Anesthesiology
62:396–405, 1985

Mechanism for Bupivacaine Depression of Cardiac Conduction: Fast Block of Sodium Channels during the Action Potential with Slow Recovery from Block during Diastole

Craig W. Clarkson, Ph.D., and Luc M. Hondeghem, M.D., Ph.D.†*

The effects of bupivacaine and lidocaine on cardiac conduction were compared in guinea pig ventricular muscle. Membrane potential was controlled using a single sucrose gap voltage clamp technique, and the maximum upstroke velocity of the action potential ($\dot{V}_{max}$) was used as an indicator of peak sodium current. Bupivacaine blocked cardiac sodium channels in a time- and voltage-dependent fashion. Although bupivacaine has a low affinity for rested and activated sodium channels, it avidly blocks inactivated channels ($K_d = 9 \times 10^{-7}$ M). Bupivacaine-associated channels do not conduct and have their voltage dependence of inactivation shifted by about 33 mV to more negative potentials. At bupivacaine concentrations above 0.2 μg/ml, a substantial fraction of the channels become blocked during the cardiac action potential, while recovery from block during diastole proceeds relatively slowly with a time constant (τ) of 1,557 ± 304 ms (n = 8). Thus, bupivacaine blocks sodium channels in a fast-in-slow-out fashion, and substantial block accumulates at 60–150 beats/min. In comparison, 5–10 μg/ml lidocaine also blocks a substantial fraction of channels during the action potential, but diastolic recovery from block is more rapid (τ = 153.8 ± 51.2 ms, n = 4). Thus, lidocaine blocks channels in a fast-in-fast-out fashion. Consequently, even at toxic doses of lidocaine (*i.e.,* 10 μg/ml), little accumulation of block occurs at normal heart rates. Sodium channel block by bupivacaine can be minimized by reducing heart rate, hyperpolarization, and shortening of action potential duration. However, alteration of these variables over clinically applicable ranges does not produce marked changes in bupivacaine effect. Our results provide a possible explanation for the clinical observation that when bupivacaine accidently gains access to the general circulation, cardiac conduction can be depressed seriously and such depression may be difficult to reverse. (Key words: Anesthetics, local: bupivacaine; lidocaine. Heart: conduction; excitability. Toxicity: local anesthetics.)

This paper is accompanied by an editorial. Please see: Kendig JJ: Clinical implications of the modulated receptor hypothesis: Local anesthetics and the heart. ANESTHESIOLOGY 62:382–384, 1985.

BUPIVACAINE has become a popular local anesthetic because of its long duration of action (up to two or three times as long as lidocaine[1,2]), excellent sensory anesthesia, and, for obstetrics, its lack of adverse neonatal neurobehavioral effects.[3] Unfortunately, these advantages may be offset by the potential for cardiac toxicity when bupivacaine accidently is administered iv.[4,5]‡ In a recent report to the Food and Drug Administration,§ the manufacturers of bupivacaine reported 12 well-documented cases of cardiac arrest associated with the use of bupivacaine, 10 of them fatal.

Depression of cardiac conduction appears to be one of the primary mechanisms underlying bupivacaine's cardiotoxicity.[4]‡ Depression of conduction by local anesthetics in both nerve and cardiac tissue results from block of sodium channels. Furthermore, the degree of sodium channel block by local anesthetics is dependent upon the state of the sodium channel.[6–8] Local anesthetic drugs typically have a high affinity for channels in the open or inactivated states, but a very low affinity for channels in the rested state.[6,7] Consequently, block of sodium channels develops during the upstroke and plateau of the action potential and dissipates during the diastolic interval between beats (fig. 1). Since local anesthetic effect is both state and time dependent, changes in both heart rate and diastolic membrane potential substantially may alter drug action.[7,9]

To better understand the basis for bupivacaine's cardiotoxicity, we studied its electrophysiologic effects on guinea pig ventricular muscle and compared them with those of lidocaine. In particular, we defined both the time course of block development during the cardiac action potential and the time course of block recovery during diastole. The dependence of local anesthetic effect upon both stimulation rate and diastolic membrane potential also was determined.

---

* Postdoctoral Research Fellow in Pharmacology.

† Associate Professor of Pharmacology. Dr. Hondeghem is an Established Investigator of the American Heart Association.

Received from the Department of Pharmacology, University of California, San Francisco, California 94143. Accepted for publication October 12, 1984. Supported by NIH grant HL 21672. Results were presented in part at the annual meeting of the International Anesthesia Research Society, Anesth Analg 63:199, 1984.

Address reprint requests to Dr. Clarkson.

‡ Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. Regional Anesthesia 8:55–61, 1981.

§ Adverse reactions with bupivacaine. FDA Drug Bulletin 13:23, 1983.

Methods

Guinea pigs of either sex and weighing 250–450 g were stunned by cervical dislocation. Their thoraces were opened and the hearts removed as quickly as possible. Papillary muscles having a diameter of less than 0.8 mm and a length of at least 3 mm carefully were dissected and installed in a standard three-compartment sucrose-gap chamber.[9] The base of the papillary muscle was placed in the current injection chamber, which was perfused with HEPES buffered solution (described below) in which the NaCl (143 mM) was replaced by KCl. The middle 2 mm was placed in the center chamber, which was perfused with an isotonic sucrose solution enriched with 40 μM calcium. The tip of the muscle (less than 0.5 mm) was placed in the experimental chamber, which was perfused with a HEPES buffered salt solution of the following composition: (mM): NaCl 143, KCl 4, $CaCl_2$ 1.8, $MgCl_2$ 1.1, d-glucose 5 and HEPES 5. The *p*H of the solution was titrated to 7.38 ± 0.01 with approximately 3 mM NaOH. All solutions were kept at 36 to 37° C and equilibrated with 100% oxygen.

The transmembrane potential was measured using conventional microelectrodes filled with 3 M KCl and attached to a high-input impedence voltage follower with input capacitance and series resistance compensation. Current used for stimulation and voltage clamping the tissue in the experimental chamber was passed from the current injection chamber through the sucrose gap. The command pulses were generated by a Z8253A microprocessor-based stimulator (Micro Data Collection Inc., Novato, California). Action potential upstrokes were elicited by 1 ms current pulses. The intensity of the current pulse was adjusted continuously to maintain a constant latency between the stimulus and time at which the maximum upstroke velocity ($\dot{V}_{max}$) of the action potential was achieved.[10] $\dot{V}_{max}$ was measured by electronically differentiating the action potential upstroke[11] and was used as a measure of the sodium current and recorded on either a polygraph or by photographing the signal displayed on an oscilloscope. During voltage clamping the membrane potential was controlled at all times except during the initial 5 ms of the upstroke of the action potential (during which $\dot{V}_{max}$ was measured) and during the 20-s rest periods separating successive clamp protocols. Different voltage clamp pulse protocols were used to determine the time courses of block development and recovery from block, dependence of block upon stimulation rate, and diastolic membrane potential. To clarify how the results were obtained, pulse protocols are illustrated as diagrams in the appropriate figures. Some protocols are also briefly described in the text.

