Use-dependent effects of lidocaine on conduction in canine myocardium: application of the modulated receptor hypothesis in vivo

JESSE DAVIS, M.D., TETSU MATSUBARA, M.D., MELVIN M. SCHEINMAN, M.D., BERTRAM KATZUNG, M.D., PH.D., AND LUC H. HONDEGHEM, M.D., PH.D.*

ABSTRACT  Lidocaine is a commonly used antiarrhythmic drug that causes use-dependent blockade of sodium channels in vitro and reduces conduction velocity in vitro and in vivo. According to the modulated receptor hypothesis of antiarrhythmic drug action, lidocaine has a low affinity for rested sodium channels but a high affinity for open and inactivated channels. In the present experiments, we characterized use-dependent conduction slowing and recovery from slowing by lidocaine in anesthetized dogs. The His-to-ventricular conduction interval was used as the indicator of conduction velocity. We found that prolongation of conduction time was greater as the stimulation frequency was increased. Moreover, on abruptly changing the stimulation frequency, a new steady-state conduction time was approached in two to three depolarizations. On discontinuation of stimulation, the conduction time of progressively less premature extrastimuli shortened exponentially with a terminal phase time constant of 152 ± 115 msec. These effects by lidocaine were enhanced during acidosis and enhancement was reversed by correction of the acidosis. It is concluded that the effects in vivo of lidocaine on conduction under several conditions of rate, rhythm, and pH are similar to its effects on the maximum upstroke velocity of the action potential in vitro. Although these experiments were not designed to validate the modulated receptor hypothesis, it appears that the modulated receptor hypothesis can predict the effects of lidocaine on conduction in vivo.


LIDOCAINE blocks sodium channels in a voltage- and time-dependent fashion.1 These effects of lidocaine on the sodium current2 and the maximum upstroke velocity3,4 of the cardiac action potential can be accounted for by the modulated receptor hypothesis.5,6 Briefly, when sodium channels are in the rested state, they have a low affinity for lidocaine, but when they are opened or inactivated by depolarization their affinity for lidocaine increases by several orders of magnitude.2,5 As a result, during each action potential, the fraction of channels blocked by lidocaine increases, whereas during each diastole the fraction blocked decreases. Thus the more closely the action potentials are coupled, the more time is available for block development and the less time for recovery from block. This accounts for frequency- or use-dependent effects on sodium-channel block and action potential upstroke velocity by lidocaine. Use-dependent behavior is also compatible with an alternative model, in which affinity for open and inactivated channels is constant, but drug access to the channel varies with changes in gate configuration during the action potential.6 The modulated receptor predictions have been extensively tested in vitro but not in vivo.7 Both sodium current and maximal upstroke velocity of action potential Vmax have been decreased by lidocaine in studies in vitro. Since maximum upstroke velocity is a major determinant of conduction velocity,8,9 we predicted that lidocaine should produce use-dependent slowing of conduction in vivo. Conduction velocity is also an important variable in the pathophysiology of arrhythmia and in correction of arrhythmia by drugs.

By applying the modulated receptor hypothesis to sodium channel-dependent conduction, we predicted
that (1) the slowing of conduction by lidocaine will increase as the cycle length is reduced, (2) on shortening the cycle length, a new steady state of conduction will be reached in less than 3 beats,3 and (3) after a fast driving train, conduction rate will recover as the coupling interval of an extrasystole is increased. Furthermore, since acidosis enhances the use-dependent block produced by lidocaine and slows the recovery from block,4 we also predicted that acidosis would result in (4) more use-dependent slowing of conduction and (5) slower recovery of conduction.

