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# Recovery From Ropivacaine-Induced or Levobupivacaine-Induced Cardiac Arrest in Rats: Comparison of Lipid Emulsion Effects

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**BACKGROUND:** Lipid emulsion treatment appears to have application in the treatment of local anesthetic–induced cardiac arrest. To examine whether the efficacy of lipid resuscitation in the treatment of local anesthetic–induced cardiac arrest is affected by lipophilicity, the effects of lipid infusions were compared between levobupivacaine-induced (high lipophilicity) and ropivacaine-induced (lower lipophilicity) rat cardiac arrest model.

**METHODS:** A total of 28 female Sprague-Dawley rats were anesthetized using sevoflurane, which subsequently underwent tracheostomy, followed by femoral artery and vein cannulation. Two hours after the discontinuation of sevoflurane, either levobupivacaine 0.2% (n = 14) or ropivacaine 0.2% (n = 14) was administered at a rate of 2 mg/kg/min to the awake rats. When the pulse pressure decreased to 0, the infusion of local anesthetic was discontinued, and treatment with chest compressions and ventilation with 100% oxygen were immediately initiated. The total doses of local anesthetics needed to trigger the first seizure and pulse pressure of 0 mm Hg were calculated. The 2 groups were each subdivided into a lipid emulsion group (n = 7) and a control group (n = 7). In the lipid emulsion group, 20% lipid emulsion was administered intravenously (5 mL/kg bolus plus continuous infusion of 0.5 mL/kg/min), while in the control group, the same volume of normal saline was administered. Chest compressions were discontinued when the rate-pressure product had increased by more than 20% of baseline.

**RESULTS:** The cumulative doses of levobupivacaine and ropivacaine that produced seizures and 0 pulse pressure showed no significant difference. Mean arterial blood pressure (MAP) values were higher in the levobupivacaine group than in the ropivacaine group after resuscitation was initiated ($P < .05$). In levobupivacaine-induced cardiac arrest, heart rate and MAP values were higher in the lipid group than in the control group after starting resuscitation ($P < .05$); all rats in the lipid group achieved spontaneous circulation (rate-pressure product >20% baseline), while only 2 of 7 rats in the control group achieved spontaneous circulation at 10 minutes. In ropivacaine-induced cardiac arrest, there were no significant differences in heart rate and MAP between the lipid and control groups from the start of resuscitation to 10 minutes; spontaneous circulation returned in 6 of 7 lipid group rats, but in only 2 of 7 control group rats at 10 minutes.

**CONCLUSIONS:** Lipid emulsion treatment was more effective for levobupivacaine-induced cardiac arrest than for ropivacaine-induced cardiac arrest. Although lipid therapy is also effective for ropivacaine-induced cardiac arrest, it takes more time than in levobupivacaine-induced cardiac arrest. This suggests that the lipophilicity of local anesthetics influences the efficacy of lipid infusion when treating cardiac arrest caused by these drugs. (Anesth Analg 2017;125:1496–502)

Levobupivacaine and ropivacaine are 2 long-acting local anesthetics that have been developed since the recognition of the severe toxicity caused by bupivacaine. These 2 drugs are pure left-handed enantiomers, and are associated with less potential for both central nervous system and cardiovascular system toxicity than bupivacaine.[1,2] However, there have been several clinical reports of cardiovascular collapse induced by both ropivacaine and levobupivacaine.[3–10]

Comparative studies investigating the systemic toxicity of levobupivacaine and ropivacaine have been published. The cumulative dose of ropivacaine to induce circulatory collapse was greater than that of levobupivacaine in anesthetized ewes and dogs[11,12] Additionally, the cumulative doses of ropivacaine that produced dysrhythmias and asystole were larger than corresponding doses of levobupivacaine immediately after the discontinuation of anesthesia in rat models.[13] Thus, ropivacaine is required more to produce cardiac collapse than levobupivacaine in ewe, dog, and rat models. In contrast, it has been reported that levobupivacaine is less toxic than bupivacaine, but is no different from ropivacaine for lethality in anesthetized swine.[14] In rats, significantly less epinephrine was needed to treat ropivacaine-induced cardiac arrest than to treat levobupivacaine-induced or bupivacaine-induced

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cardiac arrest under ventilation with 100% oxygen and external cardiac compressions.[13] Ropivacaine-induced cardiac arrest also appeared to respond better to epinephrine than cardiac arrest induced by bupivacaine or levobupivacaine.[12,13] As noted above, reports of the systemic toxic effects of these 2 local anesthetics have been variable.

