Anesthesiology
72:322–329, 1990

Cardiac Electrophysiologic Properties of Bupivacaine and Lidocaine Compared with Those of Ropivacaine, A New Amide Local Anesthetic

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Ropivacaine is a new amino-amide local anesthetic whose anesthetic profile appears similar to that of bupivacaine. Moreover, in intact animals ropivacaine was reportedly less arrhythmogenic than bupivacaine. These experiments evaluated the cardiac transmembrane electrophysiologic effects of ropivacaine compared with those of lidocaine and bupivacaine in an isolated rabbit Purkinje fiber-ventricular muscle preparation. Only bupivacaine (3–5 μg/ml, 0.92–1.5 × 10^{-5} m) significantly decreased Purkinje fiber maximum diastolic potential. Action potential amplitude and maximal rate of depolarization ($\dot{V}_{max}$) were significantly decreased by all agents in the following order: bupivacaine, ropivacaine, lidocaine. High concentrations of bupivacaine and ropivacaine caused premature depolarizations during phase 3 in some preparations. In addition, bupivacaine altered the action potential configuration by producing "notching" not seen with either ropivacaine or lidocaine. This may reflect effects caused by changes in Ca^{2+}, K^+, or electrotonic effects. Ropivacaine and bupivacaine (30 μg/ml, 9.2 × 10^{-5} m) and lidocaine (100 μg/ml, 3.74 × 10^{-4} m) caused Purkinje fiber inexcitability and Purkinje fiber-ventricular muscle conduction block. However, the duration of PF inexcitability following exposure to ropivacaine and lidocaine was significantly shorter than in bupivacaine-treated preparation. Duration of PF-VM conduction block also tended to be shorter for ropivacaine than bupivacaine, but significantly longer than lidocaine. In general, ropivacaine is less potent than bupivacaine but more potent than lidocaine in terms of its depressant effect on cardiac excitation and conduction. (Key words: Anesthetics, local: bupivacaine; lidocaine; ropivacaine. Heart: action potential; maximal rate of depolarization ($\dot{V}_{max}$).)

SUDDEN CARDIOVASCULAR COLLAPSE has been reported following the accidental intravascular injection of bupivacaine in some patients.[1–4] Studies in a variety of animal species have demonstrated that convulsant and supraconvulsant doses of bupivacaine but not lidocaine may cause severe ventricular arrhythmias and ventricular fibrillation.[5–10] As a result, interest exists in developing a new local anesthetic with a clinical profile similar to bupivacaine but with significantly less cardiotoxic potential.

Ropivacaine (S-(-)-1-Propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate, the form to be commercially available) is a new amino-amide local anesthetic agent that is similar in structure to mepivacaine and bupivacaine. Ropivacaine's lipid solubility is intermediate between lidocaine and bupivacaine while its pK_a and protein binding are similar to that of bupivacaine.[11,12] *In vitro* and *in vivo* studies indicate that the anesthetic profile of ropivacaine is comparable to that of bupivacaine,[13,14] while its arrhythmogenic potential is less than that of bupivacaine.[15,16] The present study was initiated to compared the electrophysiological effects of ropivacaine, bupivacaine, and lidocaine on an isolated rabbit Purkinje fiber-ventricular muscle preparation. Prior investigations of this type have shown that bupivacaine is significantly more cardiodepressant than lidocaine and that the cardiac electrophysiologic alterations caused by bupivacaine can result in the development of premature action potentials probably reentrant in origin.[17]

Methods

A detailed description of the methods has been reported previously.[17] Healthy, male, white New Zealand rabbits weighing 2.5–4 kg were anesthetized with thiamylal and then killed by iv air injection. The hearts were quickly removed and placed in a beaker of warm, aerated Tyrode's solution. A piece of tissue consisting primarily of the right ventricular septal wall was dissected and placed in a recording chamber and superfused with warm (36.5° C) Tyrode's solution that was aerated with 95% O_2–5% CO_2 to maintain a *p*H of about 7.35. The content of the Tyrode's solution was (in mM/l): NaCl, 137; KCl, 4.0; $CaCl_2$, 1.2; $MgCl_2$, 0.9; NaH_2PO_4, 1.2; $NaHCO_3$, 24; d-glucose, 11.

Extracellular stimulating and intracellular recording electrodes were positioned at the Purkinje fiber (PF) and ventricular muscle (VM) cells. The preparation was paced orthogradely through bipolar Teflon®-coated silver wires, placed on the right bundle branch, at a rate of 2.5 Hz by rectangular pulses, two times the diastolic threshold and 1 ms in duration. The use of this pacing rate was to control for the high degree of spontaneous activity often seen in these preparations. Premature stimuli, used to measure the effective refractory period and membrane responsiveness, consisted of rectangular pulses 2 ms in duration with an amplitude three times threshold. These premature stimuli were applied only after every tenth action potential during the recording period.