Methods

Adult mongrel dogs of either sex weighing 19 to 29 kg were anesthetized with morphine sulfate (2 mg/kg) and α-chloralose (100 mg/kg) dissolved in warm saline (45°C). Endotraheal intubation allowed mechanical ventilation with room air. The ventilator was adjusted to maintain a normal Pco2 and the air was enriched with oxygen as required to maintain the Po2 above 100 mm Hg. To detect aberrancy, surface electrocardiographic leads V1, I, and III were continuously monitored from subcutaneous needle limb electrodes and recorded at 0.1 and 500 Hz band-pass filter settings. His bundle electrograms were recorded from No. 6F quadripolar catheters introduced into the right carotid artery and advanced under fluoroscopic guidance to the aortic root to record the largest His electrogram. Constant current pacing stimuli were developed by a programmable stimulator (Digital Cardiovascular Instruments Inc., Emeryville, CA). The right atrium was paced with the distal electrode pair of a No. 6F quadripolar catheter introduced via a jugular vein; the proximal electrode pair was used for recording atrial electrograms. A No. 5F plastic cannula allowed continuous monitoring of femoral arterial pressure with a transducer (Gould Statham P23ID). To study the effects of slow heart rates, right vagal stimulation was used. The right vagus nerve was isolated from the right carotid sheath and carefully cleared of adventitia. The nerve was secured by 2-0 silk suture and cut to allow stimulation of afferent fibers to the heart. All recordings were made on photosensitive paper running at 100 mm/sec, with use of an Electronics for Medicine DR-8 oscilloscope recorder. Serum potassium, sodium, and lidocaine concentrations, and blood pH, Po2, and Pco2 were all measured from femoral arterial blood. Drug was infused via a right femoral vein cannula. To study the effects of acidosis, 0.25N HCl was infused via the left femoral vein. Reversal of acidosis was accomplished by infusion of 1N NaHCO3 as required to return pH to between 7.39 and 7.44. Constant infusion was maintained by a Harvard pump.

Serum potassium and sodium concentrations were determined with an ion-selective electrode (Beckman-Astra); evaluations were performed in the Clinical Laboratories at the University of California, San Francisco. Serum lidocaine concentrations were determined by an immunoassy method (EMIT; Bioscience Laboratories, Oakland, CA). Arterial blood gases were measured in freshly sampled blood with a blood gas analyzer (Radiometer-Copenhagen).

Pacing protocols. These studies were designed to determine the influence of pacing rate on His-Purkinje conduction under control conditions and in the presence of lidocaine at normal pH, lidocaine during acidosis, and lidocaine after reversal of acidosis. We examined the onset, magnitude, and duration of use-dependent effects on conduction. The onset of use-dependent change was monitored during rapid His bundle pacing. The magnitude of steady-state conduction change was monitored by examining the His-ventricular (HV) interval during rapid atrial pacing. The duration of use-dependent change was determined by monitoring recovery from HV prolongation after rapid atrial pacing.

Onset of conduction slowing. Direct His bundle pacing was required to examine the onset of rate-related conduction change. Attempts to observe onset during rapid atrial pacing were complicated by refractoriness (accommodation) within the atroventricular (AV) node. To avoid this limitation, we paced the His bundle directly with electrodes at the aortic root (sinus of Valva). To be sure that the His bundle was paced selectively, we required that the following criteria be met: (1) QRS and T wave morphology had to be similar to that during sinus rhythm and identical to that during atrial pacing at comparable rates. (2) stimulus-to-ventricular depolarization (SV) interval had to be within 5 msec of the HV interval recorded during atrial pacing, and (3) AV dissociation or retrograde ventriculoatrial conduction had to be present.

To monitor onset, the His bundle was paced rapidly at a cycle length of 200 msec. Five trains of 10 complexes were developed for each dog. The interval between the pacing stimulus and the subsequent ventricular depolarization (SV) was determined for each complex in the sequence 1 through 10 for all five trains. Next, mean SV value for the first depolarization of the five trains was calculated for each dog. Similarly, mean SV values for each numbered depolarization (1 through 10) were calculated for the five trains. A reference SV interval was obtained before drug, by pacing at a rate 10 per minute faster than the sinus rate. The change in mean SV interval or delta SV was expressed as a percentage of the reference SV value for each dog (see Data evaluation). Delta SV values for the first through the tenth stimulations at a cycle length of 200 msec were compared under the following conditions: control, lidocaine, lidocaine in acidosis, and lidocaine after reversal of acidosis.

Steady-state HV interval change. The magnitude of steady-state change in the HV interval was examined during atrial pacing. In preliminary experiments, we found that on abruptly changing the frequency of stimulation, AV node accommodation and stable His-to-His intervals developed within three to seven depolarizations. We also verified that administration of atropine did not measurably influence the HV interval in anesthetized dogs during sinus rhythm or rapid atrial pacing. Therefore measurements were taken after 10 depolarizations. Atroine (0.5 mg bolus) was given before pacing to facilitate accommodation within the AV node and to encourage 1:1 AV conduction at rapid rates.1 If AV conduction did not stabilize or AV Wenckebach periodicity was observed, the data were discarded. All atrial stimuli were 2 msec in duration and were applied at two to three times diastolic threshold.