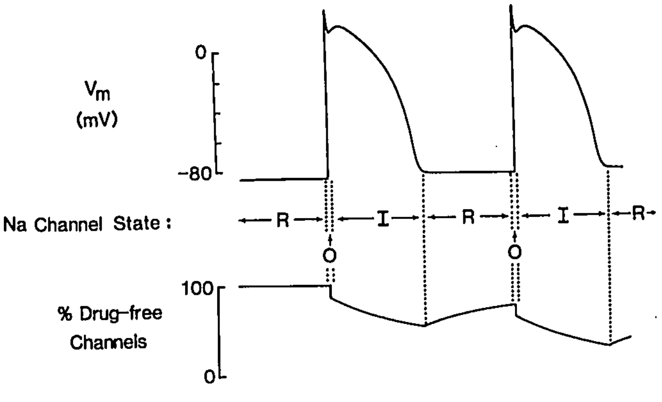

FIG. 1. Schematic diagram illustrating time-dependent changes in sodium channel states (middle) and block of sodium channels (bottom) associated with the cardiac action potential (top) in the presence of a local anesthetic drug. The top trace shows two simulated ventricular muscular action potentials. V_m = transmembrane voltage. The drug binds to sodium channels in open (O) and inactivated (I) states but has a very low affinity for channels in the (R) rested state. As indicated (middle), sodium channels are in the rested state during diastole, open transiently during the action potential upstroke, and are in an inactivated (closed) state during the action potential plateau. As indicated at the bottom, all channels are in a drug-free state after a long rest, but drug binding to open and inactivated channels develops during the action potential. Drug dissociation during diastole is time dependent and incomplete, resulting in an accumulation of drug-associated (blocked) channels with successive beats.

All results reported in the present study were obtained from preparations where $\dot{V}_{max}$ had a constant amplitude in a latency window of at least 1 ms and where a single cell impalement was maintained throughout the study. Even when these precautions are taken there is some controversy as to what extent $\dot{V}_{max}$ is related linearly to peak sodium conductance.[10,12–15] A nonlinear relationship between $\dot{V}_{max}$ and peak sodium conductance could result in an underestimate in the level of channel block when $\dot{V}_{max}$ is used as an indicator of drug-free sodium channels. This controversy only can be resolved when $\dot{V}_{max}$ and peak sodium current have been measured under identical physiologic conditions. For the purpose of the present study, $\dot{V}_{max}$ only needs to be a qualitatively accurate indicator of the peak sodium current, so that a decrease in $\dot{V}_{max}$ reflects a decrease in peak sodium current. Recent studies suggest that this is a valid assumption.[10,12,16]

The time course of block development and recovery was analyzed by using least-squares error nonlinear exponential fitting. Paired comparisons were evaluated using Student's paired *t* test. Comparisons between more than two groups were evaluated by one-way analysis of variance and Scheffe's test for critical difference. Differences were considered significant if *P* values were less than 0.05. Results are represented as mean plus/minus a standard deviation.

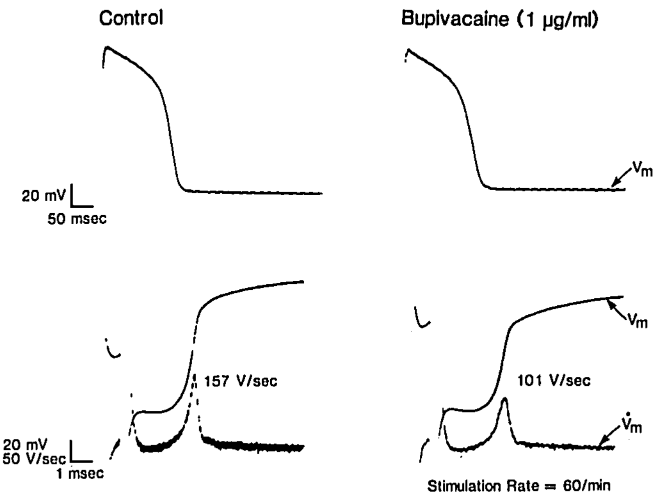

FIG. 2. Effects of 1 μg/ml bupivacaine on the ventricular action potential. The top panels show action potentials recorded in drug-free solution (control) and 30 min after addition of 1 μg/ml bupivacaine. The bottom panels show membrane potentials (V_m) during the action potential upstroke, along with its first derivative ($\dot{V}_m$). The maximum height of the $\dot{V}_m$ trace during the action potential upstroke is referred to as $\dot{V}_{max}$. As indicated, addition of bupivacaine reduced $\dot{V}_{max}$ by approximately one-third at 60 beats/min.

Estimates of drug affinity for different channel states were determined by fitting experimental data with a least-squares error search and a mathematic model of the modulated receptor hypothesis.[7] The experimental data fit was obtained from pulse protocols used to define the effects of rate, recovery from block, and the initial 500 ms of block development at +20 mV.

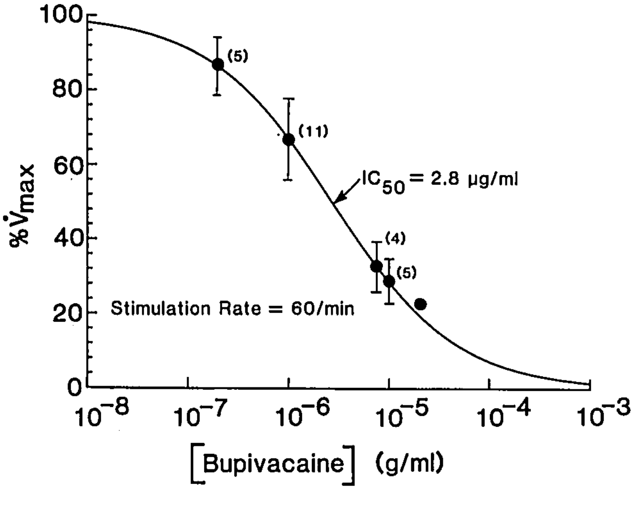

FIG. 3. The concentration–response relationship of bupivacaine-induced reduction of $\dot{V}_{max}$ at 60 beats/min. Data points are mean values of $\dot{V}_{max}$ (normalized to control) obtained in the presence of 0.2, 1.0, 7.5, and 10 μg/ml bupivacaine, and the value at 20 μg/ml represents data from a single preparation. The numbers in parentheses indicate the number of experiments contributing to each point. Vertical bars represent standard deviation. IC_{50} indicates the concentration of bupivacaine required to reduce $\dot{V}_{max}$ by 50%.

