

Comparison of the Effects of Racemic Bupivacaine, Levobupivacaine, and Ropivacaine on Ventricular Conduction, Refractoriness, and Wavelength

An Epicardial Mapping Study

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Background: The study was designed to compare the effects of equimolar concentrations of racemic bupivacaine, levobupivacaine, and ropivacaine on ventricular conduction, anisotropy, duration and homogeneity of refractoriness, and wavelengths, and to provide a potency ratio for effects on conduction velocity.

Methods: Isolated frozen rabbit hearts (which leave a thin layer of surviving epicardial muscle) were treated with 0.1, 1, and 10 μM racemic bupivacaine, levobupivacaine, or ropivacaine. Left ventricular longitudinal and transverse conduction velocities, anisotropic ratio, minimum pacing cycle length, use dependency, duration and dispersion of ventricular effective refractory period, and wavelengths were studied. A high-resolution mapping system was used for data acquisition. In addition to two-way analysis of variance for repeated measures, data for conduction velocities were fitted simultaneously using a nonlinear mixed-effect modeling program to allow intergroup comparison.

Results: Each agent induced a concentration- and use-dependent slowing of conduction velocities, with no change of the anisotropic ratio. The use-dependent effect of levobupivacaine is similar to that of racemic bupivacaine concerning longitudinal conduction velocity. Fitting of conduction velocities provided a racemic bupivacaine to levobupivacaine and to ropivacaine ratio of 1:1.38 for concentration effect at 1,000-ms pacing cycle length, and 1:0.74 for use-dependent effect at 600-ms pacing cycle length. Racemic bupivacaine and levobupivacaine prolonged the ventricular effective refractory period, whereas ropivacaine did not. No dispersion in ventricular effective refractory period values occurred. All three agents induced significant decreases in wavelengths. This effect was not different among groups.

Conclusions: Differences among racemic bupivacaine, levobupivacaine, and ropivacaine at equimolar concentrations are mainly caused by the use-dependent effects on conduction velocities and the concentration-dependent effects on ventricular effective refractory period. Therefore, one must take into ac-

count the corresponding pacing rates when comparing the potency ratios of local anesthetics.

LIFE-THREATENING ventricular tachycardia or fibrillation and cardiac arrest were reported in patients accidentally given a large intravascular dose of racemic bupivacaine.¹ Because of the potential cardiotoxicity of racemic bupivacaine, ropivacaine and levobupivacaine have been developed as safer alternatives.²⁻⁴ Experimental and clinical data showed that these two agents are as potent or less potent but less toxic than racemic bupivacaine. Although clinical data provided ropivacaine and levobupivacaine to racemic bupivacaine equipotency ratios of approximately 0.6 and 0.98, respectively,^{5,6} data from animals and isolated heart studies suggested that this ratio may be different in cardiac tissue. Using the prolongation of the QRS interval in spontaneous rhythm as a parameter of electrophysiologic toxicity, a toxicity ratio of 15:6.7:1 was reported for racemic bupivacaine, racemic ropivacaine, and lidocaine,² and a toxicity ratio of 2.1:1.2:1 was reported for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.⁷ Using the calculated maximal QRS widening in isolated buffer-perfused and paced rabbit hearts, Mazoit *et al.*⁸ showed that the three agents induce a QRS widening in the ratio 1:0.4:0.3.

Cardiac arrhythmias mainly account for the fatal outcome of animals given large intravenous doses of racemic bupivacaine. One mechanism of these cardiac arrhythmias is that racemic bupivacaine induces a concentration- and use-dependent slowing of ventricular conduction, facilitating the occurrence of ventricular conduction blocks and therefore of arrhythmias by reentry.⁹ The current study was designed to compare the effects of equimolar concentrations of racemic bupivacaine, levobupivacaine, and ropivacaine on parameters critical for the occurrence of reentrant circuits on ventricles: conduction velocity, anisotropy, use dependency, duration and spatial dispersion of refractory periods, and ventricular wavelengths. We also attempted to provide a potency ratio for the effects on conduction velocity.

Methods

Heart Preparation

The principles for the care and treatment of experimental animals complied with the national guidelines of

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the French Ministry of Agriculture. The procedure for heart preparation was described in detail in previous studies from our laboratory.^{10,11} Briefly, hearts were rapidly removed from New Zealand rabbits (weight, 3.4 ± 0.7 kg) during etomidate anesthesia (1 mg/kg administered intravenously followed by an infusion of $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and were connected to a Langendorff perfusion system using Tyrode solution. The heart was perfused with a constant flow of 40–50 ml/min, resulting in a pressure of 70 ± 10 mmHg. The composition of the Tyrode solution was as follows: 130 mM NaCl, 20.1 mM NaHCO_3 , 4.0 mM KCl, 2.2 mM CaCl_2 , 0.6 mM MgCl_2 , 1.2 mM NaH_2PO_4 , and 12 mM glucose. The solution was saturated with a mixture of 95% O_2 and 5% CO_2 , pH was adjusted at 7.40 ± 0.02 , and the temperature of the heart was maintained at 37°C throughout the experiment.

In all hearts, an endocardial cryotechnique was used to freeze the complete right ventricle, the interventricular septum, and the endocardial and intramural layers of the free wall of the left ventricle (frozen heart). The cryotechnique was also previously described^{10,11} and allowed us to obtain a thin surviving epicardial layer of the free wall of the left ventricle, approximately 1 mm thick. It was previously demonstrated that in this thin surviving layer, refractoriness and conduction velocity are not affected by the procedure and remain stable for hours.¹² The cryoprotocol was used to allow complete and bidimensional mapping of electrical activation. At the end of the experiments, the hearts were dissected to verify the efficacy of the cryoprotocol, and their results were excluded from the study if the freezing was inadequate.

Protocol

After a 60-min stabilization period, hearts were given 0.1, 1.0, and 10 μM racemic bupivacaine, levobupivacaine, or ropivacaine at increasing concentrations, each concentration being infused for 20 min. Bupivacaine-HCl (Qualimed, Lyon, France), levobupivacaine-HCl (Abbott, Rungis, France), and ropivacaine-HCl (Astra, Rueil Malmaison, France) were obtained commercially as 5-, 2.5-, and 10-mg/ml solutions, respectively.

