This study examined whether combining lipid emulsion and advanced cardiac life support (ACLS) improves survival in an unanesthetized swine model of bupivacaine- and hypoxia-induced cardiovascular collapse. Arterial and venous catheters and a tracheostomy were surgically placed in 26 swine receiving inhalation anesthesia. After a 1-hour recovery period, bupivacaine (5 mg/kg) was administered intravenously over 15 seconds. Following 1 minute of observation and 3 minutes of mechanical airway obstruction, during which all animals exhibited complete cardiovascular collapse, ACLS was initiated.

Animals were randomized to receive either intravenous saline or 20% lipid emulsion commencing with the initiation of ACLS. Survival was defined as a return of spontaneous circulation (ROSC) with unsupported blood pressure greater than 60 mm Hg for 10 minutes after 25 minutes of resuscitation effort. Data collection included electrocardiogram, arterial blood pressure, and arterial and mixed venous oxygen saturations.

There was no significant difference in survival between the saline group (4/12, 33%) and lipid emulsion group (6/12, 50%; P > .05). Additionally, there was no significant difference between groups of surviving animals in the time to ROSC (P > .05). The combination of lipid emulsion and ACLS did not improve survival from bupivacaine- and hypoxia-induced cardiovascular collapse in unanesthetized swine.

**Keywords:** Bupivacaine, hypoxia, lipid emulsion, local anesthetic toxicity, resuscitation.
cardiopulmonary resuscitation (CPR) concurrently with intravenous lipid emulsion for local anesthetic-induced complete cardiovascular collapse. The specific contribution of each agent and intervention that ultimately contributed to successful resuscitation is unclear in these cases. In 3 additional cases, patients with severe ventricular arrhythmias that did not result in complete cardiovascular collapse recovered following lipid administration. Mazoit et al have demonstrated in isolated perfused rat hearts that recovery from local anesthetic-induced cardiovascular toxicity may occur spontaneously as the local anesthetic redistributes from the myocardial tissue. The patients without complete cardiovascular collapse may have spontaneously recovered from severe but incomplete bupivacaine-induced cardiac toxicity in the absence of lipid administration.

To our knowledge, no previously published studies have examined the concomitant use of ACLS interventions and lipid emulsion therapy for treatment of combined bupivacaine- and hypoxia-induced cardiovascular collapse in an awake, unanesthetized animal model. The purpose of this randomized, investigator-blinded study was to examine the efficacy of the addition of lipid emulsion infusion to conventional ACLS resuscitation in an unanesthetized swine model of combined bupivacaine- and hypoxia-induced cardiac arrest.

**Materials and Methods**

The study was approved by the Institutional Animal Care and Use committees of the medical center and university. Twenty-six male Yorkshire pigs weighing 43 to 82 kg were acclimated for 7 to 14 days to the research facility. All animals were fasted overnight but had free access to water. One hour before surgery, the animals were premedicated with 1,200 μg of intramuscular buprenorphine. Buprenorphine produces analgesia for moderate to severe pain for up to 12 hours and therefore was used to provide pain relief throughout the study period. The time course for the experimental protocol is shown in Figure. Anesthesia was induced by mask with a combination of oxygen, nitrous oxide, and desflurane and was maintained with 100% oxygen and 9% to 18%
desflurane. An ear vein was canulated and infused with lactated Ringer's solution at 10 mL/kg per hour for the remainder of the preparatory surgery, anesthetic recovery, and experimental treatment period. Standard electrocardiogram (ECG) pads and multifunction adult defibrillation electrodes were applied and sutured in place (M3501A, Philips Healthcare, Andover, Massachusetts). Body temperature was monitored using an esophageal probe (ER400-9, Smiths Medical North America, Dublin, Ohio) during the preparatory surgery and via pulmonary artery catheter during the anesthetic recovery and experimental treatment period. Temperature was maintained at approximately 39.5°C throughout the study period using a heating blanket.

