Lipid Emulsion Reverses Bupivacaine-induced Asystole in Isolated Rat Hearts

Concentration-Response and Time-Response Relationships

Quanguang Wang, M.D.,* Yun Xia, M.D., Ph.D., † Le Liu, M.D., † Tong Shi, M.D., † Kejian Shi, B.S., § Quanguang Wang, M.D., || Limei Chen, M.D., † Thomas J. Papadimos, M.D., M.P.H., # Xuzhong Xu, M.D.**

ABSTRACT

Background: The concentration-response and time-response relationships of lipid emulsions used to reverse bupivacaine-induced asystole are poorly defined.

Methods: Concentration response across a range of lipid concentrations (0–16%) to reverse bupivacaine-induced asystole were observed using isolated rat heart Langendorff preparation. Cardiac function parameters were recorded during infusion. Concentrations of bupivacaine in myocardial tissue were measured by liquid chromatography and tandem mass spectrometry at the end of the experiment.

Results: Although all lipid-treated hearts recovered (cardiac recovery was defined as a rate-pressure product more than 10% baseline), no nonlipid-treated hearts (control group) did so. The ratio of the maximum rate pressure product during recovery to baseline value demonstrated a concentration-dependent relationship among lipid groups, with 0.25, 0.5, 1, 2, 4, 8, and 16%. Mean ± SD values for each corresponding group were 22 ± 4, 24 ± 5, 29 ± 6, 52 ± 11, 73 ± 18, 119 ± 22, and 112 ± 10%, respectively (n = 6, P < 0.01). Rate-pressure product in lipid groups with 4–16% concentrations was lower at 15–40 min than at 1 min, showing a decreasing tendency during recovery phase (P < 0.01). The concentration of myocardial bupivacaine in all lipid-treated groups was significantly lower than in the control group (P < 0.01). It was also lower in lipid groups with 2–16% concentrations than in those with concentrations at 0.25–1% (P < 0.05), with the 16% group lower than groups with 2–8% concentrations (P < 0.001).

Conclusion: Lipid application in bupivacaine-induced asystole displays a concentration-dependent and time-response relationship in isolated rat hearts.

What We Already Know about This Topic

❖ Intravenous administration of lipid emulsion reverses cardiotoxicity from local anesthetics, but the concentration-response and time-response relationships for this treatment are unclear.

What This Article Tells Us That Is New

❖ In isolated rat hearts, lipid emulsions reversed bupivacaine-induced asystole with increasing efficacy from 1% to 8% concentrations, paralleled by decreasing bupivacaine concentrations in the myocardium.

BUPIVACAINE is a commonly used, low cost, long-acting local anesthetic. In cases of unintentional administration either intra-arterially or intravenously, and/or over-absorption from peripheral tissues, bupivacaine can result in serious cardiotoxicity, contributing to a difficult recovery. Laboratory studies1–3 and clinical reports4–5 have indicated that lipid emulsion is effective in reversal of local anesthetic–induced cardiac toxicity. However, it is uncertain whether greater benefits exist with higher concentrations of lipid emulsions or if lower concentrations are just as effective. Cardiac function after recovery has not been intensively evaluated in these studies. Recently, Marwick et al.6 reported the recurrence of cardiovascular instability 40 min after completion of intralipid administration for bupivacaine cardiotoxicity.
Lipid Reverses Bupivacaine-induced Asystole

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Materials and Methods

Experimental Animals
Adult male Sprague Dawley rats weighing 300–350 g were obtained from the animal center of Wenzhou Medical College (Zhejiang, China). All work was approved by the college’s Animal Care and Use Committee.