Use of intravenous (IV) lipid emulsion has been reported as a rescue therapy for local anesthetic toxicity, especially in the situations of local anesthetic--induced cardiovascular collapse.[15,16] The mechanism of lipid emulsion therapy is not completely understood, and several new important mechanisms have been proposed; however, its effect may, in part, appear related to its ability to extract bupivacaine (or other lipophilic drugs) from plasma or tissue. This theorized mechanism of action, known as the "lipid sink" effect, may relate to the lipophilicity of local anesthetics.[15,16] To the best of our knowledge, there have been no comparisons of lipid emulsion therapy between levobupivacaine-induced and ropivacaine-induced cardiac arrest.

To test the hypothesis that lipid therapy is more effective for resuscitation of levobupivacaine-induced (high lipophilicity) cardiac arrest than of ropivacaine-induced (lower lipophilicity) induced cardiac arrest, the difference in efficacy of lipid infusion to treat cardiac arrest induced by these drugs was examined in awake rats.

## METHODS

Approval was obtained from the institutional animal care committee of Akita University Graduate School of Medicine (a-1-2652) before initiation of the study. This article adheres to the applicable ARRIVE guidelines of the EQUATOR network. Twenty-eight healthy, nonpregnant female Sprague-Dawley rats weighing between 200 and 284 g were studied. The rats were fasted for 12 hours before the experiments, with free access to water.

Anesthesia was induced in an acryl box, using 5% sevoflurane in a mixture of 33% oxygen in nitrogen. After sedation, the rats were placed on a surgical board, and anesthesia was maintained via mask using 3% sevoflurane in a 33% oxygen in nitrogen mixture, breathing spontaneously. A tracheostomy was performed, followed by tracheal intubation using a 14-gauge plastic cannula. Catheters were inserted into the left femoral artery to monitor blood pressure (BP) and measure arterial blood gases, as well as the right femoral vein for infusion of drugs. The catheters were directed to run subcutaneously in the animals, were pierced over the posterior midthorax, and were fixed by a sutured swivel, allowing the rats to move spontaneously in their cages after they had awakened from anesthesia. Rectal temperature was maintained at 37.5°C ± 0.5°C throughout the procedure by placing the rats on a temperature-controlled heating pad (CMA/150, Stockholm, Sweden) and under a heating lamp.

After the procedure, sevoflurane was discontinued, and the rats were left in their cages for 2 hours and allowed to move freely to exclude the effect of residual sevoflurane before commencing the study. Before the experiment, rats were blindly randomized by number drawing into 1 of 2 groups: the levobupivacaine group (n = 14) and the ropivacaine group (n = 14). Each group was then divided into a lipid emulsion group (n = 7) and a control group (n = 7). Before the local anesthetic challenge, BP and heart rate (HR) values were measured, and arterial blood was sampled to analyze arterial blood gases (ABL510; Radiometer Co, Copenhagen, Denmark) to confirm an arterial carbon dioxide tension between 30 and 46 mm Hg, and a pH between 7.35 and 7.46 (breathing spontaneously on room air). An anesthesiologist who was not related to the study prepared the local anesthetic solution, and the researchers who performed this experiment were blinded to the type of local anesthetic that was administered. Throughout the experiment, an electrocardiogram was recorded using 2 subcutaneous needle electrodes, and femoral arterial pressure was also recorded (CM−615G; Nihon Koden, Tokyo, Japan).

Rats in the levobupivacaine group received levobupivacaine 0.2%, while those in the ropivacaine group received ropivacaine 0.2% at a rate of 2 mg/kg/min. The cumulative doses of local anesthetic required to induce the first seizure activity (a tonic-clonic seizure) and a pulse pressure of 0 mm Hg were calculated.

When pulse pressure decreased to 0, continuous infusion of local anesthetic was discontinued, and this point was defined as time 0. Mechanical ventilation with 100% oxygen through the tracheostomy tube was started immediately using a rodent ventilator (Ugo Basile Cat. No. 7025; Muromachi Kikai Co, Ltd, Tokyo, Japan) to deliver a tidal volume of 2.5 mL at a rate of 60 breaths/min. At the same time, external manual chest compressions were commenced at a rate of 240/min to obtain a systolic arterial pressure >40 mm Hg. The lipid emulsion group received an IV infusion of 20% lipid emulsion as a 5 mL/kg bolus immediately after commencing mechanical ventilation and chest compressions, followed by a continuous infusion of 0.5 mL/kg/min for 10 minutes (Intralipid 20%; Fresenius Kabi AB, Uppsala, Sweden). Chest compressions were continued to achieve a rate-pressure product (RPP; RPP = systolic pressure × HR) of at least 20% of baseline, which was defined as the criterion for the return of spontaneous circulation. Chest compressions were interrupted for 5 seconds every minute to assess whether the native RPP had increased by >20% of baseline. The operator who was assigned to the role of chest compressions commenced the training 1 month in advance. Competence in the application of chest compressions was assured by the demonstration of 20 consecutive successful applications at a rate of 240/min and at a pressure of 45 mm Hg, using a metronome and weighing scale. The selected operator performed chest compression in all experiments and was blinded to the type of local anesthetic infused. Mechanical ventilation with 100% oxygen was continued from time 0 (when infusion of local anesthetic was discontinued) until the end of the experiment (10-minute time point). Chest compressions and mechanical ventilation with 100% oxygen were stopped at the 10-minute time point, even if native RPP had not increased by >20% of baseline. At the 10-minute time point, arterial blood gas analysis was performed. The saline control group received an infusion of the same volume of saline, similar to the rats receiving lipid emulsion. Other procedures were the same as in the lipid emulsion group.

