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Sodium bicarbonate reverts electrophysiologic cardiotoxicity of ropivacaine faster than lipid emulsions in a porcine model

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Abstract

Ropivacaine has been described as a safer local anaesthetic (LA); however, serious cardiotoxic accidents have been reported. Intravenous-lipid-emulsion (ILE) therapy during LA intoxication seems to act as an antidote. Sodium bicarbonate is the standard treatment for sodium channel blocker drug toxicity. We compared both antidotes on the reversion of electrophysiologic toxicity induced by ropivacaine. Ropivacaine 5 mg kg^{-1} was administered in 24 pigs, and 3 min later, the animals received ILE: 1.5 ml kg^{-1} + 0.25 ml kg^{-1} min^{-1} (ILE group); sodium bicarbonate: 2 mEq kg^{-1} + 1 mEq kg^{-1} h^{-1} ($NaHCO_3$ group); saline solution (CTL group). Electrophysiological parameters were evaluated for 30 min. The area under the curve (AUC) for the first 5 or 30 min was compared between groups. Ropivacaine induced a lengthening of the PR interval by 17% ($P = 0.0001$), His-ventricle-interval by 58% ($P = 0.001$), sinus QRS complex by 56% ($P = 0.0001$), paced QRS at 150 bpm by 257% ($P = 0.0001$), and at 120 bpm by 143% ($P = 0.0001$) in all groups. At 5 min after treatment, sinus QRS in the $NaHCO_3$ group was shorter than that in the CTL group (AUC_{QRS5}, $P = 0.003$) or ILE group (AUC_{QRS5}, $P = 0.045$). During the first minute, seven of the animals in the $NaHCO_3$ group vs. two in the ILE or 0 in the CTL group recovered more than 30% of the sinus QRS previously lengthened by ropivacaine ($P = 0.003$). Sodium bicarbonate reversed the electrophysiological toxicity of ropivacaine faster than ILE and control groups.

KEYWORDS
cardiotoxicity, lipid emulsions, ropivacaine, sodium bicarbonate

1 | BACKGROUND

Ropivacaine is a long-lasting local anaesthetic (LA) that is structurally related to bupivacaine. Furthermore, ropivacaine has clinical properties comparable to those of bupivacaine. However, compared to bupivacaine, ropivacaine has less potential for systemic toxicity. Regardless of these considerations, numerous clinical reports have shown that accidental administration of toxic doses causes severe complications, including arrhythmias, ventricular tachycardia, and cardiac arrest.[1–4]

Intravenous lipid emulsions (ILEs) have been used as salvage treatment for severe local anaesthetic systemic toxicity (LAST). Their efficacy is related to the lipophilicity of LAs, especially bupivacaine. However, the mechanisms underlying lipid therapy are not fully understood. Its efficacy has been considered to have a multimodal mechanism including a scavenging and shuttle effect by facilitating tissue redistribution of the toxin.[5,6]

The efficacy of ILEs highly depends on the degree of lipid solubility of the toxins.

Ropivacaine is less liposoluble than bupivacaine, and some experimental studies have not shown the efficacy of ILEs as an antidote for ropivacaine intoxication.[7,8] The cardiotoxicity of LAs, including ropivacaine, derives mainly from their inhibition of cardiac sodium channels.[9] Sodium bicarbonate ($NaHCO_3$) administration is one of the standard treatments for sodium channel blocker drug intoxications.[10] We have recently demonstrated that the administration of sodium bicarbonate reverses bupivacaine-induced cardiac electrophysiological alterations more rapidly than ILEs in a swine experimental model.[11]

Our main objective was to evaluate the differences in the speed of reversal of QRS interval widening affected by ropivacaine after the administration of ILE or $NaHCO_3$ and the differences between each treatment group and the control group (CTL). We hypothesized that the administration of sodium bicarbonate increases the recovery speed of electrophysiological parameters affected by ropivacaine in comparison with intralipid treatment.

2 | METHODS

2.1 | Ethics

Ethical approval for this study (Ethical committee N° PROEX-260/16) was provided by the Ethical Committee on Animal Studies of our Institution Gregorio Marañón University Hospital and the Consejería del Medio Ambiente of Madrid, Spain (Chainman Jesús Carpintero Hervás) on 22 November 2016. Experimental animals were cared for and treated according to national and local recommendations of the Spanish Ministry of Agriculture. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[12]

2.2 | Experimental animals

The experiment involved a series of male and female pigs between 35 and 55 kg (Sach miniature pigs). The animals fasted for 12 h before the experiment; however, free access to water was provided.

2.3 | Interventions

We used a previously described closed-thorax porcine experimental model that allowed reliable cardiac electrophysiological evaluation of LA agents.[11,13]

Intramuscular ketamine (20 mg kg^{-1}) was administered as premedication.[14] Subsequently, the pigs were anaesthetized with sodium thiopental sodium via the caudal auricular vein.

After intubation, anaesthesia was maintained by inhalation of sevoflurane (2.6%).[15] The tidal volume and respiratory rate were set at 6 to 8 ml kg^{-1} and 12 breaths/min, respectively. Ventilation of the animals was adjusted to maintain normocapnia. Normal saline was administered continuously (5 ml kg^{-1} h^{-1}). A computer-based digital amplifier/recording system (LABSYSTEM PRO EP Recording System; Boston Scientific Corporation, Marlborough, MA, USA) allowed uninterrupted cardiac rhythm monitoring and storage. It also permitted the recording of intracardiac signals.

