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Measurement of the efficacy of 2% lipid in reversing bupivacaine- induced asystole in isolated rat hearts

Hongfei Chen[1], Yun Xia[3], Binbin Zhu[1], Xiawei Hu[1], Shihao Xu[1], Limei Chen[1], Thomas J Papadimos[3], Wantie Wang[2], Quanguang Wang[1] and Xuzhong Xu[1*]

Abstract

Background: The reversal efficacy of 2% lipid emulsion in cardiac asystole induced by different concentrations of bupivacaine is poorly defined and needs to be determined.

Methods: Forty-two male Sprague–Dawley rats were randomly divided into seven groups: B40, B60, B80, B100, B120, B140 and B160, n = 6. The Langendorff isolated heart perfusion model was used, which consisted of a balanced perfusion with Krebs-Henseleit solution for 25 minutes and a continuous infusion of 100 μmol/L bupivacaine until asystole had been induced for 3 minutes. The hearts in the seven groups were perfused with Krebs-Henseleit solution containing a 2% lipid emulsion, and 40, 60, 80, 100, 120, 140 or 160 μmol/L bupivacaine, respectively. Cardiac recovery was defined as a spontaneous and regular rhythm with a rate-pressure product > 10% of the baseline value for more than 1 minute. Our primary outcome was the rate-pressure product 25 minutes after cardiac recovery. Other cardiac function parameters were also recorded.

Results: All groups demonstrated cardiac recovery. During the recovery phase, heart rate, rate-pressure product, the maximum left ventricular pressure rise and decline in heart rate in the B120-B160 groups was significantly lower than those in the B40-B80 groups ($P < 0.05$). The concentration of bupivacaine and the reversal effects of a 2% lipid emulsion showed a typical transoid S-shaped curve, $R^2 = 0.9983$, IC_{50} value was 102.5 μmol/L (95% CI: 92.44 - 113.6).

Conclusions: There is a concentration-response relationship between the concentrations of bupivacaine and the reversal effects of 2% lipid emulsion.

Keywords: Anaesthetics local-bupivacaine, Complications-cardiac arrest, Lipid emulsion

Background

Rapid infusion of a lipid emulsion to treat cardiotoxicity induced by bupivacaine, as originally proposed by Weinberg et al. [1] is now well established [2-8]. Although the mechanism of lipid emulsion has not yet been fully elucidated, it is generally accepted that a "lipid sink" resulting from the lipid emulsion causes bupivacaine to be removed from the serum [1,4,9].

Recently, the use of a rapid infusion of lipid emulsion for the management of severe local anaesthetic toxcity has been incorporated into the 2010 safety guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) [10]. These guidelines indicate that the maximum dose of a 20% lipid emulsion is 12 ml/kg, with a theoretical plasma concentration of about 2.9%. Meanwhile, the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines recommend a maximum dose of 10 ml/kg, with a theoretical plasma concentration of about 2.5% [11,12]. Subsequent to these guidelines Chen et al. [13] demonstrated that a 2% lipid emulsion was an effective resuscitative concentration when added to an isolated rat heart perfusate consisting of 40 μmol/L bupivacaine. However, the reversal efficacy of 2% lipid emulsions for higher concentrations of bupivacaine in the circulation has not been studied.

* Correspondence: xuzhong@263.net
[1]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, 2 Fuxue Road, 325000 Zhejiang, China
Full list of author information is available at the end of the article

Here we report the measurement of the reversal efficacy of a 2% lipid emulsion in cardiac asystole induced by varied concentrations of bupivacaine, and demonstrate a concentration-response relationship between these varied concentrations and the reversal efficacy of the 2% lipid emulsion. Our primary outcome was the calculation of the rate-pressure product (RPP) after resuscitation of bupivacaine-induced asystole in isolated rat hearts using a model that varied the concentrations of bupivacaine. We also examined the secondary outcomes of heart rate (HR), left ventricular developed pressure (LVdevP = left ventricular systolic pressure - left ventricular end-diastolic pressure), and the maximum rates of left ventricular pressure change ($\pm dP/dt_{max}$) that resulted from the resuscitation.

Methods

The study was conducted with the approval of Wenzhou Medical College's Animal Care and Use Committee (Zhejiang, China). The entire study was performed at the Wenzhou Medical College.

Experimental animals

Forty two male Sprague–Dawley rats, weighing 280 ~ 330 g were provided by the animal center of Wenzhou Medical College (Zhejiang, China).