Animal Preparation and Setup
Rats were anesthetized by 350 mg/kg chloral hydrate intraperitoneal injection. Hearts were rapidly excised after systemic heparinization and cannulation through the ascending aorta with suspension from a Langendorff apparatus (ML870B2; ADInstruments, Sydney, Australia). Retrograde perfusion was at a constant pressure of 120 mmHg with Krebs-Henseleit buffer comprised of 118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 1.2 mM KH2PO4, 25.0 mM NaHCO3, 10.0 mM glucose, and 2.5 mM CaCl2. The solution was continuously bubbled with 95% oxygen and 5% carbon dioxide and its pH was maintained at 7.40 in a 37°C countercurrent flow water bath. A balloon was inserted into the left ventricle and inflated with water to achieve a constant left ventricular end-diastolic pressure of 4–10 mmHg and pressure was transduced and analyzed continuously (Powerlab Data Analysis System, Chart 5.5.6; ADInstruments). After Krebs-Henseleit buffer had been perfused for 25 min (baseline time, designated Tb), a 100 µM bupivacaine infusion was initiated and sustained for 180 s beyond asystole.

The control group was then perfused with 40 µM bupivacaine. Seven experimental groups were perfused with 40 µM bupivacaine along with lipid emulsions (20% intralipid; Huarui Pharmaceuticals Co., Ltd., Wuxi, China) at concentrations of 0.25, 0.5, 1, 2, 4, 8 and 16%. There were six hearts in each group. Group assignment was randomized with investigators blinded to group assignments. All groups were perfused for 45 min after asystole (the final time designated Te). The cardiac apex of each heart was then dissected and immediately frozen in liquid nitrogen and stored at −70°C for further analysis.

Determination of Cardiac Function
The time from initiation of bupivacaine infusion to asystole (designated Ts) and the time from the end of 100 µM bupivacaine infusion to cardiac recovery (designated Tr) were recorded. The following cardiac function parameters were recorded/calculated: left ventricular developed pressure (LVdevP = systolic – diastolic pressure), maximum change rate of LVdevP fall (dP/dtmax), heart rate (HR), and rate-pressure product (RPP; = HR × LVdevP). Parameters of cardiac function were continuously monitored until the end of reperfusion, and were recorded at the following times: the balance, asystole, 1 min after restoration of cardiac rhythm (1 min), every 5 min from restoration for 40 min. The ratio of the highest RPP (RPPh) during the recovery to baseline RPP (RPPr) was also recorded. Finally, the ratio of RPP at Te to baseline RPP (RPPe) was documented.

Cardiac Tissue Bupivacaine Content
Frozen hearts were homogenized with perchloric acid 0.4 M. Precipitated proteins were separated by centrifugation at 3,000g for 15 min. The supernatant was neutralized with KOH 2 M. Samples were then centrifuged for another 15 min and the supernatant was stored at −70°C until analysis was performed.

A liquid chromatography-tandem mass spectrometric method with a rapid and simple sample preparation was developed and validated for the detection of bupivacaine. The liquid chromatography-tandem mass spectrometric system (Bruker Esquire; Bruker Company, Karlsruhe, Germany) was equipped with an electrospray interface. A Zorbax SB-C18 column (150 × 2.1 mm, 5 µm; Agilent Technologies, Inc., Santa Clara, CA) was used with the mobile phase of methanol and formic acid 0.1% solution (55:45 v) and lidocaine was used as the internal standard. Electrospray ionization source was applied and operated in positive ion mode. Multiple-reaction monitoring mode was used to quantify bupivacaine. The mass-to-charge ratio (m/z) for detected ions were m/z 289→140 for bupivacaine and m/z 235→86 for the internal standard. It was linear and ranged from 0.01 to 20.0 µg/g for bupivacaine in myocardium. The limit of detection for bupivacaine was 4 ng/g. Retention time in bupivacaine was 2.3 min. Recovery of bupivacaine from myocardium ranged from 66.45 to 74.47% with intra- and interday relative standard deviations less than 7%. We performed a regression analysis between cardiac bupivacaine concentrations and the corresponding RPPe to determine their relationship.

Concentration-Response Curve Fitting
We used the following equation to generate the concentration-response curve for lipid emulsion to reverse bupivacaine-induced cardiac arrest in isolated rat heart:

\[ Y = \text{bottom} + (\text{top} - \text{bottom}) \left[ \frac{1}{1 + 10^{(X-EC_{50})/\text{HillSlope}}} \right] \]

where \( Y \) = RPPr and \( X \) = the logarithm of lipid concentration.