The recording electrodes were 3M KCl filled micropipettes with resistances between 10–30 megohms. They

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Received from the Department of Anesthesia, Research Laboratories, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. Accepted for publication September 19, 1989. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1986.

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were placed into cells of the specialized conducting system (PF) and of the VM. The transmembrane action potentials from PF and VM were passed through wideband electrometers and displayed simultaneously upon an oscilloscope screen along with their first derivatives. Some parameters were measured initially by digitizing the analog signal with a Tektronix® waveform digitizer. The displayed signals were recorded permanently on Polaroid® film and some parameters were measured later from these photographs.

A variety of electrophysiological PF and VM parameters were measured, including: maximum diastolic potential (MDP); action potential amplitude (AP); maximal rate of depolarization of phase zero ($\dot{V}_{max}$); action potential duration at 50 and 75% of repolarization ($APD_{50\&75}$); conduction time (CT); and the ratio of effective refractory period to APD_{75} (ERP/APD). APD_{75} was chosen to compare with ERP, fortuitously during baseline recording this ratio was close to one. ERP was determined by applying a rectangular stimulating pulse three times threshold and 2 ms in duration at varying intervals during repolarization following every tenth action potential during the recording period. The shortest interval between the rising phase of the normally paced action potential and the first premature, normally conducted action potential whose amplitude reached 0 mV, was chosen as the ERP. We also measured membrane responsiveness which is a graph of the maximal rate of depolarization of premature action potentials evoked during repolarization and the membrane potential from which they arose. Although action potentials were recorded from both Purkinje fiber and ventricular muscle cells, only Purkinje fiber action potential parameters are reported since all drugs caused some degree of conduction block to the muscle. Therefore, the VM action potential was used solely to calculate conduction time. Conduction time was calculated as the time from the stimulus artifact to the rising phase of the ventricular action potential minus the comparable measurement for the Purkinje fiber.

Initially, these parameters were recorded in paced preparations. Following termination of electrical stimulation, the tissue was allowed to become spontaneously active. The rate of action potential generation was then recorded.

Two experimental studies were carried out. In Study I, the tissue was equilibrated in normal Tyrode's solution for 60 min and then exposed to three increasing concentrations of lidocaine (5, 10, and 20 μg/ml), bupivacaine (1, 3, and 5 μg/ml), and ropivacaine (1, 3, and 5 μg/ml) for a period of 60 min at each concentration.

Study II was designed to mimic drug concentrations that may occur following an accidental iv injection. After the baseline readings, the tissues were exposed to three decreasing concentrations of lidocaine (100, 10, and 2.5 μg/ml), bupivacaine (30, 3, and 1 μg/ml), and ropivacaine (30, 3, and 1 μg/ml). The preparation was exposed to the high concentration for 2 min, intermediate concentration for 28 min, and low concentration for 30 min. In both studies, all drugs were solubilized in protein-free solutions.

The molar concentrations of bupivacaine and ropivacaine are essentially equivalent with ropivacaine base being 95% of the bupivacaine molar concentration. This is not surprising since ropivacaine varies from its homologue bupivacaine by having one less CH_2.[12] The concentrations of bupivacaine and ropivacaine used in Study 1 were in protein-free solution. The corresponding plasma concentrations would be (for bupivacaine) 1 μg/ml in Tyrode's = 5.5 μg/ml in plasma assuming 90% binding; 3 μg/ml in Tyrode's = 10 μg/ml in plasma at 70% binding and 5 μg/ml in Tyrode's = 14 μg/ml in plasma at 65% binding[19,20] (bupivacaine · HCl: 1 μg/ml = 3.08×10^{-6} M base; ropivacaine · $HCl^{-1} \cdot H_2O^{-1}$: 1 μg/ml = 3.04×10^{-6} M; lidocaine · $HCl^{-1} \cdot H_2O^{-1}$: 5 μg/ml = 1.89×10^{-5} M base).

As we discussed previously, these drug concentrations were high;[17] animal studies have reported plasma concentrations of bupivacaine at 60 μg/ml.[20] If a 50% protein binding is assumed at this concentration[18,19] that would leave 30 μg/ml not bound. For lidocaine at this concentration, protein binding is on the order of about 25%.

In Study I, ten experiments were carried out with each drug, while in Study II, six experiments were carried out with each agent. In addition, ten control experiments were performed to determine if any changes occurred during a 3-h observation period.

All animals were housed, handled, and killed in accordance with the Harvard Medical School and NIH-approved guidelines.

Solutions were prepared fresh daily by solubilizing specific drug quantities calculated as the base in 20 ml of purified deionized water (Millipore® cartridge system) and then adding appropriate amounts of this stock to the superfusate reservoir.

