THE ANTIARRHYTHMIC drug lidocaine is a tertiary amine with a pKa of 7.86 (Swinyard, 1975). Over the pH range of common biological fluids, it may exist both as the uncharged amine (B) and the cation (BH⁺), the relative proportions being determined by the pH of the milieu. The facility with which the drug molecule crosses biological membranes and associates with its receptor site(s) may depend on the state of dissociation of the molecules. The state of dissociation may therefore influence the pharmacological effects of the drug. The problem of the pH dependence of the pharmacological effect has been investigated extensively in nerve for lidocaine and a number of related secondary and tertiary amine local anesthetics (Ritchie and Greengard, 1966; Narahashi et al., 1970; Frazier et al., 1970; Strobel and Bianchi, 1970; Catchlove, 1972). The results indicate that local anesthetics produce greater conduction block at alkaline pH compared to neutral pH in desheathed nerve (Ritchie and Greengard, 1966). The conclusions drawn from these experiments were that local anesthetics penetrate the nerve membrane in the uncharged form but react with receptor site(s) in the cationic form to block conduction. Results from internal perfusion experiments of giant axons of squid with tertiary and quaternary ammonium analogues of lidocaine confirmed these findings (Narahashi et al., 1970; Frazier et al., 1970).

Lidocaine is used most as an antiarrhythmic drug for arrhythmias associated with acute myocardial infarction. Recent studies indicate that both intracellular and extracellular pH and [K⁺] are very different in regions of myocardial ischemia compared with normal regions (Poole-Wilson, 1978; Hill and Gettes, 1977). In vivo studies have shown that lidocaine delays activation, prolongs the effective refractory period, and decreases excitability in regions of myocardial ischemia but not in normal regions (Kupersmith et al., 1975; Hondeghem, 1976). In vitro lidocaine produces greater decreases in action potential duration, maximum upstroke velocity, and automaticity in Purkinje fibers removed from infarcted hearts compared with normal hearts (Lazzara et al., 1978; Allen et al., 1978). Also, decrease of PO₂ increases the depressant effects of lidocaine in vitro (Hondeghem et al., 1974). It has been speculated that this difference in drug effect may be the result of the high extracellular [K⁺] or low pH is the ischemic region (Kupersmith et al., 1975). Microelectrode studies have confirmed that

SUMMARY Lidocaine has been reported to be more depressant in ischemic than normal myocardium. To determine the influence of pH on the electrophysiological effects of lidocaine, we recorded transmembrane potential and dV/dt max from guinea pig papillary muscles mounted in a single sucrose gap. Recovery kinetics of dV/dt max were studied by introducing progressively early premature responses during phase 4 at a drive rate of 0.5 Hz. In Krebs-Henseleit solution (HCO₃⁻ = 25 mM, CO₂ = 5%, pH 7.4), lidocaine (1.5 × 10⁻⁵ M) did not significantly change action potential characteristics. The recovery time constant (τ) of dV/dt max was increased from 10 ± 4 (mean ± SD) to 91 ± 12 msec. In the presence of lidocaine, τ increased from 91 ± 12 to 212 ± 5 msec when the extracellular pH (pHₑ) was lowered by increasing the [CO₂] to 20% (HCO₃⁻ = 25 mM, pHₑ = 6.95). Similarly, when pHₑ was lowered by decreasing [HCO₃⁻] (HCO₃⁻ = 7.5 mM, CO₂ = 5%, pHₑ = 6.95), τ increased from 96 ± 11 to 185 ± 41 msec. However, if the [CO₂] was increased to 20% while the pHₑ was maintained at 7.4 [HCO₃⁻ = 85], τ was unchanged compared to a [CO₂] of 5%. Drug-free solutions of pHₑ = 6.95 (CO₂ = 5% or 20%; HCO₃⁻ = 7.5 or 25 mM) did not increase τ. The increase in τ with a decrease in pHₑ was greater than that predicted by a change in distribution of the drug across the membrane. These data are consistent with the view that local anesthetics bind to a receptor in the sodium channel thereby inactivating it. The process of recovery from inactivation during the resting state occurs by exit of uncharged drug through the membrane. The degree of protonation of receptor-bound drug is increased by extracellular acidosis. This decreases the proportion of drug that may leave the receptor via the membrane and hence causes a slowing of the recovery from inactivation.