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Table 1. Baseline Values of Key Parameters for the Eight Groups (N = 48)

<table>
<thead>
<tr>
<th>Group by Lipid Concentration</th>
<th>Weight, g</th>
<th>LVdevP, mmHg</th>
<th>−dp/dtmax, mmHg/s</th>
<th>Heart Rate, Beats/min</th>
<th>RPP, mmHg · Beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, 0%</td>
<td>318 ± 7</td>
<td>145 ± 18</td>
<td>3,082 ± 490</td>
<td>305 ± 39</td>
<td>40,112 ± 10,548</td>
</tr>
<tr>
<td>0.25%</td>
<td>311 ± 14</td>
<td>149 ± 12</td>
<td>3,030 ± 178</td>
<td>302 ± 37</td>
<td>44,270 ± 6,664</td>
</tr>
<tr>
<td>0.5%</td>
<td>323 ± 10</td>
<td>147 ± 20</td>
<td>2,790 ± 138</td>
<td>276 ± 30</td>
<td>39,554 ± 7,857</td>
</tr>
<tr>
<td>1%</td>
<td>322 ± 17</td>
<td>130 ± 14</td>
<td>2,753 ± 81</td>
<td>314 ± 54</td>
<td>38,792 ± 6,583</td>
</tr>
<tr>
<td>2%</td>
<td>321 ± 11</td>
<td>149 ± 13</td>
<td>3,104 ± 136</td>
<td>297 ± 43</td>
<td>44,242 ± 5,648</td>
</tr>
<tr>
<td>4%</td>
<td>307 ± 10</td>
<td>138 ± 17</td>
<td>2,791 ± 190</td>
<td>317 ± 38</td>
<td>44,138 ± 6,884</td>
</tr>
<tr>
<td>8%</td>
<td>322 ± 10</td>
<td>139 ± 16</td>
<td>2,791 ± 175</td>
<td>274 ± 11</td>
<td>36,677 ± 5,970</td>
</tr>
<tr>
<td>16%</td>
<td>309 ± 26</td>
<td>150 ± 28</td>
<td>3,098 ± 55</td>
<td>298 ± 28</td>
<td>45,120 ± 10,271</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SD unless otherwise specified. For each concentration group, n = 6. Baseline values for major parameters showed no significant differences among the eight groups.

Table 2. Results of Ts, Tr, RPPr, RPPe, and Myocardial Bupivacaine Concentration for All Study Groups (N = 42)

<table>
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<tr>
<th>Group by Lipid Concentration</th>
<th>Ts, s</th>
<th>Tr, s</th>
<th>RPPr, %</th>
<th>RPPe, %</th>
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<tr>
<td>Control, 0%</td>
<td>40 ± 5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>30.0 ± 5.0</td>
</tr>
<tr>
<td>0.25%</td>
<td>38 ± 6</td>
<td>59.3 ± 14.0</td>
<td>22 ± 4</td>
<td>10 ± 5</td>
<td>22.4 ± 4.8</td>
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<tr>
<td>0.5%</td>
<td>39 ± 13</td>
<td>46.6 ± 10.3</td>
<td>24 ± 5</td>
<td>12 ± 5</td>
<td>22.6 ± 1.8</td>
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<tr>
<td>1%</td>
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<td>29 ± 6</td>
<td>16 ± 7</td>
<td>23.5 ± 4.0</td>
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<td>33 ± 10</td>
<td>20.4 ± 3.7</td>
<td>52 ± 11</td>
<td>21 ± 9</td>
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Results

Baseline Values

There were no differences in baseline weight and cardiac function among the eight groups in the study (table 1).