Power analysis was based on the results of preliminary experiments comparing RPP at 10 minutes between levobupivacaine and ropivacaine groups and yielding a sample size of n = 5 for each group; power was set at 0.8; significance was set at 0.05, and effect size was estimated as 2, with sigma at 0.9. Data from blood gas analysis are expressed as medians and ranges. Values were compared among groups

using the Mann-Whitney *U* test. Mean arterial blood pressure (MAP) and HR values are expressed as mean ± standard deviation. The unpaired Student *t* test was used to compare the MAP and HR values between the levobupivacaine and ropivacaine groups receiving lipid emulsion, as well as between the lipid emulsion and control groups in each levobupivacaine or ropivacaine group, respectively. The MAP and HR variables of the 2 groups measured across time were analyzed using 1-way repeated-measures analysis of variance and post hoc Student-Newman-Keuls testing (the results are applied to Figure 2). The $\chi^2$ test was used to compare the number of rats attaining return of spontaneous circulation at 10 minutes in the levobupivacaine and ropivacaine group treated with lipid emulsion. For all comparisons, $P < .05$ was considered to be statistically significant.

## RESULTS

Arterial blood gas values, MAP, and HR before infusion of local anesthetics did not differ among the 4 groups (Table 1). The levobupivacaine and ropivacaine groups showed no significant difference in term of the total amount that induced the first seizure activity (11.5 ± 3.5 vs 12.2 ± 4.3 mg/kg, respectively) and a pulse pressure of 0 mm Hg (18.0 ± 4.3 vs 19.8 ± 4.7 mg/kg, respectively) (Figure 1). MAP and HR did not differ among the 4 groups when pulse pressure decreased to 0 mm Hg (Table 2).

MAP values were higher in the levobupivacaine group than in the ropivacaine group at 2, 3, 4, 5, and 10 minutes after the start of resuscitation with lipid infusion ($P < .05$). The HR values were higher in the levobupivacaine group than in the ropivacaine group at 5 minutes after the start of resuscitation with lipid infusion ($P < .05$) (Figure 2, A-1, A-2).

MAP values were higher in the lipid group than in the control group at 2, 3, 4, 5, and 10 minutes after the start of resuscitation from levobupivacaine-induced cardiac arrest ($P < .05$). However, there was no significant difference in MAP values between the lipid and the control groups in ropivacaine-induced cardiac arrest (Figure 2, B-1, B-2). HRs of the lipid group were higher than that of the control group from 4 to 10 minutes after the initiation of resuscitation from levobupivacaine-induced cardiac arrest; however, in ropivacaine-induced cardiac arrest, significant differences between the lipid and control groups were not found ($P < .05$) (Figure 2, C-1, C-2). There were no significant differences in MAP and HR values between ropivacaine and levobupivacaine in the control groups. Data from all animals for which native RPP is ≤20% of baseline value were included (Figure 2).

Table 3 summarizes the number of animals attaining return of spontaneous circulation (native RPP >20% of baseline value) in each group over time. In the lipid-infusion group, all rats were resuscitated successfully at 10 minutes after levobupivacaine-induced cardiac arrest, while 1 of 7 rats had not achieved successful resuscitation 10 minutes after ropivacaine-induced cardiac arrest. In contrast, in the control group, 5 of 7 rats were not successfully resuscitated at 10 minutes after both levobupivacaine-induced and ropivacaine-induced cardiac arrest. There was no significant difference between the numbers of rats attaining return of spontaneous circulation at 10 minutes in the levobupivacaine and ropivacaine group treated with lipid emulsion.

Metabolic values at 10 minutes after resuscitation are shown in Table 4. In the saline group (for both levobupivacaine and ropivacaine), the sample size was reduced to 4 because arterial blood could not be drawn due to the low BP. Base excess and pH values were higher in the levobupivacaine group than in the ropivacaine group when lipid emulsion was infused ($P < .05$). There were no significant differences in the other values because of the sample size reduction in the saline groups.

