Epinephrine Impairs Lipid Resuscitation from Bupivacaine Overdose

A Threshold Effect

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Background: Lipid emulsion infusion reverses local anesthetic-induced cardiac toxicity, but the effect of adding epinephrine has not been studied. We compared escalating doses of epinephrine on recovery with lipid infusion in a rat model of bupivacaine overdose.

Methods: Rats anesthetized with isoflurane received an IV bolus of 20 mg/kg bupivacaine, producing asystole (zero time) in all animals. Ventilation (100% oxygen) and chest compressions were started immediately, and at 3 min the rats received one of six IV treatments (n = 5 for all groups): 5 ml/kg saline followed by infusion for 2 min at 1.0 ml · kg^{-1} · min^{-1}, and a second 5 ml/kg bolus at 5 min; or the same bolus and infusion treatment using 30% lipid emulsion plus a single injection of epinephrine at one of five doses: 0 (lipid control), 1, 2.5, 10, or 25 mcg/kg. An electrocardiogram and arterial pressure were monitored continuously, and arterial blood gas was measured at 7.5 and 15 min.

Results: Epinephrine improved initial return of spontaneous circulation (rate-pressure product > 30% baseline) but only 3 of 5 rats at 10 mcg/kg and 1 of 5 rats at 25 mcg/kg sustained return of spontaneous circulation by 15 min. Lipid alone resulted in slower but more sustained recovery. Epinephrine doses above a threshold near 10 mcg/kg increased lactate, worsened acidosis, and resulted in poor recovery at 15 min, as compared with lipid controls.

There was tight correlation of epinephrine dose to serum lactate at 15 min.

Conclusions: Epinephrine over a threshold dose near 10 mcg/kg impairs lipid resuscitation from bupivacaine overdose, possibly by inducing hyperlactatemia.

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Harvey M, Cave G: Bupivacaine-induced Cardiac Arrest: Fat is Good. Is Epinephrine Really Bad? ANESTHESIOLOGY 2009; 111:467–9.

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LIPID emulsion therapy is gaining acceptance as an antidote to systemic local anesthetic toxicity.[1] There is substantial experimental evidence that lipid emulsion can mitigate the cardiotoxic effects of bupivacaine overdose.[2,3] Recent case reports[4–8] support these findings and indicate that lipid infusion can rapidly reverse cardiovascular collapse secondary to systemic local anesthetic toxicity, even when conventional resuscitation measures have failed.

No study to date has specifically examined the effect of epinephrine on the efficacy of lipid reversal of local anesthetic-induced cardiac toxicity. Because patients will generally receive vasopressor therapy recommended in the Advanced Cardiac Life Support protocol during severe local anesthetic-induced cardiac toxicity, it is important to determine the effects of lipid infusion in the presence of epinephrine. We have previously shown that lipid provides superior recovery from bupivacaine overdose as compared with repeated bolus injections of epinephrine.[9] Despite rapid initial recovery of systolic blood pressure, rats treated with epinephrine uniformly showed declining hemodynamic function after 10 min. We use an intact animal model of bupivacaine overdose to test the effect of escalating doses of epinephrine on recovery from local anesthetic overdose during resuscitation with lipid infusion. Based on our previous findings, we hypothesized that injection of high-dose epinephrine could impair recovery. However, we further theorized that smaller epinephrine doses could speed early resuscitation without adverse effects on longer-term recovery.

Materials and Methods

Experimental Model

The following protocol was 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). Thirty healthy, male Sprague-Dawley rats weighing between 370 and 425 g were 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) to deliver a tidal volume of 2.5 ml at a starting rate of 65–70 breaths/min. Catheters were inserted into the left internal jugular vein, the left carotid artery, and the left femoral vein. Electrocardiography information using three subcutaneous needle electrodes and the carotid pressure were recorded continuously throughout the experiment by a PowerLab data archiving and retrieval system using Chart 5.2.1 (ADInstruments, Colorado Springs, CO). All animals were allowed to stabilize for 10 min at 1.5% isoflurane and 100% oxygen, and arterial blood gas measurements (i-STAT1 Analyzer, i-STAT Corp., East Windsor, NJ) before the bupivacaine challenge were made to confirm a pH between 7.35 and 7.45 and a serum lactate below 2.0. Arterial blood gas samples were analyzed at the experimental midpoint (7.5 min) and at the end of the experiment (15 min after onset of asystole). Animals were randomized by blind number drawing in advance of the experiment to one of six treatment groups: Saline control or lipid plus a single bolus of epinephrine at one of five doses: 0 (lipid control), 1, 2.5, 10, or 25 mcg/kg. The laboratory personnel were not blinded to the treatment; however, a subsequent offline data compilation was made from archived files of each experiment, which were blinded regarding the group.

