

Hemodynamic and Cardiac Electrophysiologic Effects of Lidocaine-Bupivacaine Mixture in Anesthetized and Ventilated Piglets

Jean-Yves Lefrant, M.D., Ph.D.,* Laurent Muller, M.D., M.Sc.,* Jean E. de La Coussaye, M.D., Ph.D.,† Laurent Lalourcey, M.D., M.Sc.,‡ Jacques Ripart, M.D., Ph.D.,† Pascale A. Peray, M.D., Ph.D.,§ Xavier Mazoit, M.D., Ph.D.,|| Michel Dauzat, M.D., Ph.D.,# Antoine Sassine, M.D.,** Jean-Jacques Eledjam, M.D.†

Background: The sensory blockade induced by a lidocaine-bupivacaine mixture combines the faster onset of lidocaine and the longer duration of bupivacaine. The current study compared the effects of large doses lidocaine (16 mg/kg), bupivacaine (4 mg/kg), and a mixture of 16 mg/kg lidocaine-4 mg/kg bupivacaine on hemodynamic and cardiac electrophysiologic parameters in anesthetized and ventilated piglets.

Methods: After carotid artery cannulation, a double micromanometer measured mean aortic pressure, left ventricular end diastolic pressure, and the first derivative of left ventricular pressure. Electrocardiogram recording and a bipolar electrode catheter measured RR, PQ, QRS, QT_c, JT_c, AH, and HV intervals. Lidocaine, bupivacaine, or the mixture was administered intravenously over 30 s, and studied parameters were measured throughout 30 min.

Results: Mean aortic pressure decreased in all groups ($P < 0.05$). The first derivative of left ventricular pressure was decreased in all groups ($P < 0.001$) but to a greater extent with the mixture compared with lidocaine ($P < 0.04$). RR, QT_c, and JT_c intervals were similarly increased in all groups ($P < 0.05$). In all groups, PQ, AH, HV, and QRS intervals were widened ($P < 0.001$). The lengthening of PQ was greater with bupivacaine ($P < 0.02$). The lengthening of AH was greater and delayed with bupivacaine compared with lidocaine ($P < 0.03$). The lengthening of HV and the widening of QRS were greater and delayed with bupivacaine ($P < 0.01$). The widening of QRS was greater with the mixture than with lidocaine ($P < 0.01$).

Conclusions: The alterations of ventricular conduction parameters are greater with 4 mg/kg bupivacaine than with a mixture of 16 mg/kg lidocaine-4 mg/kg bupivacaine, whereas the hemodynamic parameters are similarly altered.

LIDOCAINE and bupivacaine are widely used in regional anesthesia. Bupivacaine provides a good sensory anesthesia with a long duration of action, but the onset of its sensory blockade is longer than with lidocaine.¹ More-

over, cardiac arrests were reported after accidental intravenous injection of bupivacaine.² A lidocaine-bupivacaine mixture is used to combine the faster onset of sensory blockade of lidocaine and the more profound and longer duration of sensitive blockade of bupivacaine.³ Previous studies demonstrated that the action duration of the mixture tends to be similar than that obtained with bupivacaine alone.^{3,4} However, the toxicity of the lidocaine-bupivacaine was not fully investigated, and no *in vivo* study focused on the cardiotoxicity of the mixture. A mixture could potentially add the toxicity of each component. Using a single sucrose gap technique to stimulate guinea pig papillary muscle, Clarkson and Hondeghem⁵ demonstrated that lidocaine could reduce the inhibition of maximum upstroke velocity of the fast action potential induced by bupivacaine. In anesthetized dogs, we demonstrated that 16 mg/kg intravenous lidocaine induced a marked decrease in mean aortic pressure (MAoP) and in the peak of the first derivative of left ventricular pressure (LVdP/dt_{max}), and an increase in left ventricular end-diastolic pressure (LVEDP).⁶ In the same study, 4 mg/kg intravenous bupivacaine similarly altered LVdP/dt_{max} and LVEDP but dramatically impaired ventricular electrophysiologic variables (QRS interval widening and His ventricle interval lengthening).⁶ Therefore, the aim of the present study was to compare the cardiotoxicity of large doses of lidocaine (16 mg/kg), bupivacaine (4 mg/kg), and a mixture of 16 mg/kg lidocaine-4 mg/kg bupivacaine in an *in vivo* model of anesthetized and ventilated piglets.

Methods

The principles for the care and treatment of experimental animals complied with the national guidelines of the French Ministry of Agriculture (Paris, France).

Animals Preparation

Piglets, weighing 10-25 kg, were intramuscularly premedicated with ketamine (250 mg), midazolam (15 mg), and atropine (1 mg). Within 15 min, an ear vein was catheterized. Piglets were anesthetized with intravenous sodium thiopental (10 mg/kg). Tracheostomy was quickly performed. The trachea was intubated and the lungs were mechanically ventilated with room air (tidal volume = 10 ml/kg; respiratory rate = 15 breaths/min; Bennett MA 1-B, Puritan Bennett, Los Angeles, CA). Body

* Staff Anesthesiologist, † Professor of Anesthesiology, Division of Anesthesiology, Critical Care, Pain, and Emergency, ‡ Staff Anesthesiologist, Department of Anesthesiology, Clinique Val d'Aurel Paul Lamarque, § Associate Professor in Biostatistics, Department of Epidemiology and Biostatistics, University-Hospital of Nîmes, || Staff Anesthesiologist, Laboratory of Anesthesiology, UPRES EA 392, Faculté de Médecine, Université Paris Sud, # Professor of Physiology, ** Senior Research Officer (retired), Laboratory of Anesthesiology and Cardiovascular Physiology, UPRES EA 2992, Medical School of Montpellier-Nîmes.

