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The Effect of Amrinone on Recovery from Severe Bupivacaine Intoxication in Pigs

Leena Lindgren, M.D., Ph.D., Tarja Randell, M.D., Ph.D.,† Nobuaki Suzuki, M.D.,‡ Juha Kyttä, M.D., Ph.D.,§ Arvi Yli-Hankala, M.D., Ph.D.,† Per H. Rosenberg, M.D., Ph.D.**

Cardiovascular collapse following intravascular bupivacaine may be resistant to treatment. The effect of amrinone on recovery from bupivacaine-induced severe cardiovascular depression was evaluated in 20 pigs (13–26 kg) in a placebo-controlled randomized double-blind study. Under 0.7% isoflurane anesthesia at $F_{I_{O_2}}$ 0.21, 0.5% bupivacaine 2 $mg \cdot kg^{-1} \cdot min^{-1}$ was infused until mean arterial pressure was 40% of the baseline. Cardiac output and heart rate decreased 75% and 50% from the baseline, respectively. The total dose of bupivacaine was 17 ± 6 (SD) $mg \cdot kg^{-1}$ in the control and 19 ± 5 $mg \cdot kg^{-1}$ in the amrinone group, resulting in mean plasma concentrations of 42 ± 6 and 53 ± 19 $\mu g \cdot ml^{-1}$, respectively. A bolus of amrinone 4 $mg \cdot kg^{-1}$ (n = 10) was given immediately after cardiovascular depression, followed by an infusion of 0.6 $mg \cdot kg^{-1} \cdot min^{-1}$. The control animals received corresponding volumes of physiologic saline (n = 10). After cardiovascular depression, the lungs were ventilated with $F_{I_{O_2}}$ 1.0 without anesthetics or sympathomimetic support. Electric activity of the heart ceased in all control animals in 3.9 ± 2 min after cardiovascular depression despite atropine and external cardiac compression. All animals in the control group and 5 of 10 animals in the amrinone group were given atropine ($P < 0.01$). The animals receiving amrinone survived without cardiac compression ($P < 0.0001$). During bupivacaine infusion, all animals developed burst suppression in the electroencephalogram. At the time of cardiovascular depression, in 8 of 10 control and in 6 of 10 amrinone animals, the electroencephalogram was isoelectric. Mean arterial pressure, heart rate, cardiac output, and electroencephalogram recovered during the amrinone therapy. In conclusion, profound cardiovascular depression by bupivacaine in pigs was effectively reversed by amrinone, possibly through intracellular Ca^{2+}-release mechanisms. (Key words: Anesthetics, local: bupivacaine; Heart: cardiovascular depression. Pharmacology: amrinone.)

DEATHS after accidental intravascular injection of bupivacaine have been reported.[1,2] Bupivacaine causes profound cardiac depression[3] by cardiac sodium channel blockade[4] and by potassium channel inhibition[5] associated with serious cardiac arrhythmias[6–10] that may also be mediated by effects in the central nervous system.[11,12] It has been alleged that the cardiovascular collapse by bupivacaine is difficult to treat.[4,13]

Lynch[14] demonstrated that bupivacaine directly depresses myocardial contractility by alteration of Ca^{2+} release from the cardiac sarcoplasmic reticulum. Furthermore, Coyle and Sperelakis[15] showed that bupivacaine affects the slow Ca^{2+} channels. Amrinone, a bipyridine compound, increases cardiac output (CO) through actions on cyclic adenosine monophosphate (cAMP) and intracellular Ca^{2+}[16–18] in situations where sympathomimetics are without effect.[19]

We therefore evaluated whether amrinone would have an effect in cardiovascular collapse induced by bupivacaine in a double-blind randomized placebo-controlled study in pigs.