Bupivacaine Infusion and Resuscitation Protocol

Isoflurane was discontinued and bupivacaine was immediately infused as a 20 mg/kg bolus over 20 s—a dose that reliably produces asystole from which hemodynamic recovery will not occur with only ventilation and chest compressions. All rats developed asystole by the end of the bupivacaine infusion, and this was taken as zero time. Manual chest compressions to achieve a rate-pressure product (RPP; RPP = systolic pressure x heart rate) of at least 50% of baseline were started immediately and interrupted for 5 s every minute to assess native RPP and QRS duration. RPP correlates closely with myocardial oxygen consumption[10] and can be taken as an indication of myocardial work. Mechanical ventilation with 100% oxygen was continued throughout the experiment. All IV treatments were initiated at 3 min according to the following regimens: Saline control, 5 ml/kg bolus over 20 s followed by a continuous infusion of $1.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 2 min and another 5 ml/kg bolus at the 5 min time point; lipid groups, 30% Intralipid (Fresenius Kabi, Uppsala, Sweden) was given by bolus (at 3 and 5 min) and by infusion at volumes and rates identical to that of the saline control (bolus 5 ml/kg, infusion $1.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 2 min, bolus 5 ml/kg). This regimen was found in preliminary experiments to optimize recovery

in this model of bupivacaine overdose. In the lipid control, no epinephrine was administered, while the other groups received a single injection of epinephrine with the initial lipid bolus at doses of 1, 2.5, 10, or 25 mcg/kg. Chest compressions were stopped for native RPP $\geq 30\%$ of baseline value, which was our criterion for return of spontaneous circulation (ROSC). All chest compressions were stopped at the 10 min time point regardless of RPP and subjects were evaluated for sustained or nonsustained recovery until the 15 min time point when arterial blood was drawn for analysis and animals were euthanized by anesthetic overdose.

We define a recovery index which incorporates both the fraction of time after treatment spent in spontaneous circulation (minutes in ROSC/12 min) and the RPP at 15 min (recovery index = fractional ROSC $\times$ RPP15 min). In this index, early ROSC increases the first term and high RPP at experiments' end increases the second term; similarly, slow recovery or late failure are penalized and decrease the recovery index.

Statistical Analysis

Power analysis was based on results of previous experiments comparing RPP at 10 min among various treatment groups; specifically, power was set at 0.8, significance criteria was set at 0.05, effect size was estimated as 2, and sigma (SE) at 0.9. The null hypothesis is that no difference exists between treatments regarding recovery of hemodynamics or metabolic measures during resuscitation from bupivacaine-induced arrest. This yielded a sample size of n = 5 for each group. All data were analyzed using GraphPad Prism 4 (GraphPad Software, San Diego, CA). Baseline parameters were analyzed by one-way ANOVA; posttests were not required as there were no intergroup differences in any parameter. All experimental parameters were compared across time by two-way ANOVA with repeated measures and Bonferroni posttests when significance was achieved (alpha set at 0.05) for differences over time between groups. Only differences compared with the lipid control group at 15 min are reported, though other significant within- and between-group differences were found at various times. Differences at 15 min were only considered to be significant when posttests indicated $P < 0.05$ for differences found by two-way ANOVA across the entire time course of the experiments. By the experiments' end, cardiovascular collapse in three animals in two groups (epinephrine 10 and 25 mcg/kg) had progressed to the point of no cardiac (electrical or pressor) activity. We recognized that the zero-value RPPs could be considered statistically problematic, and chose to carry forward each animal's RPP from the 12.5 min time-point. We believe that this is a statistically conservative approach that reduces the chance of a Type I error but avoids losing important and meaningful data. Values for the derived recovery index

