 animals developed ven-

TABLE 2. Effect of Epinephrine on Hemodynamic Response to Bupivacaine Infusion

	Baseline	0.5 min into Bupivacaine Infusion	1.0 min into Bupivacaine Infusion	1.5 min into Bupivacaine Infusion	2.0 min into Bupivacaine Infusion	2.5 min into Bupivacaine Infusion	3.0 min into Bupivacaine Infusion
Systolic BP (mmHg)							
Plain	158 ± 7	157 ± 20	150 ± 17	147 ± 15	173 ± 27	176 ± 36	181 ± 34
Epinephrine	151 ± 16	156 ± 28	205 ± 22*	216 ± 15*	212 ± 18*	192 ± 32	188 ± 31
Diastolic BP (mmHg)							
Plain	94 ± 11	100 ± 18	96 ± 17	103 ± 15	116 ± 19	111 ± 33	113 ± 26
Epinephrine	97 ± 7	101 ± 20	135 ± 19*	144 ± 16*	137 ± 18*	110 ± 27	103 ± 30
Heart rate (beats/min)							
Plain	160 ± 27	158 ± 23	152 ± 24	159 ± 20	161 ± 23	165 ± 16	155 ± 18
Epinephrine	132 ± 16*	148 ± 17	129 ± 15*	140 ± 21	143 ± 18	147 ± 15*	143 ± 13
SVR (dynes·s^{-1}·cm^{-5})							
Plain	3,465 ± 1,290	—	2,753 ± 968	—	4,447 ± 2,434	—	4,720 ± 1,947
Epinephrine	3,094 ± 1,004	—	5,030 ± 1,190*	—	6,463 ± 2,923	—	5,007 ± 1,704
CVP (mmHg)							
Plain	5.9 ± 2	—	7.2 ± 3	—	10 ± 4	—	12 ± 4
Epinephrine	6.4 ± 3	—	9.6 ± 3	—	13 ± 4	—	14 ± 3

Values are mean ± SD, n = 10. Blank lines indicate that the measurements were not made at that particular time.

* $P < 0.05$.

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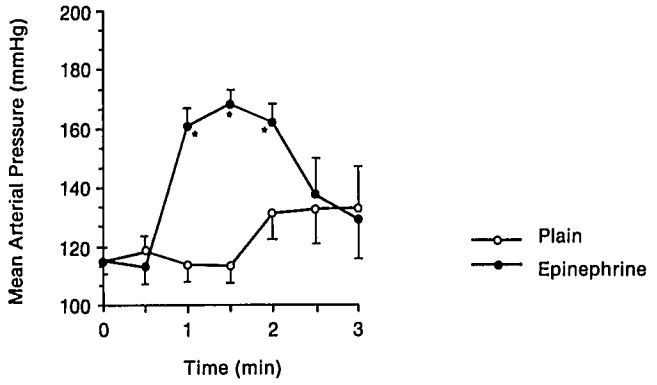

FIG. 1. Effect of plain bupivacaine and bupivacaine with epinephrine (5 μg/ml) on the mean arterial pressure response to bupivacaine infusion; n = 10 for all data points. Values are mean ± SEM. *$P < 0.05$.

tricular fibrillation during resuscitation and those animals that we were unable to resuscitate died of refractory ventricular fibrillation.

There was no difference between the two groups with respect to the ease with which animals were successfully resuscitated. Ease of resuscitation was quantified by the duration of resuscitation from initiation until successful (plain group, 369 ± 388 s; epinephrine group, 333 ± 329 s), the number of animals that developed ventricular fibrillation during resuscitation (plain group: 3/10; epinephrine group 5/10), the number of animals successfully resuscitated (plain group 8/10; epinephrine group 7/10), and the average dose of epinephrine administered per minute during resuscitation (plain group, 27 ± 14 $\mu g \cdot kg^{-1} \cdot min^{-1}$; epinephrine group, 23 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$). For successfully resuscitated animals, there was no difference between the groups in the amount of additional bupivacaine administered at collapse (plain group, 49 ± 29% of dose to collapse; epinephrine group, 33 ± 28% of dose to collapse, $P > 0.05$) or in the plasma