Cardiac output (CO) was quantified by transpulmonary thermodilution using a 5-Fr catheter (PiCCO; Pulsion Medical Systems AG, Munich, Germany) located in the femoral artery. The contralateral femoral artery was used for arterial blood sampling and blood pressure monitoring.

An electrode catheter with a deflectable tip and another two quadripolar catheters (Marinr; Medtronic, Minneapolis, MN, USA) were introduced through the femoral veins under fluoroscopic guidance. The catheters enabled intracardiac recordings and pacing; they were located in the right atrial appendage, right ventricular apex, and across the His bundle recording areas.[11] Intracardiac electrograms were filtered between 70 and 500 Hz. A customized programmable stimulator (CS3 Cardiostimulator; A.S.P. Electronic Medical, Madrid, Spain) was used to perform the stimulation protocols.

After instrumentation, a 10-min stabilizing period was allowed and the pigs were randomly assigned to one

of three groups ($n = 8$ in each group): the lipid emulsion (ILE) group, $NaHCO_3$ group, or control (CTL) group.

Block randomization was performed (program available at: http://www.randomizer.org/), and the generated data were stored in opaque envelopes under the custody of the study coordinator (M.Z.). The investigator (I.F.) accessed the randomization code immediately before the procedure, and the animals were assigned to the study groups. The investigators were not blinded during the experiments given the typical "white colour" of lipid emulsions.

The experimental model was intended to induce relevant electrophysiological alterations without causing animal death. Previous studies have reported that this objective could be achieved with ropivacaine at a dose of 6 mg kg^{-1}; however, the administration of this dose to the first two animals caused serious cardiovascular collapse resulting in death, which indicated that the ropivacaine dose should be reduced to 5 mg kg^{-1} during the following experiments.[16] Ropivacaine was administered as a 30-s bolus through the caudal auricular vein of the animal.

Three minutes after the ropivacaine bolus, the pigs received their assigned treatment (ILE, $NaHCO_3$, or saline in CTL group). Animals in the ILE group received 1.5 ml kg^{-1} ILE (20% Intralipid; Fresenius Kavi AB, Uppsala, Sweden) during 1 min via the caudal auricular vein[17]; then, an infusion of 0.25 ml kg^{-1} min^{-1} was initiated. Animals in the $NaHCO_3$ group were administered a dose of 2 mEq kg^{-1} of $NaHCO_3$ for 1 to 2 min; then, an infusion of 1 mEq kg^{-1} h^{-1} was started.[11,18] Pigs in the control (CTL) group were administered 50 ml of saline solution with perfusion at 1 ml kg^{-1} h^{-1}. The antidote perfusions were maintained until the end of the study, ≈30 min.

To assess the stability of the experimental model, haemodynamic, electrophysiological, and biological variables of a sham control group ($n = 3$ animals) were evaluated for the same period as that used for the experimental groups.

When the procedure was completed, propofol and potassium chloride were used to euthanize the animals. A flowchart of the experimental protocol is presented in Figure 1.

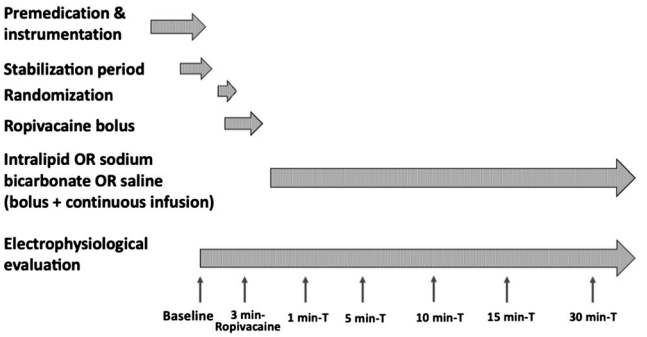

FIGURE 1 Experimental protocol. Twenty-nine animals were anaesthetized and instrumented. After the stabilization period, all pigs received 5 mg kg^{-1} of ropivacaine. Three minutes later in random fashion, the pigs were treated intravenously with either lipid emulsion, $NaHCO_3$ or saline solution. Post-treatment follow-up continued for 30 min. Haemodynamic and electrophysiologic measurements were performed at predetermined times: Baseline, 3 min after ropivacaine administration (preantidote infusion), and at 1, 5, 10, 15, and 30 min after treatment administration. The vertical arrows indicate the electrophysiological evaluation times.

2.4 | Measurements

The following variables were assessed and measured: Sinus cycle length (SCL), heart rate, PR interval, QRS duration, AH interval (from the atrial electrogram to the onset of His deflection); HV interval (from His deflection to the ventricular activation electrogram); and corrected QT interval (Bazett formula: corrected QT interval [QTc] $= QT/\sqrt{R - R}$).[11,13]

Sodium channel blockade increases at high heart rates because the time available for sodium channels to recover from the block decreases (frequency-dependent effect).[10] Therefore, throughout the study, the frequency-dependent effect of ropivacaine on slowing conduction was assessed by measuring the QRS duration after ventricular pacing trains of 10 to 12 beats with interstimulus intervals of 400 (150 bpm) or 500 (120 bpm) milliseconds ($stQRS_{400}$ or $stQRS_{500}$, respectively). The current strength was increased to 30 mA to overcome the reduced excitability caused by ropivacaine intoxication. The pacing was bipolar, with an interelectrode distance of 5 mm and a pulse width of 1 ms.