Preparation of isolated heart perfusion model

The rats were anesthetized with a 350 mg/kg chloral hydrate intraperitoneal injection, followed by anticoagulation with an injection of 1000 U/Kg heparin via the inferior vena cava. After rapid thoracotomy coring, a Langendorff device (ML870B2, AD Instruments, Australia) was applied to establish retrograde irrigation under constant temperature (37°C) and pressure (120 mmHg). The rat hearts were then perfused with Krebs-Henseleit (K-H) solution (NaCl 118 mmol/L, KCl 4.7 mmol/L, $MgSO_4$ 1.2 mmol/L, KH_2PO_4 1.2 mmol/L, $NaHCO_3$ 25.0 mmol/L, $CaCl_2$ 2.5 mmol/L, glucose 10 mmol/L, pH 7.40 ± 0.05). The perfusate was exposed to 95% O_2 and 5% CO_2 for 30 min. Spontaneously beating hearts were warmed using an insulation cover. The left ventricular pressure was continuously monitored by a latex balloon placed in the left ventricle. Saline was intermittently injected into the balloon to maintain the left ventricular end-diastolic pressure (LVEDP) at 4–10 mmHg.

Data were collected by a PowerLab biological signal processing and analysis system (ML870, Australia Ed Instruments) and Chart 5.5.6 biological signal recording software. Parameters of cardiac function were recorded by placement of a copper wire electrode into the right atrial and apical epicardium, respectively, and an additional reference electrode was placed on the aorta. The isolated hearts were then perfused with K-H solution for 25 minutes, and when cardiac functioned stabilized further experimental interventions proceeded.

Experimental grouping and treatments

Forty-two male Sprague–Dawley rats were randomly divided into seven groups each perfused with a different bupivacaine concentration (in μmol/L): B40, B60, B80, B100, B120, B140 B160, with n = 6 in each group. The Langendorff isolated heart perfusion model was used. This consisted of a balanced perfusion with K-H solution for 25 min (baseline time, or time zero, was designated as Tb), and a continuous infusion of 100 μmol/L bupivacaine (Bupivacaine hydrochloride powder, batch number 100959032, Sigmar, USA) until asystole had been induced for 3 minutes [14,15]. The hearts in the seven groups were then perfused with a K-H solution containing a 2% lipid emulsion (20% Intralipid, Huarui Pharmaceutical Co., Ltd., Suzhou, China), and 40, 60, 80, 100, 120, 140, or 160 μmol/L bupivacaine, respectively.

When an isolated rat heart recovered its ability to beat, the perfusate was continued for an additional 25 minutes (to the final time designated as Te). In our study cardiac recovery was defined as the presence of a spontaneous heartbeat accompanied by a regular heart rhythm with a RPP > 10% of the baseline value for more than 1 minute.

Outcomes measured

We compared the time from initiation of the bupivacaine infusion to asystole (designated Ts) and the time from the end of the 100 μmol/L bupivacaine infusion to cardiac recovery (designated Tr) in all groups. The following cardiac function parameters were recorded or calculated: heart rate (HR), left ventricular developed pressure (LVdevP = left ventricular systolic pressure - left ventricular end-diastolic pressure), rate-pressure product (RPP = HR * LVdevP), and the maximum rates of left ventricular pressure rise and fall ($\pm dP/dt_{max}$). The ratio of the highest RPP (RPPh) during the recovery to baseline RPP (RPPr), and the ratio of RPP at Te to baseline RPP (RPPe) were also documented.

Time of measurements

In all groups, cardiac function parameters were recorded at baseline (Tb), and at 1 (T1), 5 (T5), 10 (T10), 15 (T15), 20 (T20) and 25 (Te) minutes after cardiac recovery.

Concentration-response curve fitting

The logarithm values of bupivacaine concentration were placed along the abscissa and the corresponding RPPr were placed on the vertical axis to provide a fit for the concentration-response curve. Non-linear regression was used to analyze and verify whether the concentration-effect relationship existed.

Statistical analysis

SPSS was the statistical software used (version 14.0, Chicago, IL). Measurement data were tested for normality. Continuous variables were presented as means ± SD. Weight, Ts, Tr, RPPr, RPPe and other non-continuous data were analyzed by one-way ANOVA, and we applied the LSD test for pairwise comparison when significance was achieved. Continuous cardiac function parameters among groups were compared by repeated-measures of analysis of variance, and the Bonferroni correction was used for further multiple comparisons. Statistical significance was considered as $P < 0.05$. The relationship between bupivacaine concentration and the reversal efficacy of the 2% lipid emulsion was fitted in non-linear fashion using GraphPad Prism 5.0 software (GraphPad software, San Diego, CA).