The trachea was intubated with a cuffed endotracheal tube, and the animals were mechanically ventilated at 15/min. Tidal volume was adjusted to maintain normocapnia (32 to 38 mm Hg end-tidal carbon dioxide [ETCO₂], model 5250 respiratory gas monitor, Datex-Ohmeda, Louisville, Colorado). The right carotid artery, right internal jugular vein, and trachea were surgically exposed. Two carotid arterial catheters were inserted: 1 for arterial blood sampling and the other for continuous arterial blood pressure monitoring. A 9-French sheath was inserted into the internal jugular vein through which a flow-directed pulmonary artery catheter with continuous CO and mixed venous oxygen monitoring capability (CCOmbo Catheter, Edwards Lifesciences, Irvine, California) was advanced into the pulmonary artery. A tracheostomy was performed and a 9.0-mm cuffed reinforced tracheostomy tube was inserted. Hemostasis was achieved, and the neck wound was closed with suture and skin staples. Blood pressure, heart rate, pulse oximetry (SpO₂), ETCO₂, and desflurane concentration were measured and recorded during the preparatory phase of the experiment.

Following completion of the preparatory procedures, the animal was placed upright in a veterinary sling, and the desflurane was discontinued. Oxygen (100%) was delivered via the anesthesia circuit for 15 minutes. The anesthesia circuit was then disconnected, and the animal breathed room air spontaneously for an additional 45 minutes. Following the recovery period (time zero), 0.5% bupivacaine was administered as a bolus of 5 mg/kg over 15 seconds via the distal infusion port of the pulmonary artery catheter. The animal was left undisturbed for 1 minute and observed for signs of central nervous system toxicity. At the end of the 1-minute observation period the tracheostomy tube was occluded with a fitted rubber stopper, and the tube cuff was inflated with an additional 10 mL of air. This procedure was performed to simulate the clinical occurrence of airway obstruction during tonic-clonic seizure activity. The animal was then transferred from the recovery sling to a U-shaped board and positioned supine.

Four minutes and 15 seconds following the start of the administration of bupivacaine, ACLS was initiated. Vecuronium (400 µg/kg) was administered intravenously to prevent potential animal movement and injury during the resuscitation. The administration of vecuronium eliminated the need for additional anesthetic agents that could impact the primary study variables. External cardiac compressions and ventilations were delivered with a combination ventilator/pneumatic compression device (Thumper 1007CCV, Michigan Instruments Inc, Grand Rapids, Michigan) at a 5:1 compression-to-ventilation ratio. Compressions were delivered at a rate of 100/min, with a sternal deflection depth of 20% of the animal’s measured thoracic anterior-to-posterior diameter and a 50:50 relaxation-to-compression ratio. Compressions were suspended briefly for cardiac rhythm analysis and countershock delivery. Ventilations were delivered with 100% oxygen at the tidal volume previously determined to maintain normocapnia in the pig being studied.

For the initial cardiac rhythms of ventricular fibrillation or pulseless ventricular tachycardia, 3 escalating monophasic countershocks were performed (200, 300, and 360 J). When the rhythm was refractory to defibrillation, epinephrine (1 mg) was administered according to the standard ACLS protocol via the distal infusion port of the pulmonary artery catheter. All medication administrations were followed with 30 mL of 0.9% normal saline. A single countershock of 360 J was then administered 30 to 60 seconds following epinephrine administration. If ventricular fibrillation or ventricular tachycardia remained, amiodarone (Cordarone, 300 mg) was administered followed by countershock at 360 J in 30 to 60 seconds. This pattern of medication administration followed by countershock at 360 J in 30 to 60 seconds continued. Epinephrine (1 mg) was administered every 3 minutes until the return of a perfusing rhythm. An additional dose of 150 mg of amiodarone was administered 5 minutes after the first dose if ventricular fibrillation or ventricular tachycardia persisted. Asystole and pulseless electrical activity were treated with 1 mg of epinephrine every 3 minutes. If the animal remained in asystole or exhibited pulseless electrical activity with a ventricular rate of less than 60/min following the first dose of epinephrine, 1 mg of atropine was administered every 3 minutes. The maximum cumulative dose of atropine was limited to 2 mg.