In all groups, electrophysiological and haemodynamic parameters were evaluated at the following predetermined times: baseline; 3 min after ropivacaine bolus (pretreatment); and 1, 5, 10, 15, and 30 min after the start of the assigned treatment. Sequential analyses (baseline, 15 min, and 30 min) of arterial blood gases were performed until the end of the study.

A different investigator blinded to the experimental groups analysed the electrophysiologic recordings.

2.5 | Ropivacaine quantification

Blood samples were separated and handled as previously described.[11,13] Ropivacaine concentrations in arterial plasma were quantified at the following predetermined times: Baseline and 1, 5, 15, and 30 min after ropivacaine bolus administration. The plasma concentrations of

ropivacaine were determined using liquid chromatography coupled with tandem spectrometry.[11,13]

2.6 | Statistical analysis

Statistical analysis was performed using SPSS statistical package (version 27.0; SPSS Inc., Chicago, IL, USA). Results are presented as medians (25th percentile and 75th percentile values) for non-normally distributed data using the Shapiro–Wilk test, and as means ± standard deviation for normally distributed variables. An appropriate 95% confidence interval was calculated.

Ropivacaine-induced electrophysiological and haemodynamic effects were evaluated by comparing the baseline and pretreatment infusions using the Wilcoxon paired test.

The area under the curve (AUC) (based on the trapezoidal rule) was used to represent the ropivacaine concentrations, haemodynamic, and electrophysiological parameters after administration of the ropivacaine bolus and at the conclusion of the procedure. The AUC calculations were performed by equally weighting (averaging) baseline-corrected values obtained at each data acquisition point from ropivacaine administration to the indicated time. Additionally, to assess the neutralization speed of the electrophysiological effects induced by ropivacaine, a truncated AUC analysis including parameters until 5 min after treatment was performed. Comparisons of the $NaHCO_3$ and ILE groups and comparisons of each treatment group and the control group were performed using the Mann–Whitney test. Kaplan–Meier survival curve analysis with the log-rank test was performed to evaluate the effect of sodium bicarbonate or intralipid on the time to recovery of the QRS interval to at least 30% of the QRS interval lengthened by ropivacaine. Discrete data were compared using X^2 or a Fisher's exact test when indicated. Statistical significance was set at $P < 0.05$. Due to repeated comparisons, the Holm–Bonferroni method adjusted for multiple groups was used for the sub-analyses.

2.7 | Sample size

In terms of electrophysiological toxicity, QRS interval widening is one of the major effects of ropivacaine cardiotoxicity. In previous reports, the QRS interval was severely affected by the administration of ropivacaine (from 60 to ≈100 ms).[16]

The primary outcome of this study was to evaluate the differences in the reversion speed of QRS interval widening affected by ropivacaine after the administration of ILE or $NaHCO_3$ and the differences between each treatment group and the CTL group.

Secondary outcomes included the speed of recovery of ventricular conduction parameters such as the HV interval and the rate-dependent effect on the QRS interval with both treatments.

It was assumed that a difference greater than 50% of animals that 1 min after the administration of the antidotes had recovered more than 30% of the value of the QRS interval (previously lengthened by ropivacaine) between the $NaHCO_3$ and both the CTL and ILE group, would be clinically relevant.[19] Using a two-sided test with an alpha risk of 0.05 and a beta risk of 0.2, seven animals per group were required. We enrolled eight animals per group to account for possible animal deaths.

3 | RESULTS

A total of 29 animals were studied. There were 26 animals in the experimental group and three in the sham group. As previously mentioned, two animals died after the administration of 6 mg kg^{-1} of ropivacaine, requiring replacement by two additional animals. The remaining animals in the experimental group ($n = 24$) completed the study.

3.1 | Effects on biological parameters

Biological variables are presented in Table S1. As expected, the pH, HCO_3^-, and base excess values were significantly higher in the $NaHCO_3$ group at 15 and 30 min than in the other two groups. The evolution of plasma electrolytes showed a significant increase in the sodium concentration and a significant decrease in the potassium and calcium concentrations in the $NaHCO_3$ group compared with the other two groups at 15 and 30 min.

3.2 | Plasma concentrations of ropivacaine

Ropivacaine plasma levels were comparable among groups over the course of the study (AUC, $P = 0.13$; maximum concentration, $P = 0.56$) (Figure 2).

3.3 | Effects on electrophysiological parameters

Ropivacaine administration affected most of the electrocardiographic and electrophysiological parameters assessed, but there were no differences among groups. Ropivacaine induced lengthening of the PR interval by

17 ± 15% (95% CI, 6.5 to 22; $P = 0.0001$), of the HV by 58 ± 20% (95% CI, 48 to 66) ($P = 0.001$), of the sinus QRS complex by 56 ± 24% (95% CI, 45 to 66) ($P = 0.0001$), and of the paced QRS at 150 bpm by 257 ± 109% (95% CI, 215 to 301) ($P = 0.0001$) (Figure 3) and at 120 bpm by 143 ± 94% (95% CI, 109 to183) ($P = 0.0001$) in all groups, without significant modifications in the SCL ($P = 0.63$), AH ($P = 0.71$), and QTc interval ($P = 0.35$).

The effects of the treatments are shown in Figure 4. There were differences in the recovery of the QRS complex among groups during the first 5 min after treatment. The median sinus QRS_{5min} duration was shorter in the $NaHCO_3$ group (78 ms; 95% CI, 76 to 84) compared to the CTL group (95 ms; 95% CI, 90 to 102; $AUC_{QRS5min}$, $P = 0.003$) and the ILE-group (89 ms; 95% CI, 82 to 94; $AUC_{QRS5min}$, $P = 0.045$). No differences were observed between the ILE group and CTL group regarding the $AUC_{QRS5min}$ ($P = 0.24$) (Figure 5).