Results

DOSE DEPENDENCE

Bupivacaine (1 μg/ml) produced no remarkable changes in the overall action potential configuration; resting potential, plateau potential and action potential duration were virtually unaffected (fig. 2). In contrast, bupivacaine reduced $\dot{V}_{max}$ by approximately one-third (from 157 to 101 V/s). In 11 preparations paced at 60 beats/min, 1 μg/ml bupivacaine reduced $\dot{V}_{max}$ by 33 ± 11% ($P < 0.001$). When the bupivacaine concentration was increased to 10–20 μg/ml (six experiments), within 5 min the action potential plateau shifted to more negative potentials, the action potential duration decreased by 20–30 ms, and $\dot{V}_{max}$ decreased by 70–80%. Because $\dot{V}_{max}$ becomes less reliable as an accurate measure of peak sodium current when it is so strongly reduced,[15] we did not study these high concentrations systematically.

In figure 3 we summarize the effects of bupivacaine obtained from 19 preparations (one or two concentrations per preparation), while being stimulated at 60 beats/min. At this heart rate, $\dot{V}_{max}$ began to decline substantially when the bupivacaine concentration was increased above 0.2 μg/ml (2×10^{-7} g/ml) and the least-squares error estimate of the concentration of bupivacaine required to reduce $\dot{V}_{max}$ by 50% (IC_{50}) was 2.8 μg/ml. Since the effects of bupivacaine were quite measurable at 1 μg/ml, and, since stable effects could be maintained for long time periods, most of our studies were done at this concentration.

USE AND RATE DEPENDENCE

In the presence of bupivacaine (1 μg/ml) $\dot{V}_{max}$ of an action potential upstroke elicited after a long rest period (≥20 s) was not reduced (*i.e.*, by only 4.6 ± 5.5%, $n = 8$, $P > 0.05$). However, as illustrated in figure 4, upon application of a train of beats (pulses), $\dot{V}_{max}$ declined with each successive action potential upstroke until a new steady state $\dot{V}_{max}$ value was reached in about 10 beats. The steady state depression of $\dot{V}_{max}$ was strongly dependent upon the number of times the channels were used per unit time. For example, at a stimulation rate of 3 beats/min, neither 0.2 μg/ml nor 1.0 μg/ml bupivacaine significantly reduced $\dot{V}_{max}$ ($P > 0.05$) (see fig. 5*A*). However, the reduction of $\dot{V}_{max}$ increased progressively as the stimulation rate was increased. Significant levels of $\dot{V}_{max}$ reduction were observed at stimulation rates between 60 and 200 beats/min in the presence of 0.2 μg/ml bupivacaine ($P < 0.05$, $n = 5$) and at stimulation rates above 3 beats/min in 1 μg/ml bupivacaine ($P < 0.01$, $n = 6$). In comparison, reduction of $\dot{V}_{max}$ by 10 μg/ml (43 μM) lidocaine was not significantly different from that produced by 0.2 μg/ml (0.6 μM) bupivacaine at rates faster than 3 beats/min ($P > 0.09$) (fig. 5*A*.) but was significantly less than that produced by 1.0 μg/ml bupivacaine ($P < 0.05$).

Although the lower concentration of bupivacaine produced a level of block similar to that of lidocaine, the rate-dependent properties of the two drugs are not identical. For example, when the stimulation rate was increased from 100 to 200 beats/min, block by lidocaine increased by 43 ± 8%, while the increase in block by 0.2 μg/ml bupivacaine was significantly less (19 ± 5%, $P < 0.01$). This difference in rate dependence indicates that estimates of potency ratios may not be identical at different heart rates. To illustrate this we estimated the ratio of block produced by bupivacaine and lidocaine at different stimulation rates (fig. 5*B*). Over a range of stimulation rates between 3–200 beats/min, the ratio of block (bupivacaine/lidocaine) varied from 0.2 to 2.6 when comparing the effects of 0.2 μg/ml bupivacaine with 10 μg/ml lidocaine and from 0.9 to 6.3 when comparing 1 μg/ml bupivacaine with 10 μg/ml lidocaine. Furthermore, the dependence of the ratio of block upon stimulation rate was biphasic, with a maximum near 100 beats/min.

OPEN VERSUS INACTIVATED CHANNEL BLOCK

Use-dependent reduction of $\dot{V}_{max}$ results whenever the block that develops during an action potential has insufficient time to fully dissipate during diastole. The block development can result from drug binding to open sodium channels (during the upstroke of the action potential) from drug binding to inactivated sodium channels (during the plateau of the action potential) or from drug binding to channels in both states (fig. 1). The extent of inactivated channel block was determined by the twin pulse protocol shown in figure 6*A*. As illustrated, a conditioning pulse of variable duration was followed after a short (100 ms) recovery interval by a test upstroke. The 100-ms recovery interval was long enough so that all drug-free channels could fully recover from inactivation[17] but short enough so that recovery from block by drug was kept minimal.

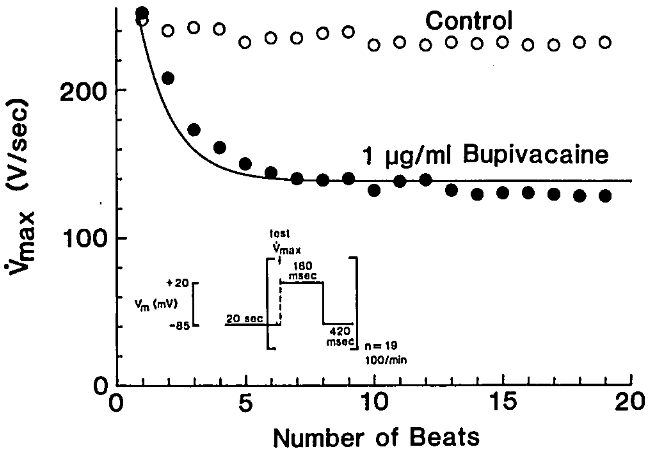

FIG. 4. Rate-dependent reduction of $\dot{V}_{max}$ by 1 μg/ml bupivacaine following a 20-s rest at −85 mV. The pulse protocol used is shown in the inset. The dotted vertical line indicates a free-running action potential upstroke of 5 ms duration. In the absence of drug (unfilled circles), there was little reduction of $\dot{V}_{max}$ during a train of 19 beats at 100 beats/min. After 30 min in 1 μg/ml bupivacaine (filled circles), $\dot{V}_{max}$ of the first beat after a 20-s rest was essentially equal to that observed prior to addition of the drug. However, during successive beats $\dot{V}_{max}$ decreased progressively toward a steady state value that was approximately 54% of that of the first beat. The solid line indicates the time course of $\dot{V}_{max}$ reduction predicted by the modulated receptor hypothesis (see text).