Table 1. Baseline Values of Key Parameters for All Six Groups

	Saline	0 (mcg/kg)	1 (mcg/kg)	2.5 (mcg/kg)	10 (mcg/kg)	25 (mcg/kg)
RPP (mmHg/min)	61,059 ± 1,961	61,764 ± 3,674	57,176 ± 1,628	58,863 ± 3,388	60,048 ± 2,517	58,926 ± 3,653
pH	7.47 ± 0.0169	7.46 ± 0.0238	7.49 ± 0.0152	7.49 ± 0.00812	7.50 ± 0.00920	7.48 ± 0.00491
Pao_2 (mmHg)	589 ± 30.2	434 ± 45.0	465 ± 52.2	519 ± 65.4	543 ± 33.5	511 ± 46.2
$Paco_2$ (mmHg)	42.5 ± 1.71	43.0 ± 2.50	39.9 ± 1.09	39.5 ± 0.998	39.0 ± 0.866	39.8 ± 0.713
Lactate (mM/l)	1.361 ± 0.1446	1.132 ± 0.1895	1.092 ± 0.1120	0.968 ± 0.0598	1.410 ± 0.1922	1.010 ± 0.0495
HCO_3 (mM/l)	30.6 ± 0.136	31.0 ± 0.757	30.5 ± 0.538	30.1 ± 0.579	30.8 ± 0.445	30.3 ± 0.662
BE (mM/l)	6.8 ± 0.374	6.8 ± 0.735	7.2 ± 0.80	7.0 ± 0.707	7.8 ± 0.583	7.0 ± 0.632

All values are mean ± SEM. Baseline values for major parameters showed no difference among the six groups. The top row defines treatment groups: Saline control (no lipid); all other groups received lipid plus a single bolus of epinephrine at one of five doses (0, 1, 2.5, 10, or 25 mcg/kg) as indicated at the top of each row; n = 5 for all groups.

BE = base excess; HCO_3 = blood bicarbonate concentration; RPP = rate-pressure product (heart rate × systolic blood pressure); $Paco_2$ = partial pressure of carbon dioxide in blood; Pao_2 = partial pressure of oxygen in blood.

were compared by one-way ANOVA and *post hoc* tests performed using the Bonferroni method.

Results

Baseline values: Mean values for all baseline physiologic parameters are shown in table 1. All individual, baseline data sets were interrogated and passed the D'Agostino-Pearson normality test. There were no differences in any parameter among the six groups.

Hemodynamics: RRP was the key metric of cardiac function in this model. All animals were asystolic by the end of the bupivacaine infusion (zero time), and none in any group achieved ROSC by 3 min (IV treatment point). Recovery in terms of mean RPP ± SE *versus* time is shown in figure 1. Table 2 identifies the number of animals attaining ROSC criteria (>30% baseline RPP) in each group over time. A fraction of animals receiving epinephrine 10 mcg/kg (1 of 5) and 25 mcg/kg (2 of 5) were found to have no heartbeat at 15 min. ROSC among all animals in a group was achieved only in the lipid control and the two groups receiving lower doses of epinephrine.

Our recovery index (units = 10^{-3} mmHg/min^{-1} given as means ± SEM are shown in parenthesis) indicated that the 1.0 (64.6 ± 3.1) and 2.5 (52.1 ± 4.4) mcg/kg treatment groups did not differ from the 0 (48.4 ± 5.1) mcg/kg group despite their rapidity of recovery; P > 0.05 for all comparisons with lipid control. However, the 10 (19.7 ± 8.0; $P < 0.01$) and 25 (6.1 ± 3.6; $P < 0.001$) mcg/kg groups scored significantly lower than the 0, 1.0, and 2.5 mcg/kg treatment groups; P values are given for comparison with the lipid control.

Metabolics

Blood gas values at 15 min are shown in table 3. All values are compared only to the lipid control. Significant depression of pH, base excess, and HCO_3 were found at 15 min in saline control, and the groups treated with 10 and 25 mcg/kg epinephrine. Significant decrements of arterial Po_2 were seen in the higher-dose epinephrine treatment groups. Animals receiving the highest dose of epinephrine reliably had the worst metabolic profiles. Mean lactate values at 15 min were different from lipid control for the groups receiving 10 ($P < 0.001$) and 25 ($P < 0.001$) mcg/kg epinephrine. At 7.5 min only the
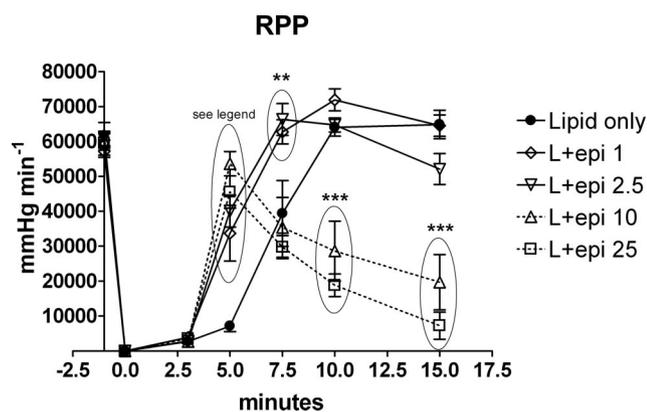
Fig. 1. Rate-pressure product *versus* time for all six experimental groups. Significance of difference *versus* lipid control is shown for each group. At 5 min, epinephrine 1 μg/kg ($P < 0.05$); epinephrine 2.5 μg/kg ($P < 0.01$), epinephrine 10 μg/kg, and epinephrine 25 μg/kg ($P < 0.001$). Asterisks represent significance of differences from lipid control for groups within the ellipses at 7.5, 10, and 15 min. Notably, no differences were found at 7.5 min for the epinephrine 10 μg/kg and epinephrine 25 μg/kg groups. This is the crossover point for the higher-dose epinephrine groups, after which they compare unfavorably to the lipid control. ** $P < 0.01$; *** $P < 0.001$; n = 5 for each group. Error bars represent SE. RPP = rate-pressure product.

