

Resuscitation with Lipid versus Epinephrine in a Rat Model of Bupivacaine Overdose

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Background: Lipid emulsion infusion reverses cardiovascular compromise due to local anesthetic overdose in laboratory and clinical settings. The authors compared resuscitation with lipid, epinephrine, and saline control in a rat model of bupivacaine-induced cardiac toxicity to determine whether lipid provides a benefit over epinephrine.

Methods: Bupivacaine, 20 mg/kg, was infused in rats anesthetized with isoflurane, producing asystole in all subjects. Ventilation with 100% oxygen and chest compressions were begun immediately, along with intravenous treatment with 30% lipid emulsion or saline (5-ml/kg bolus plus continuous infusion at 0.5 ml · kg⁻¹ · min⁻¹) or epinephrine (30 µg/kg). Chest compressions were continued and boluses were repeated at 2.5 and 5 min until the native rate-pressure product was greater than 20% baseline. Electrocardiogram and arterial pressure were monitored continuously and at 10 min, arterial blood gas, central venous oxygen saturation, and blood lactate were measured. Effect size (Cohen d) was determined for comparisons at 10 min.

Results: Lipid infusion resulted in higher rate-pressure product ($P < 0.001$, $d = 3.84$), pH ($P < 0.01$, $d = 3.78$), arterial oxygen tension ($P < 0.05$, $d = 2.8$), and central venous oxygen saturation ($P < 0.001$, $d = 4.9$) at 10 min than did epinephrine. Epinephrine treatment caused higher lactate ($P < 0.01$, $d = 1.48$), persistent ventricular ectopy in all subjects, pulmonary edema in four of five rats, hypoxemia, and a mixed metabolic and respiratory acidosis by 10 min.

Conclusions: Hemodynamic and metabolic metrics during resuscitation with lipid surpassed those with epinephrine, which were no better than those seen in the saline control group. Further studies are required to optimize the clinical management of systemic local anesthetic toxicity.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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Received from the Department of Anesthesiology, University of Illinois College of Medicine at Chicago, and the Jesse Brown Veterans Administration Medical Center, Chicago, Illinois. Submitted for publication November 4, 2007. Accepted for publication December 28, 2007. Supported in part by grant No. 1R21DA17892-01 (to Dr. Weinberg) from the National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland, and a Veteran's Administration Merit Award (to Dr. Weinberg) from the Veteran's Administration Central Research and Development Office, Washington, D.C. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 13, 2007. Dr. Weinberg was awarded US patent 7,261,903 B1, "Lipid Emulsion in the Treatment of Systemic Poisoning." He does not have equity interest or agreements with any company or commercial entity related to this method. He has never received salary or support from any company. He does not intend to prohibit or restrict the practice of this method on any patient requiring this treatment.

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LIPID emulsion therapy can rapidly restore circulation after local anesthetic-induced cardiovascular collapse. Experimental models of local anesthetic toxicity have shown accelerated return of spontaneous cardiac function after lipid infusion in both intact animals^{1,2} and the isolated heart.^{3,4} Several case reports have extended these findings to the clinical setting, where patients in cardiac arrest after regional anesthesia were quickly resuscitated with lipid.⁵⁻⁷

Epinephrine is a first-line drug for treating cardiac arrest because its α -agonist activity increases diastolic pressure and coronary perfusion pressure.⁸ The rationale for using epinephrine in local anesthetic-induced cardiac toxicity also seems compelling because of its positive chronotropic and inotropic effects. Furthermore, epinephrine has been reported as effective in promoting recovery of blood pressure in animal models of bupivacaine-induced cardiac toxicity.^{9,10} However, patients in local anesthetic-induced cardiac arrest are often resistant to adrenergic therapy and can develop severe pulmonary edema after receiving epinephrine.¹¹ Several case reports of successful lipid resuscitation had, at first, failed to achieve return of effective circulation with sympathomimetics. These disparate observations raise the question of the comparative efficacies of lipid and epinephrine for treating cardiovascular collapse in the setting of regional anesthesia. We have established an intact animal model of bupivacaine overdose to test whether there are differences in hemodynamic, electrocardiographic, and metabolic metrics during resuscitation with lipid *versus* epinephrine.

