Epinephrine Injection in Lipid-Based Resuscitation from Bupivacaine-Induced Cardiac Arrest: Transient Circulatory Return in Rabbits

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BACKGROUND: IV lipid emulsion has demonstrated to be effective therapy for bupivacaine-induced cardiotoxicity. However, the role of epinephrine when coadministered with lipid emulsion in toxin-induced cardiac arrest is unclear. We postulated superior resuscitation outcome in the absence of epinephrine in a rabbit model of bupivacaine-induced cardiac arrest resuscitated with IV lipid emulsion.

METHODS: Twenty sedated, instrumented New Zealand White rabbits received 10 mg/kg IV bupivacaine producing asystole. Mechanical ventilation and external chest compressions were commenced at 30 seconds. At 1 minute, animals received 5 mL/kg 20% lipid emulsion in addition to 1 of 4 additional IV treatments (n = 5 all groups): 0.9% saline, 2.5 μg/kg epinephrine, 10 μg/kg epinephrine, 100 μg/kg epinephrine; all at 1 mL/kg. Lipid emulsion bolus was repeated at 4 minutes. Return of spontaneous circulation and hemodynamic metrics were obtained to 15 minutes. Saline group animals additionally received high-dose epinephrine (100 μg/kg) treatment at 15 minutes, and were monitored to 20 minutes.

RESULTS: High-dose epinephrine administration was associated with increased rate of return of spontaneous circulation compared with saline control (0 of 5 saline-treated animals; 0 of 5 animals in the 2.5 μg/kg epinephrine group; 3 of 5 in the 10 μg/kg group [P = 0.167]; and 4 of 5 in the 100 μg/kg group [P = 0.048]). Spontaneous but decreasing circulation was maintained at 15 minutes in 4 of 5 animals in the 100 μg/kg group alone (P = 0.048); mean arterial blood pressure at 15 minutes was 12.8 (SEM 2.8) mm Hg saline, 12.0 (2.5) mm Hg 2.5 μg/kg epinephrine, 20.6 (2.7) mm Hg 10 μg/kg epinephrine, and 26.4 (3.9) mm Hg 100 μg/kg epinephrine (P = 0.008). Four of five animals in the saline-treated group exhibited return of spontaneous circulation after delayed epinephrine treatment (P = 0.048). High-dose epinephrine administration was associated with a significant increase in coronary perfusion pressure before return of spontaneous circulation.

CONCLUSIONS: Epinephrine seemed to be necessary for return of spontaneous circulation, but was subsequently associated with declining hemodynamic variables in this rabbit model of bupivacaine-induced cardiac arrest. Further study is required to define the role of epinephrine in lipid-based resuscitation from local anesthetic-induced cardiac arrest. (Anesth Analg 2010;111:791–6)

Intravenous lipid emulsion has demonstrated to be effective in the treatment of cardiac arrest and cardiovascular collapse secondary to bupivacaine toxicity in a variety of animal models.[1–4] Subsequent clinical application of lipid emulsion has resulted in successful resuscitation outcome in case reports of local anesthetic-induced cardiotoxicity.[5–9] On the basis of experimental and clinical efficacy, lipid emulsion is now endorsed as a component of resuscitation from local anesthetic systemic toxicity.[10]

The literature surrounding administration of vasoactive drugs in conjunction with lipid emulsion in local anesthetic toxicity is, however, far from uniform. Epinephrine and vasopressin have been compared with lipid alone in resuscitation from local anesthetic-induced cardiac arrest in porcine[11,12] and murine[13] models with conflicting results. Clinical reports of resuscitation from local anesthetic-induced cardiotoxicity likewise contain cases whereby IV lipid emulsion alone, and in combination with epinephrine and/or vasopressin, have been administered with favorable patient outcome.[5–9]