Materials and Methods

The study was approved by the Animal Care and Use Committee of Helsinki University Central Hospital. Twenty pigs weighing 13–26 kg were premedicated with intramuscular ketamine 250–500 mg after which ketamine 50 mg was given intravenously (iv). The trachea was intubated after pancuronium 6–8 mg iv. Anesthesia was maintained with isoflurane 1% in air ($F_{I_{O_2}}$ 0.21) during the preparations. Mechanical ventilation was accomplished with Servo 900 ventilator (Elema, Sweden). A pulmonary balloon-tip catheter (Swan-Ganz 5F, American Edwards Laboratories) was introduced into the pulmonary artery *via* the right internal jugular vein. The contralateral jugular vein was used for central venous pressure (CVP) monitoring and for drug administration. A femoral artery was cannulated for continuous arterial pressure monitoring and for blood sampling.

The electroencephalogram (EEG) was recorded from one bipolar channel using needle electrodes. The electrodes were placed in the midline of the skull at a distance of 2 cm from each other, with the neutral electrode in the middle. EEG was amplified and monitored with Datex ABM® EEG monitor (Instrumentarium Ltd., Finland, signal bandwidth 1.5–25 Hz [-3 dB]). Cardiac rhythm and the heart rate (HR) were monitored continuously using standard lead II. EEG and ECG were recorded on paper using a multichannel polygraph. End-tidal CO_2 (ET_{CO_2}) and arterial pressures were displayed on an oscilloscope

* Associate Professor of Anesthesiology.

† Staff Anesthesiologist, Department of Anesthesia, Fourth Department of Surgery.

‡ Visiting scientist, Miyazaki Medical College, Miyazaki, Japan.

§ Staff Anesthesiologist, Department of Anesthesia, First Department of Surgery.

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Address reprint requests to Dr. Lindgren: Department of Anesthesia, Fourth Department of Surgery, Kasarmikatu 11-13, 00130 Helsinki, Finland.

(Cardiocap®, Datex Ltd., Finland). Ringer's acetate solution was infused 100 ml · kg^{-1} · h^{-1} throughout the study to keep CVP greater than 3 mmHg. CO was measured in duplicate by a thermodilution method. Systemic vascular resistance (SVR) = (MAP − CVP)/CO × 80, where MAP = mean arterial pressure, was calculated.

About 90 min after ketamine induction and following a stabilization period of approximately 20 min at isoflurane 0.7% (FI_{O_2} 0.21), bupivacaine 0.5% was administered at a rate of 2 mg · kg^{-1} · min^{-1} in the central venous catheter until MAP was 40% of the baseline values (severe cardiovascular depression). Immediately thereafter, a bolus of amrinone (Inocor®, Winthrop Pharmaceuticals, New York, NY) 4 mg · kg^{-1} iv (mean weight 19.4 ± 4 kg) followed by an infusion of 0.6 mg · kg^{-1} · min^{-1} was instituted. The control group (mean weight 21 ± 3 kg) received a corresponding volume of physiologic saline stained with a vitamin solution (Vitafucin®, Leiras Ltd., Finland) to give the same yellow color as the amrinone preparation. Atropine 0.2 mg iv was given if HR was less than 60 beats · min^{-1}. External cardiac compression with effective arterial pressure curve was started if MAP remained less than 40% of the baseline values. Isoflurane was discontinued at cardiovascular depression. After cardiovascular depression, the lungs were ventilated with FI_{O_2} 1.0 without changing the minute volume of ventilation. No sympathomimetic agents were used during the experiments.

Baseline recordings were obtained at an inspired isoflurane concentration of 0.7% with FI_{O_2} 0.21. MAP, HR, CO, CVP, SVR, EEG and ET_{CO_2} were recorded at baseline, at cardiovascular depression, and 1, 2, 3, 5, 10, 15, 20, 25, 30, and 40 min after cardiovascular depression. Hemodynamic recordings in animals under resuscitation were obtained between the series of cardiac compression. Arterial blood samples for determination of plasma bupivacaine concentration, serum K^+, Na^+, and Ca^{2+} concentrations and blood gas analysis were taken at baseline, at cardiovascular depression, 5, 10, 15, and 20 min after cardiovascular depression. An aliquot of arterial blood was centrifuged, and plasma was collected and stored at −70° C. Plasma samples were assayed for total bupivacaine using a high-performance liquid chromatography method.[20] The detection limit was 0.01 μg · ml^{-1}, and the coefficient of variation of the intraassay variability was 3%. Other samples were assayed immediately after each experiment in the clinical chemistry laboratory of the hospital.