The right atrium was paced for 10 depolarizations at each of the following cycle lengths (msec): 500, 400, 350, 300, 250, 230, 210, 200, and in 10 msec decrements thereafter until 1:1 AV conduction was no longer achieved. A 3 sec pause (sufficiently long to allow return to steady state; see Results) separated each train of 10 depolarizations. To evaluate rate-dependent effects of lidocaine, we measured the HV conduction time of the tenth depolarization of a train. The HV interval was measured from the first high-frequency component of the His spike to the first evidence of ventricular depolarization seen in surface or intracardiac recordings. To measure QRS duration, vertical lines were drawn at the first and last evidence of QRS inscription in three electrocardiographic surface leads I, III, and V1. The interval between these lines was recorded as the QRS duration. All measurements for a given dog were obtained by the same investigator.

Recovery from conduction slowing. Recovery was monitored by sampling the HV interval at progressively earlier points in
diastole, after rapid pacing had created steady-state HV prolongation. To examine recovery, the right atrium was driven rapidly at a cycle length of 200 msec for 10 depolarizations (S1), after which a test stimulus (S2) was introduced, followed by a 3 sec pause. In successive pacing trains, the S1-S2 interval was reduced by 10 msec, starting from the longest possible S1-S2 (determined by the sinus escape complex) to the shortest possible S1-S2 (effective refractory period for AV conduction). For each programmed train, the HV interval of the tenth (H10) and test (H2) depolarizations were measured. Use of the H1-H2 coupling interval for reference avoided accommodation changes within the AV node. In early experiments, sinus tachycardia prevented sampling of recovery points in late diastole. To delay sinus recovery after pacing, we stimulated the distal ends of the cut right vagus nerve using a Grass SR-5 stimulator in five dogs. Duration of the vagal stimulus was fixed at 10 msec while voltage and frequency were varied to achieve up to 1.5 sec asystole immediately after the conditioning train. The presence or absence of vagal nerve stimulation did not affect the HV times of short coupling intervals.

**Drug infusion.** After control measurements were made, we infused 10 mg/kg lidocaine over 10 min. This was followed by a constant infusion of lidocaine at one of two rates. The infusion rate was set at 0.15 mg/kg/min to maintain serum lidocaine concentration in the 6 to 10 μg/ml range, or at 0.3 mg/kg/min to maintain serum lidocaine concentration at 10 to 12 μg/ml. After 15 min for lidocaine distribution, the measurements were repeated, followed by a determination of serum potassium and serum lidocaine concentrations, P2, Pco2, and pH.

We then induced acidosis by infusing HCl solution into the left femoral vein at 2 meq/min. Arterial blood pH was monitored every 10 to 15 min. When blood pH reached the 7.0 to 7.2 range, the acid infusion was slowed to less than 0.5 meq/min. The pH remained unchanged during the period of acidosis at 7.19 ± 0.04 and 7.19 ± 0.06 pH units (p = NS), respectively, before and after test pacing.

Acidosis was reversed by infusing NaHCO3 in an amount equimolar to the HCl used to produce acidosis (50 to 100 meq). Small additional aliquots were then administered, if necessary, until a pH between 7.40 to 7.50 was reached. After reversal of acidosis, the measurements were repeated. After infusion of NaHCO3, the pH tended to drift slightly downward from 7.46 ± 0.07 to 7.40 ± 0.04 (p < .05) during test pacing.

**Data evaluation.** Pacing-induced change in HV interval was expressed as a percentage of a reference HV interval, (HV), measured during drug-free sinus rhythm (mean value from five consecutive sinus depolarizations), according to the following formula:

\[
\%\Delta HV = (HV_i - HV_c) \cdot 100/HV_c
\]

where HVi represents the test HV interval and HVc represents the HV interval of the control sinus depolarization. During His bundle pacing, change in SV interval (%ΔSV) was expressed as a percentage of a reference SV value (SVi) obtained during pacing at 10 beats/min faster than the sinus rate:

\[
\%\Delta SV = (SV_i - SV_c) \cdot 100/SV_c
\]

The magnitude of frequency-dependent HV prolongation was characterized by plotting the change in HV interval (%ΔHV) against the His depolarization intervals (H1-H2) during rapid pacing. Recovery of HV conduction time after rapid pacing was characterized by plotting the H2V2 interval (HV response for the S2 stimulus) against the H1-H2 interval (from the His response of the last S1 pulse to the His response for the S2 stimulus). The %ΔHV points were fitted by a least-square error method to a double exponential regression equation:

\[
%\Delta HV = Ae^{-vt} + Be^{-vt} + C
\]

Single and triple exponential fits were also applied to the recovery data. Double and triple exponential fits were better than single exponential fits (p < .05, F test). Since triple exponential fits were not significantly better than double exponential fits (p > .05, F test), we report only the results of double exponential fits. Both fast and slow recovery constants are reported. Only experiments with recovery data sampled from diastolic intervals exceeding 500 msec were used for recovery constant estimates.