The rationale for administration of epinephrine during cardiopulmonary resuscitation (CPR) is to restore threshold levels of coronary and cerebral perfusion pressures and thereby blood flows. However, although epinephrine has been used universally in resuscitation, there is a paucity of evidence to show that it improves survival in humans. Both beneficial and toxic physiologic effects of epinephrine administration during CPR have been shown in animal and human studies.[14] There is evidence, however, that the use of vasopressor drugs favors initial return of spontaneous circulation.[15,16]

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A recent report of adverse outcome when epinephrine was coadministered with lipid emulsion in a rodent model of bupivacaine-induced cardiac arrest[17] raised questions regarding the clinical role of epinephrine in resuscitation from local anesthetic systemic toxicity. Given a decision to withhold epinephrine in this scenario represents a significant departure from conventional therapy; additional experimental support is clearly necessary to inform the clinician considering use of vasoactive drugs in the patient experiencing local anesthetic-induced cardiotoxicity. This study was therefore performed to further examine the role of epinephrine in lipid-based resuscitation from local anesthetic-induced cardiac arrest. Specifically, we sought to test the hypothesis that withholding epinephrine in lipid-based resuscitation from bupivacaine-induced asystole would result in superior resuscitation outcome in an established rabbit model.

METHODS

This study was performed at the Small Animals Laboratory of the Ruakura Animal Research Center, Hamilton, New Zealand. The contents of the study were reviewed and approved by the Ruakura Animal Ethics Committee. Twenty-one adult New Zealand White rabbits (aged 90–110 days) of mixed gender were studied. Animals were housed in single sex enclosures with no chance of pregnancy. Unfettered access to feed and water was permitted until the day of study.

Experimental Model

On the day of study, rabbits were sedated with ketamine (Mayne Pharma Ltd., New Zealand) at 50 mg/kg and xylazine (Bayer HealthCare, Germany) at 4 mg/kg via IM injection. Animals were placed on a surgical board and venous cannulation of the marginal vein of the ear was performed. IV ketamine bolus (10 mg) was administered before subsequent invasive procedures. Three-lead electrocardiogram (ECG) was sited with continuous monitoring of standard lead 2.

A transverse incision was made in the base of the neck and tracheostomy performed (truncated [5 cm] 3.5-mm endotracheal tube [ETT], secured by taping). Pressure-controlled mechanical ventilation (titrated to 10 cm H_2O inspiratory pressure) was then instituted with 100% oxygen at 60 breaths per minute in the absence of positive end-expiratory pressure, via a Nuffield series 200 pediatric ventilator (Penlon Ltd., Abington, England). Inspiratory/expiratory ratio was set at 1:4. End-tidal CO_2 was assessed with continuous color-change capnography (C-CO_2™; Vital Signs Colorado Ltd., Englewood, CO) and maintained in the 2% to 5% zone of the colorimeter before induced arrest. Vecuronium (Pharmaco Ltd., New Zealand) at 0.1 mg/kg was administered after establishment of mechanical ventilation.

Blunt dissection was used to expose the left common carotid artery, and confluence of internal jugular and subclavian veins on the right. One saline-filled 20-gauge cannula was advanced from the internal carotid artery to the proximal aorta and connected in standard fashion (pressure transducer; Edwards Lifesciences, Irvine, CA) to a Hewlett-Packard 78834A neonatal monitor (Hewlett-Packard, PaloAlto, CA) for continuous arterial blood pressure monitoring. Another 20-gauge cannula was advanced via the superior vena cava to the right atrium and connected in identical fashion to the monitoring system. Both pressure transducers were room-air zero calibrated with reference to the midthorax. A stabilization period of 5 minutes was given after completion of invasive procedures at which time arterial blood was obtained for analysis (I-STAT1 Analyser, CG4+ cartridge; I-STAT Corp., East Windsor, NJ).

Bupivacaine Arrest Protocol

Bupivacaine (AstraZeneca Ltd., New Zealand) 10 mg/kg was injected as an IV bolus over 5 seconds via the venous cannula in the marginal ear vein. We used 10 mg/kg as in our previous work[4] because it reliably induces asystole, from which spontaneous circulatory return with basic life support (BLS) measures is unlikely.