Table 2. Animals Attaining Return of Spontaneous Circulation for Each Group and Time

	3 min	5 min	7.5 min	10 min	15 min
Saline	0	0	0	0	1
Lipid control	0	0	4	5	5
1 mcg/kg	0	4	5	5	5
2.5 mcg/kg	0	5	5	5	5
10 mcg/kg	0	5	4	3	3
25 mcg/kg	0	5	5	3	1

n = 5 for all conditions.

Table 3. Mean Arterial Blood Gas Parameters at 15 min

	pH	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	BE mm/l	HCO_3 mmol/l
Saline	7.21 ± 0.03*	170 ± 37	45.6 ± 3.4	−7.0 ± 2.1†	20.1 ± 1.8†
Lipid control	7.31 ± 0.02	308 ± 89	49.6 ± 1.5	−1.4 ± 0.8	25.4 ± 0.6
1 mcg/kg	7.26 ± 0.02	218 ± 103	56.9 ± 1.7	−1.6 ± 0.5	26.0 ± 0.5
2.5 mcg/kg	7.26 ± 0.01	111 ± 25‡	53.6 ± 2.2	−2.8 ± 0.6	24.2 ± 0.5
10 mcg/kg	7.20 ± 0.04*	61 ± 12*	53.9 ± 6.8	−5.8 ± 1.1‡	21.7 ± 1.0‡
25 mcg/kg	7.13 ± 0.01†	104 ± 31*	42.4 ± 6.1	−10.6 ± 1.7†	16.1 ± 1.1†

Values are mean ± SEM.

The asterisk represents statistical difference at 15 min as compared with lipid control. * $P < 0.01$. † $P < 0.001$. ‡ $P < 0.05$.

n = 5 for all cells except at 10 mcg/kg, where n = 4 for PO_2, Pa_{CO_2}, BE, and HCO_3 because of failure of the blood gas machine.

BE = base excess; HCO_3 = blood bicarbonate concentration; Pa_{CO_2} = partial pressure of carbon dioxide in blood; Pa_{O_2} = partial pressure of oxygen in blood.

group receiving 25 mcg/kg differed from lipid control ($P < 0.001$).

Discussion

We found in this rodent model of bupivacaine overdose that a single injection of epinephrine of 10 mcg/kg or greater impairs lipid-based resuscitation. Comparisons with saline control confirmed that infusion of lipid emulsion alone is an effective means of reversing local anesthetic–induced cardiac collapse. While dose-response experiments suggest a potential advantage of very small epinephrine doses (1 or 2.5 mcg/kg) in terms of rapid recovery, at higher doses epinephrine clearly adversely affected both metabolic and hemodynamic recovery profiles. Although epinephrine continues to be used clinically for virtually all types of cardiac arrest, our data suggest that caution should be exercised in adding epinephrine to a lipid emulsion treatment protocol.

Lipid emulsion infusion is an effective means of treating cardiac toxicity caused by overdose of lipophilic drugs.[11] It has been shown to reverse hemodynamic compromise in experimental models of local anesthetic,[2,3] calcium channel blocker,[12] and tricyclic antidepressant[13] overdose. There are now more than a dozen reports in the peer-reviewed literature documenting successful lipid-based resuscitation of patients with apparently life-threatening overdoses of lone and combined local anesthetics[14] and other drugs, including bupropion[15] and quetiapine.[16] It is noteworthy that in many reports the patients had already failed conventional resuscitative efforts, including the use of high-dose epinephrine.‡‡

It is important to note that in our model, the higher doses of epinephrine (25 mcg/kg) are actually much lower than what is traditionally considered high-dose epinephrine treatment (0.1 mg/kg or 100 mcg/kg) as defined by the 1992 American Heart Association guidelines for cardiopulmonary resuscitation and found in

several studies to impair outcomes in clinical resuscitation.[17] However, interpretation of such interspecies dose comparisons is not straightforward, and caution should be used in extrapolating these results to a clinical situation.