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Address reprint requests to Dr. Coussaye: Département d'Urgences-Réanimation, CHU Nîmes, 5 rue Hoche, 30029 Nîmes cedex 4, France. Address electronic mail to: jean.emmanuel.delacoussaye@chu-nimes.fr. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

temperature was maintained at $38 \pm 0.5^\circ\text{C}$ with a rewarming humidifier device. Piglets were paralyzed with intravenous vecuronium bromide (0.1 mg/kg) as required, and anesthesia was maintained with an intravenous infusion of sodium thiopental ($15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). During the preparation and experiment (90–120 min), 500–750 ml of 0.9% sodium chloride were infused. In a previous study, we demonstrated that cardiac electrophysiologic, hemodynamic, and biologic parameters were stable throughout a 2-h period.⁷

The instrumentation of piglets was performed as previously described.⁷ Electrocardiographic recordings were taken from standard lead II. The left carotid artery was cannulated with a 6-French double high-fidelity micro-manometer (Millar Instruments, Houston, TX) that was advanced into the left ventricle to measure left ventricular and aortic pressures. A 6-French bipolar electrode catheter (USCI; C.R. Bard, Inc., Billerica, MA) was introduced *via* the femoral vein into the right ventricle to record the His bundle electrical activity.⁸ Another 6-French bipolar electrode catheter was introduced *via* the left jugular vein into the right atria for atrial pacing. A 5-French teflon catheter (Plastimed, Saint-Leu La Forêt, France) was inserted *via* the femoral artery into the descending aorta for arterial blood samples. After this preparation, a 15-min stability period was observed.

Experimental Protocol

A randomized study had to be performed. To avoid killing too many piglets unnecessarily, we used the data of seven piglets involved in the bupivacaine group of a recent study⁷ and added two piglets specifically for the current study to obtain nine piglets in the bupivacaine group. The previous and the current studies were achieved in a 5-month period. Because the piglets of the bupivacaine group were partly involved in a previous study, no randomization was used. Seven piglets were involved in mixture group and seven other piglets in the lidocaine group. This point of protocol was approved after consulting the methodologist (P. P.).

Lidocaine (16 mg/kg), bupivacaine (4 mg/kg), or a mixture of 16 mg/kg lidocaine–4 mg/kg bupivacaine was administered *via* the peripheral ear vein over a 30-s period. Hemodynamic, electrophysiologic, and biologic parameters were measured for a 30-min period.

Measured Parameters

The following electrophysiologic parameters were measured (in milliseconds)^{7,9}: cardiac cycle length (RR), PQ interval measured from the onset of the P wave to the Q wave of the QRS complex, atria His interval (AH) measured from the onset of the atrial depolarization to the His bundle electrogram of the endocavitary lead, His ventricle interval (HV) measured from the His bundle electrogram of the endocavitary lead to the Q wave of electrocardiogram lead II, QRS duration, QT interval, QT interval corrected by

Table 1. Animal Weight, Preparation Time, and Total Volume of Infusion

	B (n = 8)	L (n = 7)	M (n = 7)
Weight, kg	18 ± 5	13 ± 2	11 ± 2
Preparation time, min	104 ± 23	80 ± 15	93 ± 30
Total volume of infusion, ml	788 ± 88	714 ± 128	664 ± 215

Data are shown as mean ± SD. No statistical difference.

B = bupivacaine group; L = lidocaine group; M = mixture of bupivacaine and lidocaine group.

heart rate [$\text{QTc} = \text{QT} \cdot (\text{RR})^{-0.5}$, Bazett formula], and JTc interval [$\text{JTc} = (\text{QT} - \text{QRS}) \cdot (\text{RR})^{-0.5}$]. The following hemodynamic variables were measured: MAoP (millimeters of mercury), LVEDP (millimeters of mercury), and $\text{LVdp/dt}_{\text{max}}$ (millimeters of mercury per second) derived with a Gould differentiator. All of these variables were simultaneously recorded on an ES 1000 polygraph (100 mm/s; Gould Inc., Oxnard, CA). Moreover, because local anesthetics slow the ventricular conduction in a dose- and frequency-dependent manner,¹⁰ the ventricular conduction variables represented by HV interval (stHV) and QRS duration (stQRS) were measured after 10 atrial stimuli given at pacing cycle length 20% greater than the spontaneous sinus cycle length measured at baseline (Stimulator CSO; Savita, Paris, France).

Blood samples were obtained to measure the following serum concentrations: sodium (Na^+ ; millimolars), potas-

Table 2. Biologic Parameters at T_0 and T_{30}

	B (n = 8)	L (n = 7)	M (n = 7)
$\text{Na}^+ T_0$, mM	140 ± 4	139 ± 2	138 ± 1
$\text{Na}^+ T_{30}$, mM	139 ± 4	139 ± 2	140 ± 1*†
$\text{K}^+ T_0$, mM	3.1 ± 0.2	3.0 ± 0.3	2.9 ± 0.6
$\text{K}^+ T_{30}$, mM	3.4 ± 0.4	3.3 ± 0.4	3.1 ± 0.5
$\text{Ca}^{2+} T_0$, mM	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
$\text{Ca}^{2+} T_{30}$, mM	1.3 ± 0.1	1.4 ± 0.1	1.3 ± 0.1
Protein T_0 , g/l	43 ± 6	43 ± 6	46 ± 9
Protein T_{30} , g/l	45 ± 7	43 ± 4	42 ± 4
Albumin T_0 , g/l	25 ± 6	22 ± 2	23 ± 2
Albumin T_{30} , g/l	23 ± 4	22 ± 2	22 ± 2
pH T_0	7.52 ± 0.11	7.45 ± 0.05	7.54 ± 0.06
pH T_{30}	7.50 ± 0.12	7.48 ± 0.08	7.51 ± 0.10
$\text{Pao}_2 T_0$, mmHg	107 ± 32	114 ± 26	139 ± 23
$\text{Pao}_2 T_{30}$, mmHg	111 ± 42	117 ± 27	169 ± 36
$\text{Paco}_2 T_0$, mmHg	32 ± 11	34 ± 4	26 ± 3
$\text{Paco}_2 T_{30}$, mmHg	32 ± 11	32 ± 5	23 ± 3
$\text{CO}_2 T_0$, mM	26 ± 4	25 ± 2	22 ± 3
$\text{CO}_2 T_{30}$, mM	25 ± 5	25 ± 2	20 ± 4
$\text{Sao}_2 T_0$, %	98 ± 3	98 ± 1	99 ± 1
$\text{Sao}_2 T_{30}$, %	97 ± 4	98 ± 1	99 ± 1
Lactate T_0 , mM	2.8 ± 1.3	2.3 ± 1.1	4.2 ± 2.4
Lactate T_{30} , mM	3.4 ± 1.7	2.2 ± 1.4	5.3 ± 4.8