The animals were randomized using a computer-generated randomization schedule but evenly distributed to receive either 20% lipid emulsion (Intralipid 20%) or 0.9% normal saline via the side port of the 9-French central venous sheath. The lipid emulsion or saline was administered by the same investigator (J.E.V.) from a separate room through a shrouded intravenous line. All other investigators involved in the resuscitation effort and data collection were blind to the group assignment.
The lipid emulsion or saline was administered as previously described, as a bolus of 4 mL/kg over 2 minutes followed by a 0.5 mL/kg per minute continuous infusion for 10 minutes. The bolus was initiated and administered concurrently with the ACLS resuscitation protocol. Arterial blood gas samples were drawn at the end of the anesthetic recovery period (room air baseline), immediately prior to obstruction of the airway (75 seconds after bupivacaine injection) and at the initiation of the resuscitation (4 minutes 15 seconds after bupivacaine injection). Blood samples were also drawn for determination of total bupivacaine concentration at the initiation of the resuscitation and 5 minutes into the resuscitation period. These samples were centrifuged, frozen at −20°C, and shipped to a laboratory (MEDTOX Clinical Trial Services, Saint Paul, Minnesota) for determination of total plasma bupivacaine concentrations using high-performance liquid chromatography and mass spectrometry.

Resuscitation was performed for 25 minutes or until the return of spontaneous circulation (ROSC), which was defined as an unassisted pulse with a systolic arterial blood pressure greater than 60 mm Hg for a minimum of 10 minutes. Electrocardiogram, ventricular heart rate, arterial and pulmonary artery pressures, CO, SpO₂, and mixed venous oxygen saturation (SvO₂), were monitored and recorded throughout the experimental period. Upon completion of the experimental protocol, the animals were euthanized with pentobarbital and phenytoin (Beuthanasia-D Special). They underwent immediate necropsy to determine the presence of injury to the rib cage and underlying internal organs.

A 1-way analysis of variance (ANOVA) was conducted for each of the quantitative outcome variables to compare group differences. When homogeneity of variances assumption was not tenable, a Mann-Whitney (Wilcoxon rank sum) U test was conducted. For categorical data a χ² test was applied. The results are given as mean ± standard deviation. The level of significance was set at P < .05. Sample size was determined using a power analysis for contingency table testing on the number of animals with ROSC. Using a hypoxic and hypercarbic swine model, Haasio et al.17 were able to restore spontaneous circulation with epinephrine and amiodarone from bupivacaine-induced cardiac toxicity in 9 of 10 animals. However, a pilot study conducted in our laboratory with 2 pigs demonstrated resuscitation for 60 minutes with ACLS interventions and closed chest compression did not result in ROSC. Based on these results, the survival rate was predicted to be no greater than 50% for the control group. Given the recovery of all animals with lipid emulsion in 2 published resuscitation studies, the survival rate for the experimental group was predicted to be 100%. Setting α at 0.05 and power at 0.80, a sample size of 10 animals in each group was established. The sample was increased to 13 animals in each group to allow for attrition.

Results
A total of 26 animals underwent intubation, tracheostomy, and central and peripheral line placement under general anesthesia. Two animals had to be euthanized prior to application of the experimental protocol because of inadvertent loss of an arterial or central venous line during the recovery period. Data from the remaining 24 animals (12 in the saline group and 12 in the lipid group) were used in the analysis. Normothermia was maintained in all animals, with no statistically significant difference between groups. There were no significant differences between groups in blood pressure, heart rate, SpO₂, ETCO₂, or desflurane concentration during the surgical preparation and anesthesia recovery periods. Baseline arterial blood pressure, ventricular heart rate, CO, SvO₂, arterial blood gas values, and plasma bupivacaine levels were similar between groups immediately following the anesthesia recovery period (prior to bupivacaine injection) and at the time of initiation of the resuscitation protocol (4 minutes after bupivacaine injection; Table 1). Similarly, there were no significant differences in these baseline hemodynamic variables when comparing those animals that had ROSC with those that failed resuscitation. All animals were hypoxic and normocarbic at initiation of resuscitation.

