Conduction Velocity Depression and Drug-Induced Ventricular Tachyarrhythmias
Effects of Lidocaine in the Intact Canine Heart

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Depression of myocardial conduction velocity can be an important mechanism of action of antiarrhythmic drugs but it can also facilitate arrhythmogenesis. We used lidocaine in an anesthetized canine preparation to address the hypothesis that drug-induced rate-dependent conduction velocity depression causes ventricular tachyarrhythmias. A closely spaced square array of 64 electrodes was used to determine conduction velocity longitudinal and transverse to epicardial ventricular fiber direction. Lidocaine caused rate-dependent decreases in conduction velocity that were proportionately greater in the longitudinal direction at the shortest pacing cycle lengths. Conduction velocity depression developed rapidly in the presence of lidocaine with a new steady state present by the second beat of the rapid train. Recovery from rate-dependent depression of conduction velocity was exponential with a time constant of 122±20 msec (mean±SD) in the longitudinal direction and 114±30 msec in the transverse direction; this difference was not significant. The relation between conduction velocity depression and ventricular arrhythmias was assessed by pacing for 3 minutes at cycle lengths of 1,000, 500, 300, and 250 msec, and for 1 minute at a cycle length of 200 msec. Arrhythmias did not occur in the baseline period in the dogs that received lidocaine, nor in 12 control dogs that were subjected to the same stimulation protocol except that saline was administered in place of lidocaine. Sustained polymorphic ventricular tachycardia (VT) occurred in six of 16 dogs given lidocaine. VT occurred in the presence of relatively high plasma lidocaine concentrations (8.4±2.3 μg/ml) and only at pacing cycle lengths of 300 msec or shorter. The dogs that developed VT demonstrated greater rate-dependent depression of conduction velocity than the other dogs, and activation patterns obtained just before the onset of VT showed marked conduction disturbances. Furthermore, QRS prolongation, loss of one-to-one capture, and increasingly distorted activation patterns preceded the onset of VT during fixed-rate pacing, suggesting progressive sodium channel block. In summary, rate-dependent conduction velocity depression and nonuniform activation were associated with VT in this model and can be responsible for some arrhythmias induced by antiarrhythmic drugs. (Circulation 1990;81:1024–1038)

The potential for exacerbating or producing arrhythmias is a feature of most, if not all, antiarrhythmic drugs, and results in considerable morbidity and mortality. The pathophysiology of proarrhythmic events is unknown but several mechanisms might be responsible. Facilitation of reentry is one proposed mechanism. Drugs could promote reentry by increasing dispersion of repolarization, slowing conduction, or by combining these effects. It is now well established that sodium channel block, reduction of the upstroke velocity of the action potential ($V_{max}$), and conduction-velocity depression because of antiarrhythmic drugs are rate dependent. It is not known, however, if the rate-dependent effects of drugs on these properties can be arrhythmogenic.

In this investigation, we tested the hypothesis that rate-dependent effects of antiarrhythmic drugs on conduction velocity can cause ventricular tachyarrhythmia by examining the effect of lidocaine on the intact canine heart. Although the proarrhythmic effects of lidocaine are not a major clinical problem,
several characteristics make it a useful tool for examining this question. Lidocaine blocks the fast inward sodium current in a rate-dependent manner, producing minimal myocardial conduction velocity depression at the slowest heart rates achievable in the intact heart but substantial reduction at rapid rates.\(^7\)\(^9\) Moreover, previous work suggests that lidocaine’s other electrophysiological effects are not as likely to promote arrhythmias;\(^6\) it is not known to prolong repolarization\(^10\)\(^\text{--}12\) or increase nonuniformity of repolarization,\(^13\) and it does not appear to enhance automaticity even at high concentrations.\(^10\)\(^11\)\(^13\)

Lidocaine has been shown to be proarrhythmic in animal models of acute and long-term ischemic damage.\(^14\)\(^\text{--}16\) Ascertainment of the mechanisms of its proarrhythmic effects in these preparations, however, is complicated because diseased myocardium is arrhythmogenic itself, and because lidocaine’s electrophysiological effects vary with the type and degree of disease.\(^13\)\(^17\) For these reasons, our experiments were performed in healthy dogs. We are not aware of any previous reports of the electrophysiological effects of lidocaine in anisotropic canine ventricular myocardium. Therefore, in the first part of this investigation, we examined the rate-related effects of therapeutic concentrations of lidocaine on conduction, repolarization, and refractoriness.

**Methods**

**Animal Preparation**

Adult mongrel dogs of either sex (17–28 kg) were anesthetized with an intravenous bolus of sodium pentobarbital 30 mg/kg followed by a constant intravenous infusion of 0.03–0.06 mg/kg/min that was adjusted to suppress the blink reflex and spontaneous motor activity. They were then intubated and ventilated with a Harvard respirator (Harvard Apparatus, South Natick, Massachusetts). Arterial blood gases were obtained every 30 minutes, and pH was maintained at 7.35–7.45 by altering the rate and depth of ventilation. Catheters were inserted into the right femoral artery and both femoral veins for continuous arterial blood pressure monitoring, blood sampling, and drug infusion. Normal saline was infused at 1 ml/kg/hr.