Data Acquisition System and Pacing Protocol. High-resolution mapping of epicardial excitation was performed using a programmable constant current stimulator and a spoon-shaped electrode containing 256 unipolar electrodes coupled with a computerized mapping system, allowing simultaneous recording, storage, and automatic analysis of all electrograms and online presentation of color-coded activation maps (Maptech system, Maastricht, The Netherlands).¹³ Throughout the study, bipolar stimulation was applied by trains of 10 stimuli (S1–S1), with a pause of 2,000 ms introduced between successive trains. Although the basic pacing cycle length (PCL) was 300 ms, values ranged from 1,000

to 200 ms to test the use dependency. The pacing protocol used for the induction of arrhythmias consisted on application of trains of 10 stimuli at a regular cycle length, which was progressively decreased at 10-ms steps until 1-to-1 capture of the ventricle failed. The shortest PCL reached (PCL_{min} , in milliseconds) was used as an index of use dependency as it reflects the beat-to-beat recovery of excitability. This pacing protocol was applied during baseline conditions, after each dose of racemic bupivacaine, levobupivacaine, or ropivacaine, and after washout. Inducible ventricular dysrhythmias were recorded and analyzed.

Electrophysiologic Measurements. The following parameters were measured: ventricular effective refractory period (VERP, milliseconds), longitudinal ventricular conduction velocity (θL , centimeters per second), transverse ventricular conduction velocity (θT , centimeters per second), the anisotropic ratio ($\theta\text{L}/\theta\text{T}$), and PCL_{min} . During the experiment, all of these parameters were recorded using the same pacing site, which was located at the center of the thin surviving layer of the left ventricle. The procedure for the determination and the definition of each parameter was previously described.¹¹ Briefly, VERP was determined using the premature impulse technique during pacing at a 300-ms PCL. To test the dispersion of repolarization over the left epicardium, VERP was measured on a total of six sites on each heart. To increase the resolution of the spatial dispersion of VERP, the six measures were performed in the lower left quadrant of the epicardial area.¹⁰ The dispersion of refractoriness was quantified by the index of dispersion, defined as the quotient of the SD and the mean of VERP, and by the maximal dispersion, defined as the difference between the maximum and the minimum values of VERP.¹¹ Concerning conduction, it is established that the direction-dependent differences in axial resistance result in anisotropic conduction,^{14,15} which can contribute to reentrant arrhythmias. Therefore, pacing at the center of the thin surviving layer of the left ventricle produced an ellipsoidal spread of propagation, allowing the identification of the myocardial fiber orientation, with fast conduction parallel to the fiber axis (θL) and slow conduction perpendicular to the fiber axis (θT). In each experiment, θL , θT , and $\theta\text{L}/\theta\text{T}$ were measured after 10 basic stimuli (S1–S1) at 1,000-ms interval. The absolute decrease in θL and θT at 10 μM ($\Delta\theta\text{L}$ and $\Delta\theta\text{T}$, in milliseconds) was calculated for each agent and was used to compare the concentration effect among agents. To test the use dependency of the drugs, θL and θT were also measured after 10 basic stimuli at 900-, 800-, 700-, 600-, 500-, 400-, 300-, 250-, and 200-ms intervals. An attempt was made to calculate the dosing of local anesthetics that induces a 50% decrease in longitudinal and transverse conduction velocities (ED_{50}) at 1,000- and 600-ms PCL using the program NONMEM (see Statistical

Analysis), to provide a potency ratio of racemic bupivacaine, levobupivacaine, and ropivacaine. PCL at 600 ms was chosen because it was the shortest PCL for which a sufficient number of hearts could be effectively paced at 10 μM local anesthetics. Finally, the wavelength (in millimeters), defined as the product of conduction velocity and VERP, was calculated for the longitudinal and transverse directions, using respective conduction velocities measured at 300-ms PCL.

Definition of Ventricular Dysrhythmias. Induced dysrhythmias were noted and analyzed to determine the reentrant nature. We defined ventricular dysrhythmias as ventricular fibrillation and sustained and nonsustained ventricular tachycardia. Sustained ventricular tachycardia was defined as a ventricular tachycardia lasting longer than 30 s, and nonsustained ventricular tachycardia was defined as a ventricular tachycardia lasting more than 3 successive beats but less than 30 s. A separation into monomorphic and polymorphic ventricular tachycardia was made. Monomorphic ventricular tachycardia and ventricular fibrillation were expected to be terminated by overdrive pacing and administration of potassium chloride, respectively.

Statistical Analysis

All variables were expressed as mean \pm SD. Two-way analysis of variance for repeated measures followed by contrast analysis and Bonferroni correction was used for comparisons within and among groups. In addition, a curve of conduction velocity *versus* PCL was plotted for each heart at baseline and for each local anesthetic concentration. Areas under the curves of conduction velocity were calculated and used for the overall comparison of the use-dependent effect of local anesthetics. Parameters taken into account for analysis of conduction velocities were the treatment group and the PCL. Parameters taken into account for analysis of PCL_{min}, VERP, wavelengths, index of dispersion, and maximal dispersion were the treatment group and the dose. $P < 0.05$ was considered to be statistically significant.

In addition to analysis of variance, the decrease in conduction velocity (E) was fitted to the following E_{max} model:

$$E = E_0 \left(1 - \frac{E_{\text{max}_i} D}{D_{i50} + D} \right) \quad (1)$$

where E_0 is the individual measured basal conduction velocity, D is dosing of drug i (bupivacaine, levobupivacaine, or ropivacaine), E_{max_i} is the maximum decrease in conduction velocity, and D_{i50} is the drug amount producing half the maximum decrease in conduction velocity. Longitudinal and transverse velocities were considered as bivariate observations and were simultaneously fitted. Two sets of data (1,000- and 600-ms PCL) were separately fitted using nonlinear mixed-effect modeling with the program NONMEM (version V level 1.1).¹⁶

Intraindividual and interindividual variability were modeled as $f \exp(\varepsilon)$ or as $\theta \exp(\eta)$, respectively (assuming a log-normal distribution), where f and θ are the vectors of observations and of fixed-effect parameters, respectively, and ε and η are the vectors of intraindividual and of interindividual variability, respectively. We used the first-order conditional estimation method with interaction. We used a covariance term between the elements of ε , the vector of residual error caused by intraindividual and measurement variability. At each PCL, a full model with E_{max} and ED_{50} considered relevant for each of the three drugs was compared with successive reduced models with these parameters considered common among drugs. The choice between models was made using the log-likelihood ratio test.¹⁷