Materials and Methods

Experimental Model

The following protocols were approved by the Animal Care Committee and Biologic Resources Laboratory at the University of Illinois, Chicago, Illinois, and the Institutional Animal Care and Utilization Committee of the Jesse Brown Veterans Administration Medical Center, Chicago, Illinois. Healthy, male Sprague-Dawley rats weighing between 350 and 420 g were first anesthetized in a bell jar with isoflurane to allow tracheal intubation. All animals were then placed on a heated stand under a warming lamp and mechanically ventilated with 1-2% isoflurane in 100% oxygen, using a Harvard rodent ventilator model 680 (Harvard Apparatus, South Natick, MA) and a tidal volume of 2.5 ml, at a starting rate of 65-70 breaths/min. Catheters were inserted into the right and left internal jugular veins and the right carotid artery.

Table 1. Baseline Values of Key Parameters for the Three Groups

| | Lipid (n = 5) | Epinephrine (n = 5) | Saline (n = 5) |
|--|----------------|---------------------|-----------------|
| HR, beats/min | 314 ± 20 | 331 ± 31 | 337 ± 52 |
| SBP, mm Hg | 144 ± 10 | 143 ± 19 | 149 ± 17 |
| RPP, mm Hg · beats · min ⁻¹ | 45,210 ± 4,690 | 48,000 ± 9,991 | 51,120 ± 12,400 |
| pH | 7.34 ± 0.19 | 7.43 ± 0.06 | 7.46 ± 0.07 |
| PaO ₂ , mm Hg | 413 ± 77 | 378 ± 63 | 341 ± 95 |
| Paco ₂ , mm Hg | 33.9 ± 5.7 | 31.5 ± 7.6 | 33.2 ± 7.3 |
| Blood lactate, mM | 1.35 ± 0.62 | 1.03 ± 0.39 | 1.31 ± 0.62 |

Values are given as mean ± SEM. Baseline values for major parameters showed no significant differences among the three groups.

HR = heart rate; Paco₂ = partial pressure of carbon dioxide in arterial blood; PaO₂ = partial pressure of oxygen in arterial blood; RPP = rate–pressure product = SBP × HR; SBP = systolic blood pressure.

Electrocardiograms using three subcutaneous needle electrodes and the carotid pressure were recorded continuously throughout the experiment by PowerLab data archiving and retrieval system using Chart 5.2.1 (ADInstruments, Colorado Springs, CO). All animals were then allowed to stabilize for 15 min at 1.5% isoflurane and 100% oxygen, and arterial blood gas measurements were made to confirm a carbon dioxide tension between 30 and 35 mm Hg, a pH between 7.35 and 7.45, and a serum lactate below 2.0. Animals were randomly assigned in advance of the experiment to receive one of three intravenous treatments: saline, lipid, or epinephrine. The laboratory personnel were not blinded to the treatment; however, subsequent off-line data compilation from archived files of each experiment was blinded with respect to group.

Bupivacaine Infusion and Resuscitation Protocol

Isoflurane was discontinued, and bupivacaine was immediately infused as a 20-mg/kg bolus over 20 s—this dose was found in preliminary experiments to reliably produce asystole from which spontaneous recovery was unlikely with only ventilation and chest compressions. Chest compressions were started immediately at the end of the bupivacaine infusion (zero time) and were interrupted for 10 s each minute to assess native rate–pressure product (RPP = systolic pressure × heart rate) and QRS duration. RPP correlates closely with myocardial oxygen demand¹² and, in this protocol, is taken as an approximation of myocardial work. Mechanical ventilation with 100% oxygen was continued throughout the experiment (10 min). All intravenous treatments were initiated at zero time according to the following regimens: saline, 5-ml/kg bolus plus a continuous infusion of 0.5 ml · kg⁻¹ · min⁻¹; lipid, 30% Intralipid (Fresenius Kabi, Uppsala, Sweden), 5-ml/kg bolus plus a continuous infusion of 0.5 ml · kg⁻¹ · min⁻¹; epinephrine, 30-μg/kg bolus in 0.2 ml sterile water. Each of these bolus treatments was repeated at 2.5 and 5 min for a native RPP less than 20% of baseline (taken as failure to attain return of spontaneous circulation). The experiment was stopped

at the 10-min time point when arterial blood gases, central venous oxygen saturation (S_{cvp}O₂), and serum lactate were measured. All animals were then killed.

