Comparative Ventricular Electrophysiologic Effect of Racemic Bupivacaine, Levobupivacaine, and Ropivacaine on the Isolated Rabbit Heart

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Background: Numerous local anesthetics have an asymmetric tetrahedron carbon, which confers stereoselective differences between the isomers. The authors attempted to quantify the depressant effect of racemic bupivacaine, levobupivacaine, and ropivacaine on myocardial ventricular conduction and on myocardial contractility.

Methods: The authors studied the pharmacokinetics (outflow concentration) and pharmacodynamics (QRS widening) of the three drugs infused in an isolated rabbit heart preparation. All data were fitted simultaneously with use of mixed-effect modeling, thus allowing precise statistical comparison between the three drug parameters. The rate dependence of QRS widening was fitted separately.

Results: Racemic bupivacaine, levobupivacaine, and ropivacaine induced a calculated maximum increase in QRS duration in the ratio 1:0.4:0.3. Css_{50}, the dose which caused half the maximum increase in QRS duration at steady state, was similar for all three drugs (22 μM free concentration). A rate dependence of QRS widening was observed, which was in the ratio 1:0.5:0.25 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.

Conclusions: In the isolated rabbit heart, racemic bupivacaine, levobupivacaine, and ropivacaine induce an increase in QRS duration in the respective ratio of 1:0.4:0.3, which was rate dependent in approximately the same ratio. (Key words: Langendorff; NONMEM; pharmacometrics; PK-PD.)

NUMEROUS local anesthetics, including bupivacaine, have an asymmetrically substituted carbon, which confers stereoselective differences between the enantiomers.[1] Bupivacaine binding to sodium channels and to serum proteins is stereoselective,[2,3] and the levo-($S-$)-bupivacaine enantiomer is less cardiotoxic than the dextro-($R+$)-enantiomer.[4-7] However, new experiments strongly suggest that this stereospecific binding to the sodium channel is less important at the nerve site than at the heart site,[8] thus explaining that levobupivacaine may cause nerve block of similar or greater intensity and duration than the racemic mixture.[9-11] Similar observations have been made about $R(-)$- and $S(+)$-mepivacaine.[9] These findings indicate that, among local anesthetic stereoisomers, some are safer than their mirror enantiomer and than the usual racemic mixture. Ropivacaine ([$S-$]1-propyl-2′,6′-pipecoloxylidide) is the only local anesthetic available as a pure enantiomer. Ropivacaine is believed to be safer than bupivacaine.[12,13] Ropivacaine, which has one carbon less and is slightly less lipophilic than bupivacaine, is also slightly less potent than bupivacaine.[14] QRS widening, observed with lidocaine,[15] is related to ventricular conduction velocity slowing.[16] Long-acting local anesthetics, such as bupivacaine, also impair ventricular conduction, primarily by blocking voltage-sensitive sodium channels,[1,17] and this effect is more pronounced with bupivacaine than with lidocaine because of the rate dependence of the block.[18] Moreover, stereospecificity has been observed.[1,4-6,17] These effects on Na$^+$ channels may cause life-threatening arrhythmias, which are thought to be enhanced by an effect on K$^+$ channels; however, stereospecificity may vary depending on the drug and the channel studied.[19-21]

To compare racemic bupivacaine, levobupivacaine, and

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ropivacaine, we attempted to quantify the depressant effect of these agents on myocardial ventricular conduction. Because bupivacaine toxicity has been shown to be rate dependent,[22] we also studied the effect of heart rate on QRS duration changes induced by the three drugs.

Materials and Methods

We studied the effects of local anesthetics on an isolated rabbit heart model with use of a modification of our previously described procedure.[6,15] Twenty-one male New Zealand rabbits, weighing 1,550–2,040 g, were studied in a random block design of three groups of seven animals each. This study was approved by our institutional animal care committee. Care of the animals conformed to the recommendation of the Helsinki Declaration and to the guidelines of the European Communities and French laws for animal experiments (accreditation No. 1989/2559 to Dr. Mazoit). Group 1 animals were infused with racemic bupivacaine, group 2 animals were infused with levobupivacaine, and group 3 animals were infused with ropivacaine. The experimenters were blind to the drug used until study completion. Nine control animals also were studied at random to ensure the stability of the preparation. Finally, we incorporated a pilot group of five previously studied rabbit hearts that had been infused with racemic bupivacaine; the results of this group were incorporated in the rate dependence part of the study with use of the interoccasion variability concept (see Statistics).