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lidocaine is more depressant in high [K+] superfusates (Singh and Vaughan Williams, 1971; Obayashi et al., 1975). There are no data on the influence of pH on the electrophysiological effects of lidocaine in ventricular myocardium. The present study examined the electrophysiological effects of lidocaine over a range of pH that may be encountered in regions of myocardial ischemia. Our results indicate that variations of pH may account for some of the differences in the effects of lidocaine observed in myocardial ischemia and infarction. To define the mechanism of action of lidocaine, we also compared its electrophysiological effect during pH changes with that of the quaternary ammonium derivative QX 372.

Methods

Guinea pigs weighing 250-350 g were stunned by a blow to the neck and exsanguinated. The hearts were removed rapidly and dissected in Krebs-Henseleit solution. Papillary muscles 0.8-1.0 mm in diameter were excised from the right ventricle. The papillary muscles were mounted in a 3-compartment sucrose gap chamber, the length of the muscle in the test compartment being limited to 0.5-1.0 mm (Reuter and Scholz, 1968). The test compartment had a capacity of 0.7 ml and was perfused at a rate of 3 ml/min. The middle compartment was perfused with isotonic sucrose solution; the current-injecting compartment was perfused with isotonic KCl. The temperature was maintained at 36 ± 0.2°C.

The composition of the control and the various test solutions is listed in Table 1. The different test solutions were chosen partly on the assumption that they would alter the distribution of lidocaine in a reasonably predictable manner. Calculated values for the distribution of the charged and uncharged forms of the drug in the test solution are given in the Appendix. All salt solutions contained in addition the following (mM): KC1, 3.5; MgSO4-7H2O, 1.2; CaCl2, 2.5; KH2PO4, 1.2; and glucose, 11. In preparing the solutions listed in Table 1, equilibration with the gas mixture (5% CO2-95% O2 or 20% CO2-80% O2) was performed for 1 hour was performed.

After preliminary experiments had yielded similar results when pulse duration was varied between 2.5 and 5 msec, we selected current pulses 2.5 msec in duration in our experiments. A stable impalement was obtained during a 1-hour equilibration period. Recovery kinetics of dV/dtmax were determined by introducing test stimuli at varying diastolic intervals, t, after every fifth beat. Stimulus strength was increased at short coupling intervals to keep the latency constant (Chen et al., 1975).

The preparation was exposed to various solutions in the following sequence: (1) control solution, test solution (15 minutes), control solution (15 minutes); and (2) control solution with lidocaine (30 minutes), test solution with lidocaine (15 minutes), control solution with lidocaine (15 minutes). Our initial experiments indicated that the drug-free test solutions had no effect on the recovery kinetics of dV/dtmax; therefore, in some experiments, sequence 2 was started directly after data in the control solution were obtained. In two experiments, the preparations were exposed to a second test solution after sequence 2 was complete. Finally, a washout of 0.5-1 hour was performed.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Perfuse Solution Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solution</strong></td>
<td><strong>pH</strong></td>
</tr>
<tr>
<td>Control</td>
<td>7.4</td>
</tr>
<tr>
<td>Low pH-high CO2</td>
<td>6.95</td>
</tr>
<tr>
<td>Normal pH-high CO2</td>
<td>7.4</td>
</tr>
<tr>
<td>Low pH-normal CO2</td>
<td>6.95</td>
</tr>
</tbody>
</table>

* mm Hg; † mEq/liter.
The concentration-response relationship of lidocaine was determined using three drug concentrations: 1.5, 3, and 6 x 10^{-5} M (4.3, 8.6, and 17.2 µg/ml). The preparations were exposed to each drug concentration for 30 minutes, and the stimulation protocol then was repeated. The quaternary ammonium derivative QX 372 was studied at a concentration of 1.5 x 10^{-5} M. As the quaternary ammonium derivative of lidocaine has a slow onset of action, measurements also were made after exposure to drug for 1 hour. Only those experiments in which the impalement was maintained in a single fiber are reported in this study.