Comparisons between paired observations were done with Student’s t test, and multiple means were compared with one-way analysis of variance with Scheffe’s test. Data are presented as mean ± SD. Measurement error was estimated as the difference between 30 HV intervals measured by two different (blinded) investigators on different days and by repeat measurement of 30 HV intervals by one blinded investigator on different days. For 30 paired observations the measurement error was 3 ± 3 msec for the same observer on different days or 4 ± 3 msec between different observers on different days.

**Results**

An example of drug-induced use-dependent change in His-Purkinje conduction and QRS duration is displayed in figure 1. Under drug-free conditions, the HV interval did not significantly change when the spontaneous sinus cycle length of 410 msec was replaced by a paced cycle length of 210 msec (figure 1, A).

In the presence of lidocaine (10 μg/ml), the HV interval and QRS duration remained unchanged at sinus or paced cycle lengths greater than 300 msec. However, as the cycle length was reduced below 300 msec, the HV and QRS intervals lengthened. At a cycle length of 210 msec, the HV interval increased by 6 msec (20%) and the QRS increased by 11 msec or 19% (figure 1). Similar use-dependent lengthening of the HV and QRS intervals was observed in all experiments in the presence of lidocaine. Since HV intervals are better delineated than QRS duration, we shall report changes in HV interval only. It should be emphasized, however, that the observed changes in HV interval were mirrored by changes in QRS duration. Furthermore, the QRS vector never changed abruptly, so changes in conduction interval probably reflect true changes in conduction velocity rather than gross changes in conduction pathway within the His-Purkinje system.

**Onset of development of use-dependent HV lengthening.** When HV intervals are measured during atrial pacing, accommodation of the AV node to abrupt change in stimulation rate influences AV node output and the resultant cycle length of His-Purkinje depolarization. As a result, fixed-rate His stimulation is not achieved for several cycles in an atrial pacing train until a new steady state for AV node conduction is reached. This confounding factor makes it difficult to study the onset of drug-induced HV change with atrial stimulation. For this reason, the change in stimulus-to-ventricular
depolarization interval (ΔSV) was monitored during rapid His bundle pacing. Selective His bundle pacing was attempted in 10 dogs. In five of 10 dogs, we were able to maintain stable His stimulation throughout both control and lidocaine measurements. Figure 2 illustrates ΔSV for the first 10 depolarizations after abruptly shortening the cycle length to 200 msec in these five dogs. Before drug, no change was observed. In the presence of lidocaine, the SV interval was significantly increased (p < .05) to a new steady level by the second depolarization and did not increase further.

**Magnitude of steady-state HV lengthening by lidocaine.** In figure 3, A, we show the mean effect of lidocaine (9.1 ± 3.5 μg/ml) on steady-state HV interval as a

**FIGURE 1.** A, Induction of use-dependent effects by lidocaine. Surface electrocardiographic leads V1, I, and III, intracardiac electrograms from right atrium (RA) and His bundle (HBE), and femoral arterial pressure (BP) are displayed. Normal sinus rhythm was interrupted by rapid atrial pacing at a cycle length of 210 msec for 10 complexes. In the absence of lidocaine, the HV interval remained constant at 30 msec during rapid pacing. In the presence of lidocaine during rapid pacing, the HV interval was prolonged to 36 msec but quickly recovered to prepacing values upon termination of pacing. AV nodal accommodation and a stable His-to-His interval developed after six or seven rapid depolarizations. B, Enlargement of pacing termination in A. In the absence of lidocaine, neither the HV interval nor QRS duration changed during rapid pacing. The HV interval was 30 msec and QRS duration was 57 msec. In the presence of lidocaine (10 μg/ml), the HV interval was prolonged to 36 msec, an increase of 6 msec or 20%. The QRS duration also increased during rapid pacing to 68 msec. A supraventricular escape complex appearing 310 msec after pacing showed residual HV change (32 msec), but HV had recovered to the prepacing value by the next depolarization. The QRS duration measured 57 msec for both postpacing complexes.
FIGURE 2. Onset of conduction slowing during selective His pacing. Changes in the stimulus-to-ventricular depolarization interval are displayed for depolarizations 1 through 10. The SV interval increased significantly by the second depolarization and did not increase further through depolarization 10. Values are mean and SD for five dogs.

rapid depolarizations was followed by a test stimulus that scanned the subsequent diastolic interval. Delta HV was then determined for each premature interval (H₁-H₂). During control atrial pacing, the H₂-V₂ interval of an S₂-induced (test) depolarization did not change as the H₁-H₂ interval was shortened from 1000 to 180 msec (figure 4). In the presence of lidocaine, the H₂-V₂ interval increased in an exponential fashion as H₁-H₂ was shortened, and this increase in H₂-V₂ was significant (p < .05) for all H₁-H₂ intervals 300 msec and shorter (figure 4).