The heart was exposed through a median sternotomy and cradled in the pericardium. A quadrupolar electrode plaque was sewn to the right ventricle. Formalin was injected into the atrioventricular conduction system to interrupt atrioventricular conduction.\(^18\) An epoxy plaque with 64 flat unipolar silver electrodes (0.6-mm diameter) in an eight-by-eight array with 2-mm interelectrode distance was sewn to the left ventricle near the left anterior descending artery one third of the distance from apex to base. In one dog that did not have an area free of superficial vessels in this region, the 64-electrode plaque was sewn to the posterior left ventricular surface. The unipolar electrodes were referenced to a Wilson central terminal. To monitor epicardial temperature, a flat thermistor (Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio) was placed facing the left ventricular epicardium near the electrode plaque. The pericardial cradle was then taken down and the chest wall apposed.

Soon after the dog was anesthetized, a baseline rectal temperature was determined. After the chest was closed, the ventricles were paced at 120 beats/min for 30 minutes while the core temperature returned to baseline with the aid of a thermal blanket. Pacing maneuvers and measurements were then performed. Rectal and cardiac temperatures were maintained within 1.0°C of the baseline rectal temperature throughout the experiment. The mean epicardial temperature was 37.9±0.83°C. These experiments conformed to the guidelines of the American Physiological Society, and the experimental protocol was approved by the University of Utah Internal Animal Care Use Committee.

**Analysis System**

The data acquisition and analysis system has been described previously.\(^19\) Briefly, it consisted of 64 differential amplifiers (input impedance greater than 10\(^12\) Ω), each with sample and hold outputs. Electrograms were recorded at a band width of 0.03–500 Hz, sampled at a 1 kHz rate, multiplexed into a programmable-gain amplifier by four 16:1 multiplexers, and digitized by a 12-bit analog-to-digital converter. The digital output of the converter was sequentially multiplexed through a saturation detection circuit and into a first-in–first-out memory that permitted asynchronous buffering between the intermittent bursts of sampled data and the random access memory. The computer (MicroVAX II, Digital Electric, Maynard, Massachusetts) acquired the data through an optically isolated interface and, then, stored it on a fixed disk.

**Conduction Velocity**

Unipolar cathodal stimulation was applied through an electrode on the plaque array with the anodal input directed to a needle inserted into the right chest wall. Stimulation was performed with an interval generator (World Precision Instruments, New Haven, Connecticut) and a custom constant-current source with 2-msec rectangular impulses and current adjusted to twofold diastolic capture threshold. pacing thresholds were measured before each pacing sequence and were determined at the cycle length planned for that maneuver. Thresholds were determined with 0.01-mA precision.

For each experiment, two pairs of electrodes were chosen between which all conduction velocities for that experiment were calculated. The electrodes used to calculate conduction velocities were chosen by examination of the isochrone map of electrical activation. Activation time was defined as the time of the minimum negative derivative of the local potential.\(^20\) An activation map with 2-msec isochrones was constructed by the computer program by linear interpo-
lation based on the 63 available activation times. Rapid (longitudinal) and slow (transverse) directions of propagation were clearly discernible from the maps. A line was drawn from the pacing site to the outer edge of the map, perpendicular to the most widely spaced isochrones (Figure 1). Longitudinal conduction velocity was calculated between two electrode sites along this line by dividing the distance between them by the difference of their activation times. A second line, perpendicular to the first, was drawn through the densely spaced isochrones and transverse conduction velocity computed between two electrode sites along the second line. The mean (±SD) distance between the pair of electrodes used to compute conduction velocity was 9.7±1.2 mm in the longitudinal and 6.3±1.1 in the transverse direction. When isochrone maps from all pacing cycle lengths used in a given experiment were compared, the directions of maximum and minimum conduction velocities did not differ despite rate-related slowing. In seven dogs, a histological section obtained from directly beneath the electrode plaque was examined by light microscopy, and the directions of rapid and slow propagation observed from the isochrone display corresponded to longitudinal and transverse fiber orientation in the histological section. This definition of conduction velocity presumes that the path of propagation is direct and in the superficial epicardial layer. This cannot be proved without knowledge of activation in three dimensions. We carefully reviewed, however, electrode sites for evidence of indirect propagation, which can be identified by the presence of sudden changes in the density of isochrone lines. This is most likely to occur in the transverse direction in which more rapid conduction in a subepicardial layer can “preexcite” distal tissue before it is activated by the wave of excitation in the superficial tissue. To avoid such areas, the electrode sites were chosen in areas with equal spacing between isochrone lines.

The rate-dependent effects of lidocaine on conduction velocity were assessed during fixed-rate pacing at cycle lengths of 1,000, 500, 300, and 250 msec for 3 minutes and 200 msec for 1 minute. Development of drug-induced rate-related conduction velocity depression was assessed by abruptly decreasing the pacing cycle length from 1,000 msec to 300 msec and measuring the conduction velocities of the beats of the shorter cycle length.

Recovery of conduction velocity from rate-dependent depression was examined by determining the conduction velocity of the beat after a test stimulus delivered with a variable coupling interval to the last beat of a 1-minute pacing train of 300-msec cycle length. Conduction velocity (θ) data were normalized and converted to an index of fractional depression as follows: (θ_max−θ_test)/θ_max, where θ_max is the conduction velocity of the test stimulus delivered after the longest pause obtainable, and θ_test is the conduction velocity of the test impulse. To avoid the possible influence of voltage-dependent effects on conduction velocity resulting from incomplete repolarization, only test intervals 30 msec longer than the effective refractory period were used, which should allow sufficient time for complete repolarization.