Cardiac Function Parameters

All hearts developed asystole after 100 µM bupivacaine infusion. The time from initiation of the 100 µM bupivacaine infusion to asystole (Ts) did not vary among the eight groups (table 2). Cardiac recovery was defined in advance of the study as a RPP greater than 10% of the baseline value for more than 1 min. Control group hearts did not recover although all hearts in lipid-treated groups did so. The time of recovery, Tr, for the 1–16% lipid concentration groups was less than for the 0.25–0.5% lipid groups (table 2). Lipid-treated groups demonstrated no significant differences in

Statistical Analysis

All data were analyzed using SAS for Microsoft Windows (version 9.2; SAS Institute, Inc., Cary, NC) and are presented as mean ± SD. Baseline cardiac function parameters, weight, Ts, Tr, RPPr, RPPe, and myocardial bupivacaine concentration among the groups were analyzed with one-way analysis of variance and a two-sided t test. A linear mixed model was used for the cardiac factors during recovery in lipid-treated groups (7 groups × 9 times). Cardiac function parameters between lipid groups during the recovery phase and RPP ranged from 5 to 40 min compared with 1 min were analyzed using a linear mixed model with two-tailed P values that were adjusted by Holm method. A P value of less than 0.05 was considered statistically significant. Curve-fitting for the cardiac bupivacaine and lipid concentration effects were performed (Prism version 5.0; GraphPad Software Inc., San Diego, CA).
LVdevP at any time after asystole (fig. 1). Comparison among lipid groups in the recovery phase demonstrated that the \(-\frac{dp}{dt}_{\text{max}}\) in the 2 and 4% groups was greater than in the 0.25 and 0.5% groups whereas the 16% group was greater than the 0.5% group (fig. 2). During recovery phase, HR in the 2–16% lipid groups was greater than in the 0.25–1% lipid groups. Further delineation demonstrated that HR was better maintained by increasing lipid concentrations: 16% > 2%, 4%, and 8%; also, 4% and 8% > 2% (fig. 3). During the recovery phase, RPP in the 2–16% lipid groups was significant greater than that observed for the 0.25–1% groups. In addition, RPP in the 16% lipid group was greater than that of the 2–8% groups. Among the 4–16% lipid groups, RPP was lower at 15–40 min than at 1 min, with the time-response relationship showing a decreasing tendency during recovery phase. However, in the 0.25%–2% lipid groups, it did not differ at any time during recovery when data were compared at 1 min (fig. 4).

Cardiac Tissue Bupivacaine Content

The concentration of myocardial bupivacaine in all lipid-treated groups was significantly lower than in the control groups are shown during recovery from bupivacaine-induced asystole. All data are presented as mean ± SD unless otherwise specified. For all values, n = 6. P values are as follows: 2, 4, 8, and 16% vs. 0.25%; 2, 4, 8, and 16% vs. 0.5%; P < 0.001; 2 vs. 1%, P < 0.004; 4, 8, and 16% vs. 1%, P < 0.001; 4 vs. 2%, P = 0.013; 8 vs. 2%, P = 0.004; 16 vs. 2%, P < 0.001; 16 vs. 4%, P < 0.001; 16 vs. 8%, P < 0.001.

Fig. 1. Left ventricular developed pressure (LVdevP) in (A) 2–16% lipid groups and (B) 0.25–1% lipid groups are shown during recovery from bupivacaine-induced asystole. All data are presented as mean ± SD unless otherwise specified. For all values, n = 6.

Fig. 2. Maximum change rate of left ventricular pressure fall (\(-\frac{dp}{dt}_{\text{max}}\)) in (A) 2–16% lipid groups and (B) 0.25–1% lipid groups are shown during recovery from bupivacaine-induced asystole. All data are presented as mean ± SD unless otherwise specified. For all values, n = 6. P values are as follows: 2 vs. 0.25%; P = 0.025; 4 vs. 0.25%; P = 0.037; 2 vs. 0.5%; P = 0.011; 4 vs. 0.5%; P = 0.018; 16 vs. 0.5%; P = 0.03.