Data Analysis

To characterize the recovery kinetics dV/dt max, the maximum upstroke velocity of the test response was subtracted from that of the preceding basic response. This difference was normalized by dividing it by the maximum upstroke velocity of the basic response. We define the interval between the basic and test action potentials as the diastolic interval, t. The point during repolarization of the basic action potential that is 4 mV positive to the resting potential marks the onset of the diastolic interval. The onset of phase 0 of the test action potential marks the termination of the diastolic interval. The data points, normalized difference of dV/dt (Δ), and t were fitted to the regression equation: Δ = Ae^{-t/T}, where A represents the intercept and T the recovery time constant of dV/dt.

The effects of drug-free test solutions will be described first. The actions of lidocaine in control and test solutions then will be presented. The results of these initial experiments suggested two further series of experiments addressed to (1) the dose-response curve for the actions of lidocaine and (2) the action of the quaternary ammonium derivative of lidocaine, QX 372.

Effects of Drug-Free Test Solutions

In the initial experiments, we examined the effects of drug-free test solutions on action potential characteristics and the recovery kinetics of dV/dt max. The result of an experiment with low pH-high CO2 solution is compared in panels B-C and E-F. During control, test action potentials at both short (20 msec, panel B) and long (100 msec, panel C) diastolic intervals had upstroke velocities almost identical to the basic action potential. This indicates that the recovery of dV/dt max from inactivation is rapid at membrane potentials in the range of -80 to -90 mV (Gettes and Reuter, 1974). In fact, in some experiments, dV/dt max of the first test response that could be elicited when repolarization was clearly complete was equal to that of the basic action potential. Recovery of dV/dt max from inactivation appeared to coincide with complete repolarization. Panels E and F show test responses elicited at short and long diastolic intervals (22.5 and 95 msec) in the low pH-high CO2 test solution. dV/dt max of the test responses was similar to that of the basic response. The drug-free test solution did not change the recovery kinetics of dV/dt max; its influence on action potential characteristics is summarized in Table 2. The recovery time constant was 10 ± 4 msec during control and not significantly different in the test solution. In the normal pH-high CO2 solution, there were no significant changes in any action potential characteristics (Table 2), and there was no significant effect on the recovery kinetics of dV/dt max. In the low pH-normal CO2 test solution, the only significant change in action potential characteristics was a small increase in action potential duration (Table 2). There was no significant effect on the recovery kinetics of dV/dt max. In the range of membrane potentials tested, -85 to -87 mV, none of the test solutions altered the recovery kinetics of dV/dt max.

Effects of Test Solutions Containing Lidocaine

The effects of 1.5 x 10^{-5} M lidocaine were examined initially in the normal Krebs-Henseleit solu-


**Figure 2** Effects of lidocaine (1.5 × 10⁻⁵ M) on action potential characteristics and recovery kinetics of dV/dt max. The upper trace is at +7 mV. The remainder of the traces and voltage and upstroke velocity calibration are as described in Figure 1.

**Table 2** The Effects of Drug-free Test Solutions on Characteristics of the Basic Action Potential

<table>
<thead>
<tr>
<th>Condition</th>
<th>E m (mV)</th>
<th>AA (mV)</th>
<th>APD (msec)</th>
<th>dV/dt max (V/sec)</th>
<th>T (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>87 ± 2</td>
<td>125 ± 3</td>
<td>205 ± 18</td>
<td>226 ± 62</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Low pH-high CO₂</td>
<td>87 ± 2</td>
<td>123 ± 4</td>
<td>201 ± 19*</td>
<td>213 ± 54</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>87 ± 4</td>
<td>118 ± 3</td>
<td>207 ± 37</td>
<td>197 ± 39</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>Normal pH-high CO₂</td>
<td>86 ± 4</td>
<td>115 ± 4</td>
<td>185 ± 54</td>
<td>183 ± 50</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>87 ± 2</td>
<td>119 ± 3</td>
<td>142 ± 13</td>
<td>245 ± 88</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Low pH-normal CO₂</td>
<td>88 ± 4</td>
<td>117 ± 2</td>
<td>152 ± 16*</td>
<td>233 ± 80</td>
<td>11 ± 4</td>
</tr>
</tbody>
</table>

In Tables 2, 3, and 4, the following abbreviations are used: E m = resting membrane potential; AA = action potential amplitude; APD = action potential duration; T = recovery time constant of dV/dt max.