The diastolic rest period was calculated by subtracting the last repolarization interval (see next section) of the train from the coupling interval of the test.
impulse. The fractional conduction velocity versus diastolic rest-period plots were fit to a monoequational function using a nonlinear least-squares parameter fitting program.23

Repolarization Intervals and Refractory Periods

Soon after the electrode plaque was placed, recordings were obtained and analyzed immediately to construct an isochrone map. For each experiment, two electrode sites on the plaque were chosen from which refractory periods and repolarization intervals were determined. One site was in the longitudinal direction of propagation, the other in the transverse path (Figure 1). The repolarization time was defined as the time of maximum first derivative of the potential of the T wave of the local electrogram as previously described.24 This corresponds to the time of maximum rate of change of voltage during phase 3 of the action potential.25,26 The temporal correspondence between repolarization time as measured from electrograms and repolarization measured from action potentials has been demonstrated by simultaneous measurements of intra and extracellular potentials.25,26 The repolarization interval for an electrode site was defined as the difference between the repolarization time and the activation time obtained at that site. Repolarization intervals and conduction velocities were obtained for the same beat during fixed-rate pacing, that is, after 3 minutes of pacing at cycle lengths of 1,000, 500, 300, and 250 msec, and after 1 minute at a cycle length of 200 msec. Refractory period measurements were performed at cycle lengths of 1,000, 500, and 300 msec as follows: Fixed-rate pacing was continued without pause from the original pacing site (S1) after the 3-minute data acquisition; then single extrastimuli from the second site (S2) were delivered after every fourth S1. To minimize perturbation of the pacing rate, the initial S1S2 interval was set well within the refractory period and increased by 1-msec intervals until a propagated response occurred. The S1S2 interval was then decreased by 10 msec, and the process was repeated twice. The refractory period of the S2 site was defined as the mean S1S2 interval that produced a propagated response minus the activation time at that site.

Dispersion of Repolarization

Repolarization intervals obtained from each of the 63 available plaque electrodes after 3 minutes of pacing at each cycle length were used to determine dispersion of repolarization. Two measures of dispersion were assessed. The range of repolarization intervals, that is, the maximum repolarization interval minus the minimum, was used because it was the method used in most previous studies.27,28 We also examined the standard deviation of the repolarization intervals because it is the preferred measure of dispersion for most variables because it is less subject to extreme values.29

Blood Pressure

Blood pressures were measured from a catheter placed in the femoral artery and connected to a Gould-Statham P23 transducer (Gould, Inc., Cleveland, Ohio). Signals from the transducer were amplified by a Gould pressure processor and recorded on a Gould ES1000 recorder. Systolic and diastolic pressures were obtained after 3 minutes at each pacing cycle length (1 minute at cycle length of 200 msec). The mean of at least four beats was used for each pressure.

Lidocaine Administration and Concentrations

The stimulation protocols noted above were performed before and after the administration of lidocaine. Lidocaine was administered with a loading infusion of 6.0 mg/kg/min for 10 minutes followed by a maintenance infusion of 0.08 mg/kg/min. A second loading infusion, equal to the first, followed by a second maintenance infusion, 0.16 mg/kg/min, was given to three dogs. Plasma lidocaine levels were determined immediately before each stimulation protocol. For drug concentrations, 10 ml of blood was withdrawn from the arterial catheter in a heparinized tube, immediately centrifuged at 4°C, and the plasma was separated and frozen. The plasma samples were analyzed by an immunoenzymatic assay for lidocaine (Abbott Laboratories, Irving, Texas).30

Control Experiments

Twelve dogs underwent the same procedures including stimulation programs and blood withdrawal for drug concentrations, except that normal saline was infused instead of lidocaine.

Ventricular Tachyarrhythmia Induction

Ventricular tachycardia (VT) was defined as a ventricular rhythm consisting of five or more consecutive beats with a cycle length of 600–160 msec and with discrete deflections in the electrogram recorded from the right ventricle.31 Sustained meant that the arrhythmia did not terminate spontaneously. Ventricular fibrillation (VF) was defined as a ventricular rhythm with a cycle length of less than 160 msec with fractionated or disorganized electrical activity in the right ventricular lead and no distinguishable QRS complexes on the surface electrocardiographic leads. Because the purpose of this study was to assess the effect of drug-related effects of conduction velocity depression on arrhythmia development, we avoided stimulation methods that would enhance nonuniform repolarization. Although premature stimulation is commonly used to induce arrhythmias in patients, this method increases the dispersion of repolarization.27 Furthermore, if premature stimuli are delivered before repolarization is complete, the propagation velocity of the premature beat will be reduced even in the absence of drug,32 which would obscure the effect we wished to examine. Instead, arrhythmias were induced by fixed-rate pacing at increas-
ingly rapid rates (3 minutes at cycle lengths of 1,000, 500, 300, and 250 msec, and 1 minute at 200 msec). Because disparity of repolarization diminishes with faster heart rates, we could achieve progressive drug-related conduction velocity depression while reducing nonuniform recovery.

Statistical Analysis

Differences between conduction velocities obtained at several cycle lengths before and after administration of lidocaine were analyzed by analysis of variance of repeated measures (ANOVA). Scheffé’s test was used to determine the significance of differences between means involving multiple comparisons. Student’s t test was used for comparisons involving two means. Differences were considered significant when p values were less than 0.05. Average values are given as the arithmetic mean±SD.