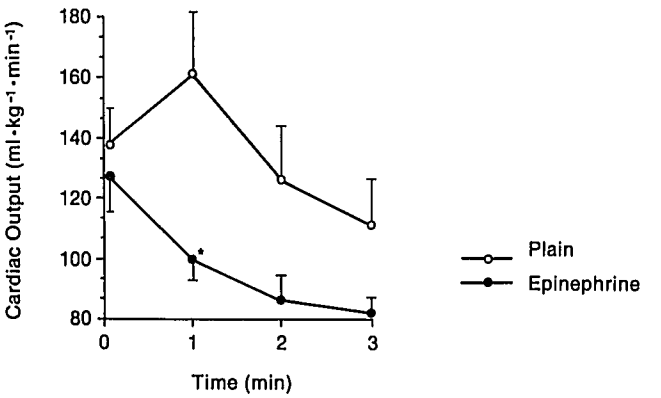

FIG. 2. Effect of plain bupivacaine and bupivacaine with epinephrine (5 μg/ml) on the cardiac output response to bupivacaine infusion; n = 10 for all data points. Values are mean ± SEM. *$P < 0.05$.

TABLE 3. Effect of Epinephrine on Bupivacaine Toxicity

	Plain	Epinephrine
Dose of bupivacaine at onset of dysrhythmias (mg/kg)	4.3 ± 2.1	2.4 ± 1.5*
Dose of bupivacaine at onset of seizures (mg/kg)	6.1 ± 1.4	4.5 ± 0.7*
Plasma concentration of bupivacaine at onset of seizures (μg/ml)	18.4 ± 3.9	18.9 ± 4.3
Dose of bupivacaine at cardiovascular collapse (mg/kg)	10.1 ± 1.9	8.9 ± 1.3
Plasma concentration of bupivacaine at cardiovascular collapse (μg/ml)	28.3 ± 7.7	27.8 ± 6.7
Plasma concentration of bupivacaine 5 min after cardiovascular collapse (μg/ml)	30.9 ± 12.3	27.8 ± 7.9

Values are mean ± SD; n = 10 for all data points.
* $P < 0.05$.

bupivacaine concentrations 5 min after collapse (plain group, 29.6 ± 13.6 μg/ml; epinephrine group, 28.1 ± 8.8 μg/ml, $P > 0.05$).

The dose of bupivacaine that produced tonic/clonic convulsions was lower in the epinephrine group (table 3). Despite the lower dose of bupivacaine required to produce seizures in the epinephrine group, the plasma concentrations of bupivacaine were not different at the onset of tonic/clonic convulsions (table 3).

Norepinephrine concentrations increased equally in both groups from baseline to cardiovascular collapse [plain group, 1,527 ± 835 pg/ml to 7,569 ± 3,868 pg/ml ($P < 0.05$); epinephrine group, 2,382 ± 2,386 pg/ml to 7,147 ± 3,955 pg/ml ($P < 0.05$)]. Epinephrine concentrations increased in both groups from baseline to collapse, but the increase was significantly greater in the epinephrine group (plain group, 12,344 ± 12,795 pg/ml to 15,699 ± 10,913 pg/ml; epinephrine group, 9,906 ± 17,690 pg/ml to 113,966 ± 47,729, $P < 0.0001$).

Animals in both groups experienced significant increases in Pa_{CO_2}, and decreases in Pa_{O_2} and *p*H as they progressed from baseline to cardiovascular collapse (table 4). With the initiation of resuscitation, *p*H, Pa_{CO_2}, and Pa_{O_2} improved significantly from their values at cardiovascular collapse (table 4).

We were unable to define a "resuscitatable dose 50" during this study because our ability to resuscitate the animals did not correlate with any measure of bupivacaine dose. Specifically, the ability to resuscitate animals did not correlate with the total dose of bupivacaine administered (resuscitated animals, 13.9 ± 4 mg/kg; unresuscitated animals, 11.5 ± 2.6 mg/kg), with the amount of

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TABLE 4. Effect of Bupivacaine Infusion on Arterial Blood Gases

	Baseline	Cardiovascular Collapse*	5 min into Resuscitation†
*p*H			
Plain	7.49 ± 0.02	7.28 ± 0.05	7.41 ± 0.1
Epinephrine	7.48 ± 0.32	7.24 ± 0.62	7.33 ± 0.1
Pa_{O_2}			
Plain	81.2 ± 7.8	21.6 ± 4.8	368.8 ± 94.9
Epinephrine	82.3 ± 5.0	20.6 ± 11.2	333.5 ± 111.2
Pa_{CO_2}			
Plain	39.4 ± 3.0	64.0 ± 5.0	28.5 ± 7.8
Epinephrine	39.5 ± 2.4	67.2 ± 7.8	33.7 ± 13.6

Values are mean ± SD; n = 10 for all data points. There are no differences between groups at any point.