In five dogs, right vagal nerve stimulation was used to increase the maximum diastolic time before sinus

FIGURE 3. A, Use-dependent effects of lidocaine on the HV interval. The atria are driven regularly for 10 depolarizations at several cycle lengths between 200 and 400 msec. ΔHV interval for depolarization 10 and the interval between the ninth and tenth His bundle deflections (H₁-H₁) are monitored. With predrug atrial pacing, the HV interval did not change as the His depolarization frequency increased, i.e., as H₁-H₁ shortened from 400 to 200 msec. After lidocaine (9.09 ± 3.5 μg/ml), the HV interval increased significantly over predrug changes as the His depolarization interval shortened to 250 msec or less. Values are mean and SD for 15 dogs. B, Use-dependent effects of lidocaine on the HV and SV intervals. The HV and SV intervals change congruently as stimulation frequency increases. Values are mean and SD for five dogs.

Recovery from use-dependent HV prolongation by lidocaine. To monitor recovery, a conditioning train of 10
infusion, we observed a reduction of plasma bicarbonate (p < .01), a small but significant increase in serum potassium concentration (p < .05), and no significant change in PaCO₂ (table 1). Although acidosis alone had no measurable effect on HV conduction time (table 1), lidocaine’s steady-state effect on conduction was markedly accentuated by acidosis. At a drive cycle length of 250 msec, the HV interval increased by 40 ± 25% (p < .01). Rate-dependent slowing by lidocaine (9.85 ± 5 µg/ml) was approximately doubled by acidosis at all cycle lengths below 400 msec (figure 5).

The kinetics of onset and of recovery from lidocaine-induced slowing were studied as previously shown in figures 2 and 4. In the one dog in which selective His pacing was achieved for all four treatments, the onset of conduction slowing after lidocaine was not altered during acidosis. SV interval reached a new level within two to three depolarizations of abruptly shortening the cycle length. In contrast, recovery from slowed conduction was significantly longer in lidocaine with acidosis than in lidocaine at normal pH, monitored after a drive interval of 200 msec (figure 6). In six dogs, τ (slow) for recovery increased from 152 ± 115 msec for lidocaine at normal pH to 686 ± 520 msec for lidocaine with acidosis (p < .05), whereas τ (fast) and serum lidocaine concentration did not significantly change (34 ± 18 to 46 ± 18 msec; p = NS). After diastolic intervals up to 1000 msec, recovery was complete after lidocaine in normal pH but not after lidocaine with acidosis (figure 6). Over a diastolic period of 1000 msec during acidosis with lidocaine, HV declined to within 7% of predrug control values (figure 6). Restoration of the pH to normal by infusion of bicarbonate reversed the effects of lidocaine on conduction toward preacidosis levels. Measured at a drive

**FIGURE 4.** Recovery from use-dependent conduction slowing by lidocaine. A conditioning train of 10 rapid depolarizations at a cycle length of 200 msec is followed by a test stimulus (extrastimulus) that scans atrial diastole. ΔHV for the test depolarization is displayed for each premature interval (His-H1). Vagal stimulation was used to delay the sinus escape depolarization, thereby creating diastolic intervals greater than 400 msec. HV prolongation progressively declined exponentially with time after the last rapid (conditioning) depolarization. Early fast and subsequent slow time constants for recovery were 34 ± 18 and 152 ± 115 msec. Values are mean and SD for six dogs.

escape. The nerve stimulation frequency was adjusted as required to obtain diastolic intervals of up to 1000 msec. In one additional dog, recovery data could be collected over a diastolic interval that spanned more than 500 msec without vagal stimulation. In these six dogs, an early fast [τ(fast)] and subsequent slow time constant [τ(slow)] were shown to characterize recovery from HV prolongation in the presence of lidocaine (8.4 ± 2.1 µg/ml); τ(fast) was 34 ± 18 msec and τ(slow) was 152 ± 115 msec.