Transitory (less than 30 seconds) tonic-clonic seizure activity was observed in all animals within the first minute following bupivacaine administration. Intraventricular conduction delay (QRS prolongation) was the earliest observed ECG finding and developed within 20 seconds of the bupivacaine administration in all animals. The mean arterial partial pressure of oxygen (Pao₂) at 1 minute following bupivacaine injection and just prior to airway occlusion was 53 ± 19 mm Hg. At the time the ACLS protocol was initiated all animals were in complete cardiovascular collapse with systolic arterial blood pressure below 60 mm Hg. The predominant terminal rhythm was asystole which occurred in 10 of 12 animals in each group. The time to onset of asystole after bupivacaine administration was less than 2 minutes for 12.5% of the animals (n = 3), 2 to 3 minutes for 54% (n = 13), and greater than 3 minutes for 17% (n = 4). The mean time to achieve asystole after bupivacaine injection was 153 ± 49 seconds; this was a mean of 93 seconds after airway occlusion. Other terminal rhythms included ventricular fibrillation (1 in each group), ventricular tachycardia (1 in the lipid group), and combined ventricular fibrillation/ventricular tachycardia (1 in the saline group). The number of animals who met the survival criteria (unassisted pulse and systolic arterial blood pressure greater than 60 mm Hg for a minimum of 10 minutes) and the time to ROSC was not significantly different between groups (Table 2).

A between groups comparison of hemodynamic variables during the first 10 minutes following return of
Table 1. Comparison of Data Before and After Bupivacaine Injection for All Animals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval</th>
<th>Saline (n = 12)</th>
<th>Lipid (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>66 ± 9</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>Total anesthesia time (min)</td>
<td></td>
<td>105 ± 20</td>
<td>98 ± 11</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>Baseline</td>
<td>39.4 ± 0.6</td>
<td>39.4 ± 0.7</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>Baseline</td>
<td>149 ± 19</td>
<td>154 ± 20</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>27 ± 15</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>Baseline</td>
<td>93 ± 14</td>
<td>91 ± 28</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>15 ± 14</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>Baseline</td>
<td>118 ± 15</td>
<td>122 ± 14</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>22 ± 13</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>Baseline</td>
<td>108 ± 11</td>
<td>103 ± 13</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac output (mL/min)</td>
<td>Baseline</td>
<td>11.2 ± 2.1</td>
<td>11.3 ± 4.1</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>Baseline</td>
<td>74 ± 8</td>
<td>69 ± 14</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>Baseline</td>
<td>99 ± 9</td>
<td>99 ± 15</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>22 ± 7</td>
<td>26 ± 11</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>Baseline</td>
<td>30 ± 7</td>
<td>31 ± 7</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>37 ± 8</td>
<td>33 ± 14</td>
</tr>
<tr>
<td>pH</td>
<td>Baseline</td>
<td>7.45 ± 0.11</td>
<td>7.41 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>4 min 15 s</td>
<td>7.33 ± 0.08</td>
<td>7.33 ± 0.13</td>
</tr>
<tr>
<td>Plasma bupivacaine level (µg/mL)</td>
<td>4 min 15 s</td>
<td>6.36 ± 2.04</td>
<td>6.52 ± 3.16</td>
</tr>
<tr>
<td></td>
<td>10 min after injection</td>
<td>5.40 ± 2.50</td>
<td>6.13 ± 1.81</td>
</tr>
<tr>
<td>Time to terminal rhythm (s)</td>
<td></td>
<td>134 ± 33</td>
<td>147 ± 49</td>
</tr>
</tbody>
</table>

Table 2. Comparison of Number of Animals Surviving and Time to ROSC

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of animals with ROSC</th>
<th>Individual animal</th>
<th>Group mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n = 12)</td>
<td>4</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Lipid (n = 12)</td>
<td>6</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 1. Comparison of Data Before and After Bupivacaine Injection for All Animals