Results

Six hearts were excluded from the study because of inadequate freezing (ineffective pacing or blocks of conduction). Thus, 26 hearts were included in the study, nine in the racemic bupivacaine and levobupivacaine groups, and eight in the ropivacaine group. All hearts could be paced until a PCL of 200 ms at baseline and at 0.1 μM in each treatment group. At 1 μM racemic bupivacaine, levobupivacaine, and ropivacaine, four, five, and three hearts could not be regularly paced at a PCL of 200 ms, respectively. At 10 μM local anesthetics, all hearts could be paced at 1,000 ms, except one heart in the racemic bupivacaine group. Furthermore, at 10 μM racemic bupivacaine, eight hearts could be paced effectively until 700 ms, seven until 600 ms, one until 500 ms, and none at a shorter PCL. At 10 μM levobupivacaine, eight hearts could be paced until 500 ms, and none at a shorter PCL. At 10 μM ropivacaine, seven hearts could be paced until 600 ms, six until 500 ms, two until 400 ms, and none at a shorter PCL. After washout, all hearts recovered their ability to be paced until 200 ms. One sustained monomorphic ventricular tachycardia was observed during pacing at 250 ms after 1 μM racemic bupivacaine. Analysis of the maps showed that the ventricular tachycardia was reentrant.

Effects on Conduction Velocity and Anisotropy

Baseline values of conduction velocities were not different among treatment groups. All three agents induced a concentration-dependent slowing of θ_L and θ_T , with no change in anisotropic ratio. Effects of increasing concentrations of racemic bupivacaine, levobupivacaine, and ropivacaine on conduction velocities and anisotropic ratio at a PCL of 1,000 ms are reported in table 1. The comparison between the three groups showed that the decrease in θ_L was not statistically different, but ropivacaine decreased θ_T less than bupivacaine ($P < 0.01$; table 2).

Table 1. Concentration-dependent Effect of Racemic (Rac) Bupivacaine, Levobupivacaine, and Ropivacaine on Longitudinal (θ_L) and Transverse (θ_T) Conduction Velocity at PCL 1,000 ms, on Anisotropic Ratio (θ_L/θ_T), and on the Shortest Pacing Cycle Length (PCL_{min})

	θ_L (cm/s)	θ_T (cm/s)	θ_L/θ_T	PCL _{min} (ms)
Rac bupivacaine (n = 9)				
Baseline	79.5 ± 11.6	39.3 ± 6.5	2.00 ± 0.29	167.5 ± 19.9
0.1 μM	75.7 ± 8.1	37.1 ± 5.9	2.02 ± 0.32	176.5 ± 25.2
1 μM	72.9 ± 7.5*	34.5 ± 6.8*	2.11 ± 0.36	179.0 ± 20.8
10 μM	59.5 ± 8.1*†‡	26.0 ± 5.6*†‡	2.03 ± 0.76	543.8 ± 82.1*
Washout	77.8 ± 9.3	36.9 ± 7.5	2.12 ± 0.39	181.1 ± 27.1
Levobupivacaine (n = 9)				
Baseline	75.9 ± 10.6	37.1 ± 5.2	2.05 ± 0.14	169.3 ± 21.7
0.1 μM	70.5 ± 11.1	35.0 ± 4.4	2.01 ± 0.22	176.1 ± 21.5
1 μM	66.3 ± 12.7*	32.8 ± 4.8*	2.02 ± 0.28	194.4 ± 25.5
10 μM	57.5 ± 9.0*†‡	28.3 ± 5.0*†‡	2.07 ± 0.40	420.0 ± 42.2*
Washout	69.5 ± 11.8	33.9 ± 4.2	2.05 ± 0.25	184.4 ± 18.8
Ropivacaine (n = 8)				
Baseline	79.4 ± 14.6	36.2 ± 4.9	2.29 ± 0.21	173.3 ± 15.0
0.1 μM	76.6 ± 13.7	34.3 ± 4.9	2.25 ± 0.25	181.1 ± 16.2
1 μM	73.8 ± 13.7	33.1 ± 4.2	2.24 ± 0.35	187.8 ± 12.0
10 μM	66.1 ± 9.8*†	28.7 ± 3.1*†‡	2.33 ± 0.35	411.1 ± 65.1*
Washout	73.9 ± 9.5	34.8 ± 3.9	2.12 ± 0.21	190.0 ± 22.9

Pacing site was located at the center of the left ventricular epicardium. Data are mean ± SD.

* $P < 0.05$ versus baseline. † $P < 0.05$ versus 0.1 μM . ‡ $P < 0.05$ versus 1 μM .

A use-dependent effect was observed with each agent. A significant increase in PCL_{min} was observed at 10 μM of each agent (table 1). The comparison between the three groups showed that racemic bupivacaine increased PCL_{min} significantly more than levobupivacaine ($P < 0.01$) and ropivacaine ($P < 0.001$), with no difference between levobupivacaine and ropivacaine. Moreover, figures 1 and 2 show that racemic bupivacaine and levobupivacaine decreased θ_L more than ropivacaine in a use-dependent manner ($P < 0.05$), but no difference occurred for θ_T . Finally, the simultaneous fitting of θ_L and θ_T allowed the analysis of these parameters at once. At 1,000-ms PCL (*i.e.*, concentration effect) and at 600-ms PCL (*i.e.*, use-dependent effect), a first reduced model considered a common ED₅₀ for all three drugs ($P > 0.2$, chi-square, 2 *df* reduced model 1 *vs.* full model). The best model was a further reduced model with E_{max} common to levobupivacaine and to ropiva-

caine ($P > 0.15$ and 0.20 for 1,000 and 600 ms, respectively, chi-square, 1 *df* reduced model 2 *vs.* reduced model 1). All other models were significantly different at $P < 0.01$. E_{max} and ED₅₀ values are shown in table 3. In summary, racemic bupivacaine and levobupivacaine-ropivacaine slowed conduction velocities in the ratio 1:1.38 at 1,000-ms PCL and induced a use-dependent slowing of conduction in the ratio 1:0.74 at 600-ms PCL. The maps in figure 3 show the PCL effect (1,000 *vs.* 300 ms) on conduction velocities in hearts given 1 μM racemic bupivacaine (figs. 3A and B), levobupivacaine (figs. 3C and D), or ropivacaine (figs. 3E and F).