**Effects of acidosis on HV interval.** When pH was reduced from 7.43 ± 0.5 to 7.19 ± 0.4 (n = 11) by acid

<table>
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<tr>
<th>Treatment</th>
<th>pH</th>
<th>K⁺ (meq/l)</th>
<th>HCO₃⁻ (meq/l)</th>
<th>Pco₂ (mm Hg)</th>
<th>Lido (µg/ml)</th>
<th>%ΔHV (msec)</th>
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<tr>
<td>Control¹</td>
<td>7.43 ± 0.05</td>
<td>4.02 ± 0.17</td>
<td>21 ± 2</td>
<td>32 ± 4</td>
<td>---</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>HCl (n = 4)</td>
<td>7.14 ± 0.05</td>
<td>4.66 ± 0.21</td>
<td>8 ± 5</td>
<td>37 ± 2</td>
<td>---</td>
<td>-3 ± 15</td>
</tr>
<tr>
<td>Lido</td>
<td>7.43 ± 0.05</td>
<td>4.05 ± 0.38</td>
<td>20 ± 2</td>
<td>32 ± 7</td>
<td>9.09 ± 3.5</td>
<td>19 ± 10²</td>
</tr>
<tr>
<td>Lido + HCl</td>
<td>7.18 ± 0.04³</td>
<td>4.60 ± 0.63³</td>
<td>11 ± 4³</td>
<td>30 ± 8</td>
<td>9.86 ± 5</td>
<td>40 ± 25³</td>
</tr>
<tr>
<td>Lido + HCO₃⁻</td>
<td>7.42 ± 0.04</td>
<td>4.01 ± 0.49</td>
<td>20 ± 4</td>
<td>32 ± 8</td>
<td>12.88 ± 12.9</td>
<td>24 ± 8³</td>
</tr>
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Lido = lidocaine; Lido + HCl = lidocaine in presence of acidosis; Lido + HCO₃⁻ = lidocaine after acidosis reversal by IN sodium bicarbonate; %ΔHV = percent change in HV time at the indicated pacing cycle lengths, compared with HV value during sinus rhythm; CL = pacing cycle length or interval between ninth and tenth His depolarizations during atrial pacing.

¹Predrug values before acidosis.

Significantly different from control: *p < .05; **p < .01. At drive cycle length 250 msec, %ΔHV during acidosis exceeded that for lidocaine at normal pH at the p < .05 level; %ΔHV values for lidocaine before acidosis and after reversal of acidosis were not significantly different. For control, lidocaine, and lidocaine + HCl, n = 11 dogs. For lidocaine + HCO₃⁻, n = 7, a subset of the 11 dogs. For HCl controls, n = 4 different dogs.
cycle length of 250 msec, HV interval was prolonged by 40% (n = 11) during acidosis and by 24% (n = 7) after restoration of pH to normal (table 1). In seven dogs receiving all four treatments and monitored at a drive cycle length of 250 msec, %ΔHV was 0 ± 5 msec for control, increased to 23 ± 11 msec with lidocaine at normal pH and to 46 ± 30 msec during lidocaine with acidosis, and declined to 24 ± 9 msec after reversal of acidosis. Use-dependent HV change with restored pH was not significantly different from preacidosis values at comparable serum lidocaine concentrations. Mean values for pH effects in drug-free and lidocaine treated periods are summarized in table 1.

Discussion

The voltage- and time-dependent actions of antiarrhythmic drugs on transmembrane sodium current or upstroke velocity (V_max) have been described by the modulated receptor hypothesis by several laboratories. Blockade of cardiac sodium channels is frequently suggested as an important mechanism by which lidocaine modifies cardiac conduction and suppresses reentrant arrhythmias but direct evidence in vivo for use-dependent actions on cardiac conduction has been lacking until recently. Our results clearly demonstrate that the effect of lidocaine on cardiac conduction in vivo is rate-dependent, i.e., the faster the heart rate the more conduction is slowed by lidocaine. In normal cardiac tissue at normal pH, lidocaine has virtually no effect on conduction at resting heart rates; only during tachycardia (cycle length less than 250 msec) does lidocaine slow conduction. Thus rate-dependent actions by lidocaine on conduction in vivo are very similar to its actions on V_max in vitro.

We measured use-dependent changes in conduction over a relatively fixed anatomic pathway, the His-Purkinje system. It should be stressed that lidocaine also prolonged QRS duration at rapid rates without significant changes in QRS vector. Thus it is unlikely that the measured effects of lidocaine on HV interval or QRS duration could have resulted from aberrant conduction.