Fig. 3. Heart rate (HR) in (A) 2–16% lipid groups and (B) 0.25–1% lipid groups are shown during recovery from bupivacaine-induced asystole. All data are presented as mean ± SD unless otherwise specified. For all values, n = 6. P values are as follows: 2, 4, 8, and 16% vs. 0.25%; 2, 4, 8, and 16% vs. 0.5%; P < 0.001; 2 vs. 1%, P < 0.004; 4, 8, and 16% vs. 1%, P < 0.001; 4 vs. 2%, P = 0.013; 8 vs. 2%, P = 0.004; 16 vs. 2%, P < 0.001; 16 vs. 4%, P < 0.001; 16 vs. 8%, P < 0.001.

Fig. 4. Rate-pressure product (RPP) in (A) 2–16% lipid groups and (B) 0–1% lipid groups are shown during recovery from bupivacaine-induced asystole. All data are presented as mean ± SD unless otherwise specified. For all values, n = 6. P values are as follows: 2, 4, 8, and 16% vs. 0.25%; 2, 4, 8, and 16% vs. 0.5%; P < 0.001; 2 vs. 1%, P = 0.003; 4, 8, and 16% vs. 1%, P < 0.001; 16 vs. 2%, P < 0.001; 16 vs. 4%, P = 0.011. Regarding RPP from 5 to 40 min compared with 1 min, P values by lipid group are as follows: 4%: 15 vs. 1 min, P = 0.016; 20–40 vs. 1 min, P < 0.001. 8%: 15 vs. 1 min, P = 0.024; 20 vs. 1 min, P = 0.018; 25 vs. 1 min, P = 0.005; 30 vs. 1 min P = 0.001; 35–40 vs. 1 min, P < 0.001. 16%: 15 vs. 1 min, P = 0.009; 20–40 vs. 1 min, P < 0.001.
product at the end of infusion time to baseline value.

Fig. 5. The concentration-response curve of lipid emulsion in reverse of bupivacaine-induced asystole in isolated rat hearts. Pharmacology parameters, from 23% as bottom to top 121.1%, 3.35% for EC50 (95% CI: 1.73–6.49%), and 2.1 for HillSlope. Therefore, we fitted these to equation 1 and got the typical S-shaped concentration-response curve. We also used equation 2, where \( Y = 0.23 + 0.98/[1 + 10^{2.1(0.93–X)}] \). Equation 2, \( R^2 = 0.9758 \).\( RPPr = \text{the ratio of the maximum rate-pressure product during recovery to baseline value.} \)

Concentration-Response Curve

RPPr demonstrated a concentration-dependent relationship among lipid groups, with cardiac function significantly improved when lipid concentration was 2% or more (table 2). However, lipid concentrations higher than 8% did not result in improved recovery, thereby demonstrating a “plateau effect” in the benefit of lipids (fig. 5).

RPPe in the 2–16% lipid groups were significant greater than in the 0.25–0.5% lipid groups, with the 8% group greater than the 1% group. The relationship between the concentration of lipid emulsion and myocardial bupivacaine and RPPe is shown in table 2 and figure 6.

Discussion

Studies7,8 from several laboratories have established the isolated heart model as a powerful tool for studying the pathophysiology, mechanisms, and treatment of bupivacaine-related cardiac toxicity. Animal studies have found that bupivacaine peaks in the blood and myocardium within seconds after intravenous injection. It rapidly declines within 3–5 min but remains in the blood and myocardium in low concentrations for a long time.9,10 Previous isolated heart model studies did not add bupivacaine to reperfusion fluid because the existence of residual plasma bupivacaine concentrations after toxic insult was questionable. In the current study, 40 \( \mu \)M bupivacaine was added as a background concentration to the reperfusion fluid to better approximate common clinical situations. Our results indicate that even low concentrations of lipid emulsion can reverse bupivacaine-induced asystole, demonstrating a concentration-effect and time-effect relationship between lipid emulsion and the recovery of cardiac function.