Statistical Analysis

Power analysis was based on results of preliminary experiments comparing RPP at 10 min among various treatment groups and yielded a sample size of n = 5 for each group; power was set at 0.8, significance criteria was set at 0.05, effect size was estimated as 2, and sigma at 0.9. The null hypothesis is that no difference exists between treatments with respect to metrics of recovery during resuscitation from bupivacaine-induced arrest. All data were analyzed using GraphPad Prism 4 (GraphPad Software, San Diego, CA). Baseline parameters were analyzed by one-way analysis of variance and Bonferroni posttests. All other parameters were compared across time by two-way analysis of variance with repeated measures and Bonferroni posttests of differences where *P* < 0.05. When differences in means at 10 min were statistically significant by posttest (*α* set at 0.05), effect sizes were calculated as Cohen *d* by the method of Thalheimer and Cook using means and standard deviations.††

Results

Baseline Values

Baseline values for key hemodynamic and metabolic parameters were compared for the three groups (table 1). No differences were found among mean baseline values for heart rate, systolic blood pressure, RPP, QRS, arterial blood gas measurements, S_{cvp}O₂, or blood lactate.

Cardiovascular Function

Hemodynamic Measurements (n = 5 for All Groups). All animals developed asystole by the zero time and showed some degree of recovery by 10 min. All lipid-treated rats received two boluses (0 and 2.5 min); four of five rats in the epinephrine group received two boluses, and the other rat received only the initial bolus; all saline-treated subjects received three boluses (at 0, 2.5, and 5 min). Return of spontaneous circulation (de-

†† http://work-learning.com/effect_sizes.htm. Accessed January 4, 2008.

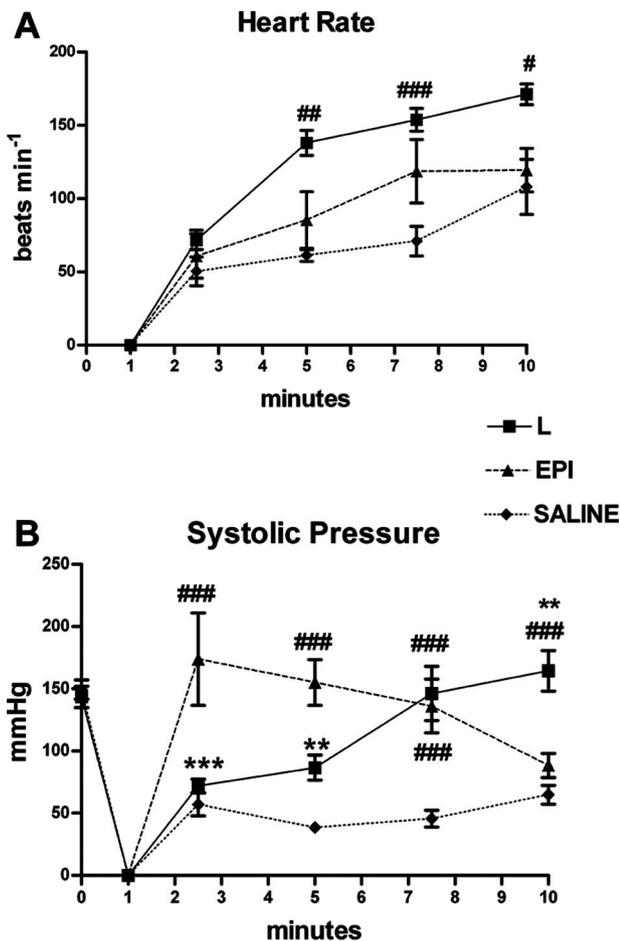


Fig. 1. Hemodynamic parameters during resuscitation. Native heart rate (A) and systolic blood pressure (B) are plotted for the 10 min after bolus bupivacaine infusion (mean \pm SEM; $n = 5$ for all values). # Significant differences with the mean value of the saline group. * Significant differences with epinephrine-treated animals. One symbol, $P < 0.05$; two symbols, $P < 0.01$; three symbols, $P < 0.001$. EPI = epinephrine-treated group; L = lipid-treated group; SALINE = control group.

