Actions of Lidocaine on Transmembrane Potentials of Subendocardial Purkinje Fibers Surviving in Infarcted Canine Hearts

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SUMMARY We compared the effects of lidocaine, $2 \times 10^{-6} \text{M}$, on transmembrane resting and action potentials of Purkinje fibers on the endocardial surface of 24- to 72-hour-old myocardial infarcts in dogs with its actions on subendocardial Purkinje fibers in normal hearts. At both proximal (near the tip of the papillary muscle) and distal (toward the apex) recording sites in noninfarcted hearts, lidocaine had no significant effect on maximum diastolic potential (MDP) or $V_{\text{max}}$. It shortened action potential duration (APD) only at the proximal site. In infarcted hearts, we arbitrarily divided Purkinje fibers at the infarcted distal site into two groups. Group I consisted of fibers which did not have a severely depressed MDP or $V_{\text{max}}$ but in which APD was markedly prolonged. Lidocaine had no effect on MDP of these fibers, significantly depressed $V_{\text{max}}$, and shortened APD. Group II consisted of fibers in which MDP and $V_{\text{max}}$ were markedly reduced. Lidocaine also reduced $V_{\text{max}}$ of these fibers further (by 60%) without altering resting potential. In addition, lidocaine depressed pacemaker activity of Purkinje fibers in infarcts. The drug did not alter conduction of premature impulses in the subendocardial Purkinje network in normal hearts but increased the maximum delay of early premature impulses in Purkinje fibers in infarcted hearts and sometimes resulted in nondriven repetitive activity. Therefore, the effects of lidocaine on transmembrane potentials of Purkinje fibers in infarcts are different from its effects on fibers in normal hearts.

THE EFFECTS of antiarrhythmic drugs on transmembrane potentials of cardiac fibers have been a subject of intensive investigation because such actions underlie both antiarrhythmic and toxic effects on the heart. These investigations have been carried out primarily on isolated, superfused cardiac tissue excised from normal hearts.

Cardiac fibers in diseased hearts may have abnormal resting and action potentials. Recently Friedman et al. and Lazzara et al. demonstrated that the subendocardial Purkinje fibers which survive in regions of extensive myocardial infarction in dogs have low maximum diastolic potentials, low rates of phase O depolarization, action potentials that are markedly prolonged in duration, and show spontaneous diastolic depolarization. They suggested that the ventricular arrhythmias present in dogs 24-72 hours after a coronary occlusion originate in these fibers. It is conceivable that the electrophysiological effects of antiarrhythmic drugs on such cardiac fibers with abnormal transmembrane potentials are different from their effects on normal cardiac fibers. The present study was undertaken to test this hypothesis. We compared the actions of lidocaine, an antiarrhythmic drug which has been used widely to treat arrhythmias caused by acute myocardial infarction, on resting and action potentials of Purkinje fibers in both normal and infarcted myocardium. The results indicate that there are differences in the electrophysiological actions of this drug on normal and abnormal tissue.

Methods

Surgical Production of Myocardial Infarction

The effects of lidocaine were studied on the transmembrane potentials of subendocardial Purkinje fibers in the left ventricle of both normal and infarcted canine hearts. For the studies on Purkinje fibers in infarcted hearts, 45 small (10-12 kg), healthy mongrel dogs were anesthetized by the intravenous administration of sodium pentobarbital (30 mg/kg), and the anterior descending branch of the left coronary artery was ligated by means of sterile techniques described previously. The dogs were allowed to recover from the anesthetic and were given penicillin intramuscularly. Thirty-five dogs survived the surgical procedure. Fourteen dogs were anesthetized again with sodium pentobarbital (20-30 mg/kg) 24 hours later, for the electrophysiological study. All these dogs had ventricular tachycardia at this time. Twenty-one dogs were anesthetized 72 hours after the surgical procedure for electrophysiological study. For the most part, these dogs showed sinus rhythm with occasional ventricular premature depolarizations.

The Isolated Preparation of Infarcted Myocardium

At the time of the electrophysiological study, the heart was excised and immersed in cool oxygenated...
Tyrode's solution, the composition of which has been described. During continuous immersion in the Tyrode's solution, the heart was dissected to yield a block of left ventricular tissue consisting of the anterior papillary muscle, the adjacent inter-papillary free wall, paraseptal free wall, and anterior interventricular septum (Fig. 1). The dissection procedure has been described previously. In each preparation, the pale area of infarction was clearly demarcated from the noninfarcted tissue (Fig. 1). The apical two-thirds of the preparation was infarcted, but approximately one-third of the anterior papillary muscle toward its tip and the basal portion of the ventricular septum around the division of the left bundle branch usually had been spared and were normal by both electrophysiological and histological criteria (see below).

The preparations were pinned to the wax floor of a tissue bath (volume = 50 ml) with the endocardial surface up and were superfused at a rate of 22 ml/min with the Tyrode's solution which had been equilibrated with 95% oxygen and 5% carbon dio-

**Figure 1** Preparation isolated from left ventricle of a dog, 24 hours after occlusion of the left anterior descending coronary artery. Arrows indicate the demarcation between normal tissue which appears dark, and the infarct which appears pale. APM is the anterior papillary muscle, VS is the intraventricular septum, and FT is the free-running false tendon. S is the location of the extracellular stimulating electrodes. The area labeled P and enclosed by the dashed lines is the location of the proximal recording site. The area labeled D and enclosed by the dashed lines is the location of the distal recording site.
The K⁺ concentration in this solution was 4.0 mM in all studies. Bath temperature was maintained constant at 36 ± 1°C. Identical preparations were prepared from the noninfarcted hearts of 11 normal dogs for studies on normal subendocardial Purkinje fibers.