Effects on Ventricular Effective Refractory Period and Wavelength

The effects of racemic bupivacaine, levobupivacaine, and ropivacaine on conduction velocities measured at 300-ms PCL, VERP, and wavelengths are shown in table 4. Racemic bupivacaine and levobupivacaine prolonged the VERP, whereas ropivacaine did not. However, no intergroup statistical difference was observed among treatment groups. In all three groups, there was no intersite variation of VERP values, as shown by the lack of increase in index of dispersion and maximal dispersion (table 5), although the baseline values of the levobupivacaine group tend to be different from those of the other groups ($P = 0.05$). Changes in conduction velocities and VERP resulted in a significant shortening in longitudinal and transverse wavelengths (table 4). Racemic bupivacaine, levobupivacaine, and ropivacaine shortened λ_L by 13.8, 16.5, and 9.9%, and λ_T by 23.0, 14.7, and 12.6%, respectively. However,

Table 2. Comparison of Absolute Decrease in Conduction Velocities by 10 μM Local Anesthetics at PCL 1,000 and 600 ms

	Rac Bupivacaine	Levobupivacaine	Ropivacaine
PCL 1,000 ms			
$\Delta\theta_L$ (cm/s)	20.5 ± 8.5	18.4 ± 8.6	13.2 ± 10.9
$\Delta\theta_T$ (cm/s)	11.9 ± 6.0	8.7 ± 3.8	7.0 ± 4.5*
PCL 600 ms			
$\Delta\theta_L$ (cm/s)	35.3 ± 10.7	28.4 ± 11.9	29.3 ± 16.6
$\Delta\theta_T$ (cm/s)	20.5 ± 4.5	13.2 ± 4.8	15.1 ± 7.5

* $P < 0.01$ versus the corresponding variable in the racemic (Rac) bupivacaine group. Racemic bupivacaine tended to decrease θ_T more than the other agents at pacing cycle length (PCL) 600 ms ($P = 0.06$).

$\Delta\theta_L$ and $\Delta\theta_T$ = absolute decreases in longitudinal and transverse conduction velocities, respectively.

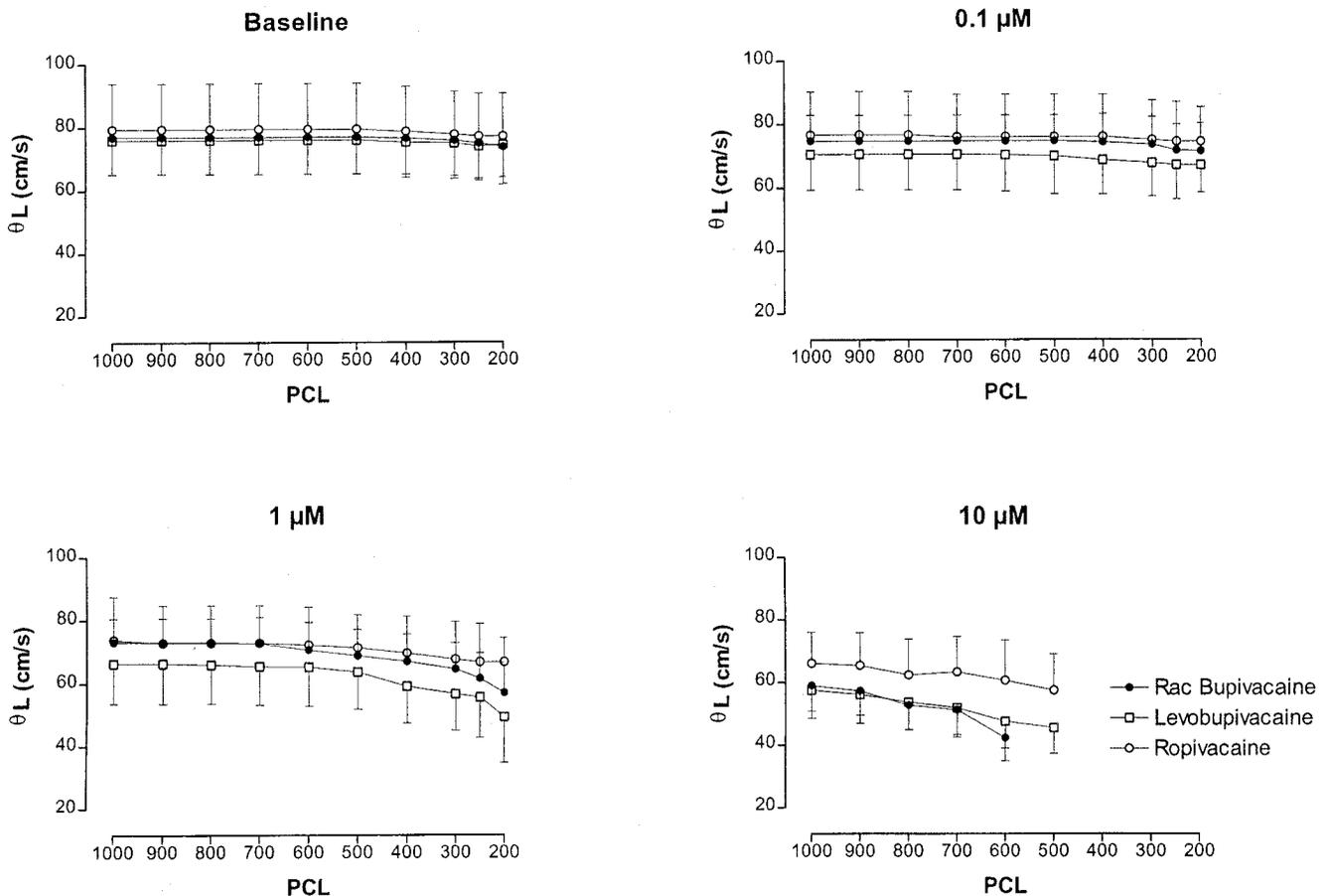


Fig. 1. Comparative use-dependent effects of racemic bupivacaine, levobupivacaine, and ropivacaine on longitudinal conduction velocity (θ_L). Data are expressed as mean \pm SD. All agents induced a significant use-dependent slowing of θ_L . At 10 μM , the use-dependent effect of racemic bupivacaine and levobupivacaine was stronger than that of ropivacaine ($P < 0.05$). PCL = pacing cycle length (in milliseconds).

there was no intergroup statistical difference on either λ_L or λ_T shortening.