The animals were considered to have been successfully resuscitated if CO reached the baseline value and EEG as well as ECG showed a pattern similar to that before bupivacaine administration. At the end of each experiment, the animal was killed with 500 mg thiopental iv followed by air embolism.

Statistical Analysis

Fisher's exact test was used for statistical analysis of the survival of the animals and of administration of atropine during the study. The hemodynamic data between the groups were tested with two-way analysis of variance. The changes within a group were tested using analysis of variance for repeated measures. Student's unpaired *t* test was used for differences between the groups in arterial blood gases and serum electrolytes. The results are given as mean ± SD. A P value < 0.05 was considered statistically significant.

Results

All animals receiving amrinone survived, whereas the control animals developed irreversible cardiac arrest in 3.9 ± 2 min after cardiovascular depression ($P < 0.0001$).

MAP decreased significantly from the baseline in both groups as a result of bupivacaine infusion ($P < 0.001$). Two minutes after cardiovascular depression, MAP was significantly higher in the amrinone than in the control group ($P < 0.05$) when a bolus of amrinone had been given and infusion had been started. In the amrinone group, MAP increased further until 10 min after cardiovascular depression. For the rest of the study (40 min), MAP remained at approximately 60 mmHg (fig. 1).

During bupivacaine infusion, HR decreased similarly in both groups from the baseline ($P < 0.001$). At 3 min after cardiovascular depression, HR was significantly greater in the amrinone than in the control group ($P < 0.05$). At 30 min after cardiovascular depression, HR

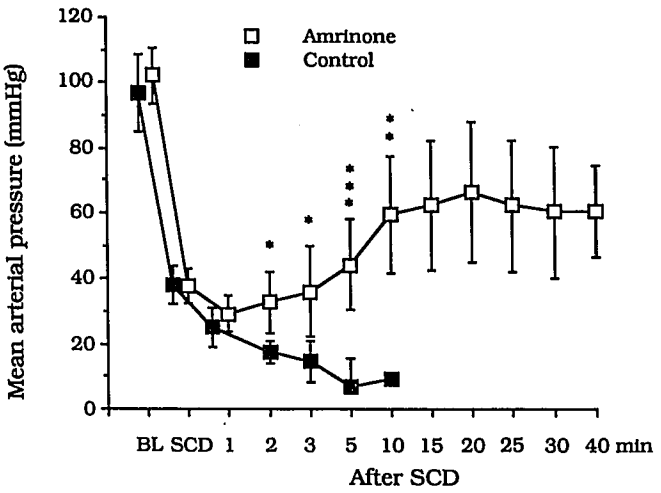

FIG. 1. Mean arterial pressure during the experiment. Mean ± SD. Ten animals in each group. BL = baseline; SCD = severe cardiovascular depression, mean arterial pressure < 40 mmHg. Data from ten animals receiving amrinone at each datapoint. At 3 min after cardiovascular depression, data from eight animals, at 5 min from four control animals; and at 10 min from one control animal. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ between the groups.