Results

Rate-Dependent Conduction Velocity Depression

Lidocaine caused marked rate-dependent reductions in both longitudinal and transverse conduction velocities as compared with baseline (p<0.0001) (Figure 2). The mean plasma lidocaine concentration during this maneuver was 5.2±1.1 μg/ml. There were no discernible differences between conduction velocities obtained at a pacing cycle length of 1,000 msec before and after lidocaine administration; however, at pacing cycle lengths of 250 and 200 msec, both longitudinal and transverse conduction velocities were significantly lower than baseline values. There was a significant correlation between the plasma lidocaine concentration and the percentage of reduction of conduction velocity when the cycle length was changed from 1,000 to 200 msec (r=0.75, p<0.01). Lidocaine caused proportionately greater reduction in longitudinal conduction velocity than in transverse conduction velocity at a pacing cycle length of 200 msec but not at longer cycle lengths. The effects of rate on conduction velocities after saline administration in the control animals did not differ significantly from baseline measurements.

Development of Conduction Velocity Depression

The rate of development of conduction velocity depression was assessed by abruptly decreasing the pacing cycle length from 1,000 to 300 msec in eight dogs (Figure 3). In the control state, conduction velocity decreased significantly in both the longitudinal and transverse directions (p<0.0001), and the decrease was significantly greater in the longitudinal direction (p<0.02). This decay in conduction velocity had a time course and magnitude similar to the ultraslow inactivation described by Clarkson et al. Lidocaine (5.8±1.8 μg/ml) caused an immediate decline in conduction velocity that did not decrease further after the second beat of the rapid train. In fact, after the tenth beat of the rapid train, conduction velocity appeared to recover slightly.

Recovery From Conduction Velocity Depression

Recovery from drug-induced, rate-related reduction of conduction velocity was determined in 13 dogs by delivering extrastimuli with variable coupling intervals after pacing at a cycle length of 300 msec. In the baseline state, a flat response between the test interval and conduction velocity was observed. In the presence of lidocaine (5.0±1.2 μg/ml), conduction velocity increased with longer intervals (Figure 4). The mean time constant (τrec) of recovery was 122±20 msec for longitudinal propagation and 114±30 msec for transverse propagation; the difference was not significant.

Refractory Periods and Repolarization Intervals

Effective refractory periods were measured at three cycle lengths and at two sites, one in the longitudinal and one in the transverse direction for each experiment (Figure 5). Refractory periods in the longitudinal direction were slightly but significantly longer than those in the transverse direction (p=0.04), a relation that was retained in the presence of lidocaine. Lidocaine tended to increase refractory periods but not significantly.

Refractory periods, which reflect action potential duration, correlated highly with refractory periods both before (r=0.96, p<0.0001) and after (r=0.95, p<0.0001) lidocaine administration. The ratio of refractory period to repolarization intervals was significantly increased by lidocaine (baseline,
Decrease in conduction velocities; after lidocaine, lidocaine levels were 1.06±0.05, lidocaine, 1.10±0.06; *p<0.001). On the other hand, repolarization intervals were not significantly changed by lidocaine. Repolarization intervals were found to be significantly longer in the longitudinal direction than in the transverse direction (*p<0.005), which is consistent with the findings of Osaka et al 34 who reported longer action potential duration with longitudinal propagation as compared with transverse propagation. This relation was not altered by lidocaine.

**Blood Pressure**

Lidocaine caused a significant decrease in blood pressure when compared with the baseline pressures in the dogs that received lidocaine, and when compared with the blood pressures obtained after saline infusion in the control dogs (Figure 6). Although blood pressure declined with shorter cycle lengths in all conditions, this rate-dependent decline was significantly greater after lidocaine, and was correlated with the plasma lidocaine levels (*r=0.66, *p<0.01*).

**Ventricular Tachyarrhythmia Induction**

The relation between conduction velocity depression and development of ventricular tachyarrhythmias was evaluated by pacing at cycle lengths of 1,000, 500, 300, and 250 msec for 3 minutes, and 200 msec for 1 minute. No arrhythmias occurred before lidocaine was given, and no arrhythmias occurred in the control dogs either before or after saline infusion. Sustained VT occurred after the administration of lidocaine in six dogs (Table 1) and was the terminal event in each case. Typically, profound widening of the paced QRS complexes preceded polymorphic VT, which had a regular cycle length 30–50 msec shorter than the pacing cycle length (Figure 7). VT became increasingly disorganized and eventually degenerated into VF. In one case, VT with a cycle length slightly longer than the pacing cycle length was observed when pacing was terminated.

The mean lidocaine plasma concentration in these dogs was 8.4±2.4 µg/ml (range, 5.8–12.2 µg/ml), which was significantly higher than the mean lidocaine level (5.1±1.3 µg/ml) determined in the
dogs that did not develop VF (range, 3.1–7.3; p=0.004).

Rate-dependent conduction velocity depression was significantly greater in the dogs that developed VT (Figure 8). Compared with the conduction velocity obtained at a cycle length of 1,000 msec, longitudinal conduction velocity decreased by a maximum of 17% at a cycle length of 200 msec and by only 7% at a pacing cycle length of 300 msec in the experiments in which VT did not occur. In contrast, in the dogs that developed VT, conduction velocity decreased by an average of 25% at a cycle length of 300 msec (p<0.05).