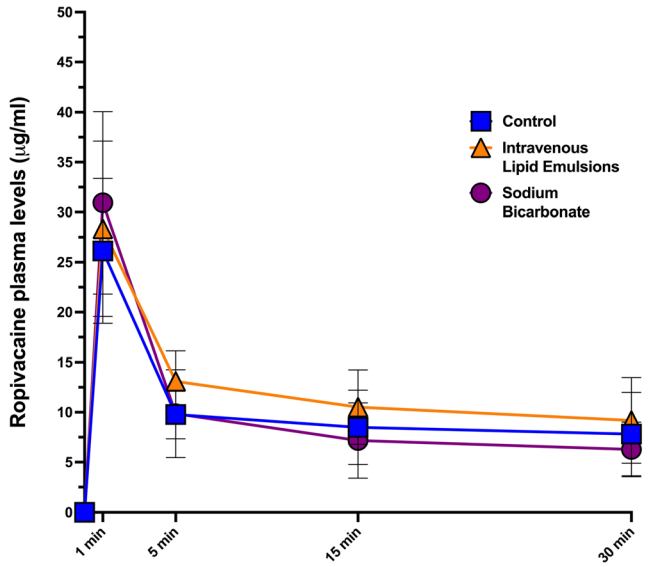

FIGURE 2 Ropivacaine plasma levels in the three study groups. No significant differences were found among groups. Data are showed as medians and interquartile values.

The analysis of the evolution of the QRS interval during 30 min yielded statistically different results between the $NaHCO_3$ group (median QRS_{30min}, 70 ms; 95% CI, 64 to 80) and CTL group (median QRS_{30min}, 72 ms; 95% CI, 70 to 80 $AUC_{QRS30min}$, $P = 0.045$); however, there were no differences between the $NaHCO_3$ group and ILE group (median QRS_{30min}, 70 ms; 95% CI, 60 to 82; $AUC_{QRS30min}$, $P = 0.39$) (Figure 3) Comparisons between the ILE group and CTL group showed no statistically significant differences in the $AUC_{QRS30min}$ ($P = 0.99$) (Figure 5).

We studied the decrease in the QRS duration after 1 min of treatment and observed that 7 (87.5%) (95% CI, 46 to 99) of the animals in the $NaHCO_3$ group had recovered ≥30% of the widening of the QRS complex lengthened by the administration of ropivacaine compared to 2 (25%) (95% CI, 3 to 65) in the ILE group and 0 (0%) (95% CI, 0 to 36) in the CTL group ($P = 0.003$).

Kaplan–Meier curves were constructed to characterize the narrowing rate of the QRS interval (recovery ≥ 30%) between the treatment groups (Figure 6). The log rank test indicated a significant difference among groups

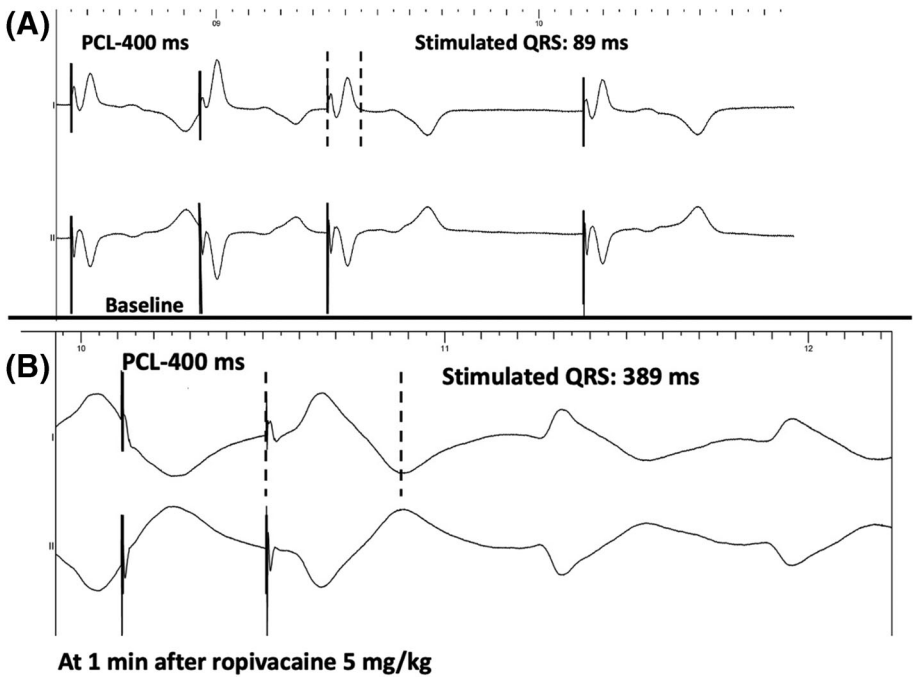

FIGURE 3 Example of the use-dependent effects of ropivacaine on ventricular conduction. The panels show ECG tracings during a train of ventricular stimulation at a PCL of 400 ms (150 bpm). The solid lines represent the ventricular stimuli. A QRS complex follows each stimulus. The QRS duration was measured in the last beat of the train of ventricular stimulation. The dashed lines represent the QRS duration in ms, measured from the pacing spike of the stimuli to the end of the QRS complex. (A) Baseline, before the administration of ropivacaine 5 mg/kg, the width of the QRS interval is 89 ms. (B) After ropivacaine 5 mg/kg, the width of the QRS interval is 389 ms.