* P < 0.05.
TABLE 3  The Effects of Lidocaine (1.5 \times 10^{-5} M) on Action Potential Characteristics in Control and Test Solutions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Em (mV)</th>
<th>AA (mV)</th>
<th>APD (msec)</th>
<th>dV/dt_{\text{max}} (V/sec)</th>
<th>\tau (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 8)</td>
<td>87 ± 4</td>
<td>122 ± 6</td>
<td>174 ± 24</td>
<td>250 ± 85</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Control + L</td>
<td>87 ± 4</td>
<td>123 ± 6</td>
<td>167 ± 23</td>
<td>250 ± 84</td>
<td>91 ± 12</td>
</tr>
<tr>
<td>Low pH-high CO$_2$ + L</td>
<td>87 ± 4</td>
<td>120 ± 9</td>
<td>176 ± 25</td>
<td>234 ± 82</td>
<td>212 ± 5*</td>
</tr>
<tr>
<td>Control + L</td>
<td>88 ± 4</td>
<td>121 ± 7</td>
<td>164 ± 26</td>
<td>214 ± 44</td>
<td>113 ± 22</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>88 ± 2</td>
<td>122 ± 7</td>
<td>196 ± 8</td>
<td>205 ± 50</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>Control + L</td>
<td>89 ± 3</td>
<td>121 ± 8</td>
<td>185 ± 12</td>
<td>205 ± 42</td>
<td>92 ± 14</td>
</tr>
<tr>
<td>Normal pH-high CO$_2$ + L</td>
<td>88 ± 4</td>
<td>121 ± 7</td>
<td>193 ± 14</td>
<td>197 ± 34</td>
<td>100 ± 17</td>
</tr>
<tr>
<td>Control + L</td>
<td>88 ± 4</td>
<td>122 ± 7</td>
<td>180 ± 15</td>
<td>208 ± 50</td>
<td>96 ± 14</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>85 ± 5</td>
<td>124 ± 4</td>
<td>174 ± 32</td>
<td>259 ± 121</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Control + L</td>
<td>86 ± 1</td>
<td>124 ± 3</td>
<td>161 ± 34</td>
<td>252 ± 116</td>
<td>96 ± 11</td>
</tr>
<tr>
<td>Low pH-normal CO$_2$ + L</td>
<td>88 ± 2</td>
<td>123 ± 4</td>
<td>170 ± 39</td>
<td>255 ± 121</td>
<td>185 ± 41*</td>
</tr>
<tr>
<td>Control + L</td>
<td>86 ± 1</td>
<td>125 ± 5</td>
<td>162 ± 42</td>
<td>210 ± 83</td>
<td>88 ± 12</td>
</tr>
</tbody>
</table>

L = lidocaine.

\* P < 0.05

an experiment with the low pH-normal CO$_2$ test solution in the presence of lidocaine. In the presence of lidocaine, \( \tau \) increased from 81 to 149 msec in changing from control to test solution and decreased to 83 msec on return to the control solution. During exposure to lidocaine in five experiments, \( \tau \)

was 96 ± 11 msec in the control solution, 185 ± 41 msec (P < 0.05) in the test solution, and 88 ± 12 msec on return to the control solution.

Dose Response Effects of Lidocaine on the Recovery Kinetics of dV/dt_{\text{max}}

The results presented up to this point indicate that extracellular acidosis exaggerated the slowing
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1.0
0.9
0.8
0.7
0.6
0.4
0.3
0.2
0.1

Lo

<table>
<thead>
<tr>
<th>pH</th>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>1.5×10^{-5} M CO_2, 5%</td>
<td>Normal</td>
</tr>
<tr>
<td>6.9</td>
<td>1.5×10^{-5} M CO_2, 5% HCO_3, 7.5 mM</td>
<td>Low pH</td>
</tr>
</tbody>
</table>

FIGURE 5 Comparison of the effects of lidocaine on the recovery kinetics of dV/dt_{max} in control and low pH-normal CO_2 solution. The plotted variables are as described in Figure 3.

of the recovery kinetics of dV/dt_{max} produced by lidocaine. It was important to determine whether this effect of pH was the result of a change in the steady state distribution of the charged and uncharged forms of lidocaine across the membrane or a slowing of the rate at which lidocaine dissociated from its receptor(s). A study of the effects of increasing the concentration of lidocaine while maintaining the preparation in the control may provide information in this regard. The results of four experiments with 1.5, 3, and 6×10^{-5} M lidocaine are illustrated in Figure 6. Over the lidocaine concentration range 1.5 to 6×10^{-5} M, τ increased by an average of 22%. For comparison, the values of τ in control and low pH-high CO_2 solutions are also shown. The slopes of the two curves are clearly different. These experiments suggest that the action of the pH change may not depend on a change in the distribution of the drug per se.