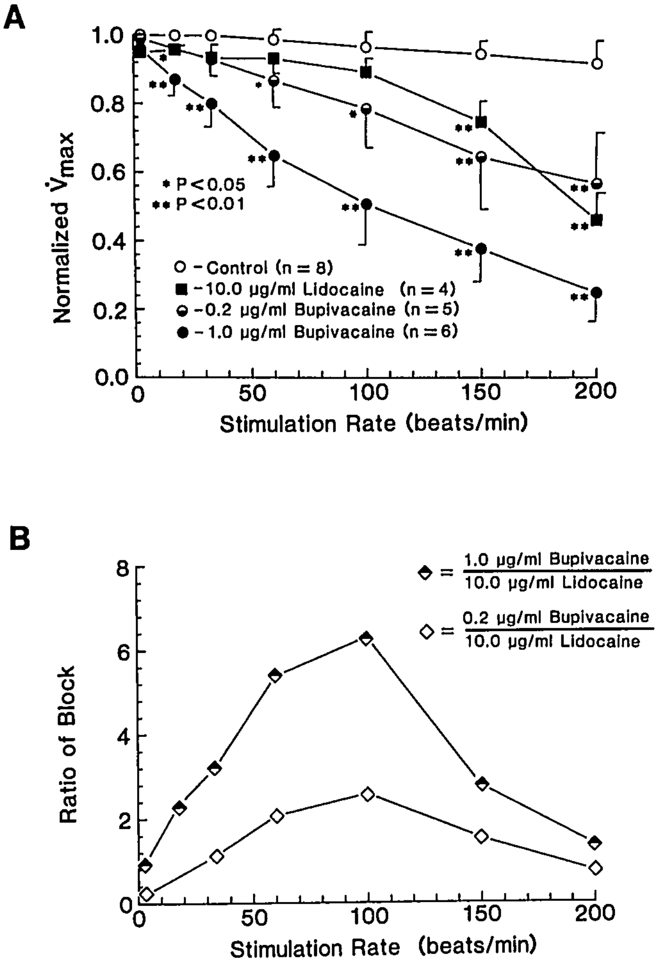

FIG. 5. The rate dependence of drug effect on $\dot{V}_{max}$. *A*. The effect of bupivacaine and lidocaine on $\dot{V}_{max}$ at different stimulation rates. Data points are mean values and vertical bars indicate standard deviation. $\dot{V}_{max}$ has been normalized to its value under control conditions at 3 beats/min. Stars indicate which values were significantly different from control as determined by one-way analysis of variance. *B*. The ratio of block caused by bupivacaine *versus* that caused by lidocaine. The amplitude of block was calculated from the mean levels of $\dot{V}_{max}$ (control–drug) shown in *A*.

A slow exponential decline in $\dot{V}_{max}$ was observed

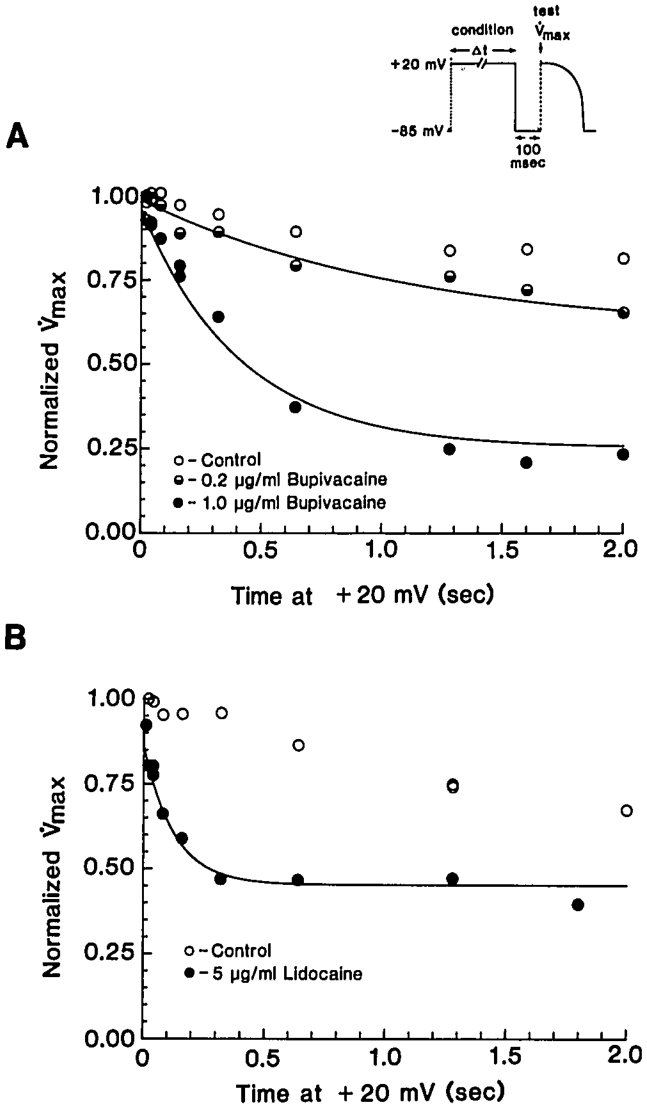

FIG. 6. Time course of block development during an action potential plateau clamped to +20 mV. The pulse protocol is shown in the inset. *A.* Development of block in bupivacaine. *B.* Development of block in the presence of lidocaine. Unfilled circles indicate control values. The small time-dependent decrease in $\dot{V}_{max}$ under control conditions is due to a slow inactivation mechanism.[22] $\dot{V}_{max}$ was normalized to its value after a long rest at −85 mV in the absence of drug. The solid curves indicate the predicted time course of block development for inactivated channels predicted by the modulated receptor hypothesis (see text).

following conditioning pulses to +20 mV in the absence of drug; time constant (τ) = 3,352 ± 2,284 ms (n = 5) (figs. 6*A* and *B*). This time-dependent decrease in $\dot{V}_{max}$ reflects slow inactivation of cardiac sodium channels.[22] However, a conditioning pulse having a duration and amplitude similar to a ventricular action potential (*e.g.*, 320 ms) reduced $\dot{V}_{max}$ by only 5.9 ± 3.8% (n = 5). In contrast, after addition of 1 µg/ml bupivacaine, $\dot{V}_{max}$ decreased much more rapidly and to a larger extent. The time constant for the development of block of inactivated channels was 625 ± 314 ms (n = 5), which was significantly less than control ($P < 0.05$). In addition, the reduction of $\dot{V}_{max}$ produced by a 320-ms conditioning pulse (40 ± 15%, n = 5) was increased significantly ($P < 0.01$) in 1 µg/ml bupivacaine. Similar effects were observed in the presence of 0.2 µg/ml bupivacaine, however, both the extent and rate of block development were much less marked (fig. 6*A*).