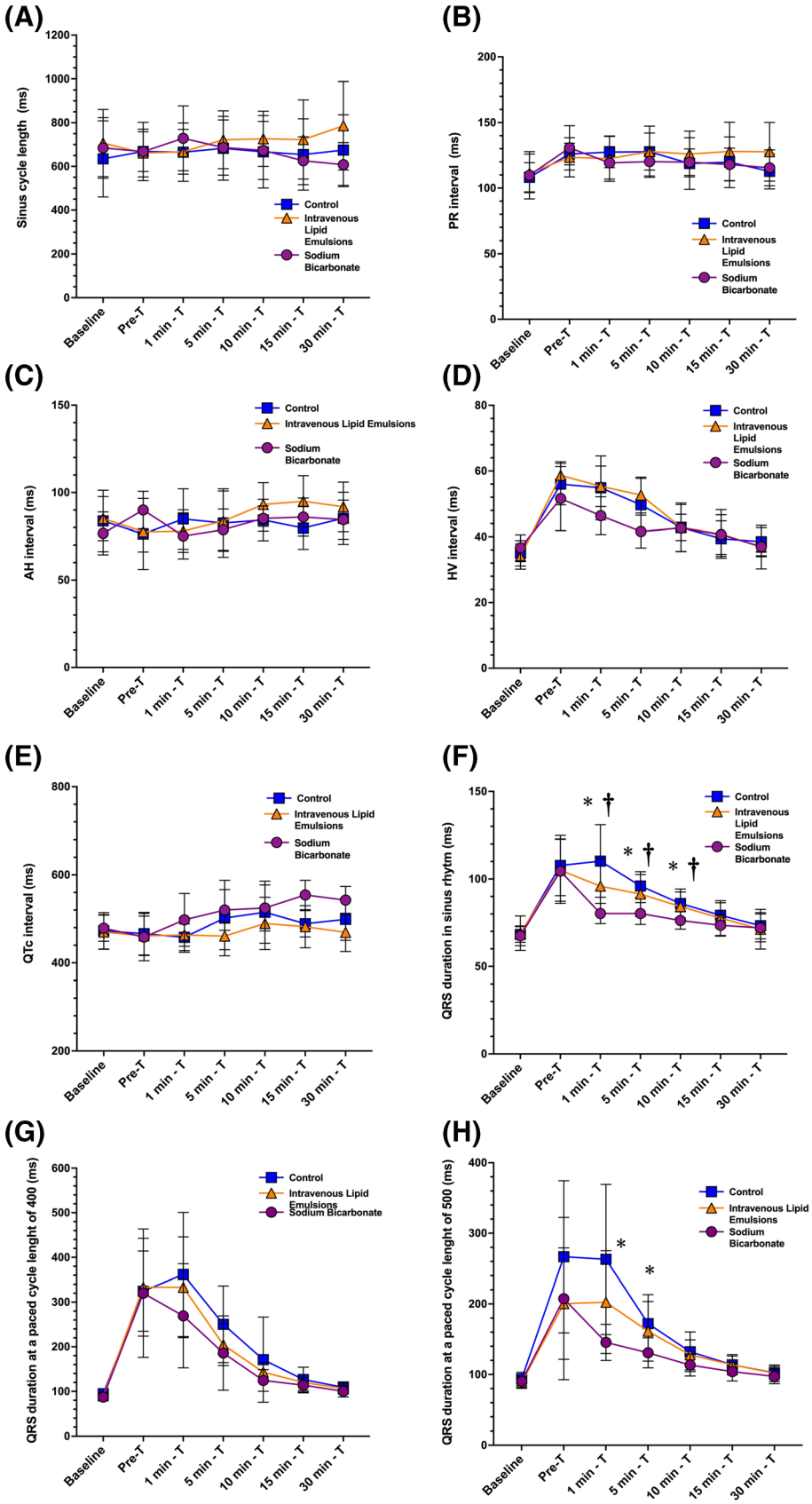

FIGURE 4 The effects of sodium bicarbonate and intravenous lipid emulsions on the electrophysiologic (SCL, PR, AH, HV, QTc, sinus QRS, stimulated QRS at a paced cycle length of 400 and 500 ms) variables 3 min after ropivacaine (pre-T), and 1, 5, 10, 15, and 30 min after administration of each treatment. Mann–Whitney test was performed at each time between the sodium bicarbonate and intravenous lipid emulsions groups and between each treatment group and the control group. Data are showed as median and interquartile values.

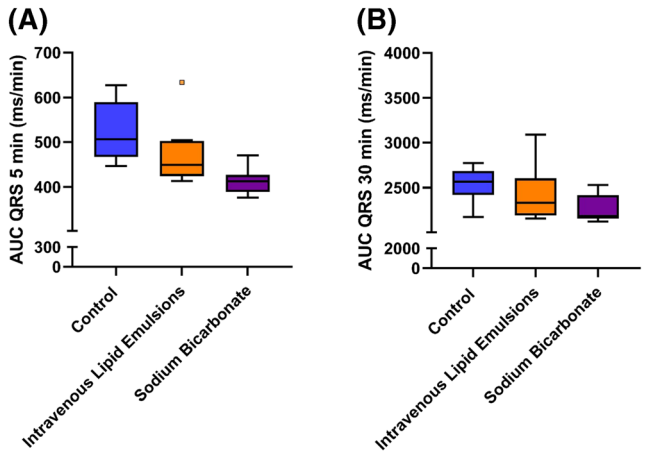

FIGURE 5 Box plots displaying the area under the curve (AUC) of the QRS interval (A) during the first 5 and (B) 30 min after treatment. The box plots were formed by the 25th and 75th percentiles, the line within the box is the median; the error bars indicate the 95% confidence intervals.