Drugs and Reagents

The drugs used were the commercial solutions for racemic bupivacaine and ropivacaine (ASTRA France, Paris, France). The solutions were tested for concentration accuracy with use of hydrochloride salts (ASTRA Pain Control, Södertalje, Sweden). Levobupivacaine hydrochloride was a gift from Chiroscience (Cambridge, United Kingdom). Racemic bupivacaine was tested with use of another hydrochloride monohydrate salt, from Sigma (St. Quentin Fallavier, France). After a concentration check, blind stock solutions of the drugs were prepared.

The same buffer, with the following composition, was used throughout the study: 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl$_2$, 1.2 mM MgSO$_4$, 1.2 mM KH$_2$PO$_4$, 25 mM NaHCO$_3$, 5.5 mM glucose, and 2.0 mM Na pyruvate. The pH of the perfusate at heart inflow was maintained between 7.37 and 7.42. Reagents for chromatography and salts for buffer were purchased from Prolabo (Paris, France).

Study Procedure

The rabbits were anesthetized with 6 mg/kg pentobarbital intraperitoneally. Tracheotomy was performed, and the animals were ventilated manually. The chest was opened, and, after intravenous heparin injection, the heart was removed and mounted quickly on a nonrecirculating Langendorff apparatus, and the coronary arteries were perfused *via* the aorta at a constant flow of 30 ml/min with use of a modified Krebs-Henseleit buffer bubbled with a mixture of 95% oxygen and 5% carbon dioxide at 37°C. The hearts were paced atrially throughout the study with a bipolar electrode at 210 beats/min using a Chronocor IV stimulator (Telectronics, SOREM, Presles en Brie, France), which delivered a square pulse of 3.5 mA. We used the following exclusion criteria for the preparation: (1) the presence of aortic valve regurgitation, (2) a rhythm (before pacing) less than 120 beats/min or greater than 170 beats/min, (3) the presence of arrhythmias, and (4) a dP/dt maximum lower than 1,000 mmHg/s. After an 8- to 12-min stabilization period, the drug (racemic bupivacaine, levobupivacaine, or ropivacaine) was infused into the inflow perfusate at 20 μM for 5 min (from T0 to T5) and at 5 μM during 15 min (from T5 to T20) with use of a model 33 Harvard pump (Harvard, Les Ulis, France). The concentrations infused correspond to amounts of 0.6 μM/min and 0.15 μM/min, respectively (at 30 ml/min buffer infusion). The hearts were studied during a total period of 60 min. The outflow perfusate was sampled with use of a fraction collector at frequent intervals up to 60 min. Pharmacodynamic variables (electrocardiography and left ventricular pressure) were recorded at the end of each effluent sampling time. Racemic bupivacaine, levobupivacaine, and ropivacaine were measured with use of gas chromatography. Electrocardiography was measured with use of surface electrodes. Data were recorded on a Gould 8000s chart recorder (Gould, Les Ulis, France). QRS duration of three consecutive beats, recorded at a paper speed of 200 mm/s, were averaged. The rate of pacing was modified between 17 and 19 min and between 50 and 52 min, with use of steps every 10 s from 170 to 350 beats/min, in increments of 20 beats/min (the starting point of the sequence [initial heart rate] and the order of change [increase or decrease in stimulation rate] were chosen at random). This additional procedure was performed to quantify the rate dependence of QRS duration. A preliminary study performed on five rabbit hearts with use of a step increase of racemic bupivacaine at 0, 1.535, 3.07, and 6.14 μM showed that, when the pacing rate was changed, ap-
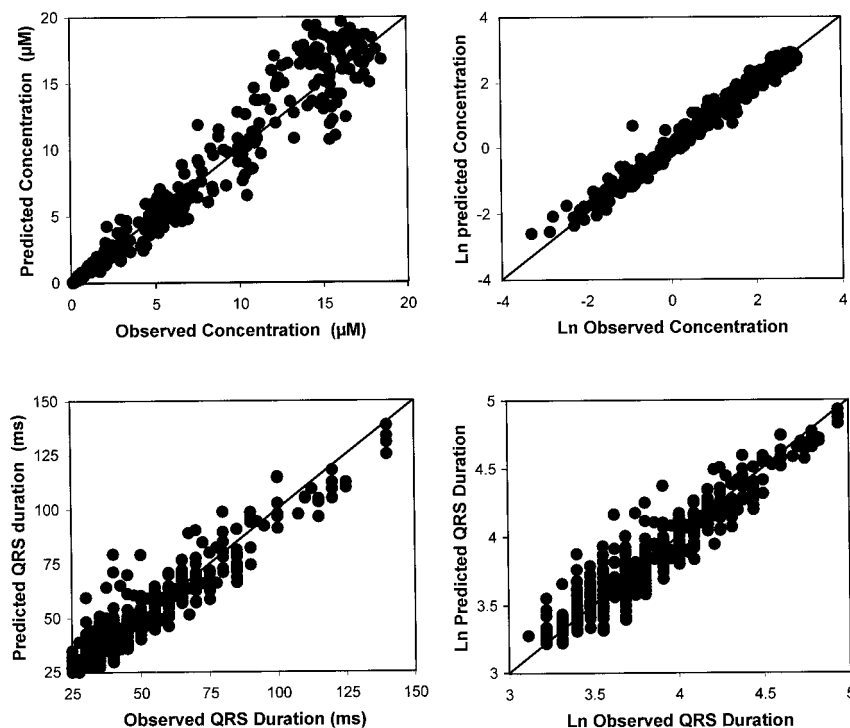
Fig. 1. Adequacy of fitting. Predicted *versus* observed outflow concentration (*top*) and QRS duration (*bottom*). Intraindividual error model for pharmacokinetic and pharmacodynamic data was modeled using a combined additive and constant coefficient of variation without interaction. A small bias in QRS duration fitting is obvious at the highest QRS durations, thus explaining the slightly different E_{max} values observed between the current study and our preceding study, in which the classic two-stage method was used.