PaO₂ indicates arterial partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide.

a Baseline indicates end of the recovery period/immediately before bupivacaine injection; 4 min 15 s, 4 minutes after completion of bupivacaine injection and the initiation of resuscitation.

b Data are mean ± standard deviation. *P > .05* between the saline and lipid groups for all variables.
spontaneous pulse and circulation was performed for surviving animals (Table 3). There were no significant differences between groups at any time interval for ventricular heart rate and CO. Mean arterial blood pressures were similar between groups except at the 2 and 4-minute time intervals, during which the lipid group had significantly higher values ($P < .05$). The mean arterial blood pressure for surviving animals in both groups was 84 mm Hg or higher at all time intervals during the 10-minute period after return of spontaneous pulse and circulation.

Table 3. Comparison of Hemodynamic Variables at Baseline and Following ROSC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>108 ± 11</td>
<td>96 ± 11</td>
<td>129 ± 32</td>
<td>151 ± 30</td>
<td>149 ± 32</td>
<td>142 ± 29</td>
<td>139 ± 29</td>
</tr>
<tr>
<td>Lipid</td>
<td>103 ± 13</td>
<td>138 ± 45</td>
<td>149 ± 30</td>
<td>165 ± 9</td>
<td>158 ± 11</td>
<td>151 ± 11</td>
<td>151 ± 13</td>
</tr>
<tr>
<td><strong>Mean arterial blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>118 ± 15</td>
<td>84 ± 16</td>
<td>86 ± 15</td>
<td>97 ± 3</td>
<td>110 ± 6</td>
<td>108 ± 10</td>
<td>108 ± 12</td>
</tr>
<tr>
<td>Lipid</td>
<td>122 ± 14</td>
<td>111 ± 36</td>
<td>128 ± 27$^a$</td>
<td>129 ± 21$^a$</td>
<td>120 ± 22</td>
<td>112 ± 22</td>
<td>108 ± 21</td>
</tr>
<tr>
<td><strong>Cardiac output (L/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>11.2 ± 2.1</td>
<td>NA</td>
<td>NA</td>
<td>7.5 ± 2.2</td>
<td>7.9 ± 1.9</td>
<td>7.2 ± 1.3</td>
<td>6.7 ± 1.1</td>
</tr>
<tr>
<td>Lipid</td>
<td>11.3 ± 4.1</td>
<td>NA</td>
<td>NA</td>
<td>8.0 ± 1.5</td>
<td>8.0 ± 1.3</td>
<td>7.4 ± 1.9</td>
<td>6.8 ± 1.7</td>
</tr>
<tr>
<td><strong>Mixed venous oxygen saturation (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>74 ± 8</td>
<td>56 ± 12</td>
<td>68 ± 11</td>
<td>73 ± 10</td>
<td>79 ± 8</td>
<td>79 ± 8</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>Lipid</td>
<td>69 ± 14</td>
<td>69 ± 16</td>
<td>72 ± 21</td>
<td>85 ± 4$^a$</td>
<td>87 ± 5</td>
<td>83 ± 4</td>
<td>83 ± 4</td>
</tr>
</tbody>
</table>

$^a$ $P < .05$ between the saline and lipid groups at these time points. (There were no significant differences between the saline and lipid groups at the remaining time points.)
Data are mean ± standard deviation.
ROSC indicates return of spontaneous circulation; NA, data not available due to monitor latency.