Resuscitation Protocol

A 30-second nonintervention period after asystole was given to mimic clinical recognition and response time. BLS (mechanical ventilation and manually performed external chest compressions [approximately 30% anterior-posterior chest diameter at 200 compressions per minute timed by metronome]) was then instituted by an investigator blinded to both group and arterial pressure tracings. Differing rates of ventilation and chest compressions from our previous work were the result of review of blood gas analysis and hemodynamic metrics in similar (as yet unpublished) models of resuscitation from toxic insults.

At 1 minute, all animals received 5 mL/kg 20% intralipid (Fresenius Kabi AB, Stockholm, Sweden) infused over a 20-second interval via the ear vein. Epinephrine (Hospira, Auckland, New Zealand) or saline was then administered over the subsequent 10 seconds (according to prior randomization) per the following groupings: control animals received 0.9% saline; low-dose epinephrine group received 2.5 μg/kg epinephrine; intermediate-dose epinephrine animals received 10 μg/kg epinephrine; and high-dose epinephrine animals received 100 μg/kg epinephrine. All treatments were diluted to 1 mL/kg volume in 0.9% saline and administered via the ear vein. Another 5 mL/kg 20% intralipid bolus was administered over a 20-second interval via the ear vein at 4 minutes. All IV treatments were purchased from their respective manufacturers and warmed to 37°C before administration.

BLS (chest compressions, mechanical ventilation) was continued for 15 minutes or until return of spontaneous circulation. Chest compressions were withheld for a 5-second period every minute to assess intrinsic cardiac rhythm and native hemodynamic metrics. Return of spontaneous circulation was defined by a mean arterial blood pressure (MAP) of ≥50 mm Hg with restoration of intrinsic cardiac rhythm, for ≥120 seconds as in our previous work.[4] Chest compressions were reinstituted in animals that developed a second period of cardiovascular collapse after initial circulatory return, defined by the development of contemporaneously recorded MAP less right atrial pressure (RAP) of ≤5 mm Hg for ≥30 seconds. Conversely, animals were considered to have evidence of native circulation if they exhibited a heart rhythm consistent with a

spontaneous circulation, and unsupported MAP-RAP differential of ≥6 mm Hg (i.e., animals not undergoing CPR). Arterial blood was additionally obtained at 15 minutes for repeat arterial blood gas (ABG) analysis and serum lactate evaluation.

All animals in the lipid-only group exhibiting cardiovascular collapse additionally underwent high-dose epinephrine treatment after completion of the initial 15-minute resuscitation phase. Epinephrine at 100 μg/kg (diluted to 1 mL/kg in 0.9% saline) was injected via the ear vein over a 10-second interval commencing at 15 minutes. Resuscitative measures were continued for a further 5 minutes (to 20 minutes) in this group alone. At completion of the study protocols, all surviving animals were killed with an IV bolus injection of 300 mg pentobarbital. Necropsy was performed to confirm correct placement of vascular catheters and ETT.

Data Acquisition

Heart rate, invasive blood pressure variables (systolic, diastolic, and MAP), and RAP were transcribed directly from the monitoring system to a standardized data collection template at baseline, commencement of resuscitative efforts (30 seconds), and 1-minute intervals from time 60 seconds until termination of the study protocol. Heart rate was recorded to the nearest bpm, and pressure metrics to the nearest mm Hg. Coronary perfusion pressure (defined as simultaneously recorded diastolic blood pressure less RAP) was retrospectively computed for each monitoring interval.