Data are shown as mean ± SD.

* $P < 0.01$ between B and M; † $P < 0.05$ between L and M.

B = bupivacaine group; L = lidocaine group; M = mixture of bupivacaine and lidocaine group; T_0 = 0 min after administration of local anesthetic; T_{30} = 30 min after administration of local anesthetic.

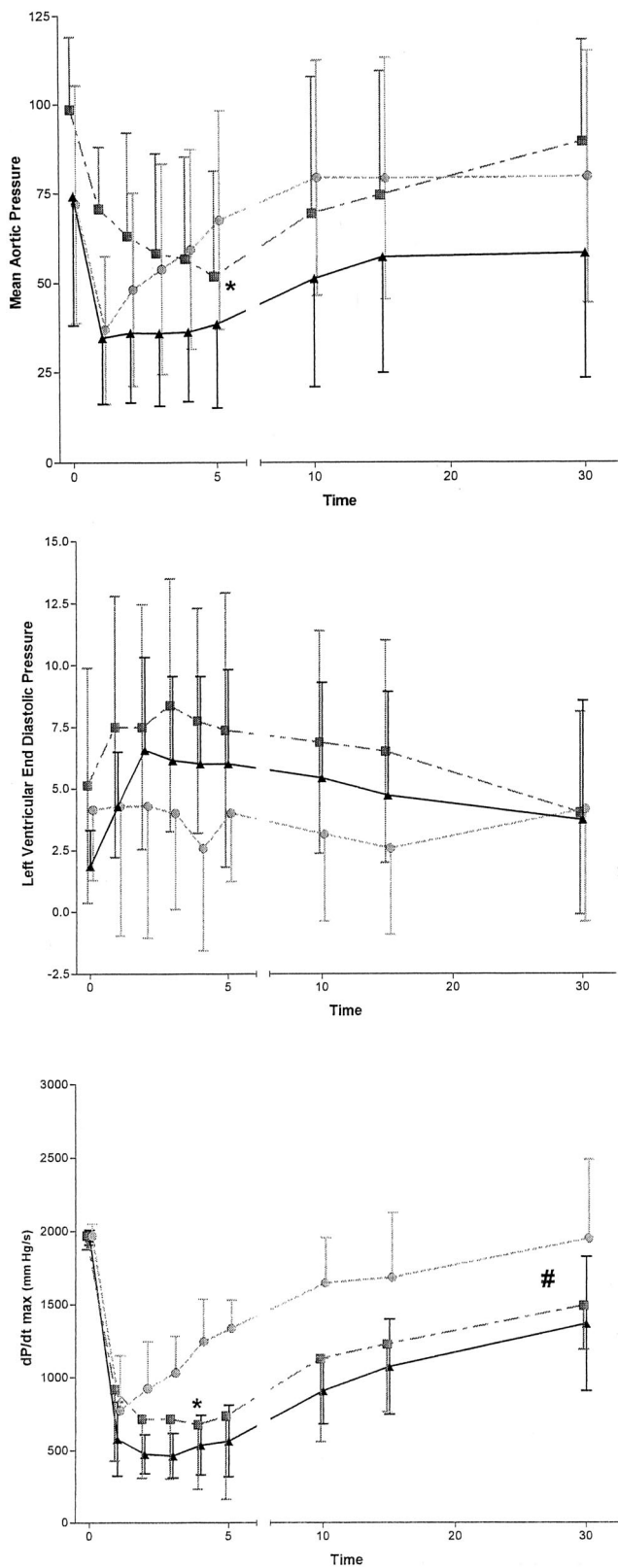


Fig. 1. Effects of 4 mg/kg bupivacaine (squares), 16 mg/kg lidocaine (circles), and a mixture of 4 mg/kg bupivacaine-16 mg/kg lidocaine (triangles) on hemodynamic parameters. Symbols indicate a statistical difference between the bupivacaine and lidocaine groups (*) and the lidocaine and mixture groups (#).