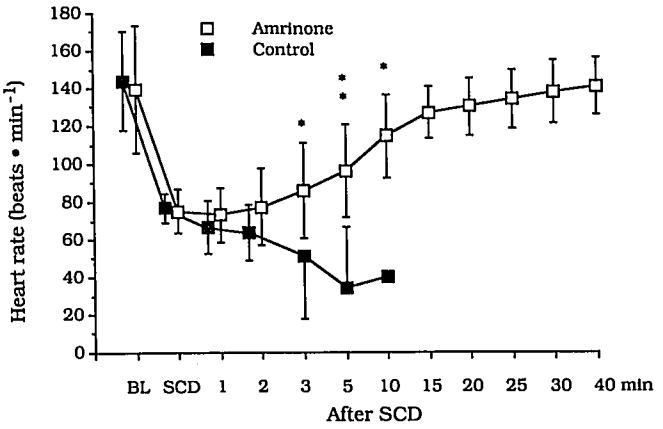

FIG. 2. Heart rate during the experiment. Symbols and abbreviations as in figure 1. *$P < 0.05$; **$P < 0.001$ between the groups.

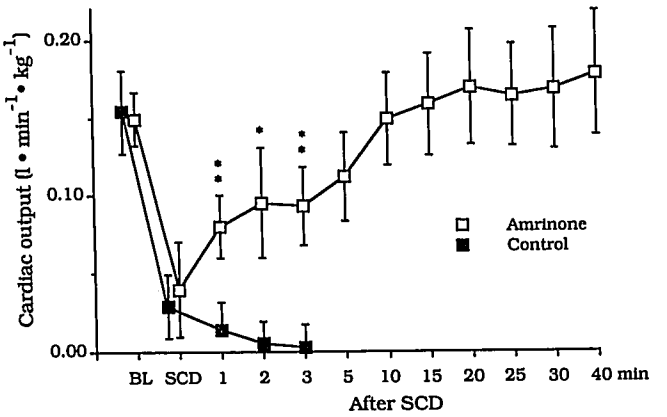

FIG. 3. Cardiac output during the experiment. Symbols and abbreviations as in figure 1. *$P < 0.01$; **$P < 0.001$ between the groups.

had reached the baseline level in the amrinone group (fig. 2). Two control animals showed multiple extrasystoles, probably by reentrant mechanism with episodes of ventricular tachycardia. In the remaining eight control animals, electromechanical dissociation or junctional bradycardia resistant to atropine was seen. Cardiac compression was continued until asystole appeared in the ECG. No defibrillation was used. All control animals received atropine (two to ten doses), whereas five pigs in the amrinone group were given atropine (one to four doses) ($P < 0.01$). In the control group, no response to atropine given at about 10-s intervals was seen. During amrinone therapy, serious cardiac arrhythmias, multiple extrasystoles, ventricular tachycardia, widening of the QRS complex, or junctional rhythms were seen in six of the ten animals 3–15 min after cardiovascular depression. All cardiac arrhythmias in the amrinone group subsided without additional pharmacologic intervention.

CO was comparable in both groups at baseline. At 1 ($P < 0.001$), 2 ($P < 0.01$), and 3 ($P < 0.001$) min after cardiovascular depression, CO was significantly greater in the amrinone than in the control group. Further increases in CO were seen during amrinone infusion, and at 15 min after cardiovascular depression, CO had reached the baseline values (fig. 3).

The baseline CVP was 4 ± 1 mmHg in both groups. During amrinone infusion, CVP remained at 3 ± 1 mmHg.

The baseline ET_{CO_2} was 4.0 ± 0.4% in the control group and 3.8 ± 0.4% in the amrinone group. At cardiovascular depression, ET_{CO_2} decreased to 2.6 ± 0.2% in the control group ($P < 0.001$) and to 2.7 ± 0.4% in the amrinone group ($P < 0.001$). During amrinone therapy, ET_{CO_2} returned to 3.5 ± 0.4% in 40 min.

Figure 4 shows that SVR was comparable at baseline and at cardiovascular depression in both study groups. One minute after cardiovascular depression, SVR was significantly greater in the control than in the amrinone group ($P < 0.05$). During amrinone infusion, SVR remained stable at a level of approximately 1,500 dyn • s • cm^{-5}.