financed in advance of the study as a RPP $> 20\%$ baseline) was attained at 10 min by five of five animals in the lipid group, four of five in the epinephrine group, and two of five in the saline group. Heart rate (fig. 1A) improved after lipid treatment beyond that of saline controls at 5 min ($P < 0.01$) and continued to increase to the end of the experiment, when the mean heart rate in the lipid group also exceeded that of the saline group ($P < 0.05$, $d = 2.22$) but not the epinephrine group. Systolic blood pressure (fig. 1B) in the lipid group steadily increased during resuscitation from values below those of the epinephrine group at 2.5 min ($P < 0.001$) to values significantly higher than both saline ($P < 0.001$, $d = 3.98$) and epinephrine ($P < 0.01$, $d = 2.88$) at 10 min. The mean RPP (fig. 2) in the lipid group exceeded those of saline-treated rats at 7.5 min ($P < 0.001$) and 10 min ($P < 0.001$, $d = 4.73$) and was greater than the mean epinephrine-treated RPP at 10 min ($P < 0.001$, $d = 3.84$). Epinephrine treatment resulted in RPP that was

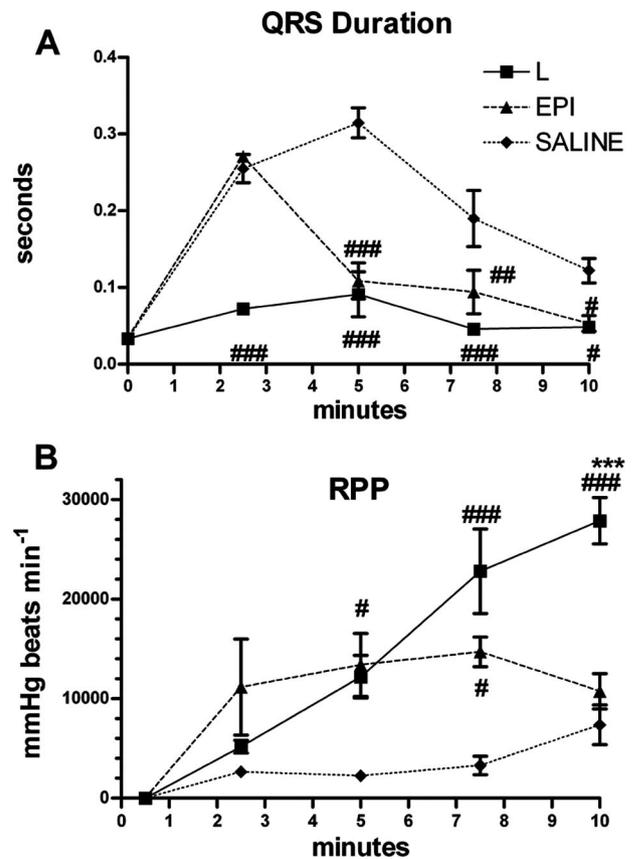


Fig. 2. Rate-pressure product (RPP) and electrocardiogram during recovery. QRS duration (A) and RPP (B) are shown during the recovery from bupivacaine-induced asystole (mean \pm SEM; $n = 5$ for all values, except QRS duration in the saline group, where $n = 4$). # Significant differences with the mean value of the saline group. * Significant differences with epinephrine-treated animals. One symbol, $P < 0.05$; two symbols, $P < 0.01$; three symbols, $P < 0.001$. EPI = epinephrine-treated group; L = lipid-treated group; SALINE = control group.

greater than that of saline treatment only at 5 and 7.5 min ($P < 0.05$ for both). However, by 10 min, the mean RPP was the same in the saline and epinephrine groups.

Electrocardiogram. Lead II was evaluated during the course of recovery for each animal except for one animal in the saline group, where the electrocardiogram was obscured by 60 cycle interference. QRS duration in both the epinephrine and saline groups was significantly prolonged at 2.5 min compared with lipid treatment ($P < 0.001$ for both comparisons). The mean QRS in the epinephrine group recovered to baseline values by 5 min, but the mean QRS duration in the saline group remained elevated throughout the experiment ($P < 0.001$ for within-group comparison of QRS at baseline vs. 10 min). QRS duration in the lipid and epinephrine groups was shorter than that for the saline group at 10 min ($P < 0.05$ for both comparisons; $d = 3.87$, 2.88 for saline vs. lipid and epinephrine treatment, respectively). Ventricular ectopy was noted throughout recovery in five of five rats in the epinephrine group, one of five in the saline group, and zero of five in the lipid group.