The ranges and standard deviations of the repolarization intervals from the plaque electrodes were used to assess dispersion of repolarization. Both measures decreased significantly with shorter cycle lengths (p<0.01). Lidocaine tended to decrease dispersion of repolarization in the dogs that developed VT (Figure 9) although the differences were not significant.

After lidocaine administration, the dogs that developed VT tended to have lower blood pressures than the dogs that did not develop VT (Figure 10) but the differences were not significant.

**Progression of Electrophysiological Changes**

The time between the onset of stimulation at the cycle length that induced VT and the time of VT development averaged 91 seconds (Table 1). There was evidence that electrophysiological changes were continuing throughout this period. In the experiments in which VT did not occur, conduction velocity after lidocaine was infused did not change significantly after two beats of pacing at a more rapid rate (Figure 3). At the final pacing cycle length in the dogs with VT, however, QRS duration increased significantly between the tenth beat of rapid stimulation (130±7 msec) to the last stimulated beats before VT (160±11 msec, p=0.002).

In the three experiments in which VT occurred more than 60 seconds after the onset of pacing, data were acquired from the 64-electrode plaque at 60 seconds after initiation of pacing at the cycle length that induced VT and just before the onset of VT. In each case, marked changes in the pattern of activation occurred between 60 seconds and the onset of VT. An example is seen in Figure 11. Before lidocaine administration there were no pronounced rate-related changes in activation sequence (Figure 11, Panel A). Conduction slowed slightly at a pacing cycle length of 1,000 msec after lidocaine was given. Greater slowing was noted at faster cycle lengths (Figure 11, Panels B, C, and D). With short cycle lengths (<300 msec), slowing of activation became nonuniform. This was unlike the patterns observed in the animals without VT, in which rate-dependent changes in activation were always uniform. We did

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**TABLE 1. Lidocaine Plasma Concentrations, Pacing Cycle Lengths, and Characteristics of Induced Ventricular Arrhythmias in Six Dogs**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Lidocaine (µg/ml)</th>
<th>Pacing CL (msec)</th>
<th>Time to VT (sec)</th>
<th>Initial CL* of VT (msec)</th>
<th>CL* at 30 sec (msec)</th>
<th>Time to VF (sec)</th>
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<tr>
<td>1</td>
<td>8.2</td>
<td>250</td>
<td>127</td>
<td>205</td>
<td>219</td>
<td>39</td>
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<td>2</td>
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<td>140</td>
<td>268</td>
<td>250</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
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<td>200</td>
<td>60</td>
<td>216</td>
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<td>132</td>
</tr>
<tr>
<td>4</td>
<td>5.8</td>
<td>200</td>
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<td>171</td>
<td>166</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
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<td>250</td>
<td>176</td>
<td>200</td>
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<td>41</td>
</tr>
<tr>
<td>6</td>
<td>8.3</td>
<td>250</td>
<td>20</td>
<td>VF</td>
<td>VF</td>
<td>imm</td>
</tr>
<tr>
<td>Mean</td>
<td>8.4</td>
<td>242</td>
<td>91</td>
<td>212</td>
<td>199</td>
<td>64</td>
</tr>
<tr>
<td>SD</td>
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<td>38</td>
<td>66</td>
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CL, cycle length; VT, ventricular tachycardia; VF, ventricular fibrillation; N/A, not available; imm, immediate onset of VF.

*Mean of 10 beats.
not attempt to estimate conduction velocity during nonuniform activation because previous work demonstrated that epicardial activation can occur by subepicardial spread in such circumstances. Slowing of activation was observed after pacing at a cycle length of 250 msec for 60 seconds but recordings obtained a few seconds before VT demonstrated pronounced abnormalities of activation (Figure 11, Panel F). The chaotic pattern observed in Panel F of Figure 11 might suggest that it was recorded during VT; however, the configuration of the electrograms did not change from beat to beat and the relation between the stimulus artifacts and the local deflections remained constant (Figure 12F).

One could legitimately question whether the deflections recorded from sites in the middle of the electrode array (Figure 11, Panel F) should be considered activation at all (Figure 12F). Instead, these electrograms could result from distant electrical activity and indicate electrically silent tissue just beneath the plaque. The absolute values of the first
time derivatives of all the extracellular potentials exceeded a previously suggested criterion of at least 1.5 V/sec \textsuperscript{35} except one site in which the derivative was \(-0.9\) V/sec. In either case, this example demonstrates the development of an area of extreme activation delay or block that could permit the development of reentrant arrhythmias. Because the recordings were obtained from a very small area of the heart, it is probable that multiple areas of such disturbed activation occurred throughout the myocardium. Examination of the individual electrograms for changes suggestive of ischemia\textsuperscript{36} revealed no elevation of the ST segments when compared with baseline recordings. Microscopic examination revealed histologically normal myocardial tissue beneath the electrode array and no anatomic abnormalities that could explain the observed electrical changes.