Results

A total of forty-two rats were included in the statistical analysis, with n = 6 in each group.

Baseline values

There were no differences in baseline weight and cardiac function parameters among the seven groups in the study.

Time to asystole (Ts) and time to recovery (Tr)

All hearts developed asystole after a 100 μmol/L bupivacaine infusion. Ts did not vary among groups (Table 1). All isolated hearts in the seven groups exhibited cardiac recovery. Tr in the B40-B80 groups was shorter than those in the B120-B160 groups ($P < 0.05$, Table 1).

Cardiac function parameters

The isolated hearts in all bupivacaine groups demonstrated cardiac recovery after being infused with a 2% lipid emulsion (although the extent of recovery varied among groups).

During the recovery phase, LVdevP in the B40 group was greater than that in the B120-B160 groups ($P < 0.05$), (Figure 1).

In regard to HR, the B40-B60 groups achieved a higher HR than the B80-B160 groups ($P < 0.01$). The B80 group exceeded B120-B160 groups ($P < 0.01$), and the B100 group exceeded the B140-B160 groups ($P < 0.01$, Figure 2). Furthermore, the maximum HR in all groups was achieved within 5 minutes after cardiac recovery, which were 128 ± 19, 118 ± 25, 91 ± 15, 74 ± 9, 55 ± 9 41 ± 7 and 35 ± 9 beats/min, respectively. The B40 group had the greatest recovery rate among all groups (45%).

In regard to RPP, the B40-B60 groups exceeded the B80-B160 groups ($P < 0.05$), and the B80-B100 groups exceeded the B140-B160 groups ($P < 0.05$, Figure 3). The maximum value of RPP in all groups was achieved within 5 minutes of cardiac recovery, these were 22551 ± 3460, 21228 ± 5546, 17025 ± 2067, 13496 ± 3611, 8690 ± 1473, 6220 ± 1139, 5236 ± 1544 mmHg•beats.min^{-1}, respectively.

The -dP/dt$_{max}$ in the B60 group was greater than that in the B160 group ($P < 0.05$), while -dP/dt$_{max}$ in the B80 group was greater than in the B120-B160 groups ($P < 0.05$); +dP/dt$_{max}$ in the B40-B100 groups were greater than in the B120-B160 groups ($P < 0.05$).

RPPr in all groups recovered within 5 minutes after cardiac recovery, which were 55, 50, 43, 33, 22, 16 and 13%, respectively (Table 1). RPPr in the B40-B60 groups were greater than those in the B100-B160 groups ($P < 0.05$), while RPPr in the B80-B100 groups were greater than in the B140-B160 groups ($P < 0.05$). Otherwise, the RPPe in the seven groups were 37, 29, 18, 14, 8, 5 and 4%, respectively, and the RPPe in the B40-B100 groups were greater than in the B120-B160 groups ($P < 0.05$, Table 1).

Table 1 The results of Ts, Tr, RPPr and RPPe for all groups

Group	Ts (second)	Tr (second)	RPPr (100%)	RPPe (100%)
B40	39 ± 7	34 ± 14	55 ± 10	37 ± 10
B60	40 ± 10	44 ± 12*†	50 ± 14*	29 ± 9*
B80	40 ± 8	62 ± 11*†	43 ± 7*	18 + 3*†
B100	39 ± 9	74 ± 10*†	33 ± 8*†‡	15 ± 4*†
B120	38 ± 11	80 ± 88*†‡	22 ± 5*†‡	8 ± 3*†‡
B140	42 ± 7	81 ± 6*†‡	16 ± 3*†‡	5 ± 1*†‡
B160	38 ± 4	84 ± 10*†‡	13 ± 3*†‡	4 ± 2*†‡

All values are given as mean ± SD, n = 6 for each group. Ts = the time from initiation of bupivacaine infusion to asystole, Tr = the time since the end of bupivacaine infusion to cardiac recovery, RPPr = the ratio of the maximum rate-pressure product during recovery to baseline value, RPPe = the ratio of the rate-pressure product at the end of infusion time to baseline value.
$^{*}P < 0.05$, compared with B40 group.
$^{\dagger}P < 0.05$, compared with B60 group.
$^{\ddagger}P < 0.05$, compared with B80 group.