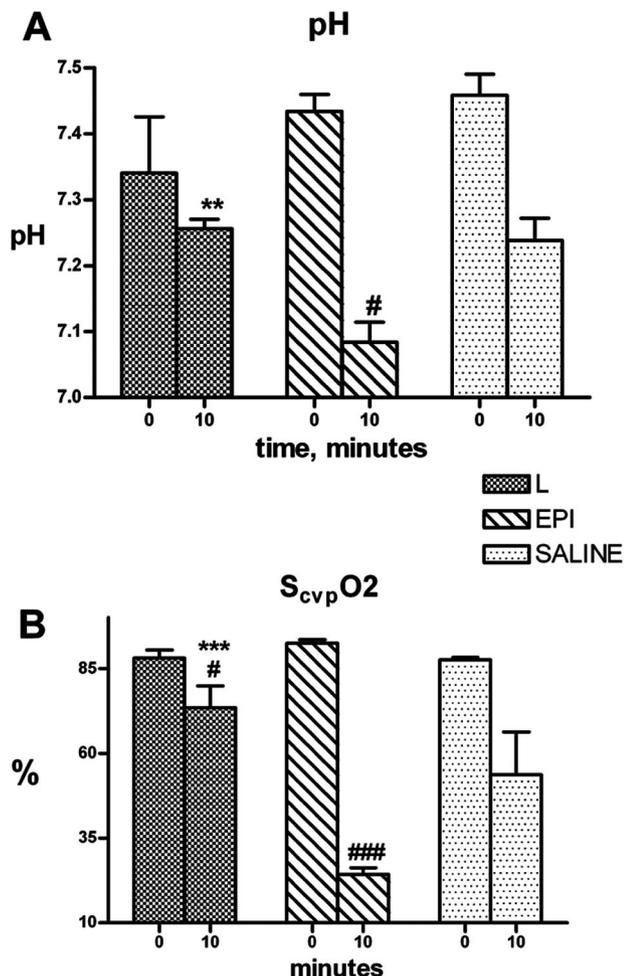


Fig. 3. Arterial pH (A) and central venous oxygen saturation (S_{cvpO_2} ; B) are shown at baseline (zero) and after 10 min of resuscitation (mean \pm SEM; $n = 5$ for all values). # Significant differences with the mean value of the saline group. * Significant differences with epinephrine-treated animals. One symbol, $P < 0.05$; two symbols, $P < 0.01$; three symbols, $P < 0.001$. EPI = epinephrine-treated group; L = lipid-treated group; SALINE = control group.

Metabolic Parameters

Arterial Blood Gas Measurements ($n = 5$ for All Groups). pH declined in all groups by 10 min ($F = 71.88$, $P < 0.0001$). However, the mean arterial pH (fig. 3) of the epinephrine-treated group at 10 min was significantly lower than those of the lipid ($P < 0.01$, $d = 3.78$) and saline groups ($P < 0.05$, $d = 2.48$). The other comparisons showed no difference at 10 min. Bupivacaine infusion and resuscitation decreased arterial oxygen partial pressure (P_{aO_2}) in all groups ($F = 243$, $P < 0.0001$; fig. 4). The mean P_{aO_2} of the lipid group at 10 min was significantly greater than that of the epinephrine group ($P < 0.05$, $d = 2.8$). There were no other significant between-group differences in P_{aO_2} at 10 min. Arterial carbon dioxide partial pressure (P_{aCO_2} ; fig. 4) was increased during recovery in all groups ($F = 56.3$, $P < 0.0001$) but most strikingly in the epinephrine-treated group, where mean values at 10 min exceeded