**Discussion**

**Rate-Dependent Effects of Lidocaine**

We measured the effects of therapeutic concentrations of lidocaine on several electrophysiological parameters to confirm the rate-dependent properties of lidocaine in our preparation. At a mean plasma concentration of 5.2 \(\mu\)g/ml, there was no significant change in conduction velocity at a pacing cycle length of 1,000 msec compared with controls; however, at a cycle length of 200 msec conduction velocity declined an average of 17% in the longitudinal direction and 13% in the transverse direction. Our results are compatible with observations obtained in other preparations.\textsuperscript{7,8,10} For example, 5.3 \(\mu\)g/ml lidocaine caused minimal changes in \(V_{\text{max}}\) in isolated canine ventricular myocytes during stimulation at 1,000-msec intervals but significant changes were observed at shorter cycle lengths in a study by Wasserstrom and Salata.\textsuperscript{10} In guinea pig papillary muscles exposed to 4 \(\mu\)g/ml lidocaine, Buchanan et al\textsuperscript{10} detected a 7% decrease in conduction velocity when the cycle length was shortened from 10,000 msec to 1,000 msec, and a 21% decrease when the cycle length was shortened to 200 msec.\textsuperscript{8}

When the pacing cycle length was decreased abruptly, a new steady state of conduction velocity occurred by the second beat of the rapid train, as others have observed.\textsuperscript{7,37,38} We noted a gradual decline in conduction velocity in the control state that developed throughout 1–2 minutes before reaching a plateau. Because the change was greater in the longitudinal direction, it seems unlikely that a reduction in cell-to-cell coupling was responsible.\textsuperscript{39} The observed change is consistent with sodium channel inactivation, and has a similar time course to the ultraslow sodium current inactivation described by Clarkson et al.\textsuperscript{33} In the presence of lidocaine, conduction velocity did not drop after the second beat of the rapid train. This suggests that lidocaine inhibits ultraslow sodium current inactivation.\textsuperscript{33} Recovery from use-dependent conduction-velocity depression occurred with a time constant of about 120 msec. This is quite similar to the results of others (138 msec,\textsuperscript{9} 152 msec,\textsuperscript{37} 161 msec,\textsuperscript{38} and 112 msec\textsuperscript{40}).

At a cycle length of 200 msec, lidocaine's effect on conduction was anisotropic, that is, longitudinal conduction velocity was reduced more than transverse conduction velocity. Recovery from depressed conduction velocity did not differ significantly with direction of propagation; therefore, differences in the kinetics of drug unbinding could not explain this. Previous work suggests that directional differences in drug binding might be responsible for this anisotropic effect. Spach et al\textsuperscript{32} developed a model that predicted greater total open time of sodium channels with longitudinal propagation than with transverse propagation, which should result in greater binding of antiarrhythmic drugs that block activated sodium channels. This was verified by the finding of greater depression of \(V_{\text{max}}\) and conduction velocity with longitudinal propagation than with transverse propagation in the presence of lidocaine and quinidine. Another explanation for greater depression of longitudinal conduction velocity is related to the finding that repolarization intervals were longer in this direction.\textsuperscript{34} Binding of drugs that block inactivated sodium channels increases in the presence of prolonged repolarization because the period of inactivation is longer.\textsuperscript{41} Because lidocaine blocks both activated and inactivated sodium channels,\textsuperscript{41} either of these mechanisms could explain lidocaine's directional selectivity of conduction velocity depression.

Lidocaine caused an accentuation of the rate-related decline in blood pressure. The most likely explanation for this observation is a frequency-dependent reduction in cardiac contractility, which has been carefully examined previously.\textsuperscript{42} Reduction in cardiac sympathetic activity by lidocaine could also contribute to this observation.\textsuperscript{43}

**Mechanism of Induced Arrhythmias**

Arrhythmias can result from abnormalities in impulse initiation or propagation. There is little
support for automaticity as a mechanism of lidocaine-induced arrhythmias\textsuperscript{10-12,44} although abnormal automaticity has been implicated as a mechanism of arrhythmias caused by antiarrhythmic drugs such as quinidine\textsuperscript{45} and digitalis\textsuperscript{46}. Indeed, lidocaine has been shown to inhibit various forms of automaticity clinically\textsuperscript{47,48} and experimentally.\textsuperscript{42} The available evidence favors reentry. Carson et al\textsuperscript{14} reported that
lidocaine increased the incidence of VF during acute myocardial ischemia and hypothesized that lidocaine promoted reentrant arrhythmias by increasing conduction delays and by producing block. In a conscious canine model of myocardial infarction (6–14 days after coronary occlusion), Patterson et al reported that lidocaine enhanced the induction of VT and VF by programmed electrical stimulation and proposed that lidocaine’s proarrhythmic effects resulted from facilitation of reentry. The role of conduction in these studies, however, could not be separated from other properties because lidocaine’s effects on conduction, refractoriness, and excitability are intensified in infarcted tissue. Lidocaine, in particular, has minimal effects on the effective refractory period in normal tissue but, in infarcted tissue, the effective refractory period is markedly increased, and this could increase the likelihood of reentrant arrhythmias by increasing the disparity of recovery. In other words, these studies demonstrate that lidocaine promotes reentry in circumstances that mimic the clinical situation; however, the heterogeneous effects of the drug on damaged tissue make it difficult to determine which effect is responsible.

A relation between the development of ventricular arrhythmias and conduction velocity depression was supported by several findings in this study. As noted previously, the predominant effect of lidocaine was a rate-dependent reduction in conduction velocity, whereas minimal effects were noted on repolarization. Moreover, the development of VT was rate dependent; VT occurred only during pacing cycle lengths of 300 msec or less, and were preceded by reductions in conduction velocity that were more pronounced than those occurring at lower concentrations of lidocaine (Figure 8). Furthermore, activation maps constructed from data obtained just before the onset of VT revealed pronounced disturbances in conduction (Figure 11).