Bupivacaine infusion caused spikes in the EEG. Silent EEG periods that were interrupted by short bursts (burst suppression pattern) were seen in all animals. Isoelectric EEG appeared before cardiovascular depression in eight of ten control and in six of ten amrinone animals. During the recovery phase, the burst suppression pattern reappeared in these amrinone animals in 25 ± 11 min after cardiovascular depression. Finally, a slow continuous EEG activity was seen 42 ± 16 min after cardiovascular depression (fig. 5).

Table 1 shows that the initial blood gas and serum electrolyte values were comparable. Five minutes after cardiovascular depression, Pa_{CO_2} had increased to near baseline level in the amrinone group (29.4 ± 3.6 mmHg) and decreased to 16.6 ± 3.5 mmHg in the control group ($P < 0.001$) (table 1).

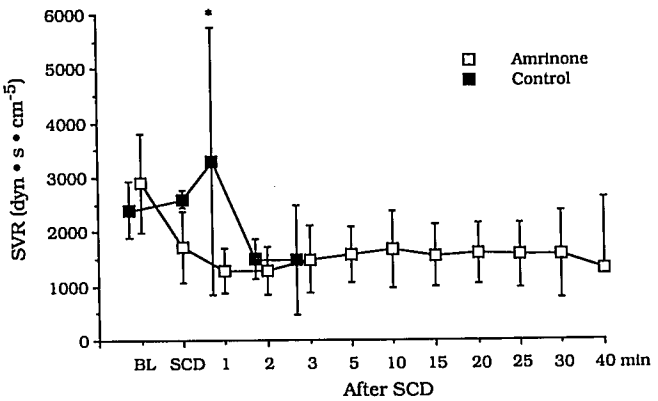

FIG. 4. Systemic vascular resistance (SVR) during the experiment. Symbols and abbreviations as in figure 1. *$P < 0.05$ between the groups.