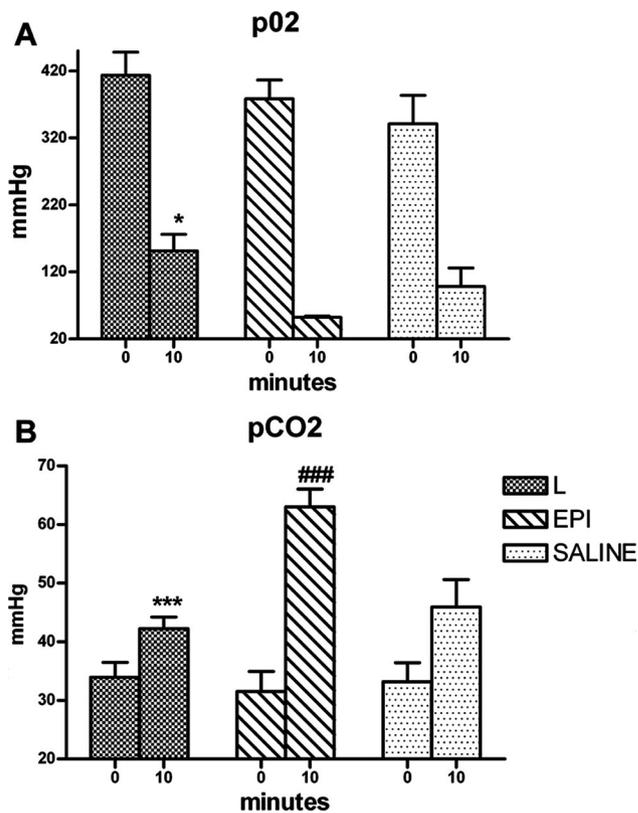


Fig. 4. Blood gas measurements. Arterial oxygen (P_{O_2} ; A) and carbon dioxide (P_{CO_2} ; B) partial pressures are shown at baseline and after 10 min of resuscitation (mean \pm SEM; $n = 5$ for all values). # Significant differences with the mean value of the saline group. * Significant differences with epinephrine-treated animals. One symbol, $P < 0.05$; three symbols, $P < 0.001$. EPI = epinephrine-treated group; L = lipid-treated group; SALINE = control group.

those in the lipid and saline groups ($P < 0.001$ for both comparisons; $d = 4.86$ and 2.16 for the comparisons with lipid and saline, respectively).

Notably, four of five rats in the epinephrine group, but none in the other groups, developed pulmonary edema shortly after the first injection of epinephrine. This was identified as fluid in the endotracheal tube and expiratory limb of the breathing circuit, which was removed by collection in a water trap on the expiratory limb. We measured the wet:dry ratios of lungs harvested immediately after the 10-min point. Values for the three groups were not statistically different (5.96 ± 0.91 , $n = 4$; 7.92 ± 1.32 , $n = 5$; 7.40 ± 1.29 , $n = 4$; mean \pm SD for lipid, epinephrine, and saline treatment, respectively). The initial experimental sample size was determined by the anticipated effect size of hemodynamic variables, and it is likely that data for the wet:dry lung ratio were underpowered for detecting a difference in means.

Blood Lactate. Lactate levels (fig. 5) showed significant increases in all groups after resuscitation ($n = 5$ for epinephrine and lipid groups, $n = 3$ for saline due to equipment failure in two experiments; $F = 97.1$, $P < 0.0001$). The mean lactate value at 10 min was lower in the lipid group than the epinephrine group ($P < 0.01$,

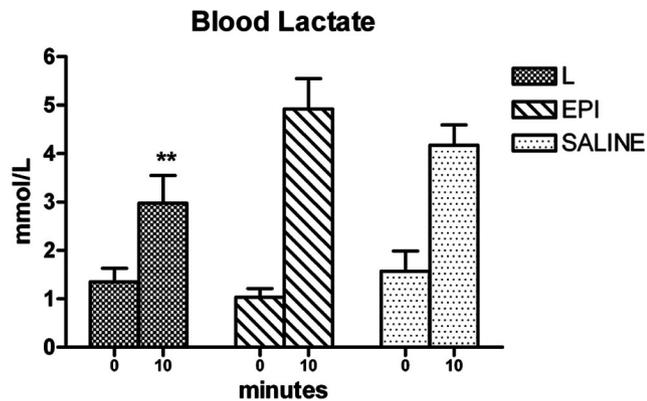


Fig. 5. Blood lactate measurements are shown at baseline (zero) and 10 min after the bupivacaine bolus (mean \pm SEM; $n = 5$ for all values except saline at 10 min, where $n = 3$). ** Significant differences with epinephrine-treated animals; $P < 0.01$. EPI = epinephrine-treated group; L = lipid-treated group; SALINE = control group.

$d = 1.48$). There was no difference in mean lactate at 10 min between the saline-treated group and either the lipid or epinephrine groups.

Central Venous Oxygen Saturation ($n = 5$ for All Groups). The bupivacaine infusion and resuscitation significantly decreased S_{cvpO_2} across all groups ($F = 83.3$, $P < 0.0001$; fig. 3). However, at 10 min, the lowest values for S_{cvpO_2} were seen in the epinephrine-treated group, with a mean value that was significantly lower than those of the lipid ($P < 0.001$, $d = 4.9$) and saline ($P < 0.01$, $d = 1.63$) groups. There were no other significant between-group differences.