Extrapolation of the least-squares exponential to time zero (intercept with the ordinate) gives an estimate of the amount of block that appears to develop instantaneously, *i.e.*, the block that cannot be accounted for as developing during inactivation and consequently must have developed during the action potential upstroke when channels were open. For bupivacaine there appeared to be no significant instantaneous or open channel block; the estimated fraction of channels blocked during the upstroke in the presence of 1 µg/ml bupivacaine was 3.2 ± 6.0% (n = 5, $P > 0.29$). This result does not, however, rule out the possibility that bupivacaine blocks a significant although small (≤3%) fraction of open channels during the upstroke. To further test this conclusion, we examined the blocking effect of bupivacaine during a train of pulses of 5 ms duration at 30 Hz. During a train of such pulses, block of inactivated channels should be small due to the short pulse duration, but block of open channels, if present, should result in a beat-by-beat accumulation of drug blockade. In three experiments the reduction of $\dot{V}_{max}$ produced by each pulse was no more than 1% greater than that expected from accumulation of inactivation block alone. Thus, if bupivacaine blocks open sodium channels at all, it must do so to a very limited extent.

For comparison with bupivacaine, we also investigated the effects of 5 µg/ml lidocaine (fig. 6*B*). In the presence of lidocaine, 26 ± 16%¶ (n = 5) of all channels became blocked during the upstroke, and, as illustrated in figure 6*B*, the rate of block development during channel inactivation was significantly faster than for bupivacaine (τ = 159 ± 53 ms, n = 5) ($P < 0.02$). In addition, following a 320-ms pulse to +20 mV, 5 µg/ml lidocaine reduced $\dot{V}_{max}$ by 67 ± 5%¶ (n = 5), which was significantly more than that produced by 1 µg/ml bupivacaine ($P < 0.01$).

REST–RECOVERY FROM BLOCK

Recovery from drug-induced block of sodium channels was studied using the pulse protocol shown in figure 7*B* (*inset*). A high level of block first was induced by applying a train of conditioning pulses at a rapid rate. The rate of recovery from block then was determined with a test upstroke elicited after a variable amount of time following the last conditioning pulse. In the absence of drug $\dot{V}_{max}$ recovered exponentially with a time constant of 22.6 ± 10.1 ms (n = 8). In the presence of either 0.2 or 1 μg/ml bupivacaine, recovery of $\dot{V}_{max}$ at −85 mV contained two components, a rapid exponential phase having a time constant similar to that obtained in the absence of drug, and a slow exponential phase having a time constant of 1,557 ± 304 ms (n = 8) in 1 μg/ml bupivacaine and 1,467 ± 664 ms (n = 4) in 0.2 μg/ml bupivacaine. For comparison, in figure 7*B* we also show the time course of recovery from block in the presence of 5 μg/ml lidocaine. Similar to the results obtained in the presence of bupivacaine, recovery could be well described by the sum of two exponentials, a rapid and a slow phase. However, the time constant of the slow phase in lidocaine (τ = 153.8 ± 51.2 ms, n = 4) was significantly shorter than that observed in bupivacaine ($P < 0.01$; one-way analysis of variance).

¶ Block by lidocaine actually is underestimated due to substantial recovery from block during the 100-ms interpulse interval (fig. 6).

VOLTAGE DEPENDENCE

In four experiments we determined the relationship between membrane potential and $\dot{V}_{max}$ at 1 Hz. Similar to most local anesthetic drugs, including lidocaine,[18,19] bupivacaine shifted the curve to hyperpolarized potentials (figs. 8*A* and *B*). At 1 μg/ml, bupivacaine shifted the midpoint of the curve by 10.7 ± 2.6 mV ($P < 0.01$). However, hyperpolarization from −85 to −120 mV did not significantly increase $\dot{V}_{max}$ toward control levels (n = 4, $P > 0.05$) (see fig. 8*A*). Only in one experiment did strong hyperpolarizations result in a partial restoration of $\dot{V}_{max}$. The inability of moderate hyperpolarization to relieve bupivacaine block is different from lidocaine block, which, essentially, can be reversed fully by hyperpolarization to potentials negative to −100 mV.[9]

Discussion

BUPIVACAINE BLOCKS NA CHANNELS BY A MODULATED RECEPTOR MECHANISM

Like lidocaine and most other local anesthetic drugs,[20,21] the depressant effects of bupivacaine on cardiac sodium channels are both time- and voltage-dependent. That is, block of sodium channels increases as stimulation rate is increased (fig. 5)[8] or membrane potential becomes more depolarized (fig. 8). The dependence of bupivacaine's inhibitory effects upon rate and membrane potential results from the fact that block increases in a time-dependent manner whenever sodium channels are inactivated (fig. 6) and decreases when the membrane potential is repolarized to potentials where channels become rested (fig. 7). Such behavior can be described adequately by the modulated receptor hypothesis.[6,7] According to this hypothesis (illustrated in fig. 9), block of sodium channels results from interaction of drugs with a single specific receptor site associated with the sodium channel. Drug affinity for this receptor site is dependent upon the state of the channel, *i.e.*, the rate constants defining association and dissociation of drug from its receptor are different for each channel state and for different drugs. Drug-associated channels do not conduct ions, and they behave as if their voltage-

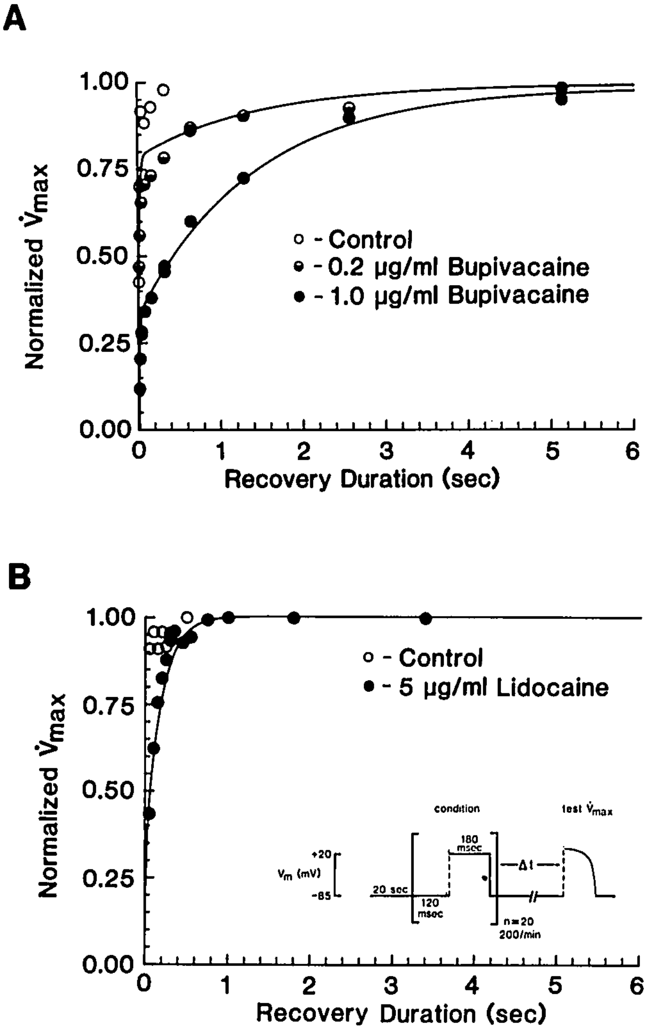

FIG. 7. The time course of recovery from block under control conditions and in the presence of bupivacaine or lidocaine. The pulse protocol is shown in the inset. *A*. The time course of recovery of $\dot{V}_{max}$ under control conditions and in the presence of bupivacaine. The solid curves represent the time course of recovery from block predicted by the modulated receptor hypothesis (see text). Both curves are biexponentials with time constants of 15 ms and 1.4 s. *B*. The recovery time course under control conditions and in the presence of lidocaine. The solid curve represents the time course predicted by the modulated receptor hypothesis. The curve is a biexponential with time constants of 15 and 189 ms.