## DISCUSSION

Lipid emulsion treatment was more effective in treating cardiac arrest induced by levobupivacaine than by ropivacaine, although there were no significant differences between the total amount of levobupivacaine and ropivacaine required to induce seizures and cardiac arrest. Lipid therapy was superior to saline in achieving resuscitation in both levobupivacaine-induced and ropivacaine-induced cardiac arrest; however, successful resuscitation from ropivacaine-induced cardiac arrest took more time when compared with levobupivacaine.

There have been many reports investigating lipid rescue in bupivacaine-induced cardiovascular collapse.[17] However, to the best of our knowledge, no studies have compared the effects of lipid emulsion on the recovery from levobupivacaine-induced versus ropivacaine-induced cardiac arrest. Ohmura et al[13] compared the number of successful resuscitations between levobupivacaine-induced and ropivacaine-induced cardiac arrest and concluded that ropivacaine-induced cardiac arrest may be more responsive to treatment than cardiac arrest induced by levobupivacaine. However, the drug used for treating cardiac arrest in their study was epinephrine, not a lipid emulsion.

Lipid emulsion therapy has become an additional option of treatment for local anesthetic–induced cardiac arrest.[18] However, the effects of lipid infusion on local anesthetic-induced cardiac arrest are not likely uniform and depend on the chemical properties of the local anesthetic concerned.

**Table 1. Baseline (Before Infusion of Local Anesthetics) Physiologic Values**

| | Levobupivacaine | | Ropivacaine | |
|---|---|---|---|---|
| | Lipid Emulsion (n = 7) | Saline (n = 7) | Lipid Emulsion (n = 7) | Saline (n = 7) |
| MAP (mm Hg) | 132 ± 15 | 138 ± 13 | 120 ± 9 | 133 ± 12 |
| HR (beats/min) | 384 ± 68 | 410 ± 45 | 384 ± 68 | 403 ± 29 |
| pH | 7.419 (7.379–7.43) | 7.450 (7.411–7.460) | 7.439 (7.396–7.459) | 7.407 (7.383–7.42) |
| $Paco_2$ (mm Hg) | 41.3 (31.9–45.4) | 36 (33.4–45.4) | 38.3 (37.4–42.8) | 39.4 (32.2–41.5) |
| $Pao_2$ (mm Hg) | 84.3 (74.0–113) | 96.3 (70.7–101.9) | 87.6 (78.9–102.6) | 84.5 (70.2–106.8) |
| BE (mEq/L) | 2.3 (−3.4 to 4.1) | 0.9 (−0.7 to 3.5) | 3.0 (−0.4 to 3.3) | 0.4 ± 2.3 |

Values of MAP and HR are mean ± SD; all other values are median (minimum, maximum). Baseline values showed no difference among the 4 groups.
Abbreviations: BE, base excess; HR, heart rate; MAP, mean arterial blood pressure.

In fact, it has been reported that lipid emulsion improves the recovery from cardiac arrest induced by bupivacaine, but not from cardiac arrest induced by ropivacaine or mepivacaine in the isolated rat heart.[19] The lipophilicity of local anesthetics might have an impact on the efficiency of lipid infusions to treat cardiac arrest.[20] Because ropivacaine and levobupivacaine have very similar characteristics in terms of *p*Ka and percentage of protein binding,[1,2] the key difference is that levobupivacaine is more lipophilic than ropivacaine.[21] However, the difference between the lipophilicity of levobupivacaine and ropivacaine may not be sufficient to support our results. In fact, some new mechanisms have been advocated. Large lipid dose could reverse the inhibition of fatty acid metabolism in cardiac mitochondria because lipids are the energy matrix of the heart. These metabolic or other direct cardiac effects may be even more important than the lipid sink because, in more recent studies, very high doses of lipid emulsion have caused a rise in arterial BP, HR, and cardiac blood flow in rats, possibly through inotropic and lusitropic mechanisms.[22,23] Moreover, a microemulsion both improves cardiac output and rapidly transports the drug away from organs subject to toxicity.[22] Other recent experiments also support these new mechanisms.[23] However, we have not proved the relationship between these mechanisms and the difference of the lipid emulsion effects on levobupivacaine and ropivacaine toxicity.

One of the characteristic observations in the present study is that elevated MAP was seen from 2 minutes after lipid resuscitation in the levobupivacaine group, whereas MAP elevation did not occur until 5 minutes in the ropivacaine group. However, it would be inappropriate to conclude that lipid emulsion is not effective for ropivacaine-induced cardiac arrest. As the result shows, 6 of 7 rats that received lipid emulsion attained return of spontaneous circulation 10 minutes after ropivacaine-induced cardiac arrest. Meanwhile, only 2 of 7 rats receiving saline recovered after ropivacaine-induced cardiac arrest. This suggests that lipid emulsion therapy for ropivacaine toxicity is not ineffective, but does takes a longer time to achieve its effect. Although the lipophilicity of the local anesthetics concerned may be 1 factor explaining the difference between the 2 groups studied, there may be other important mechanisms at play. Our results suggest that early treatment with lipid infusion is an effective strategy, as recommended in the American Society of Regional Anesthesia and Pain Medicine practice advisory on local anesthetic systemic toxicity,[18] especially in ropivacaine-induced cardiac arrest.