Discussion

We found in a rodent model of bupivacaine overdose that lipid infusion resulted in improved recovery compared with epinephrine-based resuscitation. Several measures of cardiac function and metabolic status indicated that lipid was superior to saline infusion or intravenous epinephrine in this setting. Furthermore, epinephrine caused pulmonary edema in four of five rats, which contributed to the generally poor recovery of animals that group. This is the most recent of many studies over the past three decades examining treatment of bupivacaine overdose, but it is the first comparing lipid with epinephrine. These data suggest that lipid infusion could be superior to epinephrine for treating local anesthetic-induced cardiovascular toxicity. However, substantial additional work is required to confirm this finding and translate it from an animal model to the clinical setting.

Several clinical reports of resuscitation with lipid have cited return of spontaneous circulation shortly after the emulsion infusion and despite failed trials of adrenergic therapy.^{6,7} These cases offer a form of crossover exper-

iment with each patient serving as his or her own control. An outstanding example is provided by the report of Sirianni *et al.*¹³ in which a patient in cardiac arrest after a massive overdose of bupropion was unresponsive for more than 70 min of resuscitation including 11 counter-shocks, 18 bolus injections of epinephrine, and continuous, "wide-open" infusions of epinephrine, dopamine, and norepinephrine. Her pulse returned less than a minute after lipid infusion, and she ultimately recovered without significant neurologic or cardiac deficits. Interestingly, this patient developed severe pulmonary edema before the lipid infusion and subsequently required prolonged intubation and mechanical ventilation for acute lung injury. We believe this is consonant with the findings of pulmonary edema in the epinephrine group of our experiments. Similarly, Reinikainen *et al.*¹¹ reported a case of prolonged pulmonary edema after the use of epinephrine in the setting of local anesthetic-induced cardiac arrest. This case paralleled the physiologic arc observed in our epinephrine experimental group: increased initial blood pressure (168/120) followed by severe hypotension (70/40) and pulmonary edema with a large alveolar-arterial oxygen gradient requiring prolonged mechanical ventilation (22 h).

Previous experimental models of bupivacaine toxicity have used arterial pressure as a primary measure of recovery.^{9,10,14,15} However, a key observation of our study is that the elevated systolic pressures seen at 2.5 and 5 min in the epinephrine group were not sustained and did not correlate with improved cardiac or metabolic metrics later in the experiment. At 10 min, the mean values in rats receiving epinephrine were no better (RPP, lactate, PaO_2) or were worse (S_{cvpO_2} , pH, PaCO_2) than those of the saline control. Conversely, mean systolic blood pressure in the lipid-treated group was significantly lower than readings in the epinephrine group at 2.5 and 5 min, but significantly higher by the end of the experiment. The paradox of this crossover effect suggests that at least in this model, systolic hypertension early in resuscitation does not predict good recovery from bupivacaine overdose. RPP is a useful alternative measure of cardiac recovery because it compensates for reciprocal, rate-dependent alterations in systolic pressure and, obversely, pressure-dependent effects on heart rate. The RPP of the lipid group exceeded that of saline treatment from 7.5 min until the end of the experiment, when it surpassed those of both the saline and epinephrine groups (fig. 2).

Several previous studies of bupivacaine-induced toxicity found arrhythmias produced by epinephrine to be highly problematic. Heavner *et al.*⁹ reported an increased frequency of ventricular extrasystoles in rats given epinephrine for bupivacaine-induced asystole. Similarly, Groban *et al.*¹⁴ found that nearly half of dogs with bupivacaine overdose developed refractory ventricular fibrillation after treatment with epinephrine. In con-

cert with these studies, we found persistent ventricular ectopy throughout the experiment in each animal in the epinephrine group but not the others.

QRS duration was initially prolonged by bupivacaine infusion in the epinephrine and saline groups but returned to baseline values over the course of the experiment (fig. 2). The more rapid reversal of QRS prolongation in the epinephrine group is probably indicative of the salutary effect of adrenergic stimulation on cardiac conduction. The discrepant effects on cardiac conduction and RPP in the later part of the experiment suggest a lack of improvement at the underlying molecular or cellular sites of local anesthetic toxicity. In contrast, QRS duration in the lipid group was no different from baseline from the first return of spontaneous rhythm to the end of the experiment. The apparent relief from local anesthetic tissue intoxication suggests a rapid decline in myocardial bupivacaine concentration.