Measures of contractility, such as left ventricular systolic pressure, are highly dependent on and inversely related to HR. Therefore, we used RPP as a measure of recovery because it incorporates contractility with a correction for HR. RPPr is more useful as an indicator of recovery. RPPr was improved with the increasing concentrations of lipid emulsion in a concentration-dependent manner. Postulated mechanisms of lipid emulsion in the reversal of local anesthetic toxicity include either: (1) lipid emulsion extraction of lipophilic local anesthetics from aqueous plasma or cardiac tissues2,3,11 (“lipid sink” theory), and/or (2) counteraction of local anesthetic inhibition of myocardial fatty acid oxidation.12 Our results showed that even low lipid concentrations could lead to a reversal of LVdevP, whereas increasing lipid concentration did not result in increased myocardial contractility. In addition, left ventricle diastolic function was improved in higher lipid concentration groups, although a concentration-dependent relationship was not demonstrated. The trend for RPP paralleled that for recovery of HR (fig. 3 and 4). Enhanced RPPr was mainly a result of improved HR. Lipid treatment may produce a concentration-related restoration of cardiac function primarily by counteracting bupivacaine inhibition of myocardial conduction.

A key finding of our study is the relationship between the concentration of lipid emulsion and myocardial bupivacaine concentration, and the resulting recovery of the heart from asystole. The myocardial bupivacaine concentration-effect curve (fig. 6) indicated lipid treatment hastened the removal of bupivacaine from myocardial tissue when demonstrating some degree of cardiac recovery. When lipid concentrations were 2% or more, myocardial bupivacaine concentration significantly decreased when compared with lower concentration lipid groups—thereby confirming improved cardiac function and better recovery when the lipid concentration was higher. These findings support the lipid sink theory—or at least support the premise that lipid infusion accelerates the loss of bupivacaine from myocardial tissue. In addition, our results demonstrate that higher lipid concentrations result in a larger loss, and that this loss is contemporaneous with better recovery of cardiac function.
Lipid Reverses Bupivacaine-induced Asystole

Our study time-response analysis demonstrated that, when lipid emulsion concentrations are 4% or higher, RPP peaks and then trends downward during recovery. This result may be related to the structural characteristics of lipid emulsion; high-dose lipid emulsion infusion in a short period of time may have fat embolism effects, especially when part of emulsified fat is greater than 5 μm in diameter.13,14 Hiller et al.15 found microscopic abnormalities in the lung when giving high concentrations (60 ml/kg) of 20% lipid emulsion to rats in vivo. Our study instead used an isolated rat heart model, without the effect of the “filtration” properties of an in vivo lung. It may be that future studies will link the use of high concentrations of lipid emulsions to cardiac fat embolism. The application of lipid emulsion as an antidote in the setting of bupivacaine toxicity should be done under strict monitoring conditions with paramount vigilance on the part of the physician during and after resuscitation.

Steher et al.16 found that lipid application in l-bupivacaine–induced cardiac depression resulted in improved inotropy in isolated rat hearts, but that HR did not change. The amount of lipid in their study was based on a recommendation by Weinberg.17 The effluent lipid concentration used was 8.9 ± 0.4 μl/ml, or a 0.18% concentration. Our results showed HR during recovery in the 2–16% lipid groups was higher than in the 0.25% group. This finding suggests that higher concentrations of lipid emulsion than those investigated in previous studies may demonstrate larger beneficial effects on cardiac function. It is noteworthy that, in our study, cardiac function was significantly improved in the 2% lipid group although a decreasing tendency during recovery was not observed. This result suggests an optimal concentration of lipid emulsion should exist in its application for use in local anesthetic toxicity.

Conclusion

Our study demonstrated that the effect of lipid emulsion to reverse bupivacaine cardiac toxicity was exact, showing— within specified limits—a concentration-dependent relationship during the early recovery phase. An appropriate increase in the current recommended dose of lipid emulsion may improve cardiac function after resuscitation. However, safe use of increasing concentrations of fat emulsion in patients with bupivacaine toxicity requires further study.

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References


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