Statistical Analysis

Power analysis was based on results of previous experiments comparing return of spontaneous circulation and survival to 15 minutes between treatment groupings. A difference in proportion of 0.8 was sought. That is, we were powered to find almost "all or nothing" effects in categorical outcomes only. The null hypothesis was that there is no difference between treatment groups. With power set at 80% and α level at 0.05, this equated to 5 animals in each group. Statistical analysis of all variables was performed with SPSS for Windows (version 10.0; SPSS, Chicago, IL). Return of spontaneous circulation and survival to 15 minutes were compared as primary outcome variables. Fisher exact testing was used to compare dichotomous outcomes among groups. Comparison of baseline metrics was conducted using 1-way analysis of variance following assessment for normality with Kolmogorov-Smirnov testing. Continuous hemodynamic variables were compared across time with the lipid-only group as control by 2-way repeated measures analysis of variance with Bonferroni posttesting when significance was achieved ($P < 0.05$). We performed post hoc comparison of coronary perfusion pressure at the following isolated time points: immediately before epinephrine administration, and immediately after epinephrine administration using Mann-Whitney statistics. All data are presented as mean (SEM). A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

No difference was observed in animal characteristics or hemodynamic baseline variables among groups (Table 1).

Table 1. Animal Characteristics and Baseline Hemodynamic Variables

	Lipid only ($n = 5$)	2.5 μg/kg epinephrine ($n = 5$)	10 μg/kg epinephrine ($n = 5$)	100 μg/kg epinephrine ($n = 5$)
Age (d)	105 (5)	105 (4)	101 (4)	103 (6)
Gender (male/female)	4/1	4/1	4/1	3/2
Weight (g)	2364 (74)	2390 (111)	2383 (139)	2192 (152)
Heart rate (bpm)	202 (6)	186 (14)	210 (8)	198 (11)
MAP (mm Hg)	66 (5)	72 (8)	64 (6)	75 (4)
RAP (mm Hg)	3.8 (0.4)	3.2 (0.6)	3.4 (0.4)	4.8 (0.8)
CPP (mm Hg)	54 (5)	60 (8)	52 (5)	61 (4)

MAP = mean arterial blood pressure; RAP = right atrial pressure; CPP = coronary perfusion pressure.
Continuous data are presented as mean (SEM); gender is presented as proportion.
There were no significant differences among groups.

Table 2. Arterial Blood Gas Variables at Baseline

	Lipid only ($n = 5$)	2.5 μg/kg epinephrine ($n = 5$)	10 μg/kg epinephrine ($n = 5$)	100 μg/kg epinephrine ($n = 5$)
pH	7.39 (0.03)	7.39 (0.03)	7.40 (0.02)	7.37 (0.03)
Pao_2 (mm Hg)	258 (56)	279 (75)	252 (66)	221 (61)
$Paco_2$ (mm Hg)	33.6 (5.8)	33.8 (3.1)	40.6 (4.9)	44.6 (3.5)
HCO_3 (mmol/L)	23.2 (4.8)	25.0 (4.4)	27.4 (1.9)	28.5 (3.7)
Base excess (mmol/L)	−1.6 (4.9)	4.8 (5.3)	3.0 (1.6)	3.8 (3.2)
Lactate (mmol/L)	2.5 (0.5)	1.6 (0.5)	2.4 (1.3)	2.2 (0.5)

Data are presented as mean (SEM).
There were no significant differences among groups.

Table 3. Return of Spontaneous Circulation and Repeated Cardiovascular Collapse According to Group

	Lipid only ($n = 5$)	2.5 μg/kg epinephrine ($n = 5$)	10 μg/kg epinephrine ($n = 5$)	100 μg/kg epinephrine ($n = 5$)
ROSC (0–15 min)	0	0	3*	4†
CPR in progress (at 15 min)	5	5	5	1†
ROSC (15–20 min)[a]	4†			
CPR in progress (at 20 min)[a]	1†			

ROSC = return of spontaneous circulation; CPR = cardiopulmonary resuscitation; MAP = mean arterial blood pressure.
ROSC: >50 mm Hg for ≥120 s.
CPR reinstituted when MAP − rate pressure product was ≤5 mm Hg.
[a] Lipid-only group.
*$P = 0.167$.
†$P = 0.048$.

Likewise, no difference was observed in any ABG analysis variable before induced cardiac arrest (Table 2).