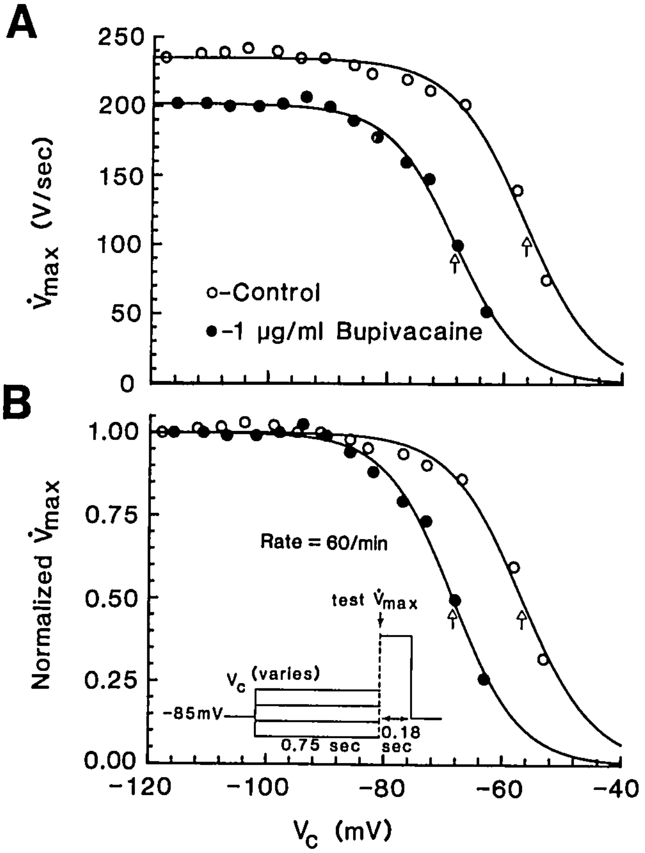

FIG. 8. Effect of bupivacaine on the voltage dependence of $\dot{V}_{max}$ availability. The pulse protocol is shown in the inset of *B.* The conditioning pulse was applied for long enough (750 ms) to allow fast inactivation to reach steady state and yet keep slow inactivation development to a minimum. *A.* The availability of $\dot{V}_{max}$ at different membrane potentials under control conditions and after addition of 1 µg/ml bupivacaine. The solid curves represent least-squares fits of the data to the equation: $Max/(1 + exp[V_c - V_{mid}]/k)$. The open vertical arrows next to each curve indicate the voltage at which $\dot{V}_{max}$ was half-maximum (V_{mid}). For control values (open circles), Max = 235 V/s, and k = −6.2, while in 1.0 µg/ml bupivacaine, Max = 201 V/s and k = −5.1. *B.* Both control and bupivacaine values normalized to their maximal values at negative potentials. Note the shift of the curve to more negative potentials in the presence of bupivacaine.

dependence for inactivation is shifted to more negative potentials.[6,7]

COMPUTATION OF MODULATED RECEPTOR PARAMETERS

To estimate bupivacaine's affinity for different channel states, we analyzed our experimental data using a least-squares fitting program based upon the mathematic model of Hondeghem and Katzung.[7] The estimated dissociation constants ($K_d = \ell/k$) for rested, open, and inactivated states in bupivacaine were $K_{d_R} = 2$ mM, $K_{d_O} = 1.0$ M, $K_{d_I} = 0.9$ µM ($k_I = 545$ ms^{-1} M, $\ell_I = 0.0005$ ms^{-1}, respectively. The estimated voltage shift for blocked channels was 33 mV. Estimated modulated receptor parameters for lidocaine have been published previously.[9] The smooth curves shown in figures 4, 6, and 7 indicate modulated receptor based simulations of the bupivacaine results upon the above values. The excellent fit of the bupivacaine data by the modulated receptor simulations supports the conclusion that most, if not all, of the effects of bupivacaine on cardiac sodium channels can be well described by a modulated receptor mechanism. In our simulations we did not attempt to correct for the effects of slow inactivation.[22] Such corrections could further improve the fit and result in slightly different estimates for the rate constants. However, due to the fact that a good fit was obtained, we did not explore the behavior of more complex models that incorporate slow inactivation.

COMPARISONS BETWEEN BUPIVACAINE AND LIDOCAINE

Bupivacaine is similar to lidocaine in that it has a high affinity for inactivated channels, but, unlike lidocaine, it has a relatively low affinity for open channels.[7,23] Furthermore, bupivacaine also may differ from lidocaine in how it interacts with rested channels. The observation that channel block by bupivacaine cannot be reduced markedly by hyperpolarizing the membrane (fig. 8*A*) suggests that bupivacaine may slowly or incompletely dissociate from rested channels. This contrasts with

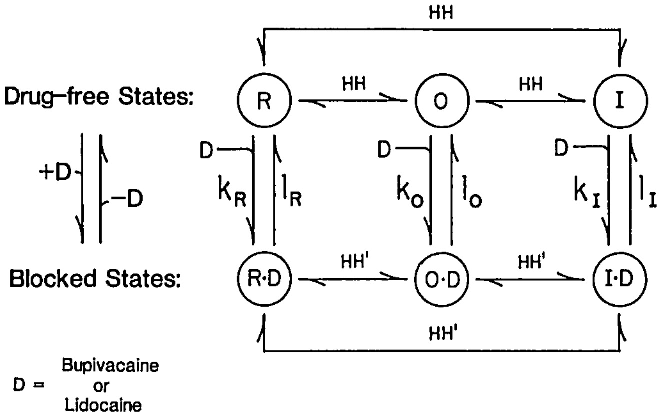

FIG. 9. Schematic diagram of the modulated receptor hypothesis. Drug-free states of the sodium channel are indicated by: R = rested; O = open, and I = inactivated, and R·D, O·D and I·D represent drug-associated channel states. Transitions between R, O, and I states are assumed to be governed by standard Hodgkin-Huxley rate constants (HH), while rate constants governing transitions between drug-associated states (HH') have had their voltage dependence shifted to more negative potentials by an amount ΔV. k_R, k_O, and k_I indicate drug association rate constants, and l_R, l_O and l_I indicate dissociation rate constants for each channel state. For further discussion see Hille[6] and Hondeghem and Katzung.[7,19]

lidocaine, which rapidly dissociates from sodium channels at potentials negative to -85 mV.[9]