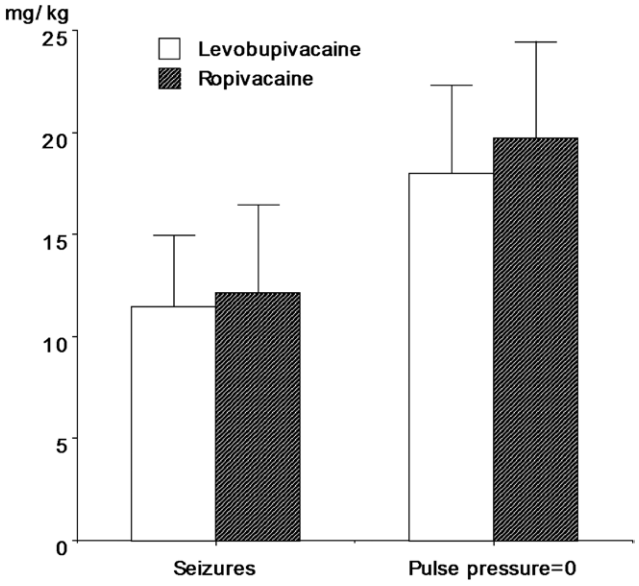


**Figure 1.** Cumulative doses of levobupivacaine (n = 14) and ropivacaine (n = 14) for inducing convulsions and cardiac arrest (pulse pressure = 0). Data are expressed as mean ± standard deviation.

It has been reported that lipid emulsion therapy was successful in treating ropivacaine-induced cardiovascular collapse.[8,10] However, in previous clinical reports, several different drugs were used during resuscitation efforts. For example, both epinephrine and lipid emulsion were infused to treat a case of ropivacaine-induced cardiovascular collapse.[8] Moreover, there have been some clinical reports describing failed reversal of ropivacaine-induced neurotoxicity.[24] In these clinical situations, it is uncertain whether lipid emulsion therapy was solely effective in treating ropivacaine-induced cardiovascular collapse.

In the present study, there were no significant differences between the total doses of levobupivacaine and ropivacaine required to induce cardiac arrest. This finding is consistent with some previous reports[14] but not with others.[11–13] The cumulative dose of ropivacaine to induce circulatory collapse was greater than that of levobupivacaine in anesthetized ewes, dogs and immediately discontinued anesthesia in rat model.[11–13] On the other hand, levobupivacaine is less toxic than bupivacaine but was no different from ropivacaine for lethality in anesthetized swine.[14] Our result indicates that there was no statistical difference of lethal doses between levobupivacaine and ropivacaine in the awake rat model. One of the causes for this difference may be the definition of "lethal." We defined lethal as a pulse pressure of 0, while previous reports defined it as a MAP ≤45 mm Hg,[12] or the lack of recognizable beat on the ECG for 1 minute after the appearance of the last systole.[13] Another cause of this difference may be attributable to whether anesthetized or awake animals were used in the experiment. In our study, general anesthesia was used only in the preparation of the animals. Experiments commenced 2 hours after discontinuation of sevoflurane to exclude the effects of this agent

**Table 2. Mean Arterial Blood Pressure and Heart Rate at a Time of Pulse Pressure = 0**

| | Levobupivacaine | | Ropivacaine | |
|---|---|---|---|---|
| | Lipid Emulsion (n = 7) | Saline (n = 7) | Lipid Emulsion (n = 7) | Saline (n = 7) |
| MAP (mm Hg) | 6.8 ± 1.5 | 8.5 ± 4.3 | 7.6 ± 1.3 | 6.1 ± 1.2 |
| HR (beats/min) | 45 ± 18 | 47 ± 15 | 35 ± 25 | 30 ± 18 |

Values are mean ± SD.
Abbreviations: HR, heart rate; MAP, mean arterial blood pressure.