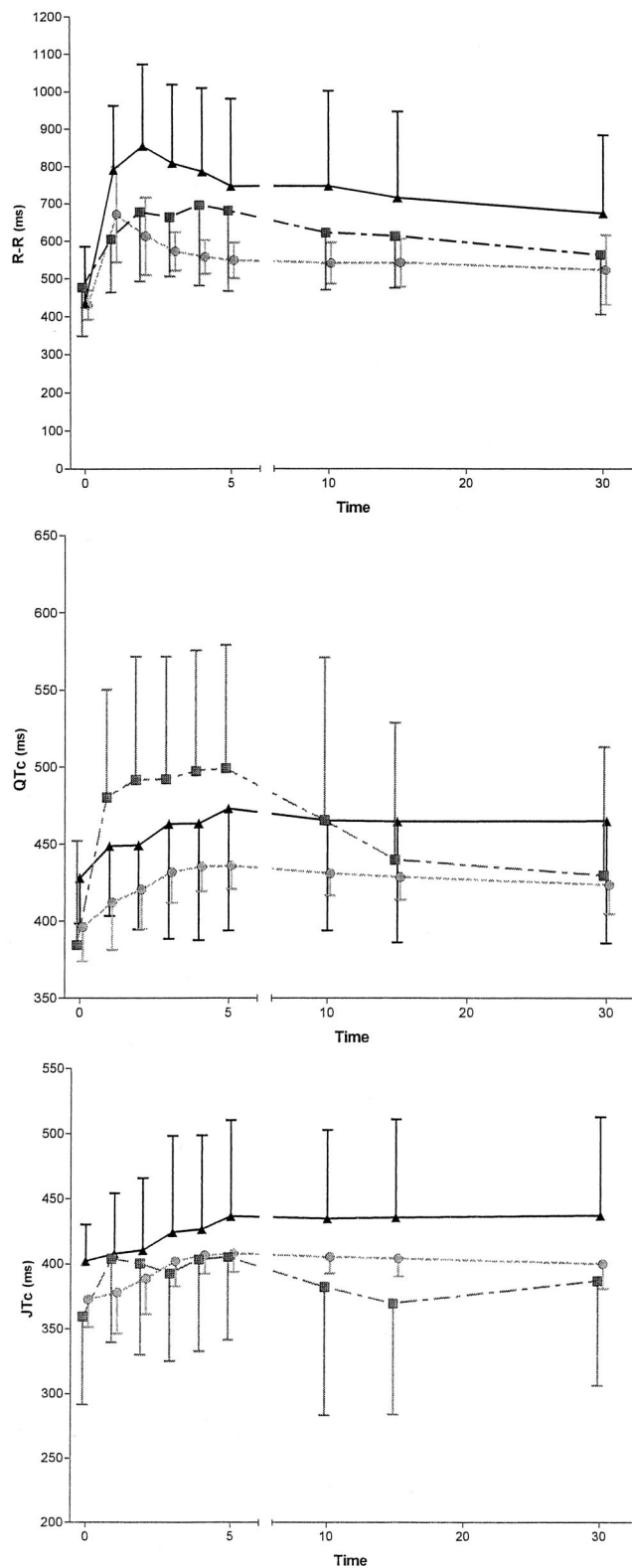


Fig. 2. Effects of 4 mg/kg bupivacaine (squares), 16 mg/kg lidocaine (circles), and a mixture of 4 mg/kg bupivacaine-16 mg/kg lidocaine (triangles) on electrophysiologic parameters (RR, AH, QT_c, JT_c, PQ, HV, QRS). Symbols indicate a statistical difference between the bupivacaine and lidocaine groups (*) and the bupivacaine and mixture groups (§).

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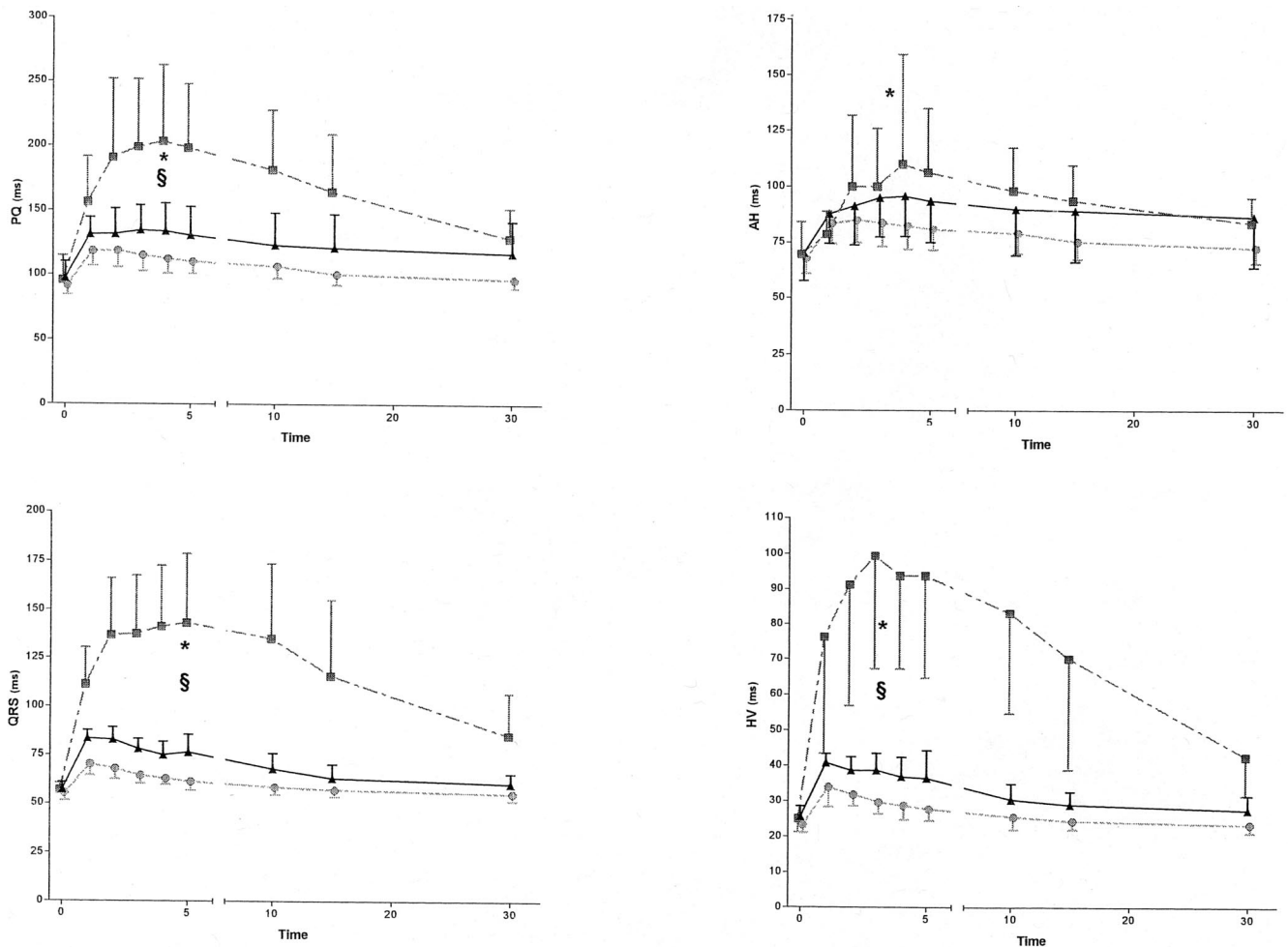