The higher potency of bupivacaine than lidocaine at physiologic heart rates results from both a higher affinity for sodium channels as well as a qualitative difference in its kinetics of interaction with cardiac sodium channels. The estimated dissociation constant for bupivacaine binding to inactivated channels is 0.9 μM (0.3 μg/ml), while a conservative estimate for lidocaine is 10 μM (2.3 μg/ml).[18] In addition, from a kinetic perspective, lidocaine rapidly blocks both open and inactivated sodium channels during the action potential (fig. 6). Block development by lidocaine during each action potential is fairly rapid ($\tau < 500$ ms), even at fairly low concentrations (1.2 μg/ml).[23] Recovery from block at diastolic potentials is also fairly rapid ($\tau = 154$ ms). Assuming that channel block results from drug binding to a site within the channel lumen,[6] lidocaine then may be considered to block sodium channels in a fast-in–fast-out manner.[19] Because recovery from block is fast, block of sodium channels by lidocaine accumulates only at fast heart rates when the time for recovery between beats is relatively short (fig. 5). The kinetics of block development and recovery for bupivacaine are different. Recovery from block at diastolic potentials is slow ($\tau = 1.5$ s), while block development is slow at low concentrations (0.2 μg/ml) but fairly rapid at higher concentrations (1 μg/ml) (fig. 6). Thus, bupivacaine blocks sodium channels in either a slow-in–slow-out manner (at low concentrations) or in a fast-in–slow-out manner (at concentrations > 0.2 μg/ml). Because recovery from block by bupivacaine is always slow, block accumulates even at very low heart rates (*e.g.*, ≤ 60 beats/min, fig. 5*A*). These differences make bupivacaine much more "potent" than lidocaine in depressing $\dot{V}_{max}$ (conduction) in ventricular muscle paced at physiologic heart rates (*e.g.*, 60–150 beats/min, fig. 5*B*) *in vitro.*

Bupivacaine is approximately four to five times more potent than lidocaine in blocking sodium channels and conduction in nerve tissues.[24,25] However, local anesthetic potencies are difficult to compare, since the effect of these drugs is heavily dependent upon the experimental conditions (*i.e.*, rate of stimulation, pattern of stimulation, and membrane potential).[6] Furthermore, the dependence of drug effect upon these parameters varies widely between different local anesthetics.[6,21,25] Consequently, estimates of drug potency can vary under different experimental conditions. As illustrated in figures 5*A* and *B*, this problem also exists when trying to compare the potencies of lidocaine and bupivacaine in cardiac tissue. Concentrations of the two drugs that produce approximately equal effects at one stimulation rate produce substantially different effects at other rates. Despite such differences in rate dependence, on a molar basis approximately 70 times more lidocaine (43 μM or 10 μg/ml) than bupivacaine (0.6 μM or 0.2 μg/ml) is needed to produce an equal depression of $\dot{V}_{max}$ at physiologic heart rates (*i.e.*, 60–150 beats/min; see fig. 5*A*). Although similar rate-dependent effects are expected to be observed in human cardiac tissue, the exact quantitative descriptions may not be identical.

The apparent difference in comparative potencies between lidocaine and bupivacaine in nerve and cardiac tissue may be due to several different factors: differences in action potential duration, levels of inactivation at the normal resting potential, frequency of impulses in each tissue, and possibly differences in individual channel state affinities between tissues.[26]

CLINICAL CORRELATIONS

A recent study using sheep found signs of bupivacaine cardiotoxicity (wide QRS complexes in all animals and arrhythmias of various types in more than half) when the whole blood concentration ranged from 3 to 11 μg/ml following intravenous injection.[4] The concentrations that produced marked effects on $\dot{V}_{max}$ in the present study using guinea pigs appear to be similar to those that produce clinical toxicity in sheep. Assuming a blood/plasma concentration ratio of 0.73,[27] 3–11 μg/ml bupivacaine in whole blood should correspond to 4–15 μg/ml in the plasma. Since bupivacaine is 66–88% bound to plasma proteins over this concentration range,[28] the free form of the drug should be approximately 0.5 to 5 μg/ml. These concentrations produce a marked depression of $\dot{V}_{max}$ in guinea pig ventricular muscle (figs. 3–5). Reduction of $\dot{V}_{max}$ will result in slowed conduction of cardiac action potentials.[16] In an intact heart this will result both in prolonged PR intervals and a widened QRS complex in the electrocardiogram. Slowed conduction also can result in unidirectional block and reentry, which in turn may result in the production of unifocal or multifocal ventricular ectopic beats and ventricular tachycardias.[29] All of these have been observed following the iv injection of bupivacaine.[4,30,31] In addition, the observation that high (>1 μg/ml) concentrations of bupivacaine shorten the duration of cardiac action potentials also may explain bupivacaine's ability to alter the ST-interval.[4]

The cardiac depressant effects of bupivacaine can be attenuated by reducing heart rate, prevention of diastolic depolarization, and shortening the action potential duration. Unfortunately, the relationship between $\dot{V}_{max}$ and stimulation rate has a fairly shallow slope over the range of physiologic heart rates (fig. 5*A*). However, large changes in heart rate such as may be brought about by abolishing a tachycardia substantially could reduce bupivacaine's depressant effect on cardiac conduction and thus may be beneficial in reducing bupivacaine cardiotoxicity.

Although hyperpolarization *per se* does not appear to be very effective in reducing bupivacaine's depressant effect on $\dot{V}_{max}$ (fig. 8*A*), even a small amount of diastolic depolarization would be expected to greatly increase bupivacaine's depressant effect on conduction as a result of the drug-induced shift of the membrane responsiveness curve to more negative potentials (figs. 8*A* and *B*). Thus, conditions that are known to depolarize the cardiac cell membrane (*e.g.*, hyperkalemia, severe hypoxia) are expected to increase bupivacaine's depressive effects.