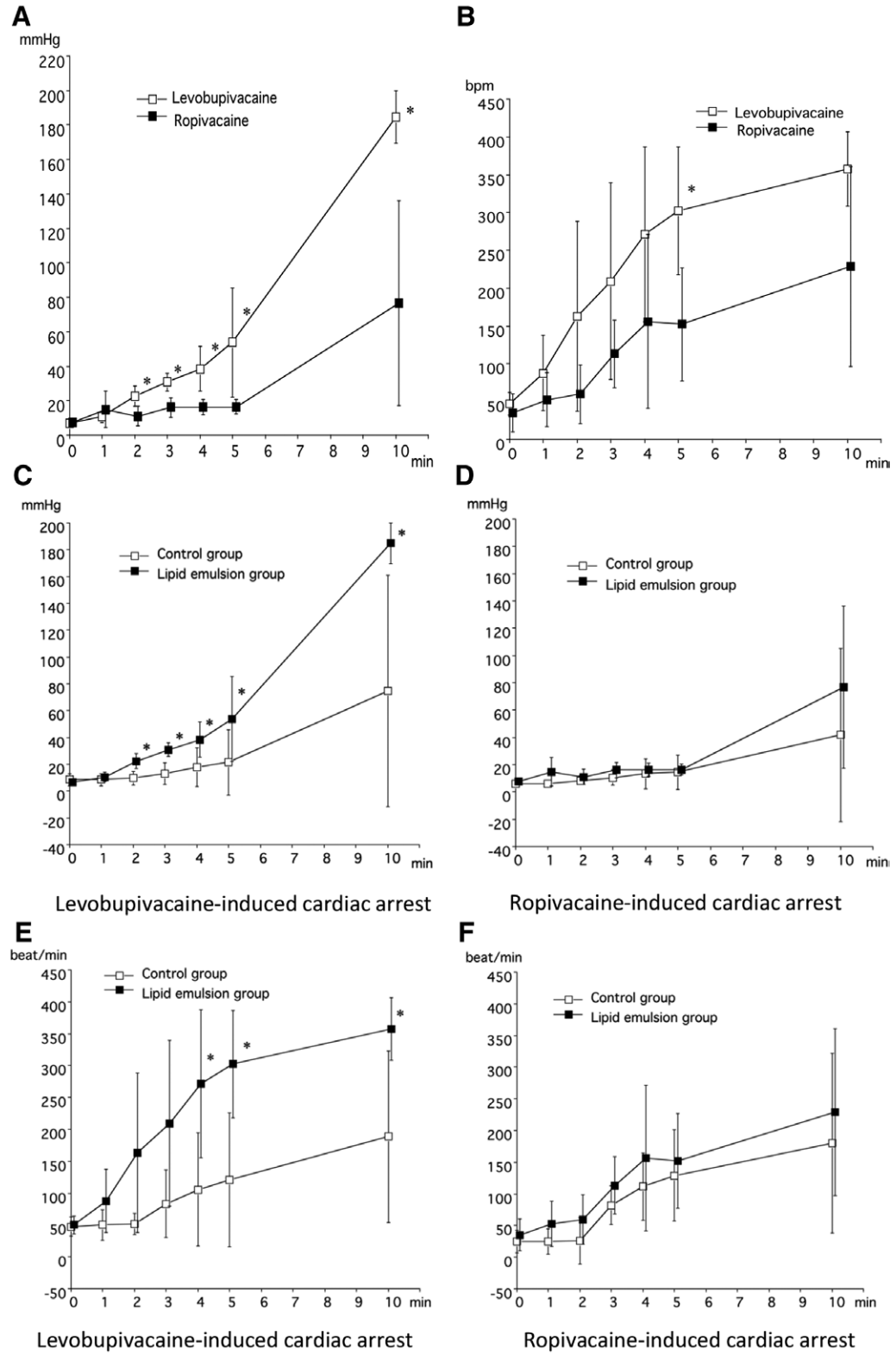


**Figure 2.** A, Changes in mean arterial blood pressure (A-1) and heart rate (A-2) after the start of resuscitation with lipid infusion in the levobupivacaine group (n = 7) and the ropivacaine group (n = 7). Data are expressed as mean ± SD. *$P$ < .05 compared with the ropivacaine group. B, Changes in MAP in the lipid emulsion group and the control group after the start of resuscitation from levobupivacaine-induced cardiac arrest (B-1) and ropivacaine-induced cardiac arrest (B-2) (n = 7 in each group). The same MAP values are presented in the lipid emulsion group of A-1 and B-1. Data are expressed as mean ± SD. *$P$ < .05 compared with the control group. C, Changes in HR in the lipid group and the control group after the start of resuscitation from levobupivacaine-induced cardiac arrest (C-1) and ropivacaine-induced cardiac arrest (C-2) (n = 7 in each group). The same HR values are presented in the lipid emulsion group of A-2 and C-2. Data are expressed as mean ± SD. *$P$ < .05 compared with the control group. HR indicates heart rate; MAP, mean arterial blood pressure; SD, standard deviation.