Discussion

The current study shows that racemic bupivacaine, levobupivacaine, and ropivacaine induce a concentration- and use-dependent slowing of conduction velocities, with no change in the anisotropic ratio. At 1,000 ms, the potency ratio of racemic bupivacaine to levobupivacaine-ropivacaine is 1:1.38. Moreover, ropivacaine slows θ_T less than racemic bupivacaine. Levobupivacaine and ropivacaine increased PCL_{\min} less than racemic bupivacaine. Racemic bupivacaine and levobupivacaine induce a stronger use-dependent slowing of θ_L than ropivacaine, and the potency ratio of racemic bupivacaine on levobupivacaine-ropivacaine is 1:0.74 at 600 ms. Finally, racemic bupivacaine and levobupivacaine prolonged VERP, whereas ropivacaine did not. All three drugs significantly shortened the ventricular wavelengths, with no interagent difference. Therefore, it appears that ropivacaine is less cardiotoxic than racemic bupivacaine because of a lesser use-dependent effect on conduction, and that levobupivacaine has an intermediate effect.

Effects on Conduction and Anisotropy

Effects of local anesthetics on cardiac electrophysiologic parameters have been fully investigated. It is widely established that racemic bupivacaine is more potent and more toxic than levobupivacaine, ropivacaine, and lidocaine.^{2,3,7,18-21} The great potency and cardiotoxicity of racemic bupivacaine result from its high lipid solubility,²² its effects on mitochondrial respiration,²³⁻²⁵ and on use-dependent slowing of conduction caused by the fast-in-slow-out pattern of sodium channel inhibition.^{9,26} However, most studies were not able to distinguish between concentration- or dose-dependent effects and use-dependent effects of anesthetic agents on conduction. Indeed, because of the design of most cell preparations, isolated heart, and animal models, the observed effects reflected additive actions of local anesthetic on conduction properties and use dependency, as pacing rates were usually too fast.

The current study confirms the published effects of racemic bupivacaine, levobupivacaine, and ropivacaine on cardiac conduction (*i.e.*, concentration- and use-dependent slowing of conduction).⁷⁻⁹ In addition, our results show that the anisotropic ratio is unchanged. Al-

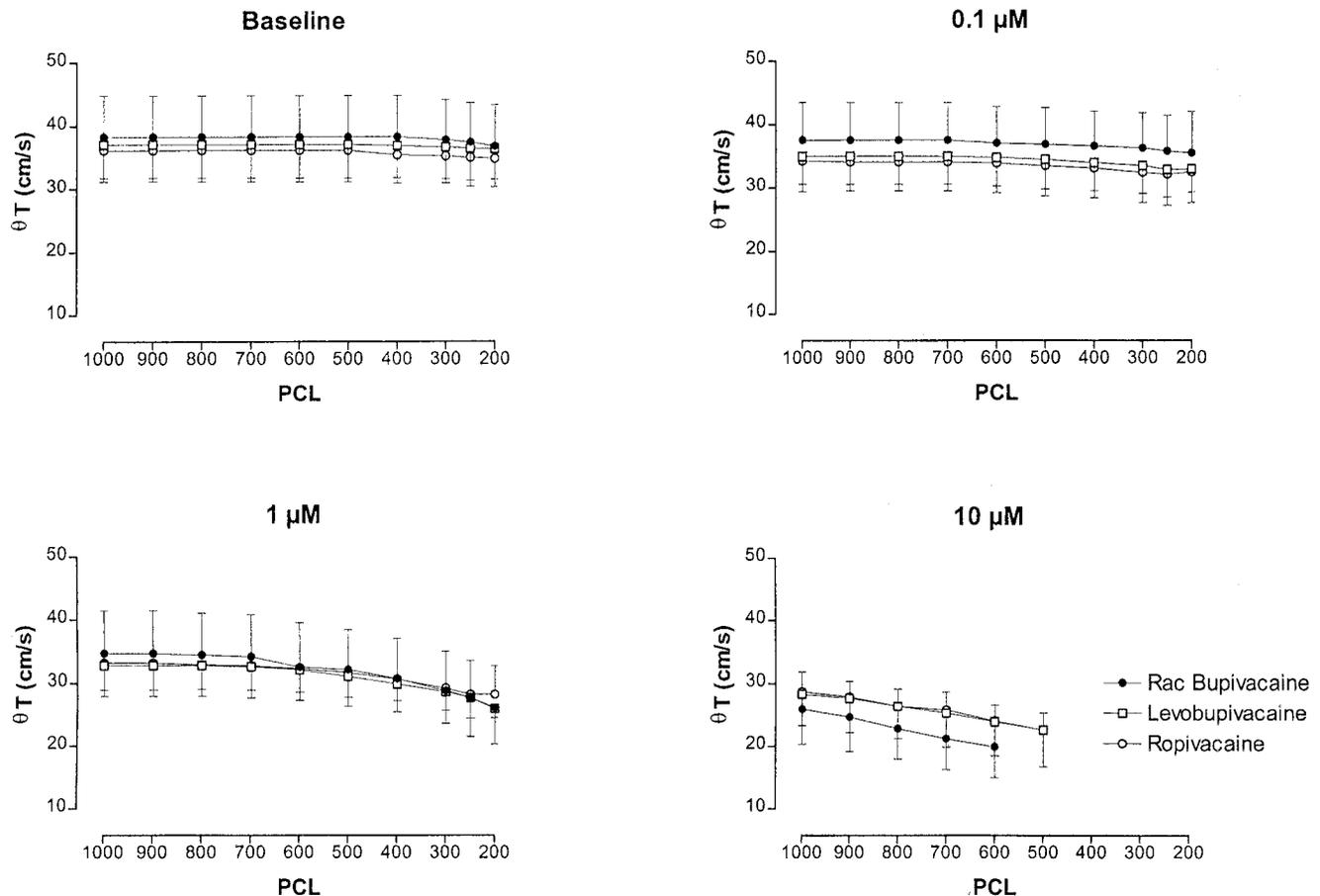


Fig. 2. Comparative use-dependent effects of racemic bupivacaine, levobupivacaine, and ropivacaine on transverse conduction velocity (θT). Data are expressed as mean \pm SD. All agents induced a significant use-dependent slowing of θT . The use-dependent effect was not different among agents ($P = 0.07$). PCL = pacing cycle length (in milliseconds).

though a greater inhibition of sodium channels^{27,28} and a greater QRS widening^{7,8} was shown with racemic bupivacaine compared with the two other agents, our study shows that, at best, the effects of racemic bupivacaine, levobupivacaine, and ropivacaine at 1,000 ms (*i.e.*, concentration effect) on θL are not different. However,