Fig. 2 (continued).

sium (K^+ ; millimolars), total and ionized calcium (Ca_{TOT} , Ca^{2+} ; millimolars), protein (grams per liter), albumin (grams per liter), and arterial lactate (millimolars) (Astra 4 Beckman Coulter Ink analyzer; Palo Alto, CA). Hematocrit was determined using micromethod. Arterial blood gas analysis (arterial oxygen partial pressure in millimeters of mercury, arterial carbon dioxide partial pressure in millimeters of mercury, pH, arterial oxygen saturation, and HCO_3^- in millimolars) was performed using a 1306 pH/blood gas analyzer (Instrument Laboratory, Lexington, MA).

In both groups, the plasma concentrations of bupivacaine and lidocaine were measured using gas chromatography.¹¹ Briefly, 100 μ l internal standard solution (10 μ g/ml mepivacaine), 100 μ l NaOH 2N, and 200 μ l pentane were added to 0.5 ml plasma. After rapid vortex agitation during 45 s and centrifugation at 3,500 g, 2 μ l of the supernatant was injected on column. The chromatograph (Varian model 3400; Varian, Les Ulis, France) equipped with a nitrogen-phosphorus detector was fitted with a megabore J&W DB-1701 column (30 m \times 0.53 mm, film thickness 1 μ m). Helium was used as carrier gas at 30 ml/min, and air and hydrogen were set at 150 and

4.5 ml/min, respectively. The temperatures were as follows: injector, 250°C; detector, 290°C; oven, 230°C. The standard curve was linear in the range 0.01–8 μ g/ml. The limit of detection at four times the basal noise was less than 0.01 μ g/ml for the two drugs. The intraday and interday coefficients of variation were 6 and 8% at 200 μ g/ml.

Times of Measurements

In the three groups, electrophysiologic and hemodynamic variables were measured at baseline (T_0) and 1 (T_1), 2 (T_2), 3 (T_3), 4 (T_4), 5 (T_5), 10 (T_{10}), 15 (T_{15}), and 30 (T_{30}) min after the administration of the local anesthetic.⁷ Biologic parameters were measured at T_0 and T_{30} . The plasma concentrations of bupivacaine and lidocaine were measured at T_0 , at the end of the intravenous bolus of local anesthetic ($T_{0.5}$), and at T_3 , T_{15} , and T_{30} .

Statistical Analysis

Results are expressed as mean \pm SD. The effects of lidocaine, bupivacaine, and the mixture were tested using two-way analysis of variance for repeated measures followed by contrast study and completed by Bonferroni correction. Comparisons between groups were per-

formed using the area under the curve (trapeze method), maximal or minimal concentrations, or maximal or minimal times. One-way analysis of variance was then performed for each variable followed by the Newman-Keuls test. The comparison of mortality between groups was performed using the Fisher exact test. For lidocaine and bupivacaine plasma concentrations, the same analyses were performed at $T_{0.5}$, T_3 , T_{15} , and T_{30} . However, because plasma concentrations at T_0 were always = 0, comparisons were performed *versus* $T_{0.5}$. $P < 0.05$ was considered statistically significant.

Results

Nine, seven, and seven piglets were included in the bupivacaine, lidocaine, and mixture groups, respectively. One piglet died during the preparation period in the bupivacaine group before the injection. Therefore, it was not included in the statistical analysis. The animal weight, the time to prepare piglets until the local anesthetics injection, and the total fluid administration during the overall experimentation were similar in all groups (table 1). Biologic parameters are shown in table 2. At baseline, all groups were similar. At T_{30} , plasma sodium concentration decreased in the bupivacaine group and increased in the mixture group ($P < 0.05$). No animal death occurred after the injection of any local anesthetics.

Effects on Hemodynamic Parameters

The alterations of hemodynamic parameters are shown in figure 1. MAoP was decreased in all groups ($P < 0.05$). The maximal decrease in MAoP was delayed in the bupivacaine group ($P < 0.03$). LVEDP was increased in all groups at T_2 and T_3 ($P < 0.05$) without difference between groups. $LVdP/dt_{max}$ was decreased in all groups ($P < 0.001$). The decrease in $LVdP/dt_{max}$ was greater in the mixture group than in the lidocaine group ($P < 0.04$), whereas its maximal decrease was delayed in the bupivacaine group compared with the lidocaine group ($P < 0.03$).