proximate steady state QRS duration was attained after 4 or 5 s. A 10-min stabilization period was observed between changes in dose amount. The results of this preliminary group have been incorporated into the study (see after).

Pharmacokinetics and Pharmacodynamics. We used the model previously described.[6,15] Briefly, linear pharmacokinetics were assumed, and the heart was described by a two-compartment open model (with the assumption of venous equilibrium). If C_0 is drug concentration in the inflow perfusate, the outflow perfusate concentration (C) can be expressed as a function of time (t) by the following relation:

$$C = k_{10} A_1/Q \qquad (1)$$

where k_{10} is the exit rate constant from the central compartment, A_1 is the amount of drug in the central compartment at time t, and Q is the perfusate flow. Fitting was performed with use of standard equations[23] with the procedure ADVAN 3 from the program NONMEM[24] (version V, level 1). The volume of the central compartment was not measurable with data from outside the heart. Therefore, we set all volumes to unity. We calculated the three rate constants, k_{12}, k_{21}, and k_{10}, from the central to the peripheral compartment, from

the peripheral to the central compartment, and from the central compartment to outflow, respectively.

The increase in QRS duration (E) was fitted simultaneously to the E_{max}:

$$E = E_0 + \frac{E_{max} A_i}{A_{i50} + A_i} \qquad (2)$$

where E_0 is the basal QRS duration, E_{max} is the maximum increase in QRS duration, and A_{i50} is the drug amount in compartment i that produces half E_{max} at steady state.[25] A special-effect compartment model, as described by Sheiner *et al.*,[26] was also tried. The steady state perfusate concentration that produced half E_{max} (Css_{50}) was calculated as $Css_{50} = A_{i50}/k_{10}$, in case of an effect occurring in the central compartment.

Statistics

Between-group comparison of QRS duration measured before and at the end of each infusion was performed using the Student *t* test with the Bonferroni correction. Results are expressed as the arithmetic mean and SD, except for figure 3, in which the standard error of the mean was used for clarity of the figure.