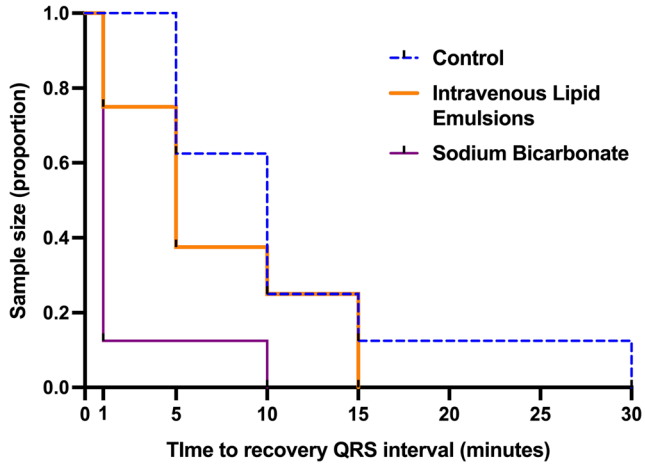

FIGURE 6 Kaplan–Meier curves analysis comparing sodium bicarbonate, intravenous lipid emulsions, and saline (control group) for the time to recovery of the QRS interval ≥30% of the widening of the QRS complex lengthened by the administration of ropivacaine. The log rank test indicated a significant difference among groups ($P = 0.021$).

($P = 0.021$). The median times to QRS recovery ≥ 30% were 1 min for the $NaHCO_3$ group (95% CI, 1to 1), 5 min for the ILE group (95% CI, 1.4 to 8.6) and 10 min for the CTL group (95% CI, 5.9 to 14) (Figure 6).

There were no significant differences among the groups regarding the changes in the SCL, PR, AH, HV, and QTc intervals after the administration of the corresponding treatment (Figure 4).

There were no statistically significant differences among groups regarding the paced QRS duration at baseline or after the ropivacaine bolus at short-paced ($StQRS_{400}$ of 150 bpm) and long-paced ($StQRS_{500}$ of 120 bpm) cycle lengths. The administration of either treatment did not affect the recovery of this parameter with short-paced cycle lengths (Figure 4). However, with long-paced cycle lengths, the median stimulated QRS duration at 5 min was shorter in the $NaHCO_3$ group (136 ms; 95% CI, 104 to 48) in comparison to the CTL group (158 ms; 95% CI, 138–200) ($AUC_{StQRS500}$, $P = 0.045$) in relation to a more rapid recovery in the $NaHCO_3$ group. However, there were no differences between the $NaHCO_3$ group and ILE group ($P = 0.24$) or between the ILE group and CTL group in the $AUC_{StQRS500}$ ($P = 0.99$) (Figure 4).

3.4 | Effect on haemodynamic parameters

Table 1 shows the haemodynamic parameters of the three groups throughout the study. The administration of ropivacaine did not significantly modify the mean blood pressure or systemic vascular resistance index, although it did induce a decrease in the cardiac index of 11% ($P = 0.035$) and a decrease in the dP/dt_{max} of 26% ($P = 0.001$). After administration of the study drugs, we observed a differential change among the three groups, with a decrease in mean blood pressure in the $NaHCO_3$ group compared to that in the ILE group (AUC_{MAP}, $P = 0.009$) and the CTL group (AUC_{MAP}, $P = 0.003$). However, the evolution in the cardiac index showed higher values in the $NaHCO_3$ group than in the ILE group, although the difference was not statistically significant (AUC, $P = 0.06$).

3.5 | Sham group

The biological and electrophysiological data of the sham group are shown in Tables S2 and S3, respectively. All parameters remained within the normal ranges throughout the study period.

4 | DISCUSSION

The main finding of the current study was that sodium bicarbonate reversed ventricular conduction disturbances altered by ropivacaine faster than spontaneous reversal (control group) and also faster than lipid infusion. In contrast, we could not demonstrate that lipid infusion resulted in faster recovery of these parameters than spontaneous reversal. Ropivacaine concentrations in our animal model were within the expected ranges after an accidental massive intravenous injection of ropivacaine.[1,4]

TABLE 1 Haemodynamic variables on the baseline, after 5 mg/kg ropivacaine ("pretreatment"), and 1, 5, 10, 15, and 30 min after treatment