Discussion

The addition of lipid emulsion to ACLS interventions failed to improve survival in an awake, unanesthetized swine model of combined bupivacaine- and hypoxia-induced cardiovascular collapse. A number of animal studies and case reports suggest the use of lipid emulsion to treat bupivacaine-induced cardiac toxicity is promising, the results of the present study and the work of both Mayr et al $^7$ and Hicks et al $^8$ suggest there may be clinical conditions in which lipid emulsion may not be as effective as suggested by Weinberg’s animal investigations or published case reports. Animal research using rat $^{3,19,20}$ dog $^6$, and rabbit $^{21}$ models of bupivacaine-induced cardiovascular collapse have found lipid emulsion significantly improves survival. In contrast, 2 previous studies of bupivacaine-induced cardiovascular collapse in swine $^{7,8}$ and the present swine study all failed to demonstrate a benefit of lipid emulsion therapy. The use of the swine model and/or the experimental design of the swine studies may account for these results. There is considerable interspecies variability for local anesthetic toxicity with respect to sensitivity, clinical manifestations, and ease of resuscitation. Dogs appear to be particularly resistant to the toxic effects of bupivacaine and therefore may not be the most suitable animal model for extrapolation of experimental results to the clinical setting. Kasten and Martin $^{22}$ found the mean dose of bupivacaine required to induce cardiac arrest in dogs is 24.6 ± 8.5 mg/kg. Following this considerable dose of bupivacaine required to induce cardiac arrest in dogs is 24.6 ± 8.5 mg/kg. Following this considerable dose of bupivacaine all study animals were easily resuscitated after several minutes of epinephrine, atropine, and open chest cardiac massage. In contrast, bupivacaine toxicity can be induced in swine with smaller doses from which resuscitation with closed chest compression, defibrillation, and intravenous epinephrine is not consistently successful. $^{23}$ The swine model is favored over the canine model for resuscitation research because the thorax, degree of collateral cardiac circulation, dynamic response to closed chest compressions, and regional blood flow more closely resemble that of humans. $^{24}$

The present study incorporated 2 fundamental design differences from previous animal studies demonstrating the efficacy of lipid resuscitation; bupivacaine toxicity was induced in unanesthetized, awake animals and exacerbated with a period of hypoxia. This design was employed to mimic the respiratory and cardiac arrest and the...
airway compromise that can occur with inadvertent intravenous injection of bupivacaine during performance of a major plexus block on an awake, unanesthetized patient. Studies to date examining the efficacy of lipid emulsion have been performed on animals receiving multiple medications, including isoflurane, at the time of or just prior to bupivacaine administration.\(^2\)\(^3\)\(^6\)\(^8\) Volatile anesthetics have been shown to have variable effects on bupivacaine toxicity in animal models. The administration of isoflurane or halothane increases the lethality of bupivacaine cardiovascular toxicity in swine.\(^2\)\(^3\)\(^6\) Conversely, the combination of sevoflurane and propofol dramatically decrease bupivacaine-induced cardiovascular and central nervous system toxicity in rats.\(^27\) Common anesthetics premedicants have also been shown to significantly affect bupivacaine-induced central nervous system and cardiac toxicity.\(^28\) Preservation of the central nervous system component of toxicity was considered an important design feature in the present study since central nervous system exposure to local anesthetics has been shown to precipitate ventricular dysrhythmias in animals.\(^29\) A recovery period of 1 hour was provided in the present study to wash out the desflurane administered for line placement and tracheostomy, and a single long-acting \(\mu\)-agonist-antagonist without appreciable cardiovascular effects was administered for postinstrumentation analgesia. These design features were an attempt to eliminate potential positive or negative effects of anesthetic agents on the resuscitation effort.