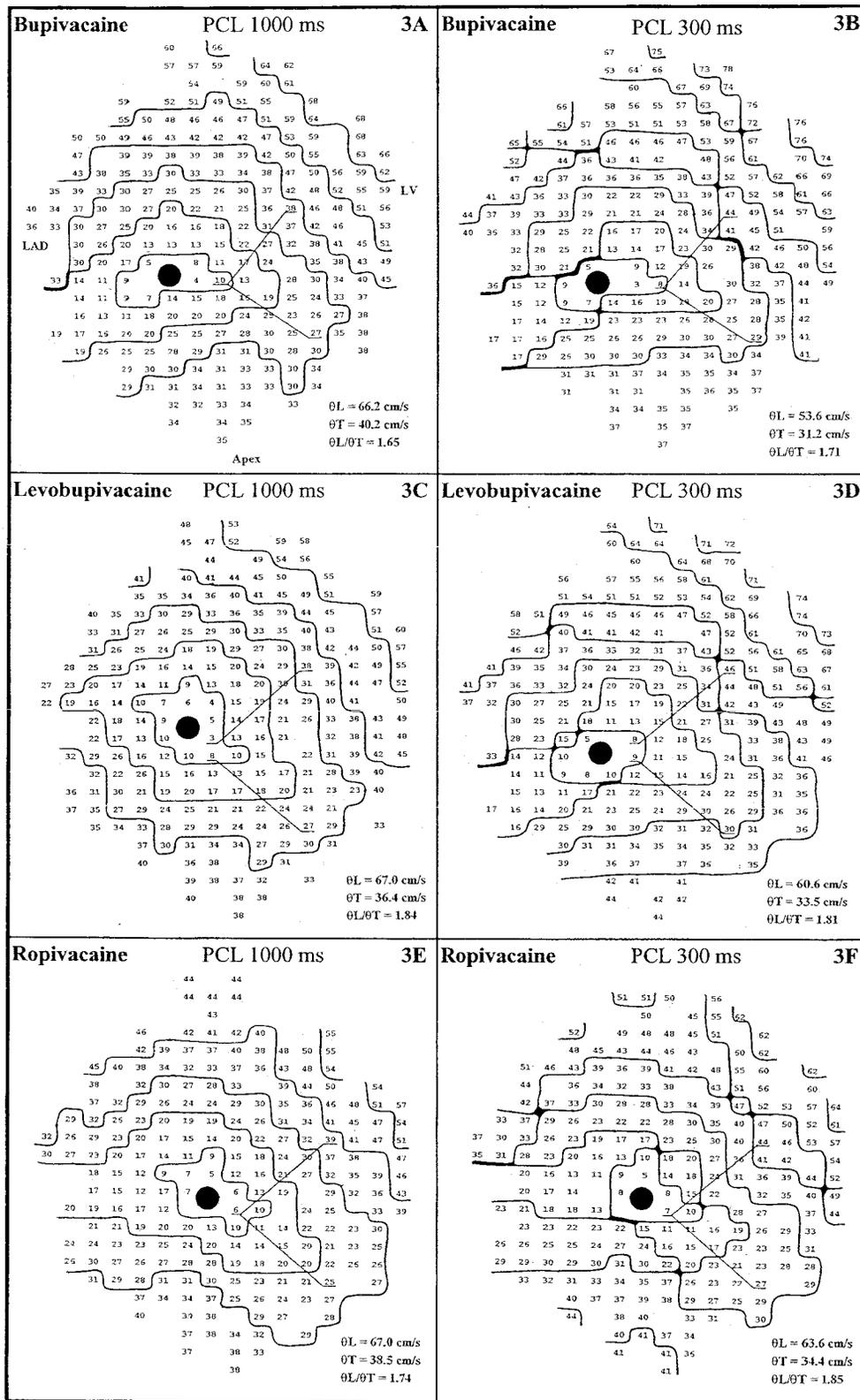
Table 3. Parameter Estimates

	ED ₅₀ (μM)	Emax Rac Bupi (% of E ₀)	Emax Levo-Ropi (% of E ₀)
1,000 ms			
Typical values	2.03	0.267	0.370
	θL	θT	θT
ω^2	3.58	1.60	0.0661
600 ms			
Typical values	3.44	0.640	0.476
	θL	θT	θT
ω^2	1.40	0.843	0.0284

Data are typical value with three significant digits. ω^2 is the variance of η , the interindividual variability. The arithmetic means of η was never significantly different from zero.

θL = longitudinal conduction velocity; θT = transverse conduction velocity; Rac Bupi = racemic bupivacaine; Levo = levobupivacaine; Ropi = ropivacaine; ED₅₀ = dosing of local anesthetic that induces a 50% decrease in conduction velocity; E₀ = individual measured basal conduction velocity; Emax = maximal decrease in conduction velocity.

θT was more affected by racemic bupivacaine than ropivacaine. One difference between our results and previous comparisons of the effects of racemic bupivacaine, levobupivacaine, and ropivacaine on cardiac conduction is that we used two conduction variables referring to different mechanisms of conduction, whereas a single variable was used in most studies, usually the QRS interval. The separation of conduction into θL and θT could have affected our results, because simultaneous fitting of these two variables resulted in a significant difference in the effects of racemic bupivacaine and levobupivacaine-ropivacaine on conduction velocity. ED₅₀ was similar for the three drugs in our study but was at least 10-fold lower than that reported by Mazoit *et al.*⁸ We have no clear explanation, but some contributing factors can be pointed out. From our data, it appears that ED₅₀ increases with increasing pacing rates. We determined ED₅₀ for conduction velocity at a PCL of 1,000 ms (60 beats/min) and 600 ms (100 beats/min), whereas the pacing rate ranged from 170 to 350 beats/min in the study by Mazoit *et al.*⁸ In addition, unlike Mazoit *et al.*, who worked on the whole isolated heart and on QRS measurements, we worked only on the epicardial tissue.



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Fig. 3. Effects of pacing cycle length (PCL) on longitudinal (θL) and transverse (θT) conduction velocities during treatment of isolated hearts with $1 \mu\text{M}$ racemic bupivacaine (A and B), levobupivacaine (C and D), or ropivacaine (E and F). The central closed circle represents the pacing site. Numbers indicate local activation times expressed in milliseconds. Isochrones are drawn at 10-ms intervals. The underlined activation times indicate the sites between which longitudinal and transverse conduction velocities were measured in panels. Conduction velocities were slowed by shortening the PCL from 1,000 to 300 ms. Heavy lines indicate coalescence of at least two isochrones because of unidirectional conduction block. LAD = left anterior descending coronary artery; LV = left ventricle.