The data were analyzed statistically using one-way analysis of variance (ANOVA), Newman-Keuls Test, and Student's *t* test where applicable. Paired *t* tests were employed to evaluate the differences between various concentrations of the same drug while unpaired *t* tests were used to evaluate differences between drugs.

The data are presented as the mean ($\bar{X}$) ± standard error of the mean (SEM). $P \leq 0.05$ was considered to be statistically significant.

Results

No significant change in the Purkinje fiber or ventricular muscle action potentials were observed in the ten

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TABLE 1. Effects of Various Local Anesthetics on Maximum Diastolic Potential (MDP) and Action Potential Amplitude (AP)

Concentration	Lidocaine	Bupivacaine	Ropivacaine
MDP (mV)			
Baseline	79.4 ± 1.4	80.5 ± 1.8	81.2 ± 1.5
1 μg/ml	—	79.4 ± 1.9	80.4 ± 1.2
3 μg/ml	—	74.4 ± 1.9*	78.4 ± 1.5
5 μg/ml	80.0 ± 1.3	72.2 ± 2.2*	76.9 ± 2.1
10 μg/ml	74.2 ± 1.4	—	—
20 μg/ml	76.4 ± 2.0	—	—
Wash period	74.3 ± 1.5	75.1 ± 1.3	80.2 ± 1.5
AP (mV)			
Baseline	114.3 ± 1.9	113.2 ± 1.8	116.0 ± 2.1
1 μg/ml	—	107.0 ± 1.8	114.4 ± 1.5
3 μg/ml	—	90.2 ± 3.8*	103.4 ± 2.2*
5 μg/ml	114.8 ± 1.2	88.5 ± 3.3*	96.0 ± 3.2*
10 μg/ml	107.2 ± 3.5	—	—
20 μg/ml	107.8 ± 2.2*	—	—
Wash period	111.5 ± 2.7	108.3 ± 1.7	111.8 ± 2.4

Values given are $\bar{X}$ ± SEM; n = 10 for each drug.
* $P < 0.05$ compared to baseline.

preparations paced at 2.5 Hz and exposed to drug-free Tyrode's solution for 3 h.

STUDY I

Maximum Diastolic Potential (MDP). Lidocaine and ropivacaine did not significantly alter the MDP of the Purkinje fiber or ventricular muscle cells. However, bupivacaine (3 and 5 μg/ml) significantly depolarized PF's MDP 6 and 8 mV, respectively, after 45 min exposure ($P < 0.05$; table 1).

Action Potential Amplitude (AP). All three drugs decrease AP, ropivacaine, and bupivacaine in a concentration-dependent manner. Ropivacaine significantly decreased Purkinje fiber AP by 11% at 3 μg/ml and 17% at 5 μg/ml ($P < 0.05$). Bupivacaine significantly decreased AP by 20% at 3 μg/ml and 22% at 5 μg/ml ($P < 0.01$). Lidocaine significantly decreased AP 6% at 20 μg/ml ($P < 0.01$; table 1). The decrease in AP produced by 3 and 5 μg/ml of bupivacaine was significantly greater than that observed with an equal concentration of ropivacaine or 10–20 μg/ml of lidocaine ($P < 0.01$). In all cases the AP returned toward baseline values during washout.

Maximal Rate of Depolarization ($\dot{V}_{max}$). Ropivacaine significantly decreased $\dot{V}_{max}$ from a baseline value of 602 ± 31 V/s to 352 ± 30 V/s at 3 μg/ml ($P < 0.01$) and 256 ± 32 V/s at 5 μg/ml ($P < 0.001$; fig. 1). Bupivacaine significantly decreased $\dot{V}_{max}$ at all concentrations ($P < 0.001$), while lidocaine significantly decreased $\dot{V}_{max}$ only at 10 and 20 μg/ml ($P < 0.01$; fig. 1). The decrease in $\dot{V}_{max}$ produced by bupivacaine was significantly greater than that seen with ropivacaine and lidocaine ($P < 0.05$). Ropivacaine at 3–5 μg/ml decreased $\dot{V}_{max}$ significantly greater than 10 μg/ml lidocaine ($P < 0.05$).