Studies with a Quaternary Ammonium Derivative

The quaternary ammonium derivatives of lidocaine have been studied extensively in nerves and to a lesser extent in cardiac tissue to gain insight as to the mechanism of action of the parent compound (Strichartz, 1973; Gliklich and Hoffman, 1978). The assumption is made that the quaternary derivatives cross the membrane to a very limited extent such that their action is restricted to the side of the membrane to which they are applied. We therefore studied the effects of the quaternary ammonium derivative of lidocaine, QX 372, on action potential characteristics and the recovery kinetics of dV/dt_{max}. Because of its slower onset of action, the total time of exposure to QX 372 was extended to 1 hour.

An experiment with 1.5×10^{-5} M QX 372 is illustrated in Figure 7. For the basic beats in panels A and D, QX 372 caused a small decrease in the action potential amplitude and duration (<5%), and dV/dt_{max} decreased from 160 to 145 V/sec. The effects on the recovery kinetics of dV/dt_{max} are illustrated in panels B–C and E–F. In contrast to

FIGURE 6 Comparison of the effects of increasing lidocaine concentrations in control solution and 1.5×10^{-5} M lidocaine in the low pH test solutions on the recovery time constant of dV/dt_{max}. The recovery time constant is plotted on the ordinate. The calculated concentration of the charged form of lidocaine in the control and various test solutions is plotted on a logarithmic scale on the abscissa. See text for discussion.

FIGURE 7 The effect of QX 372 (1.5×10^{-5} M) on action potential characteristics and recovery kinetics of dV/dt_{max}. All the traces are as described in the legend to Figure 1.
Table 4 summarizes the effects of QX 372 on action potential characteristics. A limited number of experiments with $7.5 \times 10^{-5}$ M QX 372 gave similar results. Because of the lack of the effect of QX 372 on recovery kinetics in control solution, experiments were not performed in test solutions.

### Discussion

The principal conclusions from the present study are the following. (1) Extracellular acidosis prolongs the ventricular muscle action potential duration. (2) Hypercapnia or metabolic acidosis have no effect on the recovery kinetics of dV/dt$_{\text{max}}$. (3) Lowering the extracellular pH by elevating the PCO$_2$ lowers the bicarbonate concentration causes a 2-fold increase in the slowing of the recovery kinetics produced by lidocaine. (4) In a solution of normal pH, elevating the lidocaine concentration to cover the probable range of concentration of the charged form of lidocaine in the low pH produces a smaller increase in the recovery kinetics of lidocaine. (5) The permanently charged quaternary ammonium derivative of lidocaine QX 372 does not slow the recovery kinetics of dV/dt$_{\text{max}}$ with the protocol used in this study.

The increase in action potential duration is similar to that reported for rabbit ventricular muscle by Poole-Wilson and Langer (1975) and Spitzer and Hogan (1979). It is important to point out that neither of the acidic test solutions caused a significant decrease in E$_{\text{m}}$. Weld and Bigger (1975) and Chen et al. (1975) have shown that lidocaine produced greater slowing of the recovery kinetics of dV/dt$_{\text{max}}$, at low membrane potential. The observation that E$_{\text{m}}$ was not significantly decreased in the test solution with or without drugs indicates that a decrease in E$_{\text{m}}$ can be excluded as a cause of the further slowing of the recovery kinetics of dV/dt$_{\text{max}}$ in drug-containing solutions. Similarly, the observation that the drug-free test solutions were without effect on the recovery kinetics suggest that the exaggerated slowing of the recovery kinetics in drug-containing test solution does not represent a mere additive effect of extracellular acidosis and drug effect.