The modulated receptor variables for lidocaine predict that upon an increase in the frequency of stimulation, a new level of block of sodium channels should be established after two depolarizations. This prediction, previously confirmed in vitro for V_max, also holds for the effect of lidocaine on conduction in vivo (figure 2). Thus depression of conduction by lidocaine is almost fully developed by the second beat of a tachycardia. This contrasts with the action of slower drugs like quinidine or flecainide, with which the blockade develops over 10 or more beats. These slower drugs exert their maximal effects only after several beats in the tachycardia. During rapid pacing, potassium may accumulate in the extracellular space and repolarization may be altered transiently. Such local elevations in extracellular potassium concentration might be diluted in systemic venous blood. However, rate-related changes in membrane potential and extracellular potassium occur over several seconds.

![FIGURE 5](http://circ.ahajournals.org/)

FIGURE 5. Effects of acidosis: steady-state use-dependent conduction slowing by lidocaine. During atrial pacing, the HV interval became progressively longer as depolarization frequency of the His-Purkinje system increased. This response was augmented by acidosis and reversed when blood pH was normalized with intravenous sodium bicarbonate. In the presence of lidocaine and acidosis, the increase in the HV interval significantly exceeded control and lidocaine values at all His stimulation intervals 400 msec or less (one-way analysis of variance). Values are mean and SD for 11 dogs.

![FIGURE 6](http://circ.ahajournals.org/)

FIGURE 6. Effects of acidosis: recovery from His-Purkinje conduction slowing with atrial pacing. Acidosis augmented HV prolongation by lidocaine during the conditioning train, and recovery proceeded more slowly. The τ (slow) for recovery was 152 ± 115 msec for lidocaine at normal pH and increased to 686 ± 520 msec for lidocaine during acidosis (p < .05). The serum lidocaine concentrations were 9.09 ± 3.5 and 9.85 ± 5 μg/ml before and after acidosis (p = NS).
contrast, rate-dependent effects by lidocaine on conduction occurred over three depolarizations or less and therefore are probably not related to pacing-induced potassium accumulation.

In vitro, recovery from sodium-channel block by lidocaine occurs quickly and is virtually complete in less than 700 msec at 37°C in normally polarized tissue at normal pH. Published time constants for recovery of $V_{\text{max}}$ after lidocaine at normal transmembrane resting potential are 184 ± 17 msec, 189 ± 120 msec, and 120 to 260 msec. Slower time constants have been reported for recovery of the sodium current in vitro, but these studies were conducted at lower temperatures at which recovery proceeds more slowly. In vivo, recovery of conduction also proceeded quickly after lidocaine (figure 4).

Although recovery from conduction slowing also proceeded exponentially, analytic models and actual measurements suggest a quadratic relationship between upstroke velocity and conduction. In view of this quadratic relationship, recovery kinetics for upstroke velocity and conduction may not be expected to be quantitatively identical.

Effects of acidosis. In vitro, the recovery rate of $V_{\text{max}}$ and the sodium current from lidocaine block are markedly slowed by acidosis. Our results show that recovery of conduction in the His-Purkinje system in vivo is similarly slowed by acidosis. Thus the effect of lidocaine on conduction after each rapid depolarization will persist longer in acidotic tissue than in tissue at normal pH, and the magnitude of steady-state effects will be greater. Yet, complete recovery from lidocaine effect would be expected during acidosis given a sufficiently long diastolic interval. With a $\tau$ (slow) of 686 msec, use-dependent prolongation of the HV interval will decline to less than 1% of peak change after 3 sec of diastolic quiescence.

The mechanism by which acidosis slowed recovery of conduction after lidocaine cannot be explained on the basis of these experiments alone. However, the observations are consistent with a previously postulated change in the fraction of charged lidocaine molecules. Acidosis increases the cationic form of lidocaine relative to the neutral form, and the charged form of the drug dissociates from (unblocks) the repolarized channel more slowly. Our observation is compatible with slowed dissociation or slowed egress by lidocaine from the sodium channel in acidosis. Whether increased block development during each action potential was also important cannot be determined from the present experimental results.