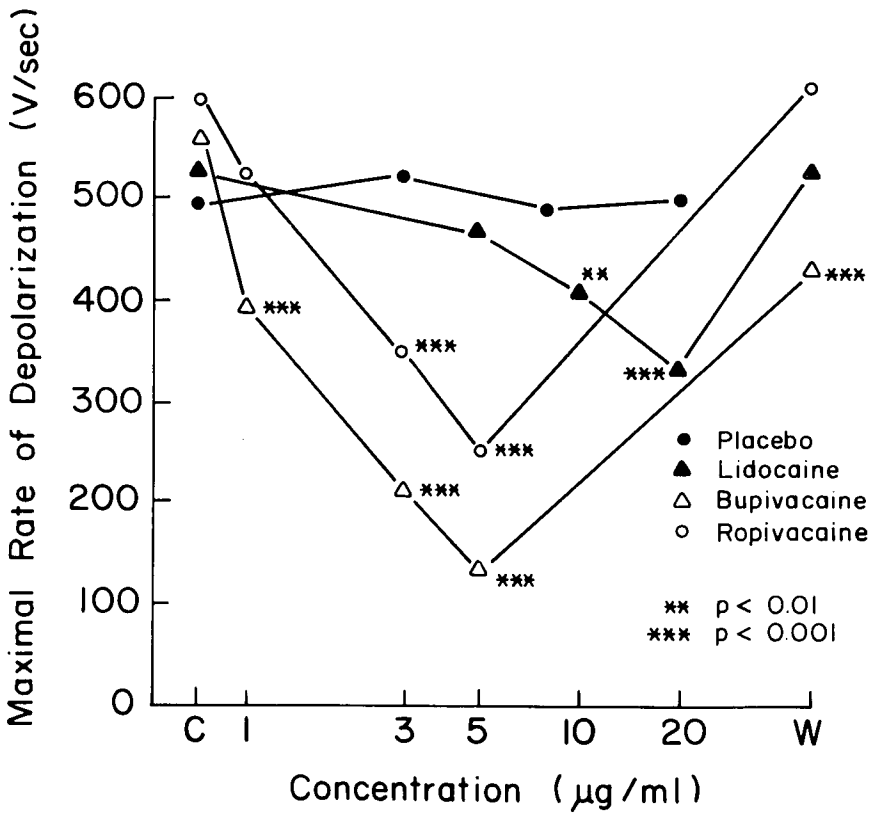

FIG. 1. Effect of lidocaine, bupivacaine, and ropivacaine on Purkinje fiber maximal rate of depolarization. (n = 10; C = control; W = washout.)

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TABLE 2. Effects of Various Local Anesthetics on the Action Potential Duration Measured at 50% and 75% of Repolarization ($APD_{50,75}$)

Concentration	Lidocaine	Bupivacaine	Ropivacaine
ADP_{50} (ms)			
Baseline	146.0 ± 9.2	157.2 ± 6.8	144.7 ± 8.5
1 μg/ml	—	119.5 ± 7.1*	129.3 ± 5.8
3 μg/ml	—	110.3 ± 10.9†	125.7 ± 4.4
5 μg/ml	119.6 ± 8.2*	138.1 ± 8.6 (n = 4)	116.8 ± 8.4† (n = 6)
10 μg/ml	115.1 ± 6.6*	—	—
20 μg/ml	112.5 ± 5.7*	—	—
Wash period	134.5 ± 6.6	131.8 ± 7.3	128.3 ± 6.1
ADP_{75} (ms)			
Baseline	168.3 ± 8.8	181.4 ± 5.4	165.6 ± 6.0
1 μg/ml	—	150.4 ± 5.0†	151.7 ± 3.8
3 μg/ml	—	143.1 ± 9.2†	152.2 ± 5.2*
5 μg/ml	144.6 ± 7.1	167.0 ± 7.3	148.7 ± 7.8 (n = 6)
10 μg/ml	140.9 ± 6.1*	—	—
20 μg/ml	139.9 ± 5.5*	—	—
Wash period	157.3 ± 5.8	152.7 ± 7.2	151.6 ± 7.0

Values are $\bar{X}$ ± SEM; n = 10 for each drug.
* $P < 0.05$ compared to baseline.
† $P < 0.01$ compared to baseline.

TABLE 3. Effect of Various Local Anesthetics on the Ratio of Purkinje Fiber Effective Refractory Period to Action Potential Duration (ERP/APD)

Concentration	Lidocaine	Bupivacaine	Ropivacaine
Baseline	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.01
1 μg/ml	—	1.20 ± 0.04*	1.09 ± 0.02
3 μg/ml	—	1.41 ± 0.08*	1.23 ± 0.05*
5 μg/ml	1.19 ± 0.05*	1.36 ± 0.09*	1.45 ± 0.10*
10 μg/ml	1.19 ± 0.04*	—	—
20 μg/ml	1.21 ± 0.04*	—	—
Wash period	1.05 ± 0.02	1.17 ± 0.06	1.08 ± 0.02

Values given are $\bar{X}$ ± SEM; n = 10 for each drug.
* $P < 0.05$ compared to baseline.