The data were fitted using the program NONMEM. Its use permits the fitting of mixed-effects models by using two levels of random errors (intraindividual and interin-

Table 1. Summary of Data‡

	Racemic Bupivacaine (n = 7)	Levobupivacaine (n = 7)	Ropivacaine (n = 7)
QRS duration			
Basal QRS duration (ms)	30 ± 4	29 ± 3	32 ± 5
ΔQRS5 (ms)	86 ± 14*†	41 ± 15†	29 ± 8†
ΔQRS20 (ms)	35 ± 11*†	15 ± 7‡	9 ± 7§
Arrhythmias			
Block	5	2	0
PVC	1	0	3
VT	2	1	0
PVC at discontinuation‖	3	0	1
Number of hearts without arrhythmias	1	4	4

* $P < 0.001$ *versus* levobupivacaine and *versus* ropivacaine.

† $P < 0.001$ *versus* baseline.

‡ $P < 0.005$ *versus* baseline.

§ $P < 0.05$ *versus* baseline.

‖ Two hearts in the bupivacaine group had episodes of bigeminy.

E_0 = basal QRS duration; ΔQRS5 and ΔQRS20 = observed absolute increase in QRS duration, respectively, at the end of the first infusion (5 min) and at the end of the second infusion (20 min); Block = intraventricular block, *i.e.*, lack of ventricular electric activity during at least one cardiac cycle despite pacing; PVC = premature ventricular contraction; VT = ventricular tachycardia lasting more than six consecutive beats.

dividual variability). By using nested models, it allows testing of the statistical difference between drugs for a specified parameter in a wide range of experiments.[27] Extended least squares were used as measure of goodness-of-fit[28] (see appendix in Web enhancement).

The concentration–time data first were fitted with use of the first-order method. The parameter estimates obtained at this step were used then (fixed at the value obtained at this step) for the calculation of the effect parameter estimates using the whole data set. The choice between the different pharmacokinetic (PK) models (one or two compartments) and pharmacodynamic (PD) models (effect in the central, peripheral, or special-effect compartment) was made with use of the Akaike criterion.[29] Thus, a full model, with all interindividual variability parameters considered to be relevant, was defined (see appendix in Web enhancement). After this full model was defined, the choice between the full model and successive reduced models was made with use of the log-likelihood ratio test.[30] To avoid overparametrization, we only considered parameters with an estimated coefficient of variation (CV) of the estimates that was less than 60%.[31,32] Intraindividual variability (assay error, model mispecification, and so forth) was modeled using a combined constant CV and additive error model without interaction for pharmacokinetic and an additive error model for pharmacodynamic. Interindividual variability was modeled as $\theta \exp(\eta)$ (assuming a log-normal distribution), in which θ is the vector of the fixed-effect parameter and η is the vector of interindividual variabil-

ity, with variance ω^2. We used the hybrid method, with the mean η corresponding to pharmacokinetic parameters set to 0. We assumed no covariance either between the elements of ϵ, the vector of residual error resulting from intraindividual and measurement variability, or between the elements of η and the elements of ϵ.

The rate dependence of QRS duration was tested with use of the following linear model:

$$QRS = \text{Intercept} + \text{Slope}_i \times C_i \times (HR - HR_0) \qquad (3)$$

where HR is heart rate and C_i is the concentration of drug i in perfusate. The slope was considered linearly dependent on drug concentration and, therefore, was set as the product of an intrinsic parameter for drug i (Slope$_i$) times the concentration of that drug (C_i). Both parameters (Intercept and Slope$_i$) had a fixed effect and a random effect (modeled as $\exp(\eta)$) component. A constant CV was used to model the residual intraindividual error. Data from a pilot study were incorporated in the fitting procedure, considering interoccasion variability with a different η and ϵ.