The values of $\tau$ observed in the control solution in the presence of lidocaine are similar to those previously reported in Purkinje fibers and ventricular muscle (Chen et al., 1975; Weld and Bigger, 1975; Iven and Brasch, 1977). In these studies, the pH of the solution was either stated or calculated to be in the range 7.2-7.4. In our study, the recovery time constant $\tau$ was doubled in the low pH solutions. Lowering the extracellular pH either by elevating the PCO$_2$ or by decreasing the bicarbonate concentration would be predicted to increase the concentration of the charged form of lidocaine, BH$^+$, in the bulk solution. In the steady state, it may be assumed that a similar change in the concentration of BH$^+$ would occur in the "unstirred" layer immediately adjacent to the membrane. Our observations of the effect of varying pH$_2$ on $\tau$ would therefore be consistent with the cationic form of lidocaine producing a slowing of the recovery kinetics of dV/dt$_{\text{max}}$ by acting on the outer surface of membrane. Data have been presented in this paper that force us to reject this explanation. (1) In control solutions, when the total concentration of lidocaine is elevated to give a level of BH$^+$ similar to that observed in the acidotic test solutions, the increase in $\tau$ was much smaller. (2) The quaternary ammonium derivative of lidocaine QX 372 does not increase $\tau$. Another quaternary ammonium derivative of lidocaine QX 314 does not increase $\tau$ (unpublished observations). Experiments by Gliklich and Hoffman (1978) involving the iontophoretic injection of QX 314 in Purkinje fibers suggest that QX 314 interacts with a site on the inner surface of the sarcolemma. Further, Strichartz (1973) has shown that externally applied quaternary ammonium derivatives produced little reduction of the sodium current, whereas the internally applied drug produced a 90% decrease.

Our results may be explained in terms of a model of the interaction of local anesthetics with the sodium channel in nerve, skeletal, and cardiac muscle initially proposed by Strichartz (1973) and Courtney (1975) and later modified by Hille (1977) and Hondeghem and Katzung (1977a). Local anesthetics are presumed to bind to a sodium channel receptor within the membrane. Channels with drug bound to receptor are assumed not to conduct. The drugs have access to the receptor through a hydrophobic pathway in the membrane and a hydrophilic pathway formed by the open channels so that both charged and uncharged forms can bind to the receptor site. Similarly, the state of dissociation of the drug will determine which route the drug will take in leaving the receptor. In the case of lidocaine, the process of recovery from inactivation during the resting state is thought to occur by the exit of the uncharged form B from the receptor though the hydrophobic pathway (Hille, 1977). The charged
form BH⁺ is able to exit only via the hydrophilic pathway, i.e., the open channels. Khodorov et al. (1976) have shown that in frog node of Ranvier the time constant of recovery from slow inactivation is increased by lowering the pH of the external medium. According to the present model, elevation of [H⁺] of the external medium protonates receptor-bound drug and decreases the proportion of drug that may leave the receptor by the hydrophobic pathway. This would result in a slowing of the recovery from inactivation. A similar explanation may account for the effects of pH that we report in recovery from inactivation. A similar explanation that may leave the receptor by the hydrophobic pathway. With increasing time, a greater proportion of receptors become drug-free. Hence the upstroke velocity of test response increases as the diastolic period increases. By elevating [H⁺] in the extracellular medium, the increased concentration of external hydrogen ions protonates more of the bound drug and decreases the proportion of uncharged drug that may leave the receptor by the hydrophobic pathway. This would lead to a slower recovery from inactivation. The results suggest that dissociation of lidocaine from the sodium channel may be similar in amphibian nerve and mammalian cardiac muscle. Hondeghem and Katzung (1977a, 1977b) have recently reported that the interaction of lidocaine with its receptor in the sodium channel may be similar in these two tissues.

The applicability of this model to our results is dependent on the extent to which changes in dV/dt max reflect, in a qualitative manner, changes in the sodium current. To date, it has not been possible to measure quantitatively the fast sodium current in naturally occurring multicellular myocardial preparations at normal temperature. In our set of experiments, the action potentials recorded in the small segment of muscle in the test compartment in this study approach a membrane action potential. In addition, test pulses were introduced only in diastole, and both the basic and test pulses were adjusted to minimize latency (Chen et al., 1975). Under these circumstances, dV/dt max is proportional to the sodium current (Hondeghem, 1978). For the purpose of the present study, all that need be assumed is that dV/dt max is a qualitative measure of the sodium current.