Effects on Cardiac Electrophysiologic Parameters

The alterations of electrophysiologic parameters are shown in figure 2. RR, QT_c , and JT_c were similarly increased in all groups ($P < 0.05$). In all groups, PQ, AH, HV, and QRS intervals were altered ($P < 0.001$). The lengthening of PQ was greater with bupivacaine than with lidocaine or mixture ($P < 0.02$). The extent of the lengthening of AH was greater and more delayed in the bupivacaine group than in the lidocaine group ($P < 0.03$). The lengthening of HV and the QRS widening were greater and more delayed with bupivacaine than with lidocaine or the mixture ($P < 0.01$). The widening of QRS was greater with the mixture than with lidocaine

($P < 0.01$). In all groups, no pacing could be achieved after an intravenous bolus of local anesthetics.

Plasma Concentrations of Lidocaine and Bupivacaine

Plasma concentrations of lidocaine were greater than those of bupivacaine ($P < 0.05$; fig. 3). Plasma concentration of lidocaine and bupivacaine were similar in the lidocaine and mixture groups and in the bupivacaine and mixture groups, respectively (fig. 3).

Discussion

The current study shows that a mixture of 4 mg/kg bupivacaine-16 mg/kg lidocaine decreased MAoP and increased LVEDP, without a major difference with 4 mg/kg bupivacaine alone. The decrease in $LVdP/dt_{max}$ was greater with the mixture compared with lidocaine. Concerning cardiac electrophysiologic parameters, RR, QT_c , JT_c , AH, PQ, HV, and QRS intervals were altered in all groups. PQ was less lengthened with the mixture than with bupivacaine, with no difference with lidocaine. QRS and HV intervals were altered to a lesser extent with the mixture than with bupivacaine. Plasma concentration of lidocaine and of bupivacaine were similar in the lidocaine and mixture groups and in the bupivacaine and mixture groups, respectively.

Assessment of the Model

In a previous study involving the same animal model, we demonstrated that hemodynamic, electrophysiologic, and biologic parameters were not altered throughout a 2-h period, and that biologic parameters were not altered by the injection of bupivacaine or ropivacaine.⁷ In the current study, plasma concentration of sodium statistically increased in the mixture group (138 ± 1 to 140 ± 1 mM) and statistically decreased in the bupivacaine group (140 ± 4 to 139 ± 4 mM). However, these alterations seemed to be clinically slight (± 1 mM). Therefore, the hemodynamic and cardiac electrophysiologic alterations reported in the current study are surely caused by local anesthetics.

Methodologic Precision

The methodology was not classic. However, this was achieved to avoid killing seven supplemental piglets in the bupivacaine group. The lack of randomization was a consequence of this point. However, because the reader of the hemodynamic and electrophysiologic recording was blinded from the drug injected, it could be supposed that the methodology mimicked a randomized study.

Effects of Bupivacaine

An intravenous bolus dose of 4 mg/kg bupivacaine was shown to induce toxic plasma bupivacaine concentrations and reproducible electrophysiologic and hemody-

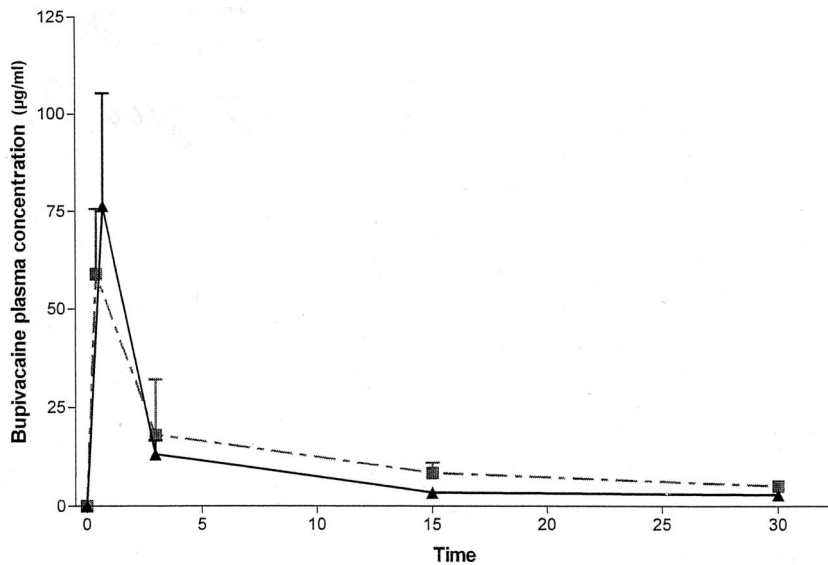
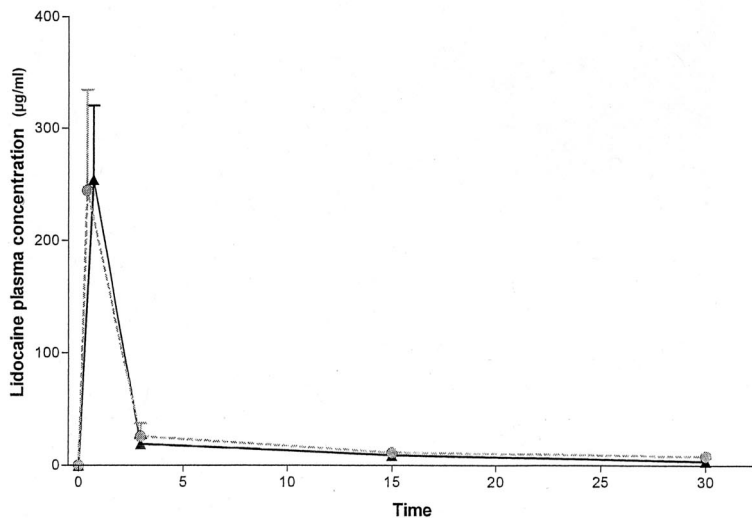