Results

QRS duration was constant throughout the study period in all control hearts. Local anesthetic infusion was followed by rapid QRS widening. Arrhythmias occurred during the rapid infusion phase (3–6 min after infusion initiation) and at the time of discontinuation of drug

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Table 2. Model Building: Statistical Significance

	Objective Function
PK model	
Full model	
k12, k21 and k10 relevant for all three drugs	$OF_1 = 196.612$
Reduced models	
k10 equal for *rac-* and levobupivacaine	$OF_2 = 196.612$
k21 and k10 equals for *rac-* and levobupivacaine	$OF_3 = 197.110$
k12, k21 and k10 equals for *rac-* and levobupivacaine	$OF_4 = 203.214^*$
* $P < 0.05$ OF_4 *vs.* OF_3	
All other models led to OFs $\gg OF_4$	
PK–PD model (QRS)	
Full model	
E_{max} and Css_{50} relevant for all three drugs	$OF_1 = 3237.001$
Reduced models	
Css_{50} equal for all three drugs	$OF_2 = 3237.231$
All other models led to OFs $\gg OF_2$	
Rate dependence model (QRS)	
Full model	
Slope relevant for all three drugs	$OF_1 = 1329.954$
Reduced models	
Slope equal for rac and levobupivacaine	$OF_2 = 1342.881$
Slope equal for levobupivacaine and ropivacaine	$OF_3 = 1344.484$
	($P < 0.001$ OF_1 *vs.* OF_2 and *vs.* OF_3)

The best model for PK was the two compartment model. The best model for PD was the model with effect in the central compartment and Css50 equal for the three drugs. The best model for rate dependence was the full model. Goodness of fit is represented by the objective function (OF).

infusion (table 1). Because of the small number of hearts used, it was impossible to compare the number of arrhythmias that occurred with each drug. In fact, onlyone heart in the racemic bupivacaine group, four hearts in the levobupivacaine group, and four hearts in the ropivacaine group had no arrhythmias (table 1). Four hearts experienced arrhythmias at infusion discontinuation.

The maximum observed increase in QRS was significantly greater with racemic bupivacaine than with the two other drugs at the end of the two infusion phases (*i.e.*, at T5 and T20) (table 1).

Fitting was adequate with use of the two-compartment open model and the QRS widening effect located in the central compartment, *i.e.*, with no delay between outflow concentration and effect (table 2 and fig. 1). Table 2 shows the statistical difference between models. Racemic bupivacaine and levobupivacaine had a similar k21 and k10. E_{max} was significantly different among the three drugs, whereas Css_{50} was similar for the three drugs (tables 2 and 3). E_{max} was more than twice as much for racemic bupivacaine than for levobupivacaine and approximately 4 times as much for racemic bupivacaine than for ropivacaine (table 3 and fig. 2). The approximate E_{max} ratio was 1:0.4:0.25 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively. QRS widening showed a marked rate dependence, which was linearly related to dose amount, at least for racemic bupivacaine (table 3 and fig. 3). The rate dependence of QRS widening (slope of the QRS duration–heart rate relation) was significantly different between the three drugs, with an approximate ratio of 1:0.5:0.2 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.