All animals were acidemic by the end of the experiment, and this was most pronounced in the epinephrine group. Lactate levels were highest and the mean $S_{cvp}O_2$ were lowest in the epinephrine group. Values of these parameters were significantly different from those of the lipid group, suggesting that epinephrine might worsen tissue perfusion, cardiac output, and oxygen delivery by comparison. Epinephrine also exerts direct metabolic effects that can increase blood lactate levels without a reduction in tissue perfusion.¹⁶ Notably, four of five rats receiving epinephrine developed visible pulmonary edema, with fluid requiring evacuation by a water trap in the expiratory limb of the breathing circuit. The 10-min mean values of P_{aO_2} and P_{aCO_2} in this group were significantly worse than those of the lipid group. The lower P_{aO_2} suggests a right-to-left shunt of sufficient magnitude to contribute to both tissue hypoxia and secondarily the low $S_{cvp}O_2$. This would exacerbate any baseline right-to-left shunt and further lower the P_{aO_2} . The hypercapnia seen in this group indicates that the pulmonary edema and resulting hypoventilation contribute to the acidosis, which has both metabolic and respiratory components. The mechanism of pulmonary edema was not studied. Nevertheless, it is likely that combined respiratory and metabolic derangements caused by epinephrine in this model of local anesthetic toxicity contributed to significant declines of cardiac function and tissue oxygen delivery seen in the later phases of the experiment. Hence, the quality of recovery after epinephrine treatment is no better than control and in many respects seems worse.

Our findings contrast with those of Mayr *et al.*,¹⁵ who reported recovery with epinephrine treatment (alone or in combination with vasopressin) in a porcine model of combined bupivacaine and asphyxial cardiac arrest. Experimental differences could explain the variance in outcomes. For example, in their model asphyxia was sustained to the point of asystole, implying that bupivacaine itself was not the cause of cardiac arrest. We

avoided this confounding factor by using a sufficiently high dose of local anesthetic that ventilation and chest compressions alone would not suffice to resuscitate the test subject. The required dose, 20 mg/kg, might be considered too high to be "clinically relevant"; however, we preferred using a single agent to be certain of the cause of cardiac arrest being treated. A difference in the definition of an endpoint such as return of spontaneous circulation could also alter the interpretation of findings. For example, the study of Mayr *et al.* defined recovery as a systolic pressure greater than 80 mm Hg for more than 5 min. Three of five animals in the epinephrine group of our study met these criteria, and only two of five in the lipid group did. Therefore, limiting our interpretation of the results to the criteria of Mayr *et al.* would alter our conclusions regarding the relative efficacies of lipid *versus* epinephrine-based resuscitation. However, our findings indicate that systolic pressure alone is not an adequate predictor of meaningful recovery in this rodent model of resuscitation from local anesthetic overdose.

Other features limit the conclusions one can draw from our study. The experiments were brief, ending at 10 min. This was necessary because all rats in the lipid group showed signs of light anesthesia by 10 min and required reinstating general anesthesia. Inhalational anesthesia profoundly decreases blood pressure in this setting, and it would be illogical to introduce this confounder unevenly across groups (*e.g.*, only in animals having return of spontaneous circulation). Furthermore, longer-term survival, neurologic recovery, and evidence of damage to other organ systems were not measured. These experiments did not address the mechanism underlying the benefit of lipid infusion which remains a key topic of debate. Most important, extreme caution must be exercised in extrapolating these results to a clinical setting.

The central finding of our study is that, for all metrics of resuscitation we examined, lipid infusion was more effective than epinephrine in treating bupivacaine overdose. Occurrence of pulmonary edema, acidemia, arrhythmias, and poor RPP suggest that epinephrine is not an effective treatment in this animal model of local anesthetic-induced cardiovascular collapse. Although it is premature to extrapolate this conclusion to the clinical setting, these data together with continued case reports of lipid infusion (successful and otherwise) and basic research will help to inform the management of such cases. Future scientific goals include identifying the mechanism of lipid's salutary effect, defining a reliable model for clinical local anesthetic toxicity, and optimizing a therapeutic regimen to treat it.

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