We previously showed in a similar rodent model of bupivacaine-induced asystole that lipid is superior to epinephrine,[9] vasopressin,[18] or the combination of those vasopressors with respect to all measured hemodynamic and metabolic variables at 10 min. However, the effects on resuscitation of combining lipid with epinephrine were unknown and comprise the main focus of this study. We measured recovery when lipid is combined with epinephrine across more than a log of doses (1–25 mcg/kg). RPP was our preferred hemodynamic metric, since it correlates closely with myocardial oxygen consumption, a surrogate for myocardial work. The 15-min values for RPP showed two discrete groups of animals among lipid-treated rats (fig. 1). All animals receiving doses of epinephrine of 0, 1, or 2.5 mcg/kg attained ROSC by 15 min, while those given larger doses of epinephrine had unfavorable recovery profiles. Notably, all animals receiving epinephrine initially achieved ROSC more rapidly than the lipid control group. This shifted the apparent recovery curves so that at 5 min all epinephrine-treated animals had attained ROSC, while no lipid controls or saline-treated animals were above ROSC criteria. However, by 7.5 min these lines crossed (fig. 1), and all animals in the lipid control group had achieved ROSC, while the mean RPPs of the groups receiving the two highest epinephrine doses were in steep but negative slopes. Mean RPP in the latter groups were at or below the criteria for ROSC by 15 min, although the lipid control animals and those receiving the lower epinephrine doses all had sustained RPPs at or above baseline values. Mean RPPs in the saline control were below ROSC criteria at all time points.

All animals receiving epinephrine appear to recover faster than the lipid control; however, sustained recovery did not occur at the two higher doses of epinephrine. It is apparent that the timing for scoring recovery has important and potentially obfuscating effects on in-

‡‡ Other anecdotal examples of successful lipid-based resuscitation can be found at the educational Web site www.lipidrescue.org. Accessed April 14, 2009.
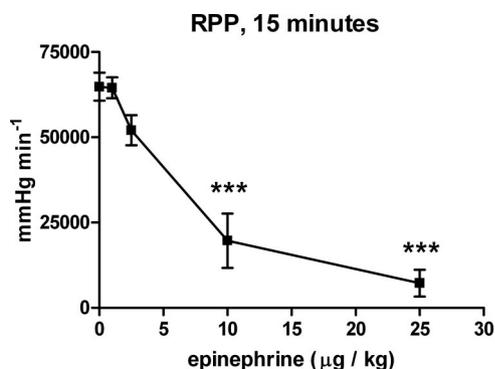
Fig. 2. Rate-pressure product at the end of the experiment (15 min) across a range of epinephrine doses. Significance of difference *versus* lipid control is shown for each of the epinephrine treated groups. *** P < 0.001. Error bars represent SEM. RPP = Rate-pressure product.

terpreting such results (table 2). Measures of RPP at 5 min alone would exactly invert our main finding that the increasing doses of epinephrine are associated with progressively poorer hemodynamic recovery at 15 min (fig. 2).

The paradox of transient recovery in the higher-epinephrine groups followed by late failure is a key finding of our study. While there appeared to be a statistical advantage in early recovery for all epinephrine-treated groups, the later decline in function of the higher-epinephrine treated groups suggests that early recovery in itself is not a sufficient or accurate predictor of recovery quality. This incongruity justified using a recovery index as an added measure that includes both early recovery and late survival as important factors in assessing recovery. In our model, a recovery index with a mean value near or equal to baseline RPP indicates an early ROSC with sustained recovery; conversely, a much lower recovery index indicates either a delayed, transient, or poor recovery. This index showed no overall recovery benefit of the lower epinephrine doses, as compared with the lipid control. However, there appears to be a threshold dose-effect in our model occurring between 2.5 mcg/kg and 10 mcg/kg, above which epinephrine is overtly deleterious.