Discussion

The current study confirms that levobupivacaine and ropivacaine induce a much lower impairment of intraventricular conduction than does racemic bupivacaine. The number of hearts used in each group does not allow statistical comparison of the number and type of arrhythmias. However, either block (defined as the absence of electrical activity during at least one cardiac cycle, despite pacing) or premature ventricular contraction was more frequent in the racemic bupivacaine group (table 1). These arrhythmias are usually described with use of bupivacaine and are associated with decreased intraventricular conduction velocity and reentry phenomenon.[22] This result is in accordance with the fact that racemic bupivacaine significantly leads to a greater impairment
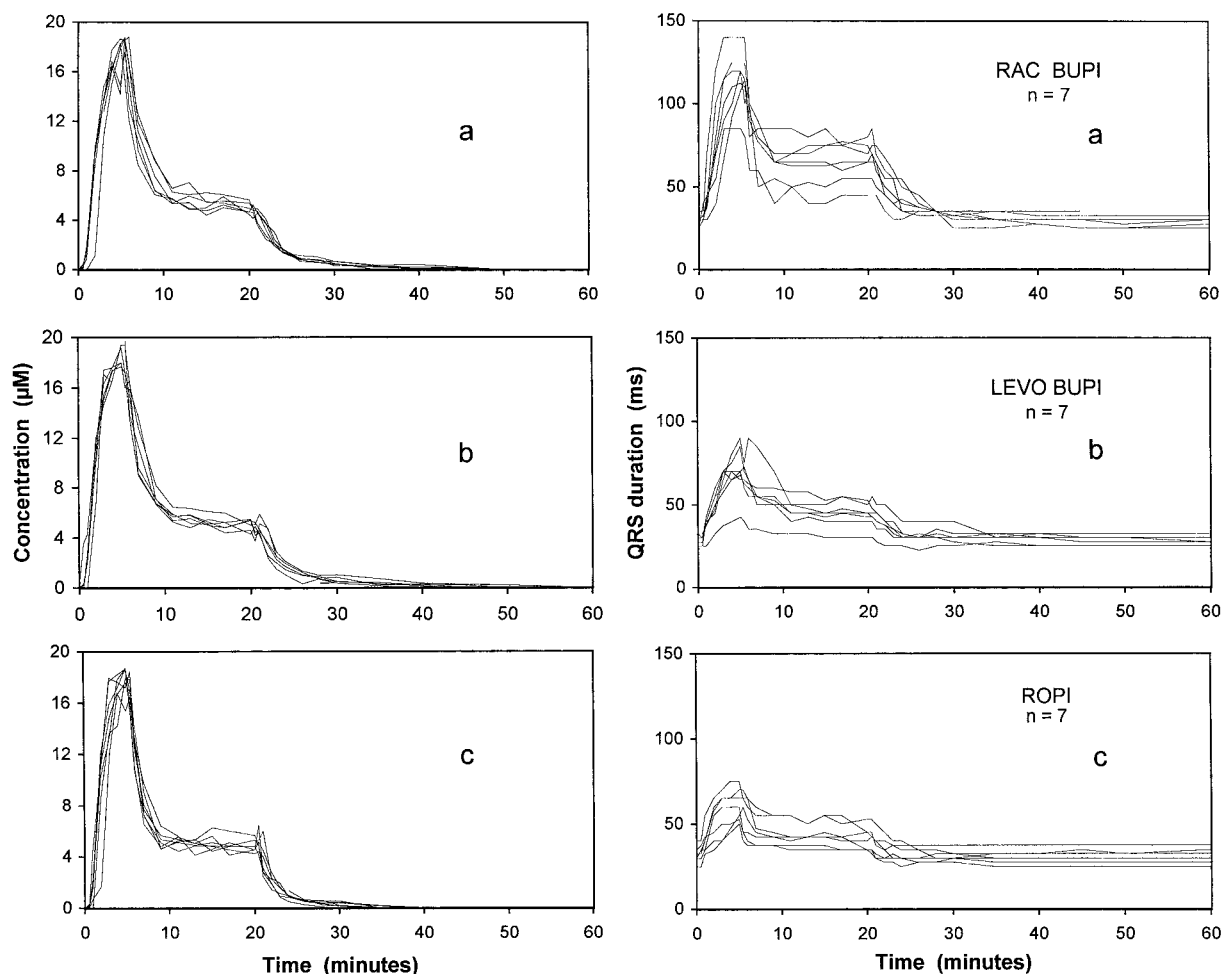
Fig. 2. Chronologic evolution of drug concentration (*left*) and QRS duration (*right*) during and after racemic bupivacaine (RAC-BUPI) (*A*), levobupivacaine (LEVO) (*B*), and ropivacaine (ROPI) (*C*) infusions. Kinetics are almost similar for all three drugs, with a rapid washout after discontinuation of drug infusion. Racemic bupivacaine induced a much higher QRS widening than did the two other drugs.

of intraventricular conduction and to a higher rate dependence. The use of nonlinear mixed-effect modeling allowed us to show that the theoretical maximum effect on QRS duration was significantly greater with levobupivacaine than with ropivacaine, whereas Css_{50} was similar for all three drugs. Therefore, at similar free concentrations in blood, the three drugs are expected to induce ventricular conduction impairment in the approximate ratio (intrinsic activity) of 1:0.4:0.25 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.