Baseline		Pre-treatment	1 min-T	5 min-T	10 min-T	15 min-T	30 min-T	Comparison between groups (AUC)
Heart rate (b/min)								
C	105(75–119)	92(73–110)	91(72–111)	89(71–112)	96(69–116)	99(71–116)	94(65–114)	AUC_{30} $NaHCO_3$ vs. C, $P = 0.99$
ILE	87(74–104)	84(81–108)	92(81–103)	85(71–97)	85(72–93)	89(72–96)	80(67–94)	AUC_{30} ILE vs. C, $P = 0.99$
B	95(78–107)	91(79–102)	87(77–94)	87(74–107)	84(75–110)	94(81–110)	94(89–113)	AUC_{30} $NaHCO_3$ vs. ILE, $P = 0.99$
MAP (mmHg)								
C	94(67–109)	89(79–94)	93(85–111)	92(85–101)	98(93–113)	98(91–109)	95(90–109)	AUC_{30} $NaHCO_3$ vs. C, $P = 0.003$
ILE	86(71–98)	90(76–102)	97(77–111)	95(86–111)	98(88–117)	104(92–125)	91(85–121)	AUC_{30} ILE vs. C, $P = 0.99$
B	77(66–84)	93(78–99)	71(52–85)	85(67–91)	83(71–85)	79(73–85)	78(67–86)	AUC_{30} $NaHCO_3$ vs. ILE, $P = 0.009$
CI ($l \cdot min^{-1} \cdot m^2$)								
C	3.1(2.5–3.2)	2.7(2.4–2.9)	2.9(2.6–3.4)	3.3(2.4–3.5)	3.3(2.8–3.6)	3.3(2.7–3.9)	3.3(2.7–3.9)	AUC_{30} $NaHCO_3$ vs. C, $P = 0.69$
ILE	3.0(2.4–3.5)	2.3(2.0–3.0)	2.6(2.4–3.5)	2.4(2.3–3.3)	2.5(2.2–2.6)	2.3(2.1–2.6)	2.4(2.0–2.9)	AUC_{30} ILE vs. C, $P = 0.16$
B	2.3(2.2–3.3)	2.3(2.1–2.9)	3.0(2.8–3.7)	3.3(2.6–4.0)	4.0(2.9–4.6)	4.0(3.1–5.0)	4.2(3.4–5.1)	AUC_{30} $NaHCO_3$ vs. ILE, $P = 0.06$
dP/dt_{max} ($mmHg \cdot s^{-1}$)								
C	595(523–739)	596(496–633)	636(553–669)	731(596–835)	729(584–897)	711(573–858)	676(561–892)	AUC_{30} $NaHCO_3$ vs. C, $P = 0.19$
ILE	719(535–909)	477(418–486)	496(418–600)	502(459–689)	480(446–659)	500(420–685)	534(504–917)	AUC_{30} ILE vs. C, $P = 69$
B	509(476–592)	369(306–481)	364(295–467)	471(357–635)	514(458–726)	500(453–742)	502(452–585)	AUC_{30} $NaHCO_3$ vs. ILE, $P = 0.99$
SVRI ($dynes^{-1} \cdot cm^5 \cdot m^2$)								
C	2139(1944–2756)	2441(2029–3003)	2380(1935–3198)	2212(1807–3101)	2391(2898–2848)	2276(1773–2916)	2182(1742–2606)	AUC_{30} $NaHCO_3$ vs. C, $P = 0.11$
ILE	2242(1573–3052)	2143(1579–2765)	2320(1703–3923)	2577(2223–3196)	2800(2074–5066)	3452(2554–5492)	2951(2532–5010)	AUC_{30} ILE vs. C, $P = 0.36$
B	2326(1900–2535)	2911(1983–3599)	1973(1332–2006)	1909(1392–2470)	1589(1321–2101)	1510(1200–1899)	1395(1116–1711)	AUC_{30} $NaHCO_3$ vs. ILE, $P = 0.027$

Notes: C: control group; B: sodium bicarbonate group; ILE: intravenous lipid emulsion group; MAP: mean arterial pressure, dP/dt_{max}: peak first derivative of femoral artery pressure, SVRI: Systemic Vascular Resistance Index. 1, 5, 10, 15, and 30 min-T: 1, 5, 10, 15, and 30 min after the treatment administration. AUC: area under the curve. AUC_{30}: during the 30 min of study duration. Data are shown as medians and interquartile values.

Ropivacaine reduces the V_{max} of the action potential by blocking sodium channels, which results in ventricular and His-Purkinje conduction slowing (represented by the duration of the QRS and HV intervals).[20–22] These effects may promote the development of re-entrant arrhythmias, but they also increase the QRS duration. In clinical practice, during an episode of possible ropivacaine intoxication, the widening of the QRS interval, which is easily observed on the patient's cardioscope tracing, should alert the anaesthesiologist to potentially serious cardiotoxicity.

Lipid resuscitation is a recommended treatment for LAST.[5,6] Lipid infusion has been reported to reverse the toxicity associated with different types of drugs that coincide with their high lipid solubility.[23–25] Because ropivacaine is one of those drugs, we anticipated rapid reversal of the electrophysiological parameters in the ILE group. However, basic research support of the use of ILE treatment for ropivacaine toxicity is inconsistent.[23,26] ILE treatment minimally reduces the total and free concentrations of ropivacaine in buffer solutions.[24,27] In rats, ILE treatment was infused after a lethal dose of ropivacaine or levobupivacaine. Of note, the blood pressure started to increase within 2 min in the levobupivacaine group. However, this did not occur in the ropivacaine group until 10 min. During the first 5 min, there was no difference with the control group (saline). The authors suggested that "lipid emulsion therapy for ropivacaine toxicity is not ineffective; however, it does require a longer time to achieve its effect".[28] In perfused rat hearts, lipid administration facilitated resuscitation after bupivacaine intoxication, with no effect on the recovery of hearts intoxicated with mepivacaine or ropivacaine.[7]

All this information suggests that ILE has some benefit, albeit of small magnitude, in ropivacaine intoxication. We also observed a trend towards faster recovery from ropivacaine intoxication with ILE treatment than with saline (Figure 3); however, it did not reach statistical significance.