Table 4. Concentration-dependent Effect of Racemic Bupivacaine, Levobupivacaine, and Ropivacaine on Longitudinal (θ L) and Transverse (θ T) Conduction Velocity at PCL 300 ms, VERP, and Longitudinal (λ L) and Transverse (λ T) Wavelengths

	θ L (cm/s)	θ T (cm/s)	VERP	λ L (mm)	λ T (mm)
Rac bupivacaine (n = 9)					
Baseline	78.5 ± 12.0	38.9 ± 6.3	172.9 ± 9.4	134.6 ± 24.4	66.5 ± 11.9
0.1 μ M	74.7 ± 8.6	36.0 ± 5.5	176.6 ± 8.0	131.6 ± 20.1	63.2 ± 9.4
1 μ M	64.3 ± 8.3*†	28.8 ± 6.1*†	182.8 ± 6.2*	117.1 ± 16.5*†	52.4 ± 10.9*†
Washout	75.2 ± 8.1	36.5 ± 7.5	176.7 ± 6.5	132.8 ± 16.5	64.5 ± 14.4
Levobupivacaine (n = 9)					
Baseline	74.9 ± 10.1	36.6 ± 4.9	169.2 ± 15.9	125.7 ± 24.7	60.4 ± 11.7
0.1 μ M	67.8 ± 10.5	33.6 ± 4.5	176.0 ± 31.0	118.9 ± 32.2	56.2 ± 12.4
1 μ M	56.6 ± 11.6*†	28.6 ± 4.2*†	182.4 ± 20.5*	104.3 ± 24.1*	50.8 ± 9.8*
Washout	69.0 ± 12.0	33.6 ± 4.2	176.7 ± 16.9	123.9 ± 26.9	60.3 ± 11.6
Ropivacaine (n = 8)					
Baseline	77.6 ± 13.6	34.3 ± 4.8	172.4 ± 10.8	134.6 ± 20.1	59.4 ± 6.5
0.1 μ M	74.9 ± 12.4	32.5 ± 4.8	176.7 ± 11.3	132.5 ± 20.7	57.3 ± 6.5
1 μ M	67.5 ± 12.0*†	29.2 ± 3.6*†	179.0 ± 10.3	121.1 ± 21.6*	52.2 ± 5.0*†
Washout	72.1 ± 9.1	33.9 ± 4.1	176.4 ± 12.4	127.4 ± 13.1	59.8 ± 6.3

Data are not given at 10 μ M because no heart could be effectively paced at 300 ms pacing cycle length (PCL). Pacing site was located at the center of the left ventricular epicardium. Data are expressed as mean ± SD.

* $P < 0.05$ versus baseline. † $P < 0.05$ versus 0.1 μ M.

VERP = ventricular effective refractory periods.

Indeed, it was shown that pharmacologic agents have different effects on different subtypes of cells constituting the ventricular wall.²⁹ Our results also confirm the difference in E_{\max} among local anesthetics previously reported by Mazoit *et al.*⁸ However, the potency ratios observed in our study are different from those previously published. Polley *et al.*⁵ reported a racemic bupivacaine to ropivacaine ratio of 0.6 in parturients. Lyons *et al.*⁶ reported a racemic bupivacaine to levobupivacaine ratio of 0.98 in parturients. It should be noted that these ratios were determined at very low concentrations and thus cannot be extrapolated to anesthetic concentrations and, *a fortiori*, to toxic concentrations. In addition, the

Table 5. Effects of Racemic (Rac) Bupivacaine, Levobupivacaine, and Ropivacaine on Dispersion of VERP

Concentration	DI	Dmax (ms)
Rac bupivacaine (n = 9)		
Baseline	0.036 ± 0.019	23.5 ± 11.8
0.1 μ M	0.037 ± 0.011	27.7 ± 13.5
1 μ M	0.043 ± 0.017	24.1 ± 12.5
Washout	0.042 ± 0.022	21.1 ± 8.6
Levobupivacaine (n = 9)		
Baseline	0.056 ± 0.027	15.0 ± 6.9
0.1 μ M	0.066 ± 0.037	17.5 ± 13.5
1 μ M	0.050 ± 0.024	24.1 ± 12.5
Washout	0.044 ± 0.017	21.1 ± 8.6
Ropivacaine (n = 8)		
Baseline	0.033 ± 0.011	14.9 ± 5.4
0.1 μ M	0.031 ± 0.007	14.0 ± 3.7
1 μ M	0.035 ± 0.016	15.9 ± 9.3
Washout	0.037 ± 0.021	16.3 ± 9.9

Ventricular effective refractory period (VERP) was measured on six sites over the left epicardium at a pacing cycle length of 300 ms. Data are expressed as mean ± SD.

DI = dispersion index; Dmax = maximal dispersion.

ratio was determined on nervous tissue, while it is shown that neuronal sodium channels are functionally different from cardiac ones.³⁰ This could explain that, using a similar equipotency ratio (0.76) in anesthetized pigs, Reiz *et al.*² showed that racemic bupivacaine prolongs the QRS interval more than ropivacaine. However, these investigators worked at spontaneous heart rate. Thus, the effect observed on QRS duration could have been modulated by the local anesthetic-induced bradycardia. In isolated perfused rabbit hearts, Mazoit *et al.*⁸ showed that racemic bupivacaine, levobupivacaine, and ropivacaine induce a calculated maximum QRS widening in the ratio 1:0.4:0.3. In the current study, the racemic bupivacaine to levobupivacaine-ropivacaine ratio at 1,000-ms PCL was 1:1.38. The level of PCL we used and the epicardial tissue could also be advocated to explain the difference between the two studies. In addition, the precision of the fitting could have been impaired by the fact that we used a wide range of concentration.