In previous animal studies demonstrating successful resuscitation from bupivacaine toxicity with lipid emulsion, the airway was secured and mechanical ventilation was initiated prior to administration of bupivacaine and cardiovascular collapse. In 4 of these studies the animals were ventilated with 100% oxygen and normocarbia was maintained.\(^3\)\(^1\)\(^9\)\(^2\)\(^1\)\(^9\)\(^2\)\(^1\) In another study, animals were ventilated with 30% oxygen, with maintenance of normocarbia until cardiovascular collapse.\(^18\) Following cardiovascular collapse all animals were ventilated with 100% oxygen. Moore and colleagues\(^3\)\(^0\) have noted from case report information that bupivacaine-induced seizures result in hypoxia, hypercarbia, and acidosis. Moore reported that in 19 consecutive cases of bupivacaine-induced seizures that deterioration into cardiac arrest was prevented by immediate ventilatory support with 100% oxygen.\(^3\)\(^1\) In contrast, initial application of supplemental oxygen and/or mask ventilation did not prevent cardiac arrest in 4 clinical cases reports of systemic bupivacaine toxicity.\(^10\)\(^3\)\(^2\)\(^3\)\(^4\) However, the effectiveness of the ventilatory support and the ability to maintain oxygenation was not described in these reports. Similarly, in case reports of successful resuscitation following ropivacaine\(^9\)\(^,\)\(^3\)\(^5\)\(^,\)\(^3\)\(^6\) and levobupivacaine\(^11\) toxicity, a description was not provided of the adequacy of ventilation and oxygenation following the onset of central nervous system toxicity but preceding cardiovascular collapse. It is unlikely in these case reports that ventilatory support and oxygenation were comparable to that provided to animals in experimental paradigms of lipid resuscitation. It is equally improbable that a secure airway with controlled mechanical ventilation delivering supplemental oxygen represents the typical clinical scenario in which bupivacaine-induced cardiovascular collapse occurs.

The methods of the present study represent a worst-case clinical scenario by permitting the animals to transiently become hypoxemic during the early phase of bupivacaine toxicity. This would be analogous to early airway obstruction with inadequate management and ventilation during a clinical event. Hypoxia and acidosis are known to significantly potentiate bupivacaine toxicity.\(^3\)\(^7\) The deliberate hypoxemia induced after bupivacaine administration in the present study may have prevented lipid emulsion from antagonizing bupivacaine inhibition of the aerobic metabolic pathway in the myocardium, as suggested by Weinberg.\(^3\)\(^8\) The period of deliberate hypoxia, however, was limited to the interval between bupivacaine injection and the initiation of the resuscitation, with arterial hypoxemia being rapidly corrected in all animals within the first 5 minutes of the resuscitative effort. In a canine model of bupivacaine-induced asystole, Weinberg and colleagues\(^6\) found that partial pressure of oxygen in the myocardial tissue declined to 0 mm Hg after 10 minutes of direct cardiac massage. The animals receiving lipid emulsion in this study were successfully recovered.\(^5\) It seems likely that the absence of a partial pressure of oxygen in the myocardial tissue contributed to the cardiovascular collapse reported in this study. In the present study, the degree of actual myocardial oxygenation was not measured but clearly could not be lower than the zero value reported by Weinberg et al.\(^5\) Lipid emulsion may have been efficacious in restoring spontaneous circulation if it had been administered at the time of cardiac arrest or if circulation had been supported with chest compression at the onset of cardiovascular collapse. Previous animal studies in rats and dogs have demonstrated ROSC within 5 minutes following initiation of lipid administration.\(^3\)\(^6\) The initial period of hypoxia in the present study may have appreciably delayed the onset of lipid rescue beyond the established resuscitation phase of 25 minutes. This time limit was selected to minimize potential iatrogenic injury from prolonged mechanical chest compressions noted in our pilot work.

It can be argued that the initial period of deliberately induced hypoxia in our study was the primary cause of cardiovascular collapse and contributed to the inability of the lipid emulsion to rescue the animals from such. The addition of lipid emulsion to standard ACLS interventions in a rabbit model of hypoxia-induced pulseless electrical activity has been shown to have a deleterious effect on the resuscitation effort. Survival in rabbits
treated only with ACLS was 7 of 11 compared with 1 of 12 animals treated with ACLS plus lipid emulsion. In contrast, the addition of lipid emulsion to ACLS treatment in the present study did not have a significant positive or negative effect on the rate of ROSC. Mayr et al compared survival rates in an anesthetized swine model of bupivacaine toxicity exacerbated by hypoxia following treatment with a combination of epinephrine and vasopressin or lipid emulsion. The airway and/or respiratory compromise that may occur during a tonic-clonic seizure was simulated by halting mechanical ventilation immediately after bupivacaine was injected and continued until asystole occurred. Manual CPR was initiated 1 minute after cardiac arrest. All animals in the vasopressor group survived, whereas none in the lipid group survived. The authors attributed this result to the fact that a coronary perfusion pressure of at least 20 to 30 mm Hg is necessary for restoration of spontaneous circulation in animals and humans, and although this threshold pressure was achieved in the vasopressor group, it was not achieved in the lipid group. Weinberg has noted, with respect to the work by Mayr et al, that cardiac standstill may have been achieved by “prolonged hypoxia” as opposed to direct bupivacaine cardiac toxicity and that lipid therapy has never been recommended as a treatment modality in this setting. However, as Mayr and colleagues have suggested, hypoxia as a result of airway compromise and the potential difficult airway management associated with bupivacaine-induced seizure activity is a clinical reality.