Since bupivacaine-induced block of cardiac sodium channels develops primarily during the action potential plateau, manipulations that shorten the duration of the plateau may be beneficial in treating bupivacaine toxicity, while conditions that lengthen action potential duration (such as exposure to quinidine or hypokalemia) may be expected to worsen the toxicity. Unfortunately, we know of no drug that markedly shortens the ventricular action potential and is not itself toxic. Although, hyperkalemia can shorten action potential duration, it also results in depolarization, which greatly may outweigh the effects on action potential duration. Indeed, hyperkalemia has been reported to markedly enhance bupivacaine cardiotoxicity.[32–34]

We conclude that bupivacaine is much more potent than lidocaine in blocking cardiac sodium channels at normal heart rates. The great difference in potency can be attributed to differences in both affinity of binding and kinetics of interaction with cardiac sodium channels. These differences may account, at least in part, for the observation that bupivacaine has a much greater potential for producing clinical cardiotoxicity than lidocaine.[4,5] Other mechanisms for bupivacaine cardiac toxicity include depression of AV node conduction and myocardial contraction.[34,35]

The authors are deeply indebted to Drs. S. Shnider, G. Albright, R. Miller, and G. Levinson for their helpful suggestions and critical evaluation of the manuscript. They also thank Dr. J. Moyer for developing the software for data analysis and D. Noack for clerical assistance.

References

1. Swerdlow M, Jones R: The duration of action of bupivacaine, prilocaine and lignocaine. Br J Anaesth 42:335–339, 1970
2. Bromage PR, Gertel M: An evaluation of two new local anesthetics for major conduction blockade. Can Anaesth Soc J 17:557–564, 1970
3. Scanlon JW, Ostheimer GW, Lurie AO, Brown WU, Jr, Weiss JB, Alper MH: Neurobehavioral response of newborn infants after maternal epidural anesthesia. ANESTHESIOLOGY 45:400–405, 1976
4. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA: Bupivacaine cardiac arrhythmias in sheep. ANESTHESIOLOGY 60:10–18, 1984
5. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. ANESTHESIOLOGY 51:285–287, 1979
6. Hille B: Local anesthetics: Hydrophilic and hydrophobic pathways for the drug-receptor reaction. J Gen Physiol 69:497–515, 1977
7. Hondeghem LM, Katzung BG: Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. Biochim Biophys Acta 472:373–398, 1977
8. Courtney KR: Fast frequency-dependent block of action potential upstroke in rabbit atrium by small local anesthetics. Life Sci 24:1581–1588, 1979
9. Hondeghem LM, Katzung BG: Test of a model of antiarrhythmic drug action. Effect of quinidine and lidocaine on myocardial conduction. Circulation 61:1217–1224, 1980
10. Walton M, Fozzard HA: The relation of $\dot{V}_{max}$ to I_{Na}, $\bar{G}_{Na}$, and h_{∞}, in a model of the cardiac Purkinje fiber. Biophys J 25:407–420, 1979
11. Hondeghem LM, Cotner C: Measurement of $\dot{V}_{max}$ of the cardiac action potential with a sample/hold peak detector. Am J Physiol 234:H312–H314, 1978
12. Bean BP, Cohen CJ, Tsien RW: Block of cardiac sodium channels by tetrodotoxin and lidocaine: sodium current and $\dot{V}_{max}$ experiments, Normal and Abnormal Conduction in the Heart. Edited by deCarvalho AP, Hoffman BF, Lieberman M. Mount Kisco, Futura, 1982, pp 189–209
13. Cohen I: Some experimental difficulties in the use of $\dot{V}_{max}$ as a measure of G_{Na}. Circ Res 44:309–311, 1979
14. Cohen IS, Strichartz GR: On the voltage-dependent action of tetrodotoxin. Biophys J 17:275–279, 1977
15. Hondeghem LM: Validity of $\dot{V}_{max}$ as a measure of the sodium current in cardiac and nervous tissues. Biophys J 23:147–152, 1978
16. Walton MK, Fozzard HA: Experimental study of the conducted action potential in cardiac Purkinje strands. Biophys J 44:1–8, 1983.
17. Gettes LS, Reuter H: Slow recovery from inactivation of inward currents in mammalian myocardial fibres. J Physiol (Lond) 240:703–724, 1974
18. Bean BP, Cohen CJ, Tsien RW: Lidocaine block of cardiac sodium channels. J Gen Physiol 81:613–642, 1983
19. Hondeghem LM, Katzung BG: Antiarrhythmic agents: modulated receptor mechanism of action of sodium and calcium channel blocking drugs. Ann Rev Pharmacol Toxicol 24:387–423, 1984
20. Strichartz GR: The inhibition of sodium currents in myelinated nerve by quaternay derivatives of lidocaine. J Gen Physiol 62:37–57, 1973
21. Courtney KR, Kendig JJ, Cohen EN: The rates of interaction of local anesthetics with sodium channels in nerve. J Pharmacol Exp Ther 207:594–604, 1978
22. Clarkson CW, Matsubara T, Hondeghem LM: Slow inactivation of $\dot{V}_{max}$ in guinea pig ventricular myocardium. Am J Physiol 247:H645–H654, 1984
23. Hondeghem LM, Matsubara T: Quinidine and lidocaine: Activation and inactivation block. Proc West Pharmacol Soc 27:19–22, 1984
24. Covino BG, Vassallo HG: Local Anesthetics, Mechanisms of Action and Clinical Use. New York, Grune and Stratton, 1976, pp 46, 49

25. Courtney KR, Kendig JJ, Cohen EN: Frequency-dependent conduction block: The role of nerve impulse pattern in local anesthetic potency. ANESTHESIOLOGY 48:111–117, 1978
26. Courtney KR: Comparative actions of mexiletine on sodium channels in nerve, skeletal and cardiac muscle. Eur J Pharmacol 74:9–18, 1981
27. Tucker GT, Mather LE: Pharmacology of local anesthetic agents: Pharmacokinetics of local anesthetic drugs. Br J Anaesth 47: 213–224, 1975
28. Coyle DE, Denson DD, Thompson GA, Myers JA, Arthur GR, Bridenbaugh PO: The influence of lactic acid on the serum protein binding of bupivacaine: Species differences. ANESTHESIOLOGY 61:127–133, 1984
29. Singer DH, Baumgarten CM, Ten Eick RE: Cellular electrophysiology of ventricular and other dysrhythmias; studies on diseased and ischemic heart. Prog Cardiovasc Dis 24:97–156, 1981
30. Edde RR, Deutsch S: Cardiac arrest after interscalene brachial plexus block. Anesth Analg 56:446–447, 1977
31. Davis NL, de Jong RH: Successful resuscitation following massive bupivacaine overdose. Anesth Analg 61:62–64, 1982
32. Avery P, Redon D, Schaenzer G, Rusy B: Cerebral and cardiac toxicity of bupivacaine in the presence of normokalemia versus hyperkalemia (abstract). ANESTHESIOLOGY 55:A164, 1981
33. Gould DB, Aldrete JA: Bupivacaine cardiotoxicity in a patient with renal failure. Acta Anaesthesiol Scand 27:18–21, 1983
34. Komai H, Rusy BF: Effects of bupivacaine and lidocaine on AV conduction in the isolated rat heart: modification by hyperkalemia. ANESTHESIOLOGY 55:281–285, 1981
35. Courtney KR: Relationship between excitability block and negative inotropic actions of antiarrhythmic drugs. Proc West Pharmacol Soc 27:181–184, 1984