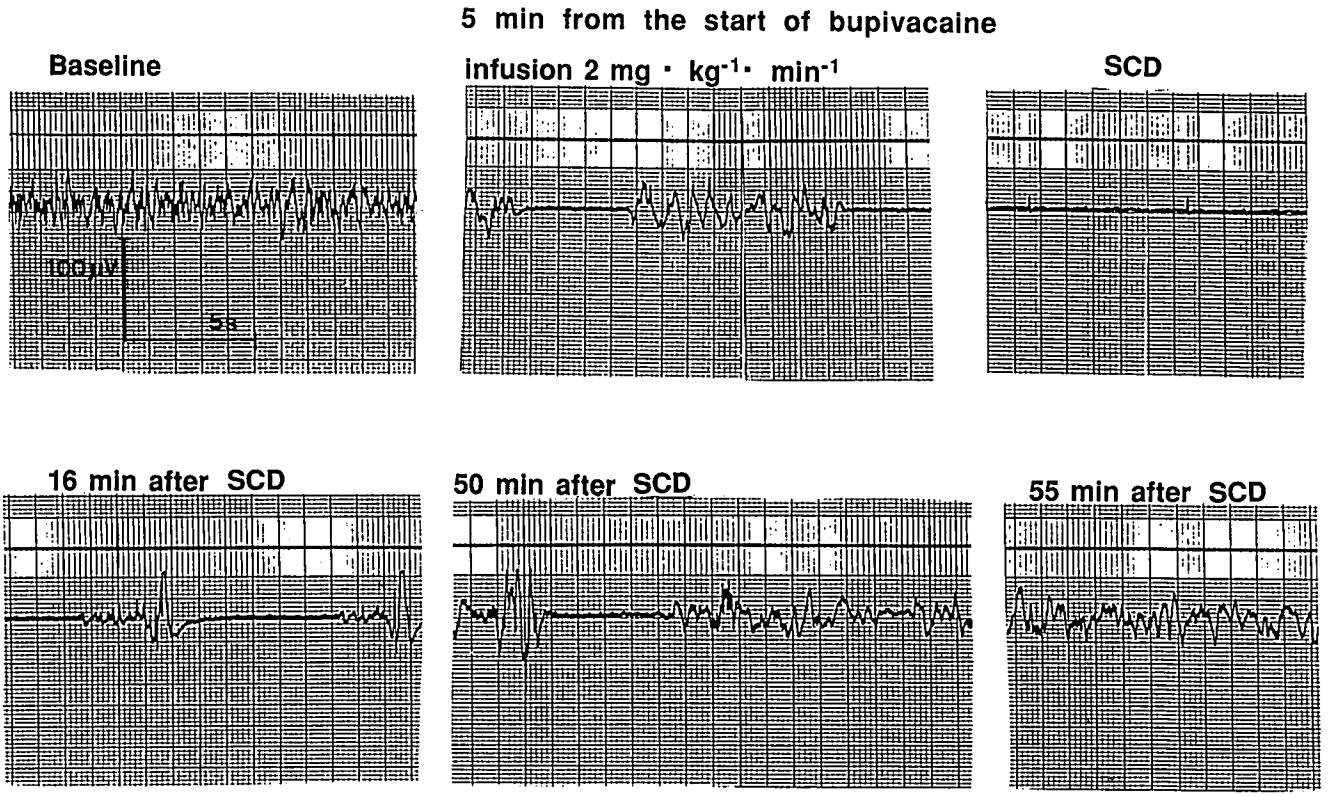

FIG. 5. EEG registration in a 22.3-kg pig. Bupivacaine was given 425 mg in 9 min. Baseline: continuous EEG activity during isoflurane anesthesia at FI_{O_2} 0.21. During bupivacaine infusion (5 min): burst suppression pattern. SCD = severe cardiovascular depression, MAP < 40 mmHg. EEG isoelectric. Amrinone 4 mg · kg^{-1} followed by an infusion of 0.6 mg · kg^{-1} · min^{-1} started. Sixteen minutes after SCD: burst suppression pattern reappeared. Fifty minutes after SCD: burst suppression turned to slow continuous EEG. Fifty-five minutes after SCD: continuous slow EEG activity.

The total dose of bupivacaine to produce severe cardiovascular depression was 16.6 ± 2 mg · kg^{-1} in the control and 19 ± 5 mg · kg^{-1} in the amrinone group. Plasma bupivacaine concentrations at cardiovascular depression were 42.5 ± 5.6 μg · ml^{-1} (2.06 ± 0.3 μg · ml^{-1} kg^{-1}) in the control and 52.8 ± 19 μg · ml^{-1} (2.75 ± 0.9 μg · ml^{-1} kg^{-1}) in the amrinone group (difference not significant). Five minutes after cardiovascular depression, there was a significant decrease in the plasma bupivacaine concentrations in both groups ($P < 0.001$) (table 2).

Discussion

This study demonstrates that severe bupivacaine-induced cardiovascular depression can be reversed by amrinone. All control animals died with bradycardia that was resistant to atropine and subsequent cardiac arrest that did not respond to cardiac compression. All animals receiving amrinone survived without cardiac compression.

The vast majority of patients in whom bupivacaine cardiotoxicity has been demonstrated have been those receiving regional anesthesia while awake and those in whom bupivacaine has been accidentally injected.[1] Isoflurane is a cardiodepressant,[21] and its administration (0.7%) during bupivacaine infusion until severe cardiovascular depression may have affected our results to some extent. The increased cardiodepression by isoflurane was not very great, however: the toxic doses of bupivacaine (mg · kg^{-1}) in the pigs were in the same range as those reported in other experimental animals.[10,22] In our study, the animals were treated with moderate hyperventilation and hyperoxia to exclude acidosis and hypoxia, which may increase the toxicity of bupivacaine.[23,24] The dose of amrinone was chosen based on the study by Raner *et al.*,[25] who demonstrated in cats that with a half of our dose, a significant increase in intestinal and renal circulation was achieved. Edelson *et al.*[26] demonstrated that in patients with congestive cardiac failure, cardiac index increased significantly after an amrinone dose of 3.5 mg · kg^{-1}.