The correlation of epinephrine with adverse outcomes is not a novel observation. Although epinephrine is recommended in the American Heart Association Advanced Cardiac Life Support guidelines[19] and is universally used in resuscitation of the pulseless patient, it has not been shown to be superior to a placebo in any clinical trial.[20] Epinephrine is arrhythmogenic, increases myocardial oxygen demand, reduces subendocardial perfusion, can cause pulmonary edema, and reduces myocardial function after resuscitation.[21] Clinical studies show no advantage to high-dose *versus* standard-dose epinephrine in resuscitation, and both clinical[22] and laboratory[23,24] data suggest that higher doses of epinephrine worsen outcome in various shock states. It is arguable whether patients in such clinical studies merely received more epinephrine support secondary to their poor baseline
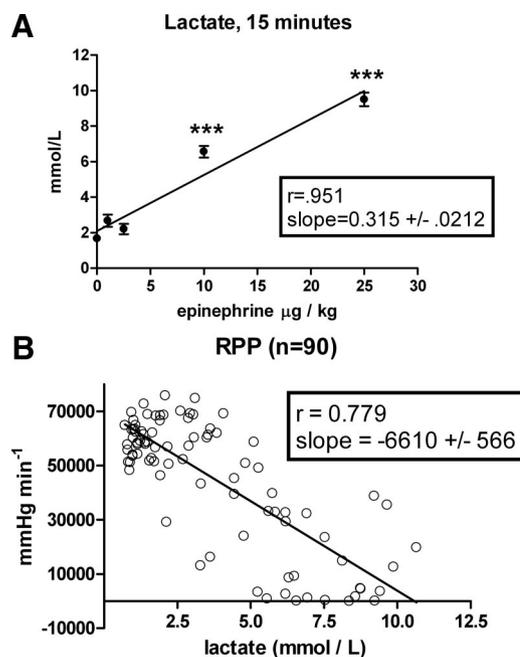

Fig. 3. Metabolic and hemodynamic correlates. (*A*) Blood lactate levels at the end of the experiment (15 min) across a range of epinephrine doses; line plotted using linear regression. Significance of difference is shown for lipid control *versus* each of the epinephrine treated groups. *** P < 0.001. Error bars represent SEM (*B*) Blood lactate levels plotted with linear regression against rate-pressure product for all treatment groups at baseline, 7.5, and 15 min. n = 90. Strength of correlation indicated by Pearson's r for both plots. RPP = rate-pressure product.

physiologic status, or if the persistent adrenergic stimulation contributed to their decline. However, the question of cause *versus* effect is addressed in our study, since all groups had the same baseline physiologic status and received the same bupivacaine challenge, cardiopulmonary resuscitation regimen, and lipid treatment. Intergroup differences in outcome were therefore attributable to the specific epinephrine dose given. Our findings clearly indicate a strong negative effect of epinephrine doses at 10 mcg/kg or greater on hemodynamic recovery. These observations support the notion that repeated epinephrine during resuscitation from local anesthetic overdose could be generally deleterious and particularly impair the efficacy of lipid-based resuscitation.

Metabolic parameters of recovery also varied according to the dose of epinephrine. Base excess, pH, and HCO_3 were all substantially reduced, and lactate was increased at 15 min in the groups receiving the higher doses of epinephrine. Negative base deficit and elevated lactate are clinical predictors of bad outcome in the critically ill.[25] Smith *et al.* found that a combination of base excess more negative than -4 mm and a lactate greater than 1.5 mm on admission to the intensive care unit had a sensitivity of 80% and specificity of 59% for mortality. We found that serum lactate levels correlated very closely with the dose of epinephrine (fig. 3A). The correlation held at the halfway point (7.5 min; $r = 0.853$; slope = 0.1804 ± 0.0230) was stronger and the slope

more positive by the end of the experiment (15 min; r = 0.951; slope = 0.315 ± 0.0212). It is well established that epinephrine enhances lactate production through direct metabolic effects mediated by activation of the beta(2)-adrenergic receptor. Epinephrine stimulates lactate production in well-oxygenated skeletal muscle by increasing the activity of the Na^+/K^+-adenosine triphosphatase,[26-28] and beta blockade inhibits this effect.[29] While shock states produce hyperlactatemia through both adrenergic stimulation (endogenous and exogenous) and tissue hypoxia, it is likely here that both mechanisms contribute. However, it is possible that the metabolic contribution is greater[30,31] and the strong dose-effect correlation we found supports this notion.

The potential relevance of this effect is borne out by the further correlation of hemodynamic function with serum lactate levels (fig. 3B). We found by plotting the RPP *versus* lactate in pooled data from all animals at three time points (baseline, 7.5 and 15 min) that there was a strong negative correlation of RPP to serum lactate under all conditions (r = 0.779; slope = −6610 ± 567; n = 90). This leads to the possibility that augmenting serum lactate could explain, in part, the apparently causal relationship of epinephrine dose to poor RPP. It is well documented in various shock states that lactic acid levels and lactic acid clearance correlate with patient survival,[32,33] suggesting that elevated lactate could be a cause as well as a sentinel of poor cardiac function.