Although disparity of repolarization always plays some role in reentry, there was little to suggest that it was primarily responsible for the observed arrhythmias. Lidocaine has been shown to shorten recovery duration in a number of studies but we are not aware that this effect varies to any great extent in ventricular myocardium. As previously reported, we found less heterogeneity of repolarization at shorter cycle lengths. Furthermore, in the dogs that developed VT, lidocaine tended to reduce dispersion of repolarization.

**Progressive Conduction Velocity Depression**

An unexpected finding was the delay between the initiation of rapid pacing and the development of VT. At therapeutic concentrations of lidocaine, the development of use-dependent conduction velocity depression was complete after the second beat (Figure 4), a finding supported by numerous previous studies. In the experiments in which VT developed, however, further electrophysiological changes occurred between the second beat of rapid pacing and VT. For instance, QRS prolongation was noted between 10 beats after the onset of rapid pacing (at which time steady-state would be expected) and the onset of VT. In some experiments, block of activation occurred, which could be overcome by increasing the stimulation current. In other experiments, activation maps obtained 60 seconds after pacing began and just before VT occurred revealed worsening disturbances in conduction (Figure 11). These findings indicate an unstable condition in which continuously electrophysiological alterations preceded sustained ventricular arrhythmias.

Myocardial ischemia could cause progressive slowing of conduction. Despite identical stimulation protocols, neither severe activation delays nor ventricular arrhythmias were observed before lidocaine administration or in the control dogs that received saline instead of lidocaine. Thus, rapid pacing per se did not cause ischemia. On the other hand, lidocaine-treated animals developed lower blood pressures that could have promoted ischemia in this group alone. Other considerations, however, suggest that ischemia was not the cause of the electrophysiological changes. After sudden, complete cessation of coronary blood flow, conduction velocity increases during the first 2–3 minutes of ischemia. Conduction slowing does not usually occur until 3–5 minutes after coronary occlusion. In this study, there was no evidence of acceleration of conduction, and slowing of activation occurred much earlier. Arrhythmias developed as early as 20 seconds after the onset of pacing (mean, 91 seconds). ST segment elevation can be recorded with unipolar electrodes from ischemic tissue after 1 minute of coronary occlusion. Electrograms recorded before VT or during nonuniform activation in our study did not reveal ST segment changes (Figure 12).

A number of other mechanisms could produce progressive conduction delays such as elevated extracellular potassium, acidosis, and increased intracellular calcium. Because we did not measure regional or cellular ion activity (arterial pH and plasma K+ and Ca2+) remained normal) we cannot exclude these possibilities. To our knowledge, lidocaine would not cause these changes in the absence of ischemia.

Nonuniform activation and ventricular arrhythmias occurred only during rapid pacing and only in the presence of high concentrations of lidocaine. We believe that extensive sodium channel blockade could explain the progressive changes we observed. Reduction of the action potential upstroke velocity (Vmax) by antiarrhythmic drugs increases the time spent at more negative membrane potentials. This will increase the time constants of sodium current activation and inactivation (τm and τh in Hodgkin and Huxley’s terminology). This will then prolong the total period of sodium channel activation and will promote further sodium channel binding by drugs. This is supported by single-channel recordings that show that sodium channels frequently reopen at more negative membrane potentials, thereby increas-
ing the total open time.\textsuperscript{55} Furthermore, slower action potential upstrokes will increase membrane capacitance,\textsuperscript{56,57} which will tend to reduce V\textsubscript{max} because of the increased current load.\textsuperscript{32} At nontoxic concentrations of drugs and at slower heart rates, these effects might be counteracted by the mobilization of additional sodium channels.\textsuperscript{58} However, in appropriate circumstances, for example, high concentrations of drugs and rapid heart rates, drug-induced reduction of V\textsubscript{max} could actually promote further binding of drug, causing further reduction of V\textsubscript{max} and so on. This would result in increasing conduction delay, decreased excitability, and conduction block because of progressive sodium channel blockade and would not require the postulation of additional metabolic or ionic abnormalities. If this concept is correct, one would expect it to occur with drugs that bind activated sodium channels but not with drugs that bind only inactivated channels, such as amiodarone.\textsuperscript{59} Voltage clamp studies will be necessary to prove or refute this hypothesis because a gradual change in membrane potential could also cause incremental sodium channel block. Multicellular preparations might be necessary to reproduce the current loading conditions that exist in vivo.\textsuperscript{54,56--58,60}

**FIGURE 12.** Electrograms from experiment in Figure 11. Extracellular potentials ($\phi$) and their first derivatives with respect to time ($\phi_t$) are shown from three electrodes on 64-electrode plaque. First rapid deflections in extracellular potentials are stimulus artifacts, and correspond to first biphasic deflections in derivative plots. Locations of electrode sites 1, 2, and 3 are noted in Figure 11. PCL, pacing cycle length; Time, duration of pacing; Fig Reference, figure letter of activation map in Figure 11 that corresponds to electrogram recordings. A: Electrograms recorded before lidocaine was given demonstrate amplitudes greater than $-80 \text{ mV}$, and derivatives greater (more negative) than $-15 \text{ V/sec}$. Activation times (time of maximum negative derivative) referenced to stimulus artifact are indicated in Figure 11, Panel A. E: Electrograms obtained in presence of lidocaine, 60 seconds after pacing at cycle length of 250 msec, demonstrated lower voltages and lower derivatives. Decrements were not uniform, however, and greater decreases were present in areas of slower conduction (see Figure 11, Panel E). F: Further changes in electrograms were noted 64 seconds after previous signals were recorded. Deflections in lead 1 became predominantly positive, which is consistent with relatively late activation. Derivative of potential was markedly diminished but was still large enough ($-2.0 \text{ V/sec}$) to be considered activation by suggested criteria.\textsuperscript{32} Progressive changes were also noted at electrode sites 2 and 3.