Action Potential Duration at 50% of Repolarization (APD_{50}). All three agents significantly decreased APD_{50} (table 2). However, ropivacaine significantly decreased APD_{50} only at 5 μg/ml ($P < 0.01$). Bupivacaine decreased APD_{50} at 1 and 3 μg/ml ($P < 0.05$), but at 5 μg/ml the APD_{50} returned toward baseline values. Lidocaine significantly reduced APD_{50} at all concentrations ($P < 0.05$). The bupivacaine- and ropivacaine-induced changes on the APD_{50} were complicated by the P-M conduction delay. In six of ten preparations superfused with 5 μg/ml of ropivacaine, the recorded APD_{50} decreased while in the remaining four preparations the APD_{50} increased. The APD_{50} prolongation was seen in all bupivacaine-treated preparations at a concentration of 5 μg/ml (fig. 2). Bupivacaine prolonged the PF-VM conduction time (below) thereby delaying activation of the myocardium. By the time the VM was activated, the PF was repolarizing. Possibly the electrotonic effects of the large mass of VM tissue affected the overlying PF tissues providing a prolongation of the PF-APD.[21,22] No preparations exposed to lidocaine showed an increase in APD_{50}. Ropivacaine (3 μg/ml) decreased APD_{50} significantly less than an equal bupivacaine concentration ($P < 0.05$).

Ratio of Effective Refractory Period to APD_{75}. All three drugs increased the ERP/APD ratio. Lidocaine significantly increased the ERP/APD ratio by approximately 20% at all concentrations, bupivacaine by 40% at 3 and 5 μg/ml, and ropivacaine by 23 and 45% at 3 and 5 μg/ml (table 3). At 3 μg/ml, ropivacaine's effect was significantly less than that of bupivacaine ($P < 0.05$).

Membrane Responsiveness. Ropivacaine (5 μg/ml) and bupivacaine (3 μg/ml) caused a similar depression of Purkinje fiber membrane responsiveness (fig. 3). Lidocaine (20 μg/ml) and ropivacaine (3 μg/ml) decreased membrane responsiveness considerably less than 3 μg/ml bupivacaine ($P < 0.05$; fig. 3).

Conduction Time (CT). Conduction time between Purkinje fiber and ventricular muscle increased dose-dependently with all agents (table 4). Three and 5 μg/ml of bupivacaine and ropivacaine caused some degree of PF-VM conduction block in 90–100% of the preparations.

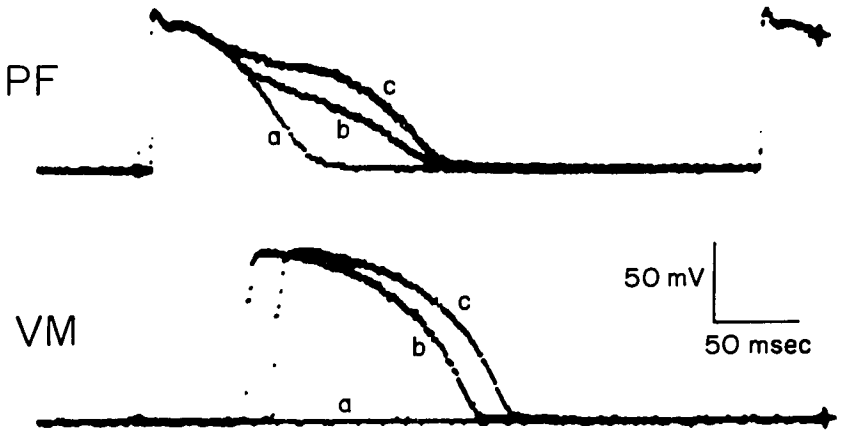

FIG. 2. Drug-induced prolongation of the action potential duration produced by bupivacaine (5 μg/ml). Three superimposed PF and VM traces. Trace A in PF was blocked in VM. Traces B and C demonstrate that the delayed ventricular muscle action potential conduction evoked an APD prolongation in the PF action potential. Ropivacaine produced similar effects but to a lesser degree.

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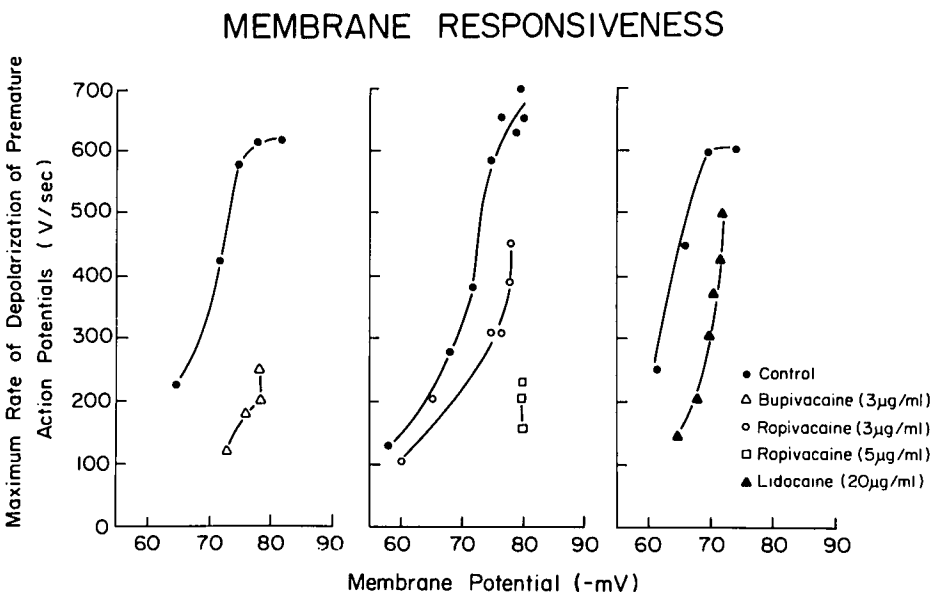