* All values differ significantly from baseline within groups, $P < 0.05$.

† All values differ significantly from collapse within groups, $P < 0.05$.

additional bupivacaine administered at cardiovascular collapse (resuscitated animals, 41.3 ± 30% of dose to collapse; unresuscitated animals; 34 ± 19.5% of dose to collapse), with the plasma concentration of bupivacaine at collapse (resuscitated animals, 29.1 ± 6.5 μg/ml; unresuscitated animals, 25.0 ± 8.4 μg/ml) or with the plasma concentration of bupivacaine 5 min after collapse (resuscitated animals, 28.9 ± 11.2 μg/ml; unresuscitated animals, 28.5 ± 8.1 μg/ml). In addition, we were unable to identify any metabolic variable (*e.g.*, baseline electrolyte values, hematocrit, epinephrine concentration, norepinephrine concentration, arterial blood gas values at collapse or during resuscitation) that distinguished between those animals that we were able to resuscitate and those animals that we were unable to resuscitate. The only event significantly associated with failed resuscitation was the development of ventricular fibrillation. Five of the eight animals that developed ventricular fibrillation could not be resuscitated. In contrast, all 12 animals that did not develop ventricular fibrillation were successfully resuscitated ($P = 0.024$ by Fisher's exact test for association between ventricular fibrillation and failed resuscitation). We identified no metabolic or hemodynamic predictors of ventricular fibrillation including the presence of epinephrine in the bupivacaine solution or the plasma epinephrine concentration at collapse.

Discussion

Epinephrine is a mainstay in the treatment of cardiovascular collapse following toxic doses of local anesthetic. This has prompted some authors to suggest that epinephrine containing local anesthetic solutions are safer than plain solutions.[11] They hypothesized that the added epinephrine will counteract local anesthetic cardiovascular toxicity in the event of accidental intravascular injection. The objective of this study was to determine if the addition of epinephrine to bupivacaine alters its toxicity in the event of accidental intravascular injection. Our markers of local anesthetic toxicity were cardiac dysrhythmias, seizures, cardiovascular collapse, and the ability to resuscitate animals following cardiovascular collapse.

Cardiovascular collapse occurred following the same dose of bupivacaine and at the same plasma concentration of bupivacaine in both groups. That is, the addition of epinephrine failed to support the cardiovascular system and to prevent or delay the inexorable decline in cardiac output that terminated in cardiovascular collapse. The presence of epinephrine produced a significantly lower cardiac output in the epinephrine group early in the bupivacaine infusion. The likely cause of this lower cardiac output is the significant increase in systemic vascular resistance experienced by the epinephrine group. The cardiac output decline experienced by both groups later in the bupivacaine infusion was likely the result of bupivacaine-induced depression of myocardial contractility, a phenomenon that has been well described in previous studies.[12,13] Whether the increase in systemic vascular resistance experienced by both groups contributed to the cardiac output decline or was a reflexive response to the falling cardiac output is unclear from the data. The increase in central venous pressure experienced by both groups confirms that decreased preload did not contribute to the decline in cardiac output.

Because epinephrine is a dysrhythmia-producing drug, it is perhaps not surprising that the epinephrine group experienced dysrhythmias at a lower total dose of bupivacaine than did the plain group. However, the dysrhythmogenicity of epinephrine does not explain why transient second degree heart block was the first manifestation of cardiac dysrhythmias in the epinephrine group. The most likely explanation for this phenomenon is a reflexive increase in vagal tone resulting from the marked increase in blood pressure produced by epinephrine. This is supported by the fact that the onset of second degree heart block in the epinephrine group coincides with the most rapid rate of blood pressure rise and with the nadir in heart rate. Although bupivacaine can produce both conduction block and bradycardia,[14,15] the absence of second degree heart block in the plain group suggests bupivacaine is not the cause of heart block in the epinephrine group. The occurrence of premature atrial and ventricular contractions as the first manifestation of dysrhythmias in the plain group is consistent with previous reports.[16,17]

Seizures occurred at a lower total dose of bupivacaine when epinephrine was added. However, plasma bupivacaine concentrations were identical in the two groups at the onset of seizures, *i.e.*, seizure threshold was not affected. A likely explanation is that the addition of epi-