**Table 3. Animals Attaining Return of Spontaneous Circulation (Native RPP >20% of Baseline Value) for Each Group and Time**

| | 2 Min | 3 Min | 4 Min | 5 Min | 10 Min |
|---|---|---|---|---|---|
| Levobupivacaine + lipid | 1 | 2 | 4 | 5 | 7 |
| Levobupivacaine + saline | 0 | 0 | 1 | 1 | 2 |
| Ropivacaine + lipid | 0 | 1 | 1 | 1 | 6 |
| Ropivacaine + saline | 0 | 0 | 0 | 1 | 2 |

n = 7 for all conditions.
Abbreviation: RPP, rate-pressure product (RPP = systolic pressure × heart rate).

**Table 4. Metabolic Values 10 Minutes After Resuscitation**

| | Levobupivacaine | | Ropivacaine | |
|---|---|---|---|---|
| | Lipid Emulsion (n = 7) | Saline (n = 4) | Lipid Emulsion (n = 7) | Saline (n = 4) |
| pH | 7.304 (7.069–7.401) | 7.134 (7.000–7.375) | 7.210 (7.012–7.241)[a] | 7.106 (6.914–7.219) |
| $Paco_2$ (mm Hg) | 29.3 (25.1–39.9) | 30.0 (23.4–53.7) | 40.7 (33.5–63.5) | 41.4 (28.5–63.9) |
| $Pao_2$ (mm Hg) | 413 (318–592) | 213 (82–373) | 381 (160–453) | 193 (75–283) |
| BE (mEq/L) | −9.5 (−11.8 to −7.0) | −13.6 (−16.3 to −7.4) | −10.5 (−14.2 to −9.3)[a] | −14.0 (−19.7 to −10.7) |

Values are median (minimum, maximum).
Abbreviation: BE, base excess.
[a]$P < .05$ compared with levobupivacaine in lipid emulsion group. The reduced sample size in the saline group (for both levobupivacaine and ropivacaine) prevented statistical comparison between the saline group and the lipid emulsion group.

because volatile anesthetic agents may increase the convulsive thresholds of local anesthetics. Sevoflurane is known to attenuate bupivacaine-induced arrhythmias and seizures in rats.[25] The doses of local anesthetic required to depress cardiac index and cause asystole were higher in the group receiving volatile anesthesia.[26] These 2 factors may account for the differences between the results of previous studies and our study. Therefore, we do not suppose that our findings are necessarily rat specific.

We used the long-chain fatty acid Intralipid for resuscitation. According to previous studies, long-chain triglyceride is more effective in vivo.[27] On the other hand, long-chain and medium-chain triglyceride is more effective in vitro, which may have been predicted based on the partition constants (log *P*) of these drugs.[28] The log *P* is a measure of the differential solubility of a compound in octanol and water, and thus is a measure of how hydrophilic a substance is, with higher log *P* values indicating greater hydrophobicity. These 2 studies draw opposite conclusions, and further study is needed to resolve which composition of lipid is effective.

There were several limitations to this study. First, serum concentrations of local anesthetics were not measured because it was believed that excessive blood sampling would have affected the results. However, had this been performed, a correlation could have been found between the efficacy of resuscitation measures and serum concentrations of local anesthetics. Second, clinical cardiac collapse induced by local anesthetic agents is usually the result of accidental IV injection of local anesthetic, whereas our protocol used an incremental increase of local anesthetic dosage. A slower rate of infusion, compared with bolus injection, requires larger doses of local anesthetic before the onset of toxicity.[29] Third, female rats were used, despite the possible effects of the sexual cycle on local anesthetic toxicity. One of the reasons we used female rats was to obtain fundamental data from females for our future experiments, which we are planning to conduct using pregnant rats. Although pregnant females may have a lower threshold for local anesthetic toxicity,[30] the effect of lipid therapy remains unknown. In fact, female humans also encounter local anesthetic toxicity; therefore, study involving female rats will be needed.

In conclusion, lipid emulsion therapy was more effective for resuscitation of levobupivacaine-induced cardiac arrest than that induced by ropivacaine. Lipid therapy was effective in our model of ropivacaine-induced cardiac arrest, but has a quicker effect for levobupivacaine-induced cardiac arrest. Our results suggest that the lipophilicity of local anesthetics can influence the efficacy of lipid infusion for treating cardiac arrest induced by these drugs.


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## DISCLOSURES

**Name:** Masashi Yoshimoto, DMD.
**Contribution:** This author helped collect the data and prepare the manuscript.
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**Contribution:** This author helped review the original study data and revise the manuscript.
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## REFERENCES


1. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? *Best Pract Res Clin Anaesthesiol*. 2005;19:247–268.
2. Leone S, Di Cianni S, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. *Acta Biomed*. 2008;79:92–105.
3. Chazalon P, Tourtier JP, Villevielle T, et al. Ropivacaine-induced cardiac arrest after peripheral nerve block: successful resuscitation. *Anesthesiology*. 2003;99:1449–1451.