With an infusion of bupivacaine comparable to that used in earlier experimental studies,[27] a significant decrease in MAP and CO was obtained in our pigs, accompanied by simultaneous decreases in ET_{CO_2} and Pa_{CO_2}. The amrinone bolus of 4 mg · kg^{-1} followed by infusion caused a significant increase in MAP and CO in 1 min. In the

TABLE 1. Blood Gases and Serum Electrolytes at Baseline with Mechanical Ventilation at FI_{O_2} 0.21 and during the Experiment at FI_{O_2} 1.0

			After SCD			
	Baseline	SCD	5 min	10 min	15 min	20 min
*p*H						
Control	7.57 ± 0.05	7.66 ± 0.04	7.73 ± 0.09*	—	—	—
Amrinone	7.59 ± 0.05	7.63 ± 0.08	7.55 ± 0.05	7.55 ± 0.04	7.56 ± 0.03	7.55 ± 0.03
Pa_{CO_2} (mmHg)						
Control	30.1 ± 3.7	21.95 ± 2.5	16.63 ± 3.5*	—	—	—
Amrinone	30.2 ± 3.7	22.90 ± 3.1	29.40 ± 3.6	30.6 ± 3.0	30.2 ± 3.0	30.6 ± 2.2
Pa_{O_2} (mmHg)						
Control	116 ± 9.7	187.4 ± 51	409 ± 112	—	—	—
Amrinone	127 ± 12.7	200.7 ± 66	483 ± 45	498 ± 60	488 ± 67	471 ± 60
BE (mM)						
Control	6.1 ± 2.7	5.2 ± 2.7	3.8 ± 2.3	—	—	—
Amrinone	6.9 ± 1.2	4.2 ± 2.7	3.9 ± 1.4	4.3 ± 1.5	4.6 ± 1.6	4.6 ± 1.7
K^+ (mM)						
Control	3.7 ± 0.2	3.6 ± 0.3	4.1 ± 0.4	—	—	—
Amrinone	3.7 ± 0.3	3.4 ± 0.4	3.4 ± 0.3	3.4 ± 0.4	3.4 ± 0.4	3.4 ± 0.4
Na^+ (mM)						
Control	136 ± 1	136 ± 1	135 ± 2	—	—	—
Amrinone	136 ± 2	136 ± 3	137 ± 2	136 ± 3	136 ± 3	136 ± 2
Ca^{2+} (mM)						
Control	1.29 ± 0.1	1.26 ± 0.1	1.32 ± 0.1	—	—	—
Amrinone	1.31 ± 0.1	1.30 ± 0.1	1.28 ± 0.8	1.28 ± 0.07	1.25 ± 0.06	1.24 ± 0.05

Values are mean ± SD; n = 10 for each data point. At 5 min, six of ten control animals in asystole and two under cardiac compression; at 10 min, all control animals in asystole. SCD = severe cardiovascular depression = mean arterial pressure 40% from the baseline.
* $P < 0.001$ between the study groups.

control animals, further decreases in MAP and CO were seen. Bupivacaine has been shown to block cardiac sodium channels in a "fast-in slow-out" fashion[4] and also to depress myocardial contractility by alteration of Ca^{2+} release from cardiac sarcoplasmic reticulum.[14–15] The reported poor success in resuscitation from bupivacaine cardiac toxicity[1,28,29] may be due to sustained sodium channel blockade. In animal studies treatment of bupivacaine cardiotoxicity has been attempted using bretylium or lidocaine[22] or amiodarone[28] with varying results. Our amrinone-treated animals, with similar bupivacaine plasma concentrations as the control animals, recovered without cardiac compression. This may be due to the beneficial cardiac effect of amrinone, which has been shown to act independently of β_1-adrenergic receptors.[19] Studies *in vitro* indicate that the drug probably inhibits the phosphodiesterase fraction III of cAMP in heart muscle to produce its positive inotropic and chronotropic effect.[30,31] Inhibition of phosphodiesterase fraction III results in an increase in intracellular cAMP, which, by activating various protein kinases, facilitates slow-channel Ca^{2+} entry into the myocardial cells.[32–34] More than one mechanism may be involved, however.[35] Since the cardiac sodium channels in our pigs were blocked,[4] the survival of our animals can probably be explained by the interaction of amrinone with cAMP and intracellular Ca^{2+}; Ca^{2+} channels are activated by amrinone, leading to greater ionic influx and maintenance of conduction by Ca^{2+} currents, which compensates in part for the blockade of sodium channels. Also, there is evidence that increased cAMP enhances sodium currents *via* phosphorylation of myosin light chain kinase.[36] Consequently, the increase in cAMP may cause improved conduction, not only permitting more Ca^{2+} channels to maintain conduction but probably