We used the global mixed-effect modeling technique, rather than the classic two-stage method because the former approach permits more accurate calculation of confidence intervals for parameter estimates than does the latter.[31,32] Two assumptions were made for interindividual variability estimation. First, we assumed a log-normal distribution for pharmacokinetic and pharmacodynamic parameters, and, therefore, we modeled interindividual variability as $exp(\eta)$. Second, we assumed a nonlinear behavior for pharmacodynamic data. Therefore, we used the hybrid method in NONMEM.

Fitting of pharmacokinetic data was adequate with use of the well-stirred, two-compartment model.[6,15,33] The three drugs showed significantly different kinetic parameters. However, these differences are relatively minor, as shown in figure 2. At the time of discontinuation of drug administration, myocardial washout was rapid, even in the racemic bupivacaine group. These results are in accordance

Table 3. QRS Widening

	k12 (min^{-1})	k21 (min^{-1})	k10 (min^{-1})	Emax (ms)	Css$_{50}$ (μM)
rac-Bupivacaine	0.079 (10%)	0.11 (8%)	0.55 (10%)	330 (50%)	43 (44%)
Levobupivacaine	0.12 (12%)	—	—	132 (31%)	—
Ropivacaine	0.15 (27%)	0.21 (18%)	0.86 (21%)	81 (29%)	—
ω^2	0.055	0.088	0.034	0.36	0.70
Rate dependence of QRS					
	HR$_0$ (beats/min)			Intercept (ms)	
	97 (13%)			29 (3%)	
ω^2	0.17			0.014	
Slope (ms · bpm^{-1} · μM^{-1})	Rac-Bupi 0.083 (12%)			Levo-Bupi 0.041 (38%)	Ropivacaine 0.019 (22%)
ω^2	$\leq 10^{-9}$/0.19			0.13	0.31

The best model was the model with k12 and E$_{max}$ significantly different for all drugs, k21 and k10 identical for rac- and levobupivacaine and Css$_{50}$ similar for all three drugs (see table 2). Data are estimates of PK, PD, and rate dependence parameters (% coefficient of variation of parameter estimate). ω^2 is the variance of interindividual variability parameter (η). Data are given with two significant digits. The rate dependence of QRS widening was tested in the range 170–350 beats/min. k12, k21, and k10 are rate constants from central compartment to peripheral compartment, from peripheral to central compartment and elimination from central compartment, respectively. Emax and Css$_{50}$ are the calculated maximum QRS duration and perfusate steady state concentration leading to half E$_{max}$, respectively.

with our previous studies, which showed that bupivacaine did not accumulate in the myocardium[6,33] and that the toxic effect of long-lasting local anesthetics was not the consequence of drug accumulation in tissue.

We used the simple E$_{max}$ model for QRS widening fitting because the addition of a sigmoid parameter resulted in overparametrization. Fitting was adequate, but a small bias that caused underestimation of the highest QRS values was observed (fig. 2). The Css$_{50}$ (the inflow or outflow steady state concentration that produced half the maximum effect) was similar for all three drugs. We have already shown that the Css$_{50}$ was similar between racemic bupivacaine and lidocaine and between racemic bupivacaine, levobupivacaine, and *R*(+)-bupivacaine. The Css$_{50}$ for the three drugs was similar to the value previously reported (43 μM *vs.* 29–39 μM in the current study and previous studies, respectively).[6,33] The calculated Css$_{50}$ (43 μM, *i.e.*, approximately 14 to 15 μg/ml) needs to be interpreted carefully because we used a protein-free perfusate solution. We may estimate that the approximate free concentration that is necessary to double the basal QRS duration at 210 beats/min was 2.4, 7.2, and 14.4 μg/ml for racemic bupivacaine, levobupivacaine, and ropivacaine.[3] These concentrations are in the range of the free concentrations expected to occur during accidental massive intravenous injection for racemic bupivacaine, but they are likely more than those expected during the same complication for levobupivacaine and ropivacaine.[34]