Sodium bicarbonate remains one of the mainstays for the treatment of sodium channel blocker intoxication.[10] From a mechanistic perspective, the administration of an antidote that reverses the blockade of sodium channels would favour recovery from the cardiac toxicity of ropivacaine because this LA potently inhibits cardiac sodium channels.[9] During a previous study, we compared the efficacy of bicarbonate and ILE treatment for recovery from bupivacaine cardiotoxicity in a porcine model. The results indicated that the recovery of electrophysiological parameters occurred quicker in the group that received bicarbonate.[11] The results regarding the reversion of ropivacaine-induced cardiotoxicity observed during the present study followed the same pattern. Remarkably, at 1 minute after bicarbonate administration, the QRS interval recovery observed during the present study was higher than that observed during the previous study of bupivacaine, probably because of the different kinetics of recovery from sodium channel blockade.[9]

The fast course of action of sodium bicarbonate can be explained by the binding capacity of ropivacaine to the sodium channel, which is diminished by sodium overload, and/or by alkalosis, which increases the dissociation rate of ropivacaine from sodium channels. The speed with which any drug reverts the toxic effects of LAs may be crucial because patients can suddenly develop cardiac arrest.

As the heart rate increases and the cardiac tissue repolarization time decreases, the frequency-dependent sodium channel block deepens with slowly dissociating LAs, including ropivacaine, manifesting as QRS prolongation. These phenomena occur with most sodium channel-blocker agents and have been observed in vitro with ropivacaine.[22] However, to the best of our knowledge, no animal model studies have investigated whether antidotes can modify the frequency-dependent effects of ropivacaine.

Consistent with our findings during sinus rhythm, the return to baseline of the paced QRS also occurred faster in the bicarbonate group. It can be assumed that the more frequency-dependent properties a LA has, the more cardiotoxic it is. Sinus tachycardia and the use of drugs, such as epinephrine, to resuscitate ropivacaine-induced cardiac intoxication could worsen ventricular conduction by enhancing the frequency-dependent depressant effects of ropivacaine, thereby facilitating the occurrence of ventricular arrhythmias by re-entry. These results indicate a rapid and potent effect of sodium bicarbonate on the reversal of the toxic electrophysiological effects of ropivacaine.

During our study, with the administration of ropivacaine, haemodynamic alterations were modest, although the cardiac index and dP/dt_{max} decreased significantly. ILEs improved haemodynamic parameters apparently due to peripheral vasoconstriction and a concomitant increase in systemic vascular resistances, which is likely to be mediated by α1-adrenergic receptor activation.[29–32] This effect has already been described in LAST, including the one induced by ropivacaine.[5,29]

Sodium bicarbonate administration transiently decreased blood pressure and systemic vascular resistance, although its infusion was associated with a concomitant increase in the cardiac index. This initial haemodynamic response to bicarbonate infusion was similar to that described during our previous study of bupivacaine. However, these results differ from those of other studies that found a similar response with both agents.[10,32,33]

To the best of our knowledge, this is the first study to evaluate the effects of treatment with two antidotes (intralipid and sodium bicarbonate) on the reversal of electrophysiological alterations associated with ropivacaine intoxication. Our study is significant because it used

a large animal model and standard doses of antidotes similar to those used in humans. Since ropivacaine is probably the most widely used LA agent, it is expected to be the most commonly involved agent in cases of accidental intoxication after regional anaesthesia techniques.[6,34]

4.1 | Limitations

A significant limitation shared by all animal models is that they do not perfectly replicate what occurs in clinical practice. However, due to the unusual and sporadic occurrence of LA overdoses, it is unlikely that randomized controlled trials will ever be performed to elucidate this topic, thus highlighting the relevance of animal models.

Some researchers have considered the pig model unsuitable for LAST research and suggested that ILE treatment is associated with hypersensitivity reactions and complement activations in pigs.[35,36] They also suggested that such hypersensitivity reactions typically increase the pulmonary arterial pressure (PAP) and decrease the systemic pressure.[36] ILE treatment for pigs has been associated with an increase in PAP without affecting oxygenation parameters.[20,36,37] Studies of critically ill patients have also shown that common doses of ILEs used for parenteral nutrition increase PAP.[38] However, the magnitude of the effect of ILE treatment on PAP at doses used for LAST (more than 50 times higher than those used for parenteral nutrition) on humans is unknown.[38] Although we did not measure the PAP directly, the fact that neither the systolic arterial pressure nor the mean arterial pressure behaved differently in the ILE group and the control group indirectly suggested that no serious increase in PAP occurred. Furthermore, there are no data regarding the impact of lipids on the PAP of other species, such as rats, rabbits, and dogs. Therefore, we do not know whether lipids have a universal effect on inducing pulmonary hypertension. During our previous study, ILE administration did not affect the cardiac electrophysiology or biological parameters of animals. Regardless of their effects on PAP, ILEs have had positive effects on pigs receiving treatment for LAST.[23,29] We evaluated the electrophysiological variables in a nonlethal model. Whether the observed effects are reproducible in a severe model, including that of cardiac arrest, is unknown.

5 | CONCLUSIONS

Sodium bicarbonate is an effective treatment that can restore established ropivacaine-induced electrophysiological alterations, including its frequency-dependent effects in an experimental porcine model. With the doses used during this study, sodium bicarbonate improved ropivacaine cardiotoxicity faster than ILE treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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