**Characteristics of Ventricular Tachycardia**

The morphologies of the induced rhythms were distinctive. They were characterized by very broad, nonuniform complexes with indefinite boundaries of depolarization and repolarization. Although polymorphic, they never resembled torsade de pointes\textsuperscript{61} and were never preceded by long-short sequences.\textsuperscript{62} Although grossly resembling ventricular flutter or coarse fibrillation, the cycle lengths were longer than is typically seen in VF due to other causes in humans\textsuperscript{63} or in dogs.\textsuperscript{64} The prolonged QRS complexes and the relatively long cycle lengths in the absence of anatomic barriers, which could create long circuits, are another indication of severely depressed conduction.

**Clinical Significance**

Is the association between rate-related conduction velocity depression and arrhythmia development relevant to clinical proarrhythmic events? Because of rapid recovery from conduction-velocity depression (recovery time constant $\tau_{cv}=0.12 \text{ sec}$), substantial depression of conduction velocity by lidocaine requires rapid heart rates in normally polarized
tissue. Drug-induced rate-dependent reduction in conduction, however, can be a more important proarrhythmic mechanism for drugs that have longer recovery times and depress conduction velocity at lower heart rates such as flecainide ($\tau_{rec}=15$ seconds$^{65}$), encainide ($\tau_{rec}=12$ seconds$^{66}$), and propafenone ($\tau_{rec}=5$ seconds$^{67}$), which are associated with a relatively high risk of arrhythmia exacerbation.$^{68-71}$ The arrhythmias associated with these drugs are characterized by very wide QRS complexes and nonuniform morphology.$^{69,70,72-75}$

Similar to the rhythms observed in this study. Furthermore, their proarrhythmic effects often seem to be rate related, occurring during exercise or during rapid atrial or ventricular pacing,$^{70,72-74,76,77}$ and sometimes in the presence of normal ventricular function.$^{74,75}$ Usually the proarrhythmic effects of these drugs occur in the presence of preexisting cardiac disease. It is probable that in certain circumstances (e.g., partial depolarization and preexisting reentrant circuit), rate-related changes in conduction velocity could be proarrhythmic at lower concentrations of drugs or at slower heart rates.

**Limitations**

Computation of conduction velocity requires knowledge of the path of conduction in three dimensions. The insertion of intramural electrodes, however, could cause tissue injury or create barriers that affect activation. To support the assumption that the distance between electrodes reflected the distance traveled by the wave of excitation, we carefully examined isochrone maps based on a closely spaced two-dimensional electrode array for evidence of indirect activation, that is, activation of epicardial tissue resulting from subepicardial spread.$^{21,78}$ and we avoided such areas in selecting the electrode sites for conduction velocity estimation. The use of conduction times rather than velocities would not have obviated the need for the essential assumption that the path of activation remain unchanged during interventions, and would not have altered our fundamental findings.

The uncertain role of excitability made it impossible to prove a causal relation between conduction velocity depression and the development of ventricular arrhythmias. Excitability is a complex function of both active and passive membrane properties for which there is no simple measurement.$^{79}$ Sodium channel blockade by lidocaine and other antiarrhythmic drugs decreases excitability in a rate-dependent manner.$^{80}$ We did not detect gross rate-dependent changes in stimulation threshold current in the presence of lidocaine but the resolution of our current generator (0.01 mA, ±5%) was not fine enough to detect small changes. On the other hand, transient loss of one-to-one capture was noted in two dogs during pacing before the development of ventricular arrhythmias, which indicates that changes in excitability accompanied delays in activation as would be expected with severe sodium channel block.$^{79,80}$ The distinction between severe conduction slowing and block of conduction is difficult because, in both cases, activation will proceed around the involved area as long as more rapid conduction is possible in the surrounding tissue. Thus, we cannot attribute with certainty the severe delays in activation shown in Figure 11 to conduction slowing. Possibly, areas of tissue became inexcitable and produced barriers around which reentrant ventricular rhythms developed.

**Conclusions**

Our findings support a role for rate-dependent sodium channel block in the genesis of drug-induced ventricular arrhythmias. We found evidence of progressive electrophysiological disturbances that preceded the onset of VT, suggesting that a vicious cycle of increasing sodium channel block might be important in the development of these arrhythmias. The relation between the arrhythmias we observed and those that occur clinically is uncertain but it is probable that some proarrhythmic events in patients are caused by the consequences of rate-dependent sodium channel block. We did not evaluate the effectiveness of therapeutic interventions in our model; therefore, therapeutic recommendations based on our findings alone would be premature. On the other hand, interventions that reduce sodium channel block would seem appropriate, and the demonstrated effectiveness of some such measures, such as reduction of heart rate and increasing plasma pH,$^{75,81}$ are compatible with our findings. Also, our results suggest that rapid pacing should be avoided in arrhythmias caused by rate-dependent sodium channel block. Because rapid pacing is effective in drug-induced arrhythmias such as torsade de pointes,$^{62}$ the distinction between arrhythmia mechanisms is of substantial clinical importance.

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