The increased slowing of recovery kinetics of phase 0 dV/dt max in acidic perfusates could in part explain the greater prolongation of refractoriness produced by lidocaine in ischemic as opposed to normal myocardium. A greater prolongation of the effective refractory period in ischemic tissue as opposed to normal tissue (Kupersmith et al., 1975) enables lidocaine to block preferentially the propagation of premature responses in ischemic ventricular myocardium, possibly explaining the effectiveness of lidocaine in suppressing ectopic activity in this tissue. At a short cycle length, prolongation of recovery kinetics of dV/dt max also will decrease dV/dt max of the basic action potential. Although the relationship between dV/dt max and conduction velocity is not direct, a substantial reduction in dV/dt max of the basic action potential may account for the slowing of conduction observed in ischemic tissue. Thus, the prolongation of the recovery kinetics in acidic perfusates may contribute to the selectivity of lidocaine's action in ischemic tissue.

In many clinical settings in patients with ischemic heart disease, this relatively selective action on ischemic tissue make this feature of the drug quite desirable. If in fact this mechanism of action is common to all local anesthetics, then identification of new compounds might be centered around identifying compounds with similar values for *he pKa and partition coefficients.

Appendix

Theory

The various test solutions shown in Table 1 were chosen partly on the assumption that they would alter the distribution of lidocaine in a reasonably predictable manner. The ratio of concentration of the uncharged B to the charged BH⁺ form of lidocaine is given by the following equation:

$$\text{pH} = \text{pK}_a + \log \frac{[B]}{[\text{HB}^+]}$$

Using the following assumption, it is possible to calculate the concentration of B and BH⁺ in the various test solutions:

1. Only the uncharged form crosses the membrane freely. Alternatively, the permeability is much greater for the uncharged than the charged

### Table 5: Concentration of the Various Forms of Lidocaine in Control and Test Solutions

<table>
<thead>
<tr>
<th></th>
<th>Control solution</th>
<th>Low pH-high CO₂</th>
<th>Normal pH-high CO₂</th>
<th>Low pH-normal CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(pH₀ = 7.4)</td>
<td>(pH₀ = 6.95)</td>
<td>(pH₀ = 7.4)</td>
<td>(pH₀ = 6.95)</td>
</tr>
<tr>
<td>BH⁺</td>
<td>1.1 × 10⁻⁵</td>
<td>1.34 × 10⁻⁵</td>
<td>1.1 × 10⁻⁵</td>
<td>1.34 × 10⁻⁵</td>
</tr>
<tr>
<td>BH₀</td>
<td>3.9 × 10⁻⁶</td>
<td>1.6 × 10⁻⁶</td>
<td>3.9 × 10⁻⁶</td>
<td>1.6 × 10⁻⁶</td>
</tr>
<tr>
<td>BH⁺</td>
<td>1.9 × 10⁻⁶</td>
<td>1.27 × 10⁻⁵</td>
<td>3.1 × 10⁻⁵</td>
<td>8.0 × 10⁻⁵</td>
</tr>
<tr>
<td>BH₀</td>
<td>3.9 × 10⁻⁶</td>
<td>1.5 × 10⁻⁵</td>
<td>3.9 × 10⁻⁵</td>
<td>1.6 × 10⁻⁵</td>
</tr>
</tbody>
</table>
form. There are data to suggest that this is true in nerve and muscle membrane (Ritchie et al., 1970).

2. When the pH of the extracellular fluid is lowered by elevating the PCO₂, the change in intracellular pH, \( \Delta pH_i \), is 0.45 \( \Delta pH_e \). (Steenbergen et al., 1977).

3. When the pH of the extracellular fluid is lowered by decreasing the bicarbonate concentration \( \Delta pH_e = 0.1 \Delta pH_i \) (Woodbury, 1966; Ellis and Thomas, 1976), the buffering capacity of ventricular muscle is approximately twice that of Purkinje fibers. In guinea pig papillary muscle superfused with a physiologic salt solution of pH 7.4, pH, has been shown to be 7.16 (Ellis and Thomas, 1976).

The predicted concentrations of each form of the drug in the test solutions are shown in Table 5. The absolute values are not critical to the presentation of our results. Rather, we are merely interested in predicting the trend in concentration changes.

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