Concentration - response relationship

The different concentrations of bupivacaine studied and their corresponding effect (RPPr) on the isolated rats hearts after cardiac recovery were fitted in a non-linear fashion using the equation, $y = 0.065 + 0.487/[1 + 10^{-4.4*(2-x)}]$, which demonstrated a transoid S-shaped concentration response curve (Figure 4), with R2 = 0.9983. The curve demonstrated that the reversal efficacy of the 2% lipid emulsion decreased with an increasing concentration of bupivacaine. The pharmacological parameters obtained from the non-linear regression analysis were a minimum value of 6.5% and a maximum value of 55.2%, IC50 value = 102.5 μmol/L (95% CI 92.44 - 113.6), LogIC50 value = 2.0, HillSlope value = −4.4.

Discussion

In our isolated rat heart model of bupivacaine-induced asystole, a 2% lipid emulsion reversed cardiac toxicity

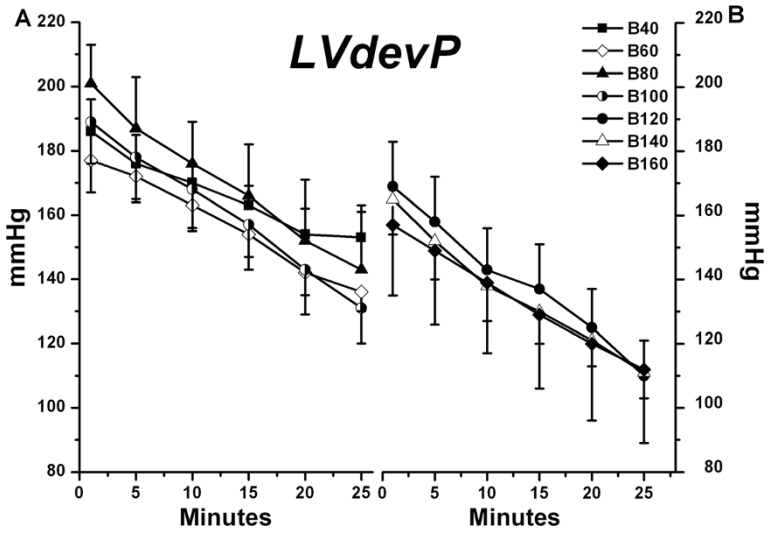

Figure 1 Left ventricular developed pressure (LVdevP) in B40 – B100 groups (A) and B120 – B160 groups (B) are shown during recovery from bupivacaine-induced asystole (mean ± SD; n = 6 for all values). LVdevp → contractility of isolated rat hearts. *P* values are as follows: B120 *vs.* B40, $P = 0.026$; B140 *vs.* B40, $P = 0.005$; B160 *vs.* B40, $P = 0.002$; B120 *vs.* B80, $P = 0.005$; B140 *vs.* B80, $P = 0.001$; B160 *vs.* B80, $P < 0.001$; B140 *vs.* B100, $P = 0.049$; B160 *vs.* B100, $P = 0.023$.

induced by 40–160 μmol/L of bupivacaine. With an increasing concentration of bupivacaine, the major cardiac function parameters including HR, RPP, RPPr, LVdevP and ± dP/dt_{max} declined in all groups. The concentration-response relationship showed a reverse S-shaped curve, with a 102.5 μmol/L IC_{50} value of bupivacaine. Cardiac recovery and function were much lower and the recovery times were much longer when the bupivacaine concentrations were above 100 μmol/L.

In our study, we used a 100 μmol/L bupivacaine infusion to induce asystole, and then added increasing concentrations of bupivacaine into the reperfusate to simulate different levels of bupivacaine-related cardiac toxicity. Liu et al. [14] reported a portion of isolated hearts in the control group that did not receive therapy with a lipid emulsion could indeed recover when the background concentration of bupivacaine was < 30 μmol/L. Previous to this, Chen et al. [13] reported that none of the isolated