FIG. 3. Effect of lidocaine, bupivacaine, and ropivacaine on Purkinje fiber membrane responsiveness. Curves are from one representative experiment per drug. The term membrane potential refers to the membrane potential during repolarization from which premature action potentials were evoked.

On the other hand, 20 μg/ml lidocaine caused conduction block in only 10% of the preparations.

Automaticity. Spontaneous impulse generation decreased with all three agents. However, ropivacaine caused a maximum decrease in rate of 35% compared to maximum significant decreases of 65% and 61% produced by bupivacaine and lidocaine, respectively (table 5).

STUDY II

Ropivacaine (30 μg/ml) inhibited PF excitability for 4.3 ± 0.3 min in 4 of 6 preparations (table 6). Bupivacaine (30 μg/ml) caused PF inexcitability in all preparations that persisted for 18.2 ± 3.6 min. Lidocaine (100 μg/ml) inhibited PF excitability for only 3.5 ± 1.5 min in two of six experiments. Ropivacaine induced PF-VM conduction block in all preparations which lasted an average of 33.2 ± 5.5 min compared to 47.8 ± 5.2 min for bupivacaine. The difference, however, was not statistically significant.

TABLE 4. Effect of Various Local Anesthetics on Purkinje Fiber—Ventricular Muscle Conduction Time (ms)

Concentration	Lidocaine	Bupivacaine	Ropivacaine
Baseline	11.5 ± 1.9	10.5 ± 1.4	16.7 ± 4.3
1 μg/ml	—	21.3 ± 4.8*	23.7 ± 5.9
3 μg/ml	—	(9)	(9)
5 μg/ml	16.8 ± 2.4*	(10)	(10)
10 μg/ml	16.9 ± 3.2*	—	—
20 μg/ml	18.0 ± 3.5* (1)	—	—
Wash period	11.9 ± 2.9	21.3 ± 4.5*	10.7 ± 2.2

Figures in parenthesis indicate number of preparations in which PF-VM conduction block occurred. Values given are $\bar{X}$ ± SEM; n = 10 for each drug.
* $P < 0.05$ compared to baseline.

Lidocaine caused PF-VM conduction block for 5.8 ± 2.3 min in only four of six preparations (table 6).

In three preparations, ropivacaine produced abnormalities in Purkinje fiber action potentials. In two preparations, these abnormalities consisted of secondary Purkinje fiber depolarizations (fig. 4). In the third preparation ropivacaine produced a transient tachyarrhythmia in the Purkinje fiber. In the latter case, conduction to the ventricular muscle was 2:1. Similar arrhythmias of both types were also observed in three preparations superfused with bupivacaine.

Bupivacaine induced a transient notching or membrane potential hyperpolarization of the phase 1–2 transition point in four of six preparations (fig. 5).[17] In two preparations an alternans between a normal action potential and one consisting of phase 0 depolarization and a phase 1 exponential repolarization to the resting potential was observed.[24] This second PF action potential elicited no action potential in the ventricular muscle. Neither lidocaine nor ropivacaine produced this effect.

TABLE 5. Effect of Various Local Anesthetics on Spontaneous Purkinje Fiber Activity (Beats/Min)

Concentration	Lidocaine	Bupivacaine	Ropivacaine
Baseline	86.4 ± 16.8	86.4 ± 13.2	69.4 ± 9.5
1 μg/ml	—	51.6 ± 8.4	59.5 ± 10.7
3 μg/ml	—	33.6 ± 9.6*	46.6 ± 4.6
5 μg/ml	43.8 ± 10.8	31.2 ± 9.6*	45.5 ± 5.3
10 μg/ml	41.4 ± 11.4	—	—
20 μg/ml	34.2 ± 12.6*	—	—
Wash period	81.6 ± 10.8	65.4 ± 15.0	66.9 ± 6.9

Values given are $\bar{X}$ ± SEM; n = 10 for each drug.
* $P < 0.05$ compared to baseline.