Several alternative factors could contribute to the increased lidocaine effect. However, these are not supported by results reported in the literature, which include the following: (1) Extracellular potassium increases during acidosis. As shown by Chen et al., depolarization by increased extracellular potassium can increase the recovery time constant. However, we do not believe that the augmented lidocaine effect in the present experiments resulted from the increase in extracellular potassium measured during acidosis. The small increase in serum potassium concentration (from 4.05 ± 0.38 to 4.59 ± 0.63 meq/liter; $p < .05$) should result in minimal effects on resting membrane potential (less than 4 mV), $V_{\text{max}}$, or conduction velocity. With abrupt-onset rapid pacing, a regional increase in myocardial extracellular potassium concentration occurs after 10 sec, but lidocaine effects on conduction develop within two to three depolarizations. (2) Acidosis reduces protein binding of lidocaine and hence increases the free lidocaine concentration in plasma. Nevertheless, preliminary observations suggest that protein unbinding during acidosis may not be an important mechanism. In three dogs, the plasma lidocaine concentration was made to double from 14.2 ± 9.2 to 27.6 ± 20 µg/ml during bicarbonate reversal of acidosis (7.15 ± 0.07) to normal pH (7.44 ± 0.05) by increasing the lidocaine infusion rate. This should have increased percent bound lidocaine from approximately 30% to 45%, and calculated free lidocaine concentration would increase from 10 to 15 µg/ml. Yet, during pacing at cycle length 230 msec, $\Delta H V$ was 64 ± 38% during acidosis and 30 ± 11% after normal pH was restored, a 53% reduction. Although lidocaine protein unbinding during acidosis did not appear to account for the increased drug effect in these three dogs, further study is required to confirm or refute this mechanism. (3) Acidosis lengthens the action potential duration under certain circumstances, which could provide more time for block development within inactivated sodium channels and less time for recovery from block at any given cycle length. However, in control experiments, we found that the QT interval (analogous to myocardial action potential duration) did not change significantly in four dogs made acidic but not given lidocaine or in nine lidocaine-treated dogs made acidic. Lidocaine effects on the duration of His-Purkinje depolarization cannot be measured in vivo because His repolarization is masked by depolarization and repolarization in ventricular muscle. However, Rosen et al. found concordance between lidocaine effects on QT interval and Purkinje action potential duration in dogs, and the magnitude of change was small. If lidocaine effects on the duration
of His-Purkinje depolarization were similarly small during acidosis, increased lidocaine exposure to inactivated receptors would not be expected and could not account for the increased lidocaine effect on the HV interval during acidosis.

Recovery from conduction slowing proceeded exponentially. In attempting to characterize the pattern of this exponential process, we found the data were better fit by double- and triple-exponential plots than by single exponentials. This probably reflects the multiple factors that have different magnitudes of influence on the HV interval as an expression of recovery from rate-dependent conduction slowing by lidocaine. These factors might include the quadratic relationship between conduction velocity and \( V_{\text{max}} \), dynamic drug ionization, and drug-channel dissociation after repolarization. Single, double, and triple exponential have been used to characterize recovery from use-dependent block by lidocaine in vitro. Although we do not have a definitive indication of the exponential equations that optimally characterize recovery in vivo, modulated receptor equations do not consider conduction explicitly and can be used only indirectly to predict the pattern of recovery for a drug given in vivo.

**Clinical relevance.** Our observations regarding the effects of lidocaine on cardiac conduction have important clinical implications. Lidocaine should be most effective in suppressing rapid clinical arrhythmias that are sensitive to drug-induced conduction slowing or conduction block, especially when occurring in acidic environments. Ischemic myocardial infarction is accompanied by profound regional myocardial extracellular acidosis (pH ≤ 7.0), along with hyperkalemia (K⁺ 12 to 14 meq/liter) and hypoxia. We observed that acidosis, even without hyperkalemia, significantly augments lidocaine's effect in vivo at very rapid rates, slowing conduction by more than 50% (figure 5). Ischemia is frequently associated with arrhythmias. Acidosis will augment and prolong lidocaine effects on conduction, and any dose of lidocaine will have more effect on conduction in ischemic tissue than in nonischemic tissue. As a result, lidocaine can selectively depress abnormal conduction associated with ischemia and tachyarrhythmias, while leaving conduction relatively unaffected in nonischemic areas.

Cardinal et al. have shown that lidocaine, by increasing the development of slowed conduction and conduction block in acutely ischemic regions and that risk for ventricular fibrillation is reduced at times when conduction slowing and/or block by lidocaine are well established. Lidocaine was less effective in suppressing ischemic ventricular tachycardia unrelated to reentry. Clinically, lidocaine has been more effective in controlling ventricular fibrillation than ventricular tachycardia in patients with acute myocardial infarction. In contrast, reentrant ventricular arrhythmia in nonischemic myocardium appears to be less responsive to lidocaine in experimental and clinical settings.

In summary, use-dependent slowing of conduction and recovery from use-dependent block can be measured in vivo. The kinetics of these effects are comparable to those previously measured in vitro. Moreover, use-dependent slowing of conduction is accentuated by tachycardia and acidosis. These effects can be accounted for by the modulated receptor hypothesis. Thus the use-dependent effects of lidocaine on conduction in vivo compare well with lidocaine effects on \( V_{\text{max}} \) and the sodium current.

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J Davis, T Matsubara, M M Scheinman, B Katzung and L H Hondeghem

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