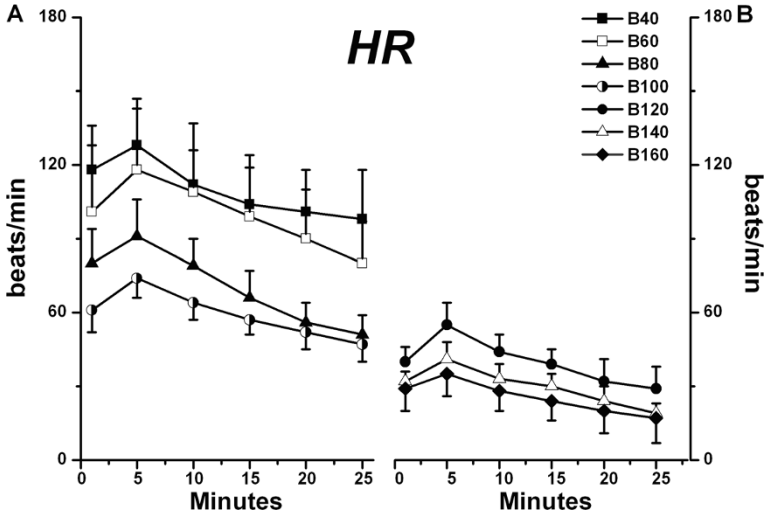

Figure 2 Heart rate (HR) in B40 – B100 groups (A) and B120 – B160 groups (B) are shown during recovery from bupivacaine-induced asystole (mean ± SD; n = 6 for all values). HR → conduction of isolated rat hearts. *P* values are as follows: B80, B100, B120, B140, B160 *vs.* B40, $P < 0.001$; B80 *vs.* B60, $P = 0.006$; B100, B120, B140, B160 *vs.* B60, $P < 0.001$; B120 *vs.* B80, $P = 0.003$; B140, B160 *vs.* B80, $P < 0.001$; B140 *vs.* B100, $P = 0.005$; B160 *vs.* B100, $P = 0.001$.

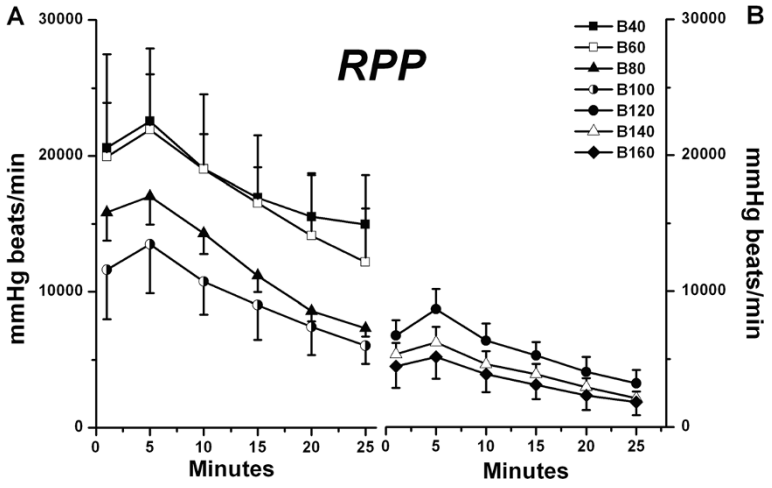

Figure 3 Rate-pressure product (RPP) in B40 – B100 groups (A) and B120 – B160 groups (B) are shown during recovery from bupivacaine-induced asystole (mean ± SD; n = 6 for all values). RPP → ventricular systolic function of isolated rat hearts. *P* values are as follows: B80 *vs.* B40, $P = 0.008$; B100, B120, B140, B160 *vs.* B40, $P = 0.000$; B100, B120, B140, B160 *vs.* B60, $P = 0.000$; B120 *vs.* B80, $P = 0.002$; B140, B160 *vs.* B80, $P < 0.001$; B140 *vs.* B100, $P = 0.014$; B160 *vs.* B100, $P = 0.004$.

hearts in the control group could be resuscitated when the background concentration of bupivacaine was ≥ 40 μmol/L. Therefore, we studied the graduated increase of bupivacaine concentrations beyond 40 μmol/L to a maximum of 160 μmol/L in order to better assess its effects. Left ventricular systolic pressure was an important method to assess the cardiac contractility, and was highly related to HR. We used RPP as a parameter of cardiac recovery because it is a good indicator of the interaction between contractility and HR; we found that RPPr is the most useful indicator of cardiac recovery.

Our work differs from previous studies in that we have focused on the reversal efficacy of a 2% fat emulsion in attenuating the cardiac toxicity induced by different concentrations of bupivacaine. We found that the reversal efficacy of a 2% fat emulsion on the isolated heart model was significantly reduced when the concentration of bupivacaine in the reperfusion solution increased, especially when it exceeded 100 μmol/L. The concentration-response relationship in this study demonstrated a typical S-shaped curve when a bupivacaine concentration of 102.5 μmol/L IC_{50} was reached. Expectations that lower and/or higher lipid concentrations may shift our bupivacaine-response curve leftward or rightward are reasonable. However, such confirmation will require further study.