The dynamics of recovery in this model are particularly interesting and lend some insight into the potentially causal association of epinephrine, lactate, and depressed cardiac function. The degree of increase or decline in RPP over the second half of the experiment is seen to correlate closely with the dose of epinephrine. This relationship can be examined by matching the change in RPP from 7.5 to 15 min (Δ-RPP) in each animal with the corresponding dose of epinephrine (fig. 4A). This plot confirms that the lipid control and the groups receiving the smaller epinephrine doses have uptrending RPP, and those receiving the higher doses of epinephrine exhibit decreasing RPP in the second half of the experiment. A parallel plot of the change in lactate can be made for each animal *versus* the epinephrine dose and yields a mirror image of the Δ-RPP plot (fig. 4B), indicating the correlation of the (unfavorable) change in lactate late in the experiment with increasing epinephrine dose. The Δ-lactate corresponds to lactate clearance, which has been reported to correlate closely with clinical recovery in specific shock states.[32,33] This relationship is confirmed for our experimental model by the double plot of Δ-lactate *versus* Δ-RPP (fig. 4C), which shows that animals with the greatest drop in lactate have the most improvement in RPP. Therefore, the nearly perfect correlation of epinephrine dose with serum lactate at the experiment's end appears to be causally related to the
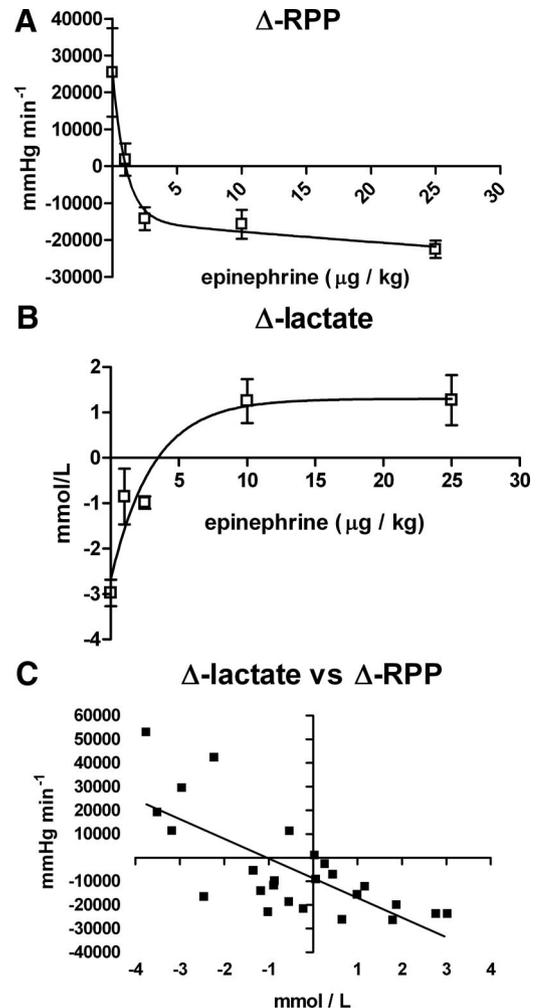

Fig. 4. Dynamics of metabolic and hemodynamic correlations. (*A*) The change in rate-pressure product (Δ-RPP) between 7.5 and 15 min over a range of epinephrine doses; curve fit by a two-phase exponential. (*B*) The change in blood lactate levels (Δ-lactate) between 7.5 and 15 min over a range of epinephrine doses; line fit to a Boltzmann sigmoidal curve. (*C*) Δ-RPP *versus* Δ-lactate; linear regression; r = 0.72. Error bars represent SEM.

adverse effect of epinephrine on overall recovery seen in figure 2 and table 2.

We also confirmed our previous observation that at higher doses epinephrine might contribute to pulmonary edema in this experimental system. Lipid alone and with smaller doses of epinephrine did not produce pulmonary edema, but injection of 10 and 25 mcg/kg epinephrine was associated with dose-related increases in fluid collected in the expiratory limb of the circuit. The same phenomenon has been reported in clinical scenarios where patients received high doses of vasopressors during resuscitation.[15,34]

These findings are consistent with the previously reported data from a similar model that indicate that the use of epinephrine is deleterious to the resuscitation from bupivacaine-induced asystole. The current model differs from the previous reports by virtue of an interval of 3 min between asystole (zero time) and treatment, a

fixed lipid treatment regimen, a longer time to end of experiment (15 min *vs.* 10 min), and use of a single epinephrine injection across a range of (much smaller) doses. The no-treatment interval was intended to more closely mimic the clinical scenario of a short delay to the availability of lipid for infusion. The fixed lipid regimen avoids the confounding variable as a result of variations in this treatment. The longer time frame allows observation of later hemodynamic recovery. The single injection across a range of epinephrine doses was designed to yield a formal dose-response for the effect of epinephrine on efficacy of lipid infusion.