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nephrine to bupivacaine produced peripheral vasoconstriction, which resulted in a reduced volume of distribution for bupivacaine. As a result, the central nervous system was exposed to a higher plasma concentration of bupivacaine than would have been the case if epinephrine were not present. This explanation is supported by epinephrine's ability to redistribute cardiac output away from skin, skeletal muscle, gastrointestinal tract, liver, and kidney[18] and by the fact that systemic vascular resistance was greater in the epinephrine group at the onset of seizures. Although epinephrine may also reduce hepatic blood flow and thereby decrease bupivacaine clearance, seizures occurred too rapidly for reduced clearance to have significantly affected plasma bupivacaine concentration. The higher systemic vascular resistance and decreased volume of distribution of bupivacaine in the epinephrine group at the onset of seizures contrasts with the situation at cardiovascular collapse. As cardiovascular collapse approached, systemic vascular resistance was no longer different between the groups and presumably neither was bupivacaine's volume of distribution. This may explain why we found no difference in the dose of bupivacaine necessary to produce cardiovascular collapse.

Although determining the maximum dose of bupivacaine that can be administered intravenously before seizures, dysrhythmias, or cardiovascular collapse occur is important clinically, it is equally important to determine the maximum dose of bupivacaine that can be administered and still permit successful resuscitation. We speculated that the presence of epinephrine in a bupivacaine solution might alter not only the threshold for dysrhythmias, seizures, and cardiovascular collapse but also the ease of resuscitation. We therefore attempted to define a "resuscitatable dose 50" for intravenously administered bupivacaine. It is difficult to explain why we were unsuccessful in our attempt, *i.e.*, why we were unable to demonstrate a relation between total dose of bupivacaine and the ability to resuscitate animals in our study. Although inconsistent quality of resuscitation would explain this inability, arterial blood gases measured during resuscitation demonstrate adequate ventilation in all animals. Furthermore, systolic blood pressure $\geq$ 90 mmHg during compressions suggests adequate perfusion in all animals as does the absence of a profound metabolic acidosis. Similarly, investigator inexperience with the resuscitation protocol does not explain the results because these same investigators successfully resuscitated 26 of 30 animals in a previous study using this model.[17] In addition, during this study unsuccessful resuscitations occurred at the beginning, middle, and end of the study. It is possible that compression of coronary arteries and myocardium during cardiac massage produced myocardial injury or ischemia, which rendered some animals refractory to defibrillation. Another possibility is wide individual variation in the ability of pigs to tolerate a toxic dose of bupivacaine. Although we were unable to demonstrate a difference in the ease of resuscitation, we caution that our data do not prove that epinephrine is *not* beneficial. There may be other factors important to the success of resuscitation that we were unable to identify.

Independent of our ability to define a "resuscitatable dose 50," it is notable that some animals were successfully resuscitated despite receiving total doses of bupivacaine as large as twice the dose that caused cardiovascular collapse. Successful resuscitations occurred following doses of bupivacaine as high as 20 mg/kg and plasma concentrations as high as 40 μg/ml at the time of resuscitation. The successful resuscitation of these animals following such large doses of bupivacaine suggests that epinephrine in the supraphysiologic doses that we used for resuscitation is capable of counteracting the myocardial depressant effects of toxic doses of bupivacaine.

A criticism of our study is that the two groups had different mean heart rates at baseline. The difference in mean heart rate between the two groups is the result of three "outliers" in the plain group with baseline heart rates between 180 and 200 beats/min. Baseline blood pressure, cardiac output, systemic vascular resistance, central venous pressure, hematocrit, Pa_{O_2}, Pa_{CO_2}, *p*H, epinephrine, and norepinephrine concentrations did not differ between these animals and the remainder of the animals in either group. However, baseline heart rate did correlate inversely with animal weight ($P = 0.04$), and these three animals represent three of the smallest animals in the study (18.9 $\pm$ 1.6 kg *vs.* 23.4 $\pm$ 3.4 kg). To determine if these three animals unduly influenced our results, we repeated all analyses eliminating their data and found that no previously significant results became insignificant at the $P = 0.05$ level except heart rate at 1 min and diastolic blood pressure at 2 min. These differences are insignificant; we therefore included data from these three animals in all statistical analyses.

In summary, our model reproduces the clinical situation in which an awake spontaneously breathing patient receives an accidental intravascular injection of bupivacaine. In this situation the addition of epinephrine to bupivacaine did not protect against bupivacaine-induced cardiovascular collapse or render the animals any easier to resuscitate after collapse. The addition of epinephrine did produce cardiac dysrhythmias and seizures at a lower dose of bupivacaine. We were unsuccessful in our attempt to define a "resuscitatable dose 50," but we did demonstrate that animals could be successfully resuscitated following doses of bupivacaine twice as large as the dose that initially caused cardiovascular collapse.

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