4. Huet O, Eyrolle LJ, Mazoit JX, Ozier YM. Cardiac arrest after injection of ropivacaine for posterior lumbar plexus blockade. *Anesthesiology*. 2003;99:1451–1453.
5. Klein SM, Trenton P, Yair R, Nielsen KC, Steele SM. Successful resuscitation after ropivacaine-induced ventricular fibrillation. *Anesth Analg*. 2003;97:901–902.
6. Reinikainen M, Hedman A, Pelkonen O, Ruokonen E. Cardiac arrest after interscalene brachial plexus block with ropivacaine and lidocaine. *Acta Anaesthesiol Scand*. 2003;47:904–906.
7. Gielen M, Slappendel R, Jack N. Successful defibrillation immediately after the intravascular injection of ropivacaine. *Can J Anaesth*. 2005;52:490–492.
8. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia*. 2006;61:800–801.
9. Foxall G, McCahon R, Lamb J, Hardman JG, Bedforth NM. Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. *Anaesthesia*. 2007;62:516–518.
10. Ludot H, Tharin JY, Belouadah M, Mazoit JX, Malinovsky JM. Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. *Anesth Analg*. 2008;106:1572–1574.
11. Santos AC, DeArmas PI. Systemic toxicity of levobupivacaine, bupivacaine, and ropivacaine during continuous intravenous infusion to nonpregnant and pregnant ewes. *Anesthesiology*. 2001;95:1256–1264.
12. Groban L, Deal DD, Vernon JC, James RL, Butterworth J. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. *Anesth Analg*. 2001;92:37–43.
13. Ohmura S, Kawada M, Ohta T, Yamamoto K, Kobayashi T. Systemic toxicity and resuscitation in bupivacaine-, levobupivacaine-, or ropivacaine-infused rats. *Anesth Analg*. 2001;93:743–748.
14. Morrison SG, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. *Anesth Analg*. 2000;90:1308–1314.
15. Weinberg GL, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology*. 1998;88:1071–1075.
16. Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg Anesth Pain Med*. 2003;28:198–202.
17. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. *Toxicol Rev*. 2006;25:139–145.
18. Neal JM, Bernards CM, Butterworth JF IV, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med*. 2010;35:152–161.
19. Zausig YA, Zink W, Keil M, et al. Lipid emulsion improves recovery from bupivacaine-induced cardiac arrest, but not from ropivacaine- or mepivacaine-induced cardiac arrest. *Anesth Analg*. 2009;109:1323–1326.
20. Zausig YA, Zink W, Graf BM. Lipophilicity of local anesthetics and success of lipid emulsion therapy. *Crit Care Med*. 2012;40:359–360.
21. Mazoit JX, Le Guen R, Beloeil H, Benhamou D. Binding of long-lasting local anesthetics to lipid emulsions. *Anesthesiology*. 2009;110:380–386.
22. Fettiplace MR, Lis K, Ripper R, et al. Multi-modal contributions to detoxification of acute pharmacotoxicity by a triglyceride micro-emulsion. *J Control Release*. 2015;198:62–70.
23. Fettiplace MR, Akpa BS, Ripper R, et al. Resuscitation with lipid emulsion: dose-dependent recovery from cardiac pharmacotoxicity requires a cardiotonic effect. *Anesthesiology*. 2014;120:915–925.
24. Calenda E, Dinescu SA. Failure of lipid emulsion to reverse neurotoxicity after an ultrasound-guided axillary block with ropivacaine and mepivacaine. *J Anesth*. 2009;23:472–473.
25. Fukuda H, Hirabayashi Y, Shimizu R, Saitoh K, Mitsuhata H. Sevoflurane is equivalent to isoflurane for attenuating bupivacaine-induced arrhythmias and seizures in rats. *Anesth Analg*. 1996;83:570–573.
26. Badgwell JM, Heavner JE, Kytta J. Bupivacaine toxicity in young pigs is age-dependent and is affected by volatile anesthetics. *Anesthesiology*. 1990;73:297–303.
27. Li Z, Xia Y, Dong X, et al. Lipid resuscitation of bupivacaine toxicity: long-chain triglyceride emulsion provides benefits over long- and medium-chain triglyceride emulsion. *Anesthesiology*. 2011;115:1219–1228.
28. Ruan W, French D, Wong A, Drasner K, Wu AH. A mixed (long- and medium-chain) triglyceride lipid emulsion extracts local anesthetic from human serum in vitro more effectively than a long-chain emulsion. *Anesthesiology*. 2012;116:334–339.
29. Scott DB. Evaluation of clinical tolerance of local anaesthetic agents. *Br J Anaesth*. 1975;47(suppl):328–331.
30. Bern S, Weinberg G. Local anesthetic toxicity and lipid resuscitation in pregnancy. *Curr Opin Anaesthesiol*. 2011;24:262–267.