All three drugs showed a marked rate dependence of QRS widening (table 3 and fig. 3). This rate dependence was statistically different between the three drugs (table 2). With racemic bupivacaine, the slope of the relation between heart rate and QRS duration was related linearly to the dose within the range of frequencies used (fig. 3, top), and nothing indicated that this phenomenon is different with the other two local anesthetics. Therefore, for the comparison between racemic bupivacaine, levobupivacaine, and ropivacaine, we modeled QRS duration as a linear function of inflow concentration with use of equation 3. Fitting was adequate (fig. 3, bottom). The rate dependence of QRS widening was in the range of 1:0.5:0.2 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively, which approximates the ratio of E$_{max}$ calculated for these drugs. The dose–effect curve parameters (E$_{max}$ and Css$_{50}$) were calculated at a fixed frequency of 210 beats/min. Because QRS duration was related linearly to drug concentration and heart rate, changes in heart rate might change E$_{max}$, with a fixed ratio between drugs. However, it may be reasonably speculated that even drugs that rapidly dissociate from the receptor may increase intrinsic activity at extreme heart rates. In contrast, Css$_{50}$ is not expected to vary with changes in heart rate.

In conclusion, using mixed-effect modeling, we showed that racemic bupivacaine, levobupivacaine, and ropivacaine block intraventricular conduction in the rab-
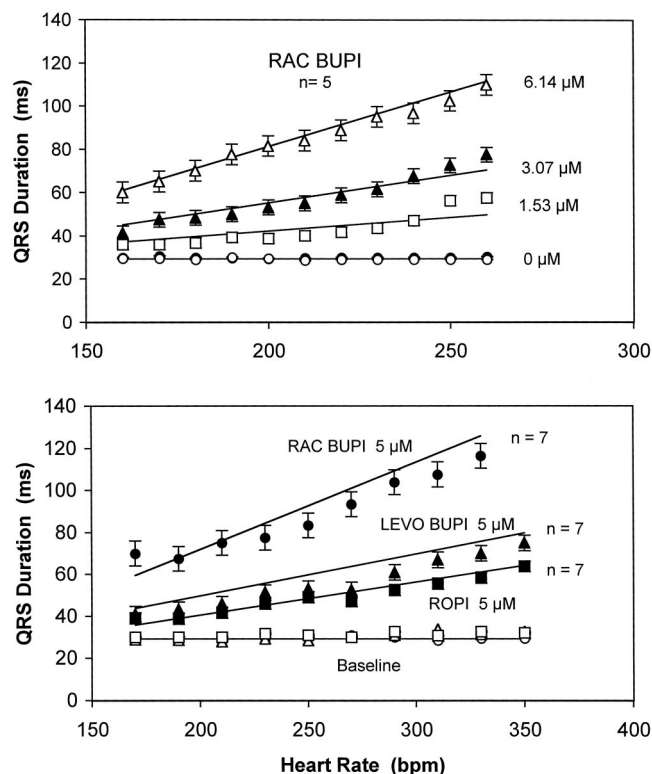
Fig. 3. Rate dependence of QRS widening. QRS duration was measured at varying frequencies. Data are mean ± SEM, for clarity of drawing. (*Top*) One group of five hearts was infused with 0 μM (closed circles), 1.535 μM (open squares), 3.07 μM (closed triangles), 6.14 μM (open triangles), and 0 μM (open circles) racemic bupivacaine (RAC-BUPI), respectively. (*Bottom*) Data obtained in the three groups during infusion of 5 μM racemic bupivacaine (closed circles), levobupivacaine (LEVO) (closed triangles), or ropivacaine (ROPI) (closed squares) and 30 minutes after cessation of drug infusion (open symbols). Because slope is the product of drug concentration and an intrinsic parameter that depends on the drug, slope increases with dose (*top*), but also when the drug is changed from ropivacaine to levobupivacaine and from levobupivacaine to racemic bupivacaine (*bottom*). bpm = beats/min.

bit heart in the respective ratio of 1:0.4:0.25. This impairment of conduction was rate dependent in approximately the same ratio (1:0.5:0.2). This must be interpreted with consideration of the supposed slightly lower nerve block potency of ropivacaine when compared with levobupivacaine and with racemic bupivacaine.[14] Bupivacaine toxicity is rare, but its potential life-threatening effect needs to be taken into account. With these conditions, extrapolation of our results to humans leads to the conclusion that levobupivacaine and ropivacaine are safer than racemic bupivacaine. The choice between levobupivacaine and ropivacaine necessitates further investigation, particularly to compare toxicity with nerve-blocking potency.

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