TABLE 2. Plasma Bupivacaine Concentration during the Experiment

		After SCD					
	SCD	5 min	10 min	15 min	20 min	25 min	30 min
Control	42.5 ± 5.6	16.8 ± 2.5*†	—	—	—	—	—
Amrinone	52.8 ± 19	16.4 ± 5.7*	11.9 ± 6.6	13.9 ± 6	12.2 ± 4.1	12.7 ± 4.1	12.4 ± 4.2

Values are mircograms per milliliter, mean ± SD; n = 10 for each datapoint.
SCD = severe cardiovascular depression (mean arterial pressure 40% from the baseline).
* $P < 0.001$ compared to the value at SCD.
† Six of ten control animals in asystole and two under cardiac compression; at 10 min all control animals in asystole.

also by increasing the number of functional sodium channels.

In the animals receiving amrinone, CO increased above the baseline values but MAP remained at a level about 60% of the baseline. SVR and CVP remained moderately low during the recovery phase. This may be due to the fact that amrinone dilates pulmonary and systemic vascular beds.[37,38] Therefore, adequate intravascular volume filling is an important supplement in the amrinone therapy.

Serious cardiac arrhythmias were seen during the amrinone therapy in 6 of 10 animals when CO was increasing. These arrhythmias, however, subsided spontaneously when CO had reached the baseline level. It is not obvious that amrinone caused arrhythmias after those induced by bupivacaine in our study, since similar arrhythmias were seen in the control group in the period between severe cardiovascular depression and cardiac arrest. Also, arrhythmias during the amrinone treatment phase were similar to those described in bupivacaine intoxication by others.[6–8,28] At seriously depressed CO states, cardiac arrhythmias can be intractable.[39] Therefore, cardiac arrhythmias in our study may have subsided due to an increase in CO and myocardial perfusion by amrinone.

In earlier reports on successful resuscitation from bupivacaine intoxication, open-chest cardiac massage[27] or cardiopulmonary bypass[40] have been used. In bupivacaine intoxication, a crucial question is how an adequate organ perfusion can be maintained when the cardiac sodium channels are blocked, CO is seriously depressed, and arrhythmias persist. Based on the present data, amrinone is a promising alternative to the above-mentioned drastic therapies.[27,40]

Burst suppression is an EEG pattern frequently seen in toxic[41] or ischemic states[42] and during deep anesthesia.[43] It is a sign of deep unconsciousness. Although we discontinued isoflurane at cardiovascular depression, the electrocortical silence or burst suppression pattern in EEG showed unconsciousness of the animals. A large dose of bupivacaine reaching the brain causes unconsciousness.[44] In our animals, EEG recovered in 42 ± 16 min after a toxic dose of bupivacaine, indicating a recovery also of the central nervous system.

In conclusion, amrinone may provide a superior alternative to presently recommended pharmacologic therapy in cases of severe bupivacaine-induced toxicity. The mechanism of action of amrinone is probably mediated through facilitation of slow-channel Ca^{2+} entry into the myocardial cells. The clinical impact of the use of amrinone in this situation deserves further evaluation.

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