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TABLE 6. Time (min) Required for Recovery of Normal Purkinje Fiber Excitability and Purkinje Fiber-Ventricular Muscle (PF-VM) Conduction Following Exposure to a High Concentration of Various Local Anesthetics

Drug	Purkinje Fiber Excitability	PF-VM Conduction
Lidocaine (100 μg/ml)	3.5 ± 1.5 min (2 of 6)	5.8 ± 2.3 min (4 of 6)
Bupivacaine (30 μg/ml)	18.2 ± 3.2 (6)	47.8 ± 5.1 (6)
Ropivacaine (30 μg/ml)	4.3 ± 0.3 (4 of 6)	33.2 ± 5.5 (6)

Lidocaine vs. bupivacaine—$P < 0.05$. Lidocaine vs. bupivacaine—$P < 0.01$.
Ropivacaine vs. bupivacaine—$P < 0.01$. Lidocaine vs. ropivacaine—$P < 0.05$.
Lidocaine vs. ropivacaine—NS. Ropivacaine vs. bupivacaine—NS.

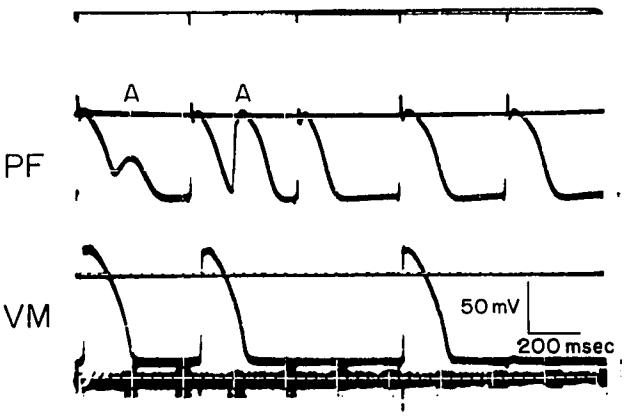

FIG. 4. Premature re-entrant action potentials (A) in Purkinje fiber following 30-min exposure to 5 μg/ml of ropivacaine. There is also a 2:1 PF-VM conduction block beginning at PF action potential 2.

Discussion

The results of the present study employing a rabbit Purkinje fiber-ventricular muscle preparation demonstrate that bupivacaine, lidocaine, and ropivacaine can significantly alter various cardiac electrophysiological parameters. Bupivacaine caused the greatest depression of cardiac excitability and conduction while lidocaine was the least depressant. Ropivacaine occupied an intermediate position. Following progressively increasing concentrations of all drugs, bupivacaine alone significantly decreased MDP which would decrease the number of available sodium channels, thereby decreasing the upstroke velocity of action potentials and thus decreasing conduction. AP was maximally decreased 5% by lidocaine, 17% by ropivacaine, and 23% by bupivacaine. Bupivacaine maximally decreased $\dot{V}_{max}$ by 76% compared to 58% for ropivacaine and 37% for lidocaine. Additionally, ERP/APD ratio was significantly prolonged at a lower concentration of bupivacaine compared to ropivacaine. In general, 5 μg/ml of ropivacaine altered cardiac electrophysiologic parameters to a similar degree as 3 μg/ml of bupivacaine, but more than 10–20 μg/ml of lidocaine.

As stated in the Methods section, 1 μg/ml of bupivacaine in Tyrode's solution is equivalent to about 5.5 μg/ml in plasma.[18,19] During normal well-achieved regional anesthesia, plasma concentrations of bupivacaine would not be expected to exceed 5 μg/ml. However, in pregnant sheep, bupivacaine induced cardiac toxicity at about one-half the plasma concentration required in nonpregnant ewes. Furthermore, accidental injections of a bupivacaine bolus onto the vascular system over a short period could raise the plasma concentration well above 14 μg/ml.

Following an initial but transient exposure to an extremely high concentration of ropivacaine and bupivacaine, both agents inhibited Purkinje fiber excitability and caused PF-VM conduction block. However, recovery of PF excitability and PF-VM conduction was more rapid with ropivacaine than bupivacaine. Although both agents caused abnormalities in PF action potentials in 50% of the preparations, only bupivacaine induced the peculiar notching at the phase 1–2 junction and subsequent development of electrical alternans.[17]