It is unlikely that the short period of hypoxia permitted in the present study would produce the observed cardiovascular collapse. It has been demonstrated in swine that a period of 7 to 13 minutes of complete airway occlusion is required to produce cardiovascular collapse. The animals were without ventilatory support for a maximum of 4 minutes in the present study. During the first minute the animals ventilated spontaneously on room air via the tracheostomy. All animals were noted to convulse and spontaneously ventilate during this 1-minute period. Physical occlusion of the tracheostomy occurred only during the subsequent 3-minute period, which was followed by mechanical ventilation with 100% oxygen. It is doubtful the 3- to 4-minute period of hypoxia was responsible for the observed cardiac arrest given that the mean time to terminal cardiac rhythm for all animals was 93 ± 49 seconds after airway occlusion. Our observations, like that of Mayr and colleagues, suggest that early airway compromise can and does occur in the clinical setting, and the ability of lipid emulsion to treat local anesthetic cardiac toxicity in this event should continue to be evaluated.

The present study was limited to a specific combination of ACLS interventions and lipid emulsion therapy. Epinephrine was administered as part of the ACLS protocol because it has traditionally been the first-line agent for vasopressor support during cardiovascular collapse. Heavern and colleagues attempted to resuscitate rats with random administration of saline, amrinone, dopamine, norepinephrine, epinephrine, or isoproterenol following intravenous bupivacaine-induced cardiovascular collapse. The survival rate was not significantly different between the groups, and epinephrine was found to promote ventricular arrhythmias. Mayr et al found that survival rates for bupivacaine toxicity were not significantly better with solo treatment of epinephrine or vasopressin versus placebo in a swine model. However, combined epinephrine and vasopressin therapy significantly improved survival over placebo. Combination therapy with epinephrine and vasopressin may have provided optimal resuscitation conditions with respect to the ACLS component of the resuscitation effort. Hiller and colleagues have recently demonstrated that “high-dose” epinephrine (10 or 25 μg/kg) decreases survival in a rat model of lipid resuscitation of bupivacaine cardiac toxicity. A single administration of epinephrine at the 1-mg dose suggested in the ACLS protocol in the clinical setting of bupivacaine toxicity resulting in asystole would exceed the dose of 10 μg/kg in a 70-kg patient. This study implies that application of the ACLS protocol with administration of epinephrine prior to administration of lipid emulsion may actually decrease the potential for successful resuscitation.

Conclusion

In this study, the addition of lipid emulsion to ACLS interventions failed to improve survival in an awake, anesthetized swine model of combined bupivacaine- and hypoxia-induced cardiovascular collapse. There remain important questions regarding the mechanism of action, dose and timing of treatment, and the clinical conditions associated with the greatest efficacy of lipid emulsion. The results of the present study, and those of Mayr et al and Hiller et al, suggest that there may be clinical conditions or resuscitation practices that alter the ability of lipid emulsion to restore cardiovascular function following bupivacaine-induced cardiovascular collapse.

Additional research is needed to determine the optimal combination of resuscitation conditions, agents and interventions, and the potential side effects of the lipid product itself. The comparability and applicability of future research in this area could be better exploited by standardizing the animal model, the experimental conditions, and the physiologic endpoints.

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