Use dependency is a major factor for the occurrence of racemic bupivacaine-induced conduction block and re-entrant arrhythmias.⁹ Arlock²⁸ showed that, at equimolar concentration, the use dependency induced by racemic bupivacaine was stronger than that induced by ropivacaine. However, the control values in this study were recorded without any drug. Thus, Arlock assessed the concentration and use dependency at once. We used three indexes of use dependency: PCL_{\min} , conduction velocities, and calculated E_{\max} at a PCL of 600 ms. Analysis of PCL_{\min} and E_{\max} modeling showed that the use-dependent slowing of conduction induced by bupivacaine is stronger than that induced by levobupivacaine and ropivacaine. This is in agreement with published data. In fact, analysis of areas under the curves showed

that racemic bupivacaine and levobupivacaine induced a similar use-dependent slowing of θL , which was stronger than that induced by ropivacaine. Irrespective of the ratio of equipotency, the stronger use dependency induced by bupivacaine is a result of the fact that sodium channels' recovery from racemic bupivacaine-induced block is slower than with levobupivacaine or ropivacaine. Indeed, it was shown that the time constant for recovery of channels from $10 \mu\text{M}$ bupivacaine is 2.1 s versus 1.4 s for the same concentration of ropivacaine.²⁸ Mazoit *et al.*⁸ showed that racemic bupivacaine, levobupivacaine, and ropivacaine induce a rate-dependent QRS widening in the ratio 1:0.5:0.25. In the current study, the racemic bupivacaine to levobupivacaine-ropivacaine ratio was 1:0.74. The level of PCL we used and the preparation also explain, at least in part, this difference. In summary, as the effects of levobupivacaine on conduction are similar to those of one or the other agent, depending on the parameter studied, the effects of levobupivacaine appear to be intermediate between ropivacaine and bupivacaine.

Effects on Refractoriness, Wavelengths, and Implication for Arrhythmogenicity

Different effects of local anesthetics on refractory periods were reported. Thus, in the anesthetized dog, Hotvedt *et al.*³¹ showed that racemic bupivacaine (1,000–2,000 ng/ml) does not change VERP or monophasic action potential duration at 50 and 90% repolarization. On a similar model, Kasten *et al.*³² showed that bupivacaine prolongs and induces a dispersion of VERP. However, VERP was measured in spontaneous rhythm, and then the results also reflected the effects of anesthesia- and racemic bupivacaine-induced bradycardia. Huang *et al.*²⁰ reported a shortening of the corrected QT interval after large doses of either racemic bupivacaine or levobupivacaine in conscious sheep. As the QT interval reflects both ventricular depolarization and repolarization, as a widening of the QRS interval also occurred in these animals, one can conclude that the repolarization was shortened in this study. On isolated hearts, conflicting effects of racemic bupivacaine on VERP were reported.^{9,33} In the current study, racemic bupivacaine and levobupivacaine induced a significant prolongation of VERP, whereas ropivacaine did not. This might be explained by a weaker inhibiting effect of ropivacaine on cardiac calcium and potassium channels in comparison with bupivacaine. No dispersion of VERP values over the left ventricular epicardium occurred, whatever the agent. Therefore, in the case of arrhythmia induced by an overdose of the three anesthetics studied, it seems that the mechanism of arrhythmia could not be caused by dispersion-based reentry.

Drugs that decrease wavelengths tend to possess arrhythmogenic potency.³⁴ As all three local anesthetics induce a concentration-dependent decrease in wave-

lengths, all are potentially arrhythmogenic. In the current study, we did not observe any difference in the shortening of wavelengths among the three local anesthetics. However, it should be noted that the wavelengths were calculated at a PCL of 300 ms. Shorter PCL, by decreasing further the conduction velocities and by limiting the increase in VERP, could enhance the shortening of wavelengths by local anesthetics. This could account for the occurrence of one reentrant ventricular tachycardia in our study, during pacing at PCL 250 ms after treatment with $1 \mu\text{M}$ racemic bupivacaine. On the other hand, wavelengths are calculated at $1 \mu\text{M}$ racemic bupivacaine, levobupivacaine, and ropivacaine, because the pacing at a PCL of 300 ms was ineffective at $10 \mu\text{M}$. However, investigators have reported that these anesthetics induce cardiac arrhythmias at higher concentrations (3–6 $\mu\text{g/ml}$, *i.e.*, 9–18 μM).^{9,19,33} Finally, a subtle interaction between the concentration- and the use-dependent effects is probably at the cornerstone of the occurrence of ventricular arrhythmias. Thus, one must keep in mind that a higher incidence of arrhythmias was observed after treatment of animals³⁵ or isolated hearts¹⁹ with racemic bupivacaine compared with levobupivacaine and ropivacaine at equal concentrations. Given the higher potency of racemic bupivacaine, one could argue that the highest arrhythmogenicity is caused by the highest potency, and that at equipotent concentrations, all three agents could be equally arrhythmogenic. Further studies are required to address this hypothesis, and similar precautions must be taken in the clinical use of all three agents to prevent tragic cardiotoxic accidents.

Limitations of the Study and Clinical Implications

Care must be taken before extrapolating the current results to the clinical setting. The interaction of the hemodynamic status and of the autonomic nervous system with the intrinsic electrophysiologic properties of the ventricular myocardium is ignored in the model. In addition, our results on the electrophysiologic parameters are obtained from a thin epicardial layer. As previously stated, because of slight differences in the electrophysiologic behaviors of cells constituting the ventricular wall,³⁶ other subtypes could be affected differently than epicardial myocytes,²⁹ and, theoretically, this could facilitate conduction blocks and reentrant arrhythmias.

Cardiotoxicity of local anesthetics results from increased blood concentrations caused by accidental intravascular injection of an expectedly epidural dose, or to the rapid absorption of the anesthetic after infiltration in a site with a rich blood supply. The most potent agents are also the more toxic, and this is accounted for by the high mortality rate in the case of toxic accident with racemic bupivacaine¹ compared with levobupivacaine³⁷ or ropivacaine.^{38,39} However, one must keep in mind that the toxic effects of local anesthetics could be amplified in patients with cardiac conduction disturbances

or in those taking medications that slow cardiac conduction.⁴⁰⁻⁴² Moreover, with regard to the mechanism of arrhythmias, one must take into account the main role of the use dependency in the occurrence of arrhythmias, especially during resuscitation by the use of positive chronotropic drugs. Indeed, the beat-to-beat slowing of conduction caused by the progressive block of sodium channels leads to conduction blocks, and therefore to the occurrence of reentrant circuits.^{9,26} Although the results of the current study suggest that patients with acute cardiotoxic accidents with levobupivacaine or ropivacaine should sustain higher heart rates than when racemic bupivacaine is involved, the acceleration of heart rate when resuscitating patients with levobupivacaine or ropivacaine cardiotoxicity should also be performed with caution.

In conclusion, the current study shows that racemic bupivacaine, levobupivacaine, and ropivacaine slow longitudinal and transverse conduction velocities in a concentration- and use-dependent manner, without changing the anisotropic ratio. Effects of all agents led to a decrease in wavelengths. The use dependency was stronger with racemic bupivacaine, and this mainly contributes to its higher arrhythmogenicity.

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