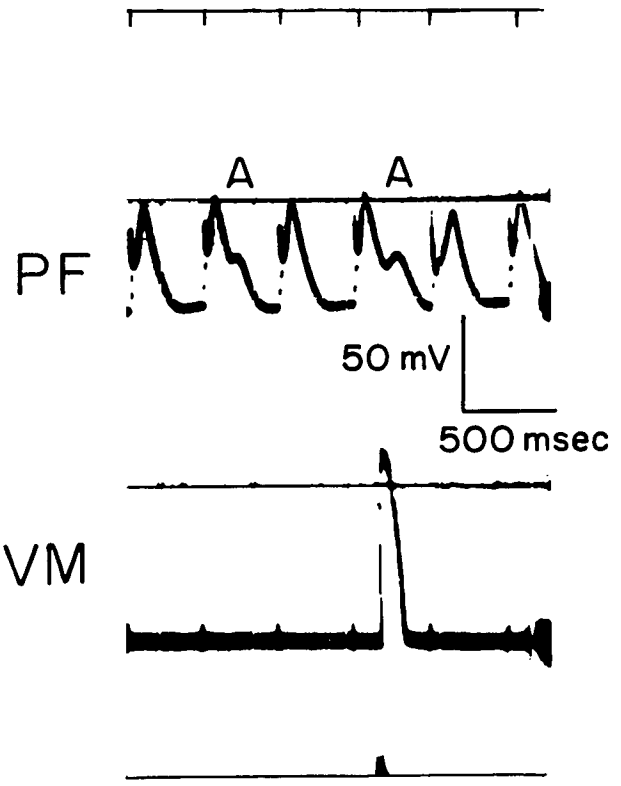

FIG. 5. Bupivacaine-induced Purkinje fiber (PF) notching. The second and fourth action potentials (A) demonstrate a premature depolarization. This is differentiated from APD prolongation by the change in the slope of repolarization from (−) to 0 or (+) as in action potential number 4. There is also profound PF-VM conduction block.

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Bupivacaine-induced electrophysiological alterations would make the development of a re-entrant-type ventricular arrhythmia more likely.[24–26] These changes include depolarized MDP, decreased $\dot{V}_{max}$, increased inhomogeneity of APD (*e.g.*, bupivacaine-induced variability in Purkinje fiber APD due to delay in ventricular muscle activation as mentioned in study 1, APD section), and decreased membrane responsiveness. A decrease in membrane responsiveness as seen with bupivacaine would indicate that action potentials arising during late action potential repolarization or shortly after complete repolarization would have a greatly reduced $\dot{V}_{max}$. Because the depolarizing sodium current determines conduction velocity as well as $\dot{V}_{max}$, the former would be greatly reduced possibly resulting in incomplete conduction throughout the conducting pathway and further increasing the inhomogeneity of the action potential duration. In general, the changes produced by ropivacaine were less severe and of shorter duration than those caused by bupivacaine. The results suggest that the arrhythmogenic potential of ropivacaine may be less than that of bupivacaine, but greater than that of lidocaine. Although ropivacaine is not completely devoid of arrhythmogenic activity, intact animal studies have demonstrated that ropivacaine is associated with a lower incidence of ventricular arrhythmia than is bupivacaine.[15,16] Ropivacaine's degree of protein binding is similar to bupivacaine's[12] although the lipid solubility is less.[11] The lipid solubility ratio of bupivacaine, ropivacaine, and lidocaine in N-heptane and buffer is 10:2.9:1, while the uptake of these agents into rat sciatic nerve was 3.3:1.8:1.[11] Obviously, ropivacaine is 2–3 times less lipid soluble than bupivacaine. Therefore, the difference between the two drugs cannot be attributed to a relatively greater concentration of bupivacaine in the protein-free solution employed in this *in vitro* study compared to intact animals.

The decrease in $\dot{V}_{max}$ produced by all three agents suggests interference with sodium conductance in the cardiac membrane that has been reported by previous investigators.[27,28] Bupivacaine exerted the most significant effect on $\dot{V}_{max}$. Additionally, the duration of bupivacaine-induced Purkinje fiber inexcitability and PF-VM conduction block was longer than after lidocaine and ropivacaine which may indicate a higher degree of bupivacaine membrane protein binding or lipid solubility.[11] The peculiar phase 1-phase 2 notching produced by bupivacaine suggests a possible effect on slow calcium[28,29] or potassium[30,31] channels or electrotonic effects[21,22] which may explain *in vitro* decreases in myocardial contractility[32,33] and arrhythmogenesis produced by bupivacaine. Tetracaine also reduced potassium currents myocytes.[34] The failure to observe similar changes with ropivacaine and lidocaine may indicate a lesser effect on calcium channels by these two agents at these concentrations.

In a recent report, ropivacaine and bupivacaine were compared for motor blockade during epidural administration in dogs.[12] In order to achieve equal duration of blockade, 1.0% ropivacaine was similar to 0.75% bupivacaine, indicating ropivacaine was less potent. In humans, 0.5% ropivacaine produced more profound motor blockade than 0.5% bupivacaine during brachial plexus block although the durations were comparable.[35] When used in epidural anesthesia in humans, ropivacaine is reported to be longer acting than bupivacaine.[36] Since ropivacaine's anesthetic potency has not been tested in rabbits, it is difficult to say whether there are species differences more similar to dog or human in comparing its neural effects to those of bupivacaine. However, ropivacaine's cardiac electrophysiologic effects are less than those of bupivacaine in this rabbit model.

All compounds supplied by Astra Alab, Sweden, as were the HCl salts, except for ropivacaine, which was the $HCl \cdot H_2O$.

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