All animals were rendered asystolic after bupivacaine injection. Data regarding return of spontaneous circulation and subsequent repeated cardiovascular collapse (at 15 minutes), and return of spontaneous circulation and repeated cardiovascular collapse (at 20 minutes, lipid-only group) are presented in Table 3. Return of spontaneous circulation occurred at median 3 (range, 2–3) minutes in the 10 μg/kg epinephrine group, median 2.5 (range, 2–5) minutes in the 100 μg/kg epinephrine group, and median

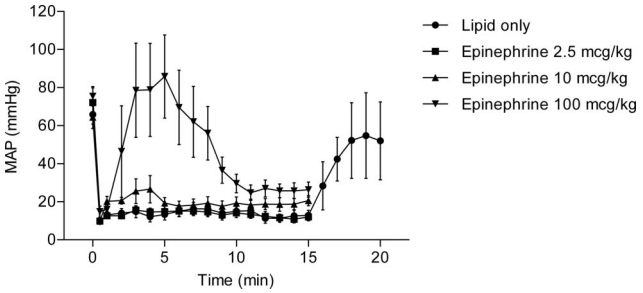

Figure 1. Mean arterial blood pressure (MAP) versus time; $n = 5$ in all groups.

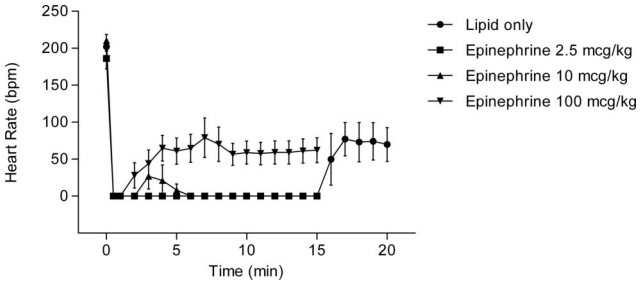

Figure 2. Heart rate versus time; $n = 5$ in all groups.

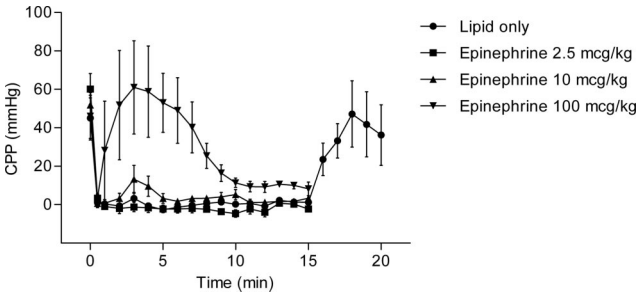

Figure 3. Coronary perfusion pressure (CPP) versus time; $n = 5$ in all groups.

17 (range, 16–18) minutes in the lipid-only group after late high-dose epinephrine administration. Duration of return of spontaneous circulation (MAP ≥50 mm Hg) was 2.3 (0.3) minutes in the 10 μg/kg epinephrine group and 7.0 (0.8) minutes in the 100 μg/kg group.

MAP in the 100 μg/kg epinephrine group was more than in lipid-only ($P = 0.05$), epinephrine 2.5 μg/kg ($P = 0.04$), and epinephrine 10 μg/kg ($P = 0.025$) groups (Fig. 1). No statistically significant difference was observed in MAP across time among lipid-only, epinephrine 2.5 μg/kg, and epinephrine 10 μg/kg groups. MAP at 15 minutes was 12.8 (SEM 2.8) mm Hg saline, 12.0 (2.5) mm Hg 2.5 μg/kg epinephrine, 20.6 (2.7) mm Hg 10 μg/kg epinephrine, and 26.4 (3.9) mm Hg 100 μg/kg epinephrine ($P = 0.008$).

Heart rate in animals exhibiting return of spontaneous circulation was invariably less than baseline with variable sinus bradycardia or junctional bradycardia as the predominant cardiac rhythm (Fig. 2). ECG QRS duration was visibly prolonged in all animals. Monitoring system limitations, however, precluded capture and more detailed interrogation of ECG variables. No animal exhibited ventricular tachycardia or ventricular fibrillation during the resuscitation phase of the experiment.