Epinephrine has been compared experimentally to lipid-based resuscitation in other laboratories with apparently conflicting results. For instance, data indicating failed recovery with lipid infusion were reported by Mayr *et al.*[35] in a porcine model of bupivacaine overdose. They gave bupivacaine 5 mg/kg and then stopped ventilating the animals until 1 min past the onset of asystole. Survival was scored as a systolic pressure greater than 80 mmHg and was found in 0 of 5 lipid-treated animals and 5 of 5 animals receiving multiple rounds of epinephrine (45, 45, and 200 mcg/kg) plus vasopressin (0.4, 0.4, and 0.8 U/kg). The difference in outcome *versus* our current study could be explained by the introduction of asphyxia as a confounder, since there is evidence that this impairs lipid-based resuscitation.[36] Alternately, the difference in endpoints could possibly result in scoring as survivors animals in the porcine study that would not have met our ROSC criteria; unfortunately, heart rate and RPP were not reported by Mayr *et al.*, and direct comparisons of recovery profiles are not possible.

Interpretation and clinical extrapolation from our study is limited by our use of a small animal; short experimental duration; lack of evaluation for a full (cardiovascular, pulmonary, and neurologic) postsurgical, postexperimental recovery; the very high dose of bupivacaine and lipid infusions; and the use of isoflurane, a potential confounder. However, similar rodent models in our laboratory have reliably predicted hemodynamics and have been translated into favorable clinical outcomes in resuscitation from local anesthetic toxicity.[37]

Physicians facing a patient with cardiac compromise as a result of local anesthetic overdose will require specific guidance on how best to integrate lipid infusion with conventional resuscitation measures. This point is particularly critical, since our results suggest the two approaches are to some degree physiologically inimical. This dilemma is aggravated by the well-entrenched, nearly universal inclination to use epinephrine for all pulseless patients. Caution must be exercised in extrapolating our findings to the clinical situation. However, our data and those of other investigators suggest that large doses of epinephrine may not always be to the patients' advantage, particularly for drug-induced car-

diac arrest. Local anesthetic cardiac toxicity reduces myocardial contractility and is worsened by tissue acidosis. Hence, the injection of repeated bolus epinephrine doses might aggravate the toxicity by intense generalized vasoconstriction and elevated lactate production. Our findings further suggest that epinephrine-induced hyperlactatemia is detrimental to hemodynamic recovery, and cast more doubt on the wisdom of using epinephrine to treat local anesthetic overdose. The clinical tendency to use epinephrine is often reinforced by a rapid, if transient, improvement in the hemodynamic profile. This phenomenon was replicated in our experimental system, but reliably predicted subsequent cardiovascular decline. The underlying mechanism of this biphasic pattern is not precisely known, but the paradox provides further evidence against a clinical advantage to using epinephrine, despite misleading appearances to the contrary.

We have confirmed that infusion of lipid emulsion reverses cardiac toxicity in this rodent model of bupivacaine overdose. However, the dose-response plot clearly indicates the adverse hemodynamic and metabolic effects of concomitant injections of epinephrine above a dosing threshold on the efficacy of lipid-based resuscitation. Analysis of the data further suggests that the hemodynamic and metabolic deterioration are interrelated, and specifically implicates epinephrine-induced hyperlactatemia as a possible mechanism of delayed cardiovascular collapse. Epinephrine remains a first-line drug for advanced cardiac life support because of its positive chronotropy, inotropy and vasopressor effects which transiently augment cardiac output and coronary perfusion pressure. However, further study will be needed to confirm or refute our conclusion that epinephrine above a threshold dose impairs recovery from bupivacaine in general and the effectiveness of lipid reversal in particular.

Note added in proof: Hicks *et al.*[38] have recently shown in the context of resuscitation using high doses of epinephrine (>100 mcg/kg) that lipid provides no recovery benefit over saline controls in a model of bupivacaine overdose. These data support our findings that predict that administering such high doses of epinephrine would preclude effective lipid reversal of bupivacaine toxicity.

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