Fig. 3. Plasma concentrations of bupivacaine (group B; squared) versus the mixture (group M; triangles) and lidocaine (group L; circles) versus group M (triangles). No statistical difference was reported.



dynamic impairment without causing immediate death by cardiovascular collapse or ventricular arrhythmias.^{7,9,10} In the current study, the same dose of bupivacaine induced dramatic decreases in MAoP and LVdP/dt_{max} with a transient increase of LVEDP, confirming the negative inotropic effect of bupivacaine.¹² The alterations in cardiac electrophysiologic parameters were also reported, with a dramatic impairment of ventricular conduction.^{6,7}

Effects of Lidocaine and Comparison of Lidocaine with Bupivacaine

An intravenous bolus of 16 mg/kg lidocaine was chosen because, *in vivo* and *in vitro*, lidocaine is four times less potent than bupivacaine.^{6,13} In the current study, the cardiac electrophysiologic and hemodynamic effects

of lidocaine were similar to those previously reported with 16 mg/kg lidocaine in dogs.⁶ Lidocaine resulted in a rapid decrease in MAoP and LVdP/dt_{max}, but this effect was more transient than with bupivacaine. The increase in LVEDP was similar to that recorded with bupivacaine. Except for RR and QTc intervals, electrophysiologic parameters were less impaired with lidocaine than with bupivacaine. Bupivacaine lengthened PQ, AH, HV, and QRS intervals much more than lidocaine did. In a previous study performed in dogs, bupivacaine had less effect on AH and PQ intervals than did lidocaine.⁶

Effects of Mixture

In clinical practice, the use of a lidocaine-bupivacaine mixture allows a smaller dose of each local anesthetic

than if they were used alone. Nevertheless, the current experiment combined 16 mg/kg and 4 mg/kg to study potential additive effects of bupivacaine and lidocaine, respectively. The mixture induced a similar increase in LVEDP to those induced by lidocaine and bupivacaine. The decrease in $LVDp/dt_{max}$ was greater with the mixture than with lidocaine, and no difference was reported in alterations of MAoP and $LVDp/dt_{max}$ between bupivacaine and the mixture. These findings suggest that the hemodynamic impairment induced by the mixture is closer to that of bupivacaine. With regard to cardiac electrophysiologic parameters, no difference was recorded in RR interval. Although AH interval was lengthened to a greater extent and with a delay with bupivacaine compared with lidocaine, there was no difference between lidocaine and the mixture. On ventricular conduction parameters, there was no statistical difference between mixture and lidocaine, while bupivacaine more dramatically impaired PQ, HV, and QRS intervals than did the mixture and lidocaine. Therefore, the mixture seemed to alter electrophysiologic parameters as does lidocaine, which is the less cardiotoxic local anesthetic.

The cardiac effects of the lidocaine-bupivacaine mixture are not well documented. In 1998, Fujita *et al.*¹⁴ showed that a mixture of bupivacaine-lidocaine decreases the ventricular fibrillation threshold in pigs. They also found that QRS was more widened with bupivacaine than with the mixture and with lidocaine, respectively. However, no measurement of AH and HV was performed. No difference in heart rate, mean arterial pressure, and cardiac output was reported among bupivacaine, lidocaine, and the mixture. In contrast, the current study shows that the mixture impairs the conduction parameters (HV, PQ, and QRS intervals) to a lesser extent than bupivacaine and tends to mimic the effects of lidocaine. Therefore, the cardiac electrophysiologic effects of the mixture, including a full dose of both lidocaine and bupivacaine, are closer to those of lidocaine than to those of bupivacaine, and it seems that lidocaine decreases the toxicity of bupivacaine on ventricular conduction parameters in the mixture group.

The mechanisms of the effects of local anesthetics on cardiac electrophysiologic parameters were widely studied. The blockade of calcium-mediated slow action potentials could explain the alteration of MAoP and $LVDp/dt_{max}$ and the lengthening of RR and AH intervals. The widening of QT_c was essentially caused by the widening of QRS. The lengthening of QRS and HV intervals are in accordance with studies showing that local anesthetics slowed ventricular conduction velocities.¹⁵⁻¹⁷ The alteration of ventricular conduction is caused by the blockade of cardiac sodium channels.¹⁸ Clarkson and Hondeghem¹⁵ showed that lidocaine, with rapid binding and unbinding kinetics, could displace a drug with slower binding kinetics such as bupivacaine. Moreover, they also demonstrated that lidocaine could partly re-

verse the sodium channel blockade induced by bupivacaine.⁵ However, in a recent *in vivo* animal model, the widening of QRS induced by bupivacaine was enhanced by a delayed intracoronary infusion of lidocaine.¹⁹

Clinical Implications

The current study shows that mixture induces different effects on hemodynamic and cardiac electrophysiologic parameters. Hemodynamically, the toxicity of the mixture is closer to that of bupivacaine. In contrast, on cardiac electrophysiologic parameters, the mixture is far less toxic than bupivacaine, and its toxicity is closer to that induced by lidocaine. Therefore, lidocaine decreases the toxicity of bupivacaine on ventricular conduction parameters without a protective effect on hemodynamic alterations. The latter finding should lead to classic cautions when a mixture is used for anesthesia.

Care must be taken before extrapolating these results to the clinical setting. First, the effects of anesthesia have to be taken into account. The hemodynamic effects of sodium thiopental could precipitate those induced by local anesthetics.²⁰ However, the current model was shown to be stable during a 2-h period.⁷ In addition to sodium thiopental, ketamine and atropine were given as premedication. Ketamine was recently shown to slow ventricular conduction velocity and to lengthen the ventricular effective refractory period in the rabbit isolated heart.²¹ With regard to midazolam, the dose given has a slight effect on cardiac electrophysiologic parameters.²² Even if hemodynamic and electrophysiologic alterations reported in the current study could be partly explained by the effect of premedication or anesthesia, the differences observed between the groups were only caused by the difference in direct cardiac impact of the local anesthetics. Second, the impact of the frequency dependence of bupivacaine could not be studied because no atrial pacing was efficiently achieved.