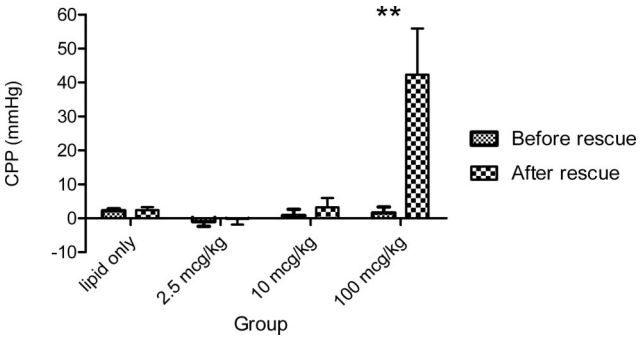

Figure 4. Coronary perfusion pressure (CPP) immediately before and immediately after saline/epinephrine rescue treatment. $**P = 0.0014$.

Table 4. Arterial Blood Gas Variables at 15 Minutes

	Lipid only ($n = 5$)	2.5 μg/kg epinephrine ($n = 5$)	10 μg/kg epinephrine ($n = 5$)	100 μg/kg epinephrine ($n = 5$)
pH	7.03 (0.04)	6.99 (0.05)	6.91 (0.03)	6.94 (0.04)
Pao_2 (mm Hg)	28.4 (4.3)	29.3 (3.9)	20.6 (3.6)	26.6 (2.0)
$Paco_2$ (mm Hg)	101.2 (9.6)	91.6 (7.6)	104.8 (7.3)	114.4 (6.1)
HCO_3 (mmol/L)	24.9 (0.99)	22.3 (2.2)	21.4 (1.9)	27.3 (0.7)
Base excess (mmol/L)	−6.2 (1.2)	−9.0 (1.8)	−10.7 (1.7)	−4.3 (1.5)
Lactate (mmol/L)	7.4 (0.6)	7.2 (0.8)	7.0 (0.9)	7.6 (0.6)

Data are presented as mean (SEM).
There were no significant differences among groups.

Coronary perfusion pressure is presented graphically in Figure 3. Coronary perfusion pressure was greater after epinephrine administration in the 100 μg/kg grouping only (Fig. 4). No difference was observed in any ABG variable or serum lactate among groups (Table 4). Similarly, no difference in lactate increment was observed among groups (15 minutes less baseline lactate: 4.9 [0.4] mmol/L lipid-only group, 5.5 [0.3] mmol/L 2.5 μg/kg epinephrine, 4.3 [0.8] mmol/L 10 μg/kg epinephrine, and 5.9 [0.6] mmol/L epinephrine; $P = 0.28$). Necropsy revealed appropriate ETT and vascular catheter positioning in all animals.

DISCUSSION

In this rabbit model of bupivacaine-induced cardiac arrest resuscitated with IV lipid emulsion and incremental-dose epinephrine, return of spontaneous circulation was not seen in the absence of moderate- or high-dose epinephrine. Circulatory recovery after late high-dose epinephrine administration in animals initially treated with lipid reinforces the association of epinephrine use and return of spontaneous circulation in this model. Although appearing prerequisite to circulatory return, however, epinephrine-treated animals subsequently exhibited deteriorating hemodynamic metrics sufficient to jeopardize survival. These results contrast with those reported in rodent models[17] wherein lipid emulsion alone resulted in less-rapid but sustained circulatory return. Disparity in experimental systems and interspecies differences in lipid responsiveness may account for these conflicting results.

In the present experiment, epinephrine-induced increases in coronary perfusion pressure appeared prerequisite to circulatory return. This finding is consistent with previous work in a similar rabbit model wherein return of spontaneous circulation was not seen in the absence of epinephrine injection and resultant increase in coronary perfusion pressure.[4] Similarly, Weinberg et al.[2] demonstrated universal survival after bupivacaine-induced asystole in intact dogs resuscitated with IV lipid emulsion alone and open chest cardiac massage, a technique known to produce greater generated coronary perfusion. In more recent work, this investigative group has additionally shown resuscitation with lipid emulsion alone to result in superior outcome compared with epinephrine[13] and vasopressin alone, or in combination.[18] In all of these reported studies, intraarrest hemodynamic metrics (rate pressure product; rate pressure product = heart rate × systolic blood pressure) were maintained at >50% baseline with external chest compressions alone. Although not directly comparable with coronary perfusion pressure (reported in the present study), it seems likely that coronary flow was significantly greater in these studies than in the pre–epinephrine-treated rabbits of the present work.