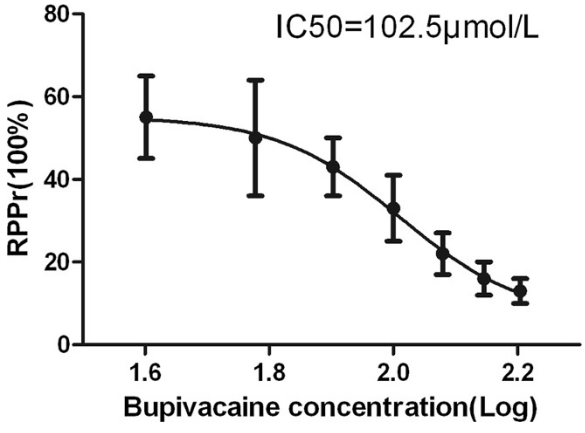

Figure 4 The concentration - response curve of the increasing concentrations of bupivacaine and the effects of 2% lipid emulsion, in reverse of bupivacaine-induced asystole in isolated rat hearts. RPPr = the ratio of the maximum rate-pressure product during recovery to baseline value.

It is of interest that Ruan et al. [15] found that a 2% fat emulsion could reduce the concentration of bupivacaine by 20-40%. Therefore, our findings may not be explained by the mechanism of "Lipid sink" alone [1,4,9]; Other mechanisms may also involved in the recovery process [16-18].

Chen et al. [13] also found that lipid administration in bupivacaine-induced asystole displayed a time-response relationship in the RPP of isolated rat hearts. We confirmed their finding that RPP decreased over the time. In our study, RPP gradually decreased after achieving its maximum at 5 minutes. RPP in groups with bupivacaine concentrations > 100 μmol/L were all less than 10% of the baseline value at the end of perfusion (25 min), which suggested that these hearts had an ineffective cardiac recovery.

The clinically recommended maximum dose of bupivaicane is 175 mg [19]. If 175 mg of bupivacaine quickly enters into the circulation of a 70 kg patient (with blood volume about 7% of body weight), the theoretical value of the blood concentration of bupivacaine will be

35.7 μg/mL (104.2 μmol/L), a concentration that approaches 102.5 μmol/L (as described above). However, if the assumption is made that the bupivacaine entering the circulation will combine with plasma proteins [20], this may make the plasma concentration of free bupivacaine much lower. We surmise that under such conditions, to achieve the lipid concentration of 2% in the circulation, a treatment dose of 7 mL/kg may be sufficient.

Our study has several limitations. Our bupivacaine-induced asystole model of isolated rat hearts used only a single factor with which to influence the model. Whereas in real clinical scenarios, cardiac arrest is often accompanied by other factors such as hypoxia, acidosis, pulmonary edema and other perturbations [21-23], thus making the pathology more complicated. Furthermore, the applicability of our findings to other species (rabbits and swine for example, let alone humans) may not be valid and requires further experimental confirmation.

Conclusion

Our study demonstrates that a 2% lipid emulsion can reverse 40–160 μmol/L concentrations of bupivacaine-induced asystole in isolated rat hearts. We have also demonstrated that there is a concentration-response relationship between the concentrations of bupivacaine and the reversal efficacy of a 2% lipid emulsion. A bupivacaine concentration of 102.5 μmol/L is the point at which the reversal efficacy of a 2% lipid emulsion will decline sharply. We encourage our colleagues to pursue further studies to better optimize the model we have proposed and any of its underlying assumptions.

Abbreviations

IC_{50}: Inhibitory concentration 50; Ts: Time to asystole; Tr: Time to recovery; HR: Heart rate; LVdevP: Left ventricular developed pressure; RPP: Rate-pressure product; $\pm dP/dt_{max}$: The maximum left ventricular pressure rise and fall rate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All those listed as authors contributed to the preparation of the manuscript. HC: Study design, animal experiment, data collection, data analysis and writing up of the first draft of the paper. YX: Study design, data analysis and editing the paper. BZ, XH, SX: Study design, animal experiment and data collection. QW, LC: Study design and data analysis. WW: Study design. TP: Editing the paper. XX: Study design, data analysis and writing up of the first draft of the paper. All authors have read and approved the final version.

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Author details

[1]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, 2 Fuxue Road, 325000 Zhejiang, China. [2]Department of Pathophysiology, Wenzhou Medical University, Wenzhou, Zhejiang, China. [3]Department of Anesthesiology, The Ohio State University Medical Center, Ohio, USA.

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