In conclusion, the current study shows that the toxicity of a lidocaine-bupivacaine mixture on ventricular conduction parameters are to a lesser extent than that of bupivacaine. However, the effects of the mixture on hemodynamic parameters are closer to those of bupivacaine. These results suggest that, for equal total doses, the lidocaine-bupivacaine mixture is less cardiotoxic than bupivacaine alone.

References

1. Watt MJ, Ross DM, Atkinson RS: A double-blind trial of bupivacaine and lignocaine. *Anaesthesia* 1968; 23:331-7
2. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *ANESTHESIOLOGY* 1979; 51:285-7
3. Magee DA, Sweet PT, Holland HJC: Epidural anaesthesia with mixture of bupivacaine and lidocaine. *Can Anaesth Soc J* 1983; 30:174-8
4. Seow LT, Lips FJ, Cousins MJ, Mather LE: Lidocaine and bupivacaine mixtures for epidural blockade. *ANESTHESIOLOGY* 1982; 56:177-83
5. Clarkson CW, Hondeghem LM: Evidence for a specific receptor site for

- lidocaine, quinidine, and bupivacaine associated with cardiac sodium channel in guinea pig ventricular myocardium. *Circ Res* 1985; 56:496-506
6. Bruelle P, Lefrant JY, de La Coussaye JE, Peray PA, Desch G, Sassine A, Eledjam JJ: Comparison of the cardiac effects of equipotent large doses of various local anesthetic drugs in anesthetized dogs. *Anesth Analg* 1996; 82:648-56
 7. Lefrant JY, de La Coussaye JE, Ripart J, Muller L, Lalourcey L, Peray PA, Mazoit X, Sassine A, Eledjam JJ: Comparative electrophysiologic and hemodynamic effects of a large dose of ropivacaine and bupivacaine in anesthetized and ventilated piglets. *Anesth Analg* 2001; 93:1598-605
 8. Moore EN, Spear JF: Acute and chronic animal models of cardiac arrhythmias, *Antiarrhythmic Drugs*. Edited by Vaughan Williams EM. Berlin, Springer-Verlag, 1989, pp 69-85
 9. de La Coussaye JE, Bassoul BP, Brugada J, Albat B, Peray PA, Gagnol JP, Desch G, Eledjam JJ: Reversal of electrophysiologic and hemodynamic effects induced by high dose of bupivacaine by the combination of clonidine and dobutamine in anesthetized dogs. *Anesth Analg* 1992; 74:703-11
 10. de La Coussaye JE, Eledjam JJ, Bruelle P, Lefrant JY, Bassoul B, Peray PA, Desch G, Sassine A: Mechanisms of the putative cardioprotective effect of hexamethonium in anesthetized dogs given a large dose of bupivacaine. *ANESTHESIOLOGY* 1994; 80:595-605
 11. Bjork M, Pettersson KJ, Osterlof G: Capillary gas chromatographic method for the simultaneous determination of local anaesthetics in plasma samples. *J Chromatogr* 1990; 533:229-3
 12. Eledjam JJ, de La Coussaye JE, Brugada J, Bassoul B, Gagnol JP, Fabregat JR, Masse C, Sassine A: In vitro study on mechanisms of bupivacaine-induced depression of myocardial contractility. *Anesth Analg* 1989; 69:732-5
 13. Covino BG: Pharmacology of local anesthetic agents. *Br J Anaesth* 1986; 58:701-16
 14. Fujita Y, Endoh S, Yasukawa T, Sari A: Lidocaine increases the ventricular fibrillation threshold during bupivacaine-induced cardiotoxicity in pigs. *Br J Anaesth* 1998; 80:218-22
 15. Clarkson CV, Hondeghem LM: Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. *ANESTHESIOLOGY* 1985; 62:396-405
 16. Eledjam JJ, de La Coussaye JE, Brugada J, Masse C, Desch G, d'Athis F, Sassine A: Cardiac electrophysiological effects of bupivacaine in the anesthetized dogs: Relation with plasma concentration. *Arch Int Pharmacodyn* 1988; 295:147-56
 17. Hotvedt R, Refsum H, Helgesen KG: Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dog. *Anaesth Analg* 1985; 64:388-94
 18. Hondeghem LM, Katzung BG: Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. *Biochim Biophys Acta* 1977; 472:373-98
 19. Simon L, Kariya N, Pelle-Lancien E, Mazoit JX: Bupivacaine-induced QRS prolongation is enhanced by lidocaine and phenytoine in rabbit heart. *Anesth Analg* 2002; 94:203-7
 20. Way WL, Trevor AJ: *Pharmacology of intravenous nonnarcotic anesthetics, Anesthesia*, 2nd edition. Edited by Miller RD. New York, Churchill Livingstone, 1986, pp 799-834
 21. Aya AGM, Robert E, Bruelle P, Lefrant JY, Juan JM, Peray P, Eledjam JJ, de La Coussaye: Effects of ketamine on ventricular conduction refractoriness, and wavelength. Potential antiarrhythmic effects: A high resolution epicardial mapping in rabbit hearts. *ANESTHESIOLOGY* 1997; 87:1417-27
 22. Stowe DF, Bosnjak ZJ, Kampine JP: Comparison of etomidate, ketamine, midazolam, propofol and thiopental on function and metabolism of isolated hearts. *Anesth Analg* 1992; 74:546-58