Conversely, in their porcine model of bupivacaine/asphyxia-induced arrest, Mayr et al.[11] demonstrated superior coronary perfusion pressure and more animals survived the vasopressor combination epinephrine and vasopressin as compared with lipid alone. Notably, coronary perfusion pressure in the lipid-alone group was low, with mean values of approximately 10 mm Hg throughout the course of the study protocol. In this minimal circulatory state, there was no evidence of a lipid sink effect, with no decrease in free bupivacaine, nor was increased total plasma bupivacaine level observed.

Disparities in the literature surrounding efficacy of lipid emulsion resuscitation from bupivacaine-induced cardiac arrest may therefore center around the simple concept of the "lipid sink," and the adequacy of myocardial perfusion during resuscitation. The sink hypothesis proposes sequestration of lipophilic drugs to an expanded plasma lipid phase, with resultant reduction in manifest toxicity. In the absence of sufficient circulation, however, not only is perfusion inadequate to support return of spontaneous circulation, but flow remains insufficient to effect toxin washout: "the sink simply cannot fill." Because human CPR typically achieves coronary perfusion pressures of 10 to 20 mm Hg,[19] measures to optimize myocardial perfusion in lipid-based resuscitation from local anesthetic-induced cardiotoxicity must be considered essential.

Our investigation has several limitations. All treatment groups in the present work exhibited profound respiratory acidosis and hypoxia at 15 minutes regardless of epinephrine administration and despite ventilation with identical settings to prearrest, and documented endotracheal positioning of the tracheal tube. The absence of positive end-expiratory pressure (known to improve ventilation and resuscitation outcome in rodents[20]) and anticipated pulmonary collapse with vigorous chest compressions may have in part contributed to such profound disturbances in ABG variables. Impaired pulmonary perfusion may have additionally proven significant in development of the observed disorders of gas exchange. IV infusions of lipid emulsions have been shown to cause profound increases in pulmonary vascular resistance in animal models[21,22] and newborn humans[23,24]: an effect worsened by intercurrent hypoxia.[22] Lipid particles >5 μm in diameter may additionally cause pulmonary fat emboli,[25] thereby further increasing pulmonary vascular resistance and impairing pulmonary flow during low-output states during CPR. Both phenomena may have contributed to the impairments in gas exchanged observed in our work; albeit in the absence of intraarrest assessment of pulmonary vascular pressures, and/or formal necropsy, we are unable to comment on the extent to which this may have influenced gas exchange in our model.

The failure of animals from any group to maintain effective circulation despite initial return of spontaneous circulation in this experiment is likely consequent on the enhancement of local anesthetic cardiotoxicity in the presence of reduced pH,[26] ongoing hypoxia, and demonstrated cardiac depression.[27] It is nevertheless informative that despite such a prohibitive metabolic milieu, epinephrine administration effected a brief period of unassisted native circulation. Although the eventual outcome in these animals is dismal, this finding further supports retention of epinephrine use.

In conclusion, in this rabbit model of bupivacaine-induced cardiac arrest resuscitated with combined IV lipid emulsion and incremental-dose epinephrine, epinephrine seemed necessary for return of spontaneous circulation, but was associated with declining hemodynamic metrics after circulatory return. Further study is required to define the role of epinephrine in lipid-based resuscitation from local anesthetic-induced cardiac arrest.

AUTHOR CONTRIBUTIONS

MH helped design and conduct the study, analyze the data, and write the manuscript. This author has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files. GC, DL, and GP helped design and conduct the study, analyze the data, and write the manuscript. These authors have seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

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