Electrophysiological Methods

Transmembrane potentials were recorded, using glass microelectrodes as previously described. For some experiments the preparations were stimulated at a cycle length of 800 msec through Teflon-coated bipolar silver-wire electrodes placed on the noninfarcted tip of the anterior papillary muscle (Fig. 1). Stimuli were rectangular pulses 3 msec in duration and twice diastolic threshold voltage. When the effects of lidocaine on conduction and refractoriness were studied (see below), premature stimuli were delivered to the preparation at variable coupling intervals after the preceding basic drive stimulus. Although the basic drive stimuli were delivered through the extracellular electrodes, the premature stimuli were delivered through an intracellular microelectrode which also was used to record an action potential at the proximal site. For intracellular stimulation, a mechanical relay rapidly switched the amplifier input to ground while connecting the microelectrode to a constant current pulse generator which delivered a rectangular pulse 2–5 times diastolic threshold and 3 msec in duration. The relay then switched the amplifier input back to the recording electrode within 3 msec after the end of this pulse.

Experimental Procedure

For studies of the effects of lidocaine on Purkinje fibers, that showed no automaticity, an interval of 2 hours was allowed for equilibration of the tissue before the effects of the drug were studied. The preparations were stimulated during this time at a cycle length of 800 msec. After equilibration, the endocardial surface of preparations from infarcted hearts was mapped by recording action potentials at intervals of 5–10 mm over the entire surface. The electrophysiological mapping procedure enabled us to localize areas of normal Purkinje fiber action potentials as well as areas in which Purkinje fibers surviving on the endocardial surface of the infarct showed abnormal action potentials.

In both normal and infarcted preparations, the effects of lidocaine were studied on Purkinje fiber action potentials, recorded from the top 1–2 cell layers in several different regions during stimulation at a cycle length of 800 msec. As a proximal site, we chose the tip of the anterior papillary muscle near the insertion of the free-running false tendon (Fig. 1). Purkinje fibers at the proximal site always were in noninfarcted regions, even in the infarcted preparations. Action potentials also were recorded from the most superficial cell layers at a distal site toward the apex of the heart (Fig. 1). In the infarcted preparations, the distal site was in the infarcted area and therefore action potential characteristics of these Purkinje fibers were quite different from those of distal Purkinje fibers in normal preparations. In each experiment, a proximal and distal site about 1 mm square was chosen where the resting membrane potential, the amplitudes, and the configurations of 10 consecutively recorded action potentials were nearly identical. At each site, resting and action potentials were recorded from 10 cells within the defined area before and after perfusion with lidocaine. Data obtained for the various parameters of the transmembrane potential of the 10 cells before exposure to drug were pooled and compared with the data obtained after drug superfusion. These data have been tabulated and form the basis for this report. Attempts also were made to maintain continuous impalements of single cells at each site during the control period and during superfusion with the drug. This often failed because of the movement of the large preparations. Data obtained from single impalements are presented in some of the figures.

During the equilibration period, four preparations studied 24 hours after ligation of the coronary artery were continuously rhythmic in the absence of electrical stimulation. The site of origin of this spontaneous electrical activity was determined by mapping the sequence of activation of the endocardial surface to determine the site of the earliest electrical activity. Purkinje fibers in regions of earliest activity showed spontaneous diastolic depolarization. Impalements were maintained in these cells during perfusion with lidocaine.

To study the effects of lidocaine on conduction of basic and premature impulses in the subendocardial Purkinje fiber network, the preparation was driven at a basic cycle length of 800 msec through the extracellular electrode on the tip of the papillary muscle. Action potentials were recorded simultaneously from a Purkinje fiber in the noninfarcted area, within several mm of these surface electrodes, and from a subendocardial Purkinje fiber at the distal site near the apex. Premature stimuli were delivered through the microelectrode in the noninfarcted area after every 10th basic driving impulse at progressively shorter coupling intervals after the preceding basic drive until conduction block occurred between the recording electrodes or until the proximal cell could not be excited. The basic drive stimuli were inhibited for 5–10 seconds after early premature stimuli to allow the appearance of nonstimulated, repetitive responses. Conduction time of the premature impulse from the proximal to the distal recording site was determined by recording the premature action potentials at a rapid sweep speed. During the premature stimulus, the transient grounding of the amplifier recording the proximal action potential resulted in failure to record the upstroke of the premature action potential of this cell. Excitation of the cell was documented by re-
cording the remainder of the action potential, and conduction time of the premature impulse from the proximal to the distal cell could be determined with reasonable accuracy by measuring from the beginning of the grounding artifact to the beginning of the premature action potential upstroke in the distal cell. By this method, the functional and effective refractory periods of the subendocardial Purkinje system were determined.

The functional refractory period was defined as the minimum interval in the distal conducting system between the basic and premature responses. The effective refractory period was defined as the maximum interval between the basic and premature stimuli during which conduction of a premature impulse did not occur to the distal cell.

For the majority of studies, we used $2 \times 10^{-5} \text{ M}$ lidocaine hydrochloride (4.68 mg/ml), a concentration considered to be therapeutic. In studies on automaticity, the effects of a higher concentration ($4 \times 10^{-5} \text{ M}$) also were determined. Concentrations refer to the salt.

The $t$-test for comparing means of nonindependent samples was used to ascertain the significance of any change observed at a given site in a preparation. To compare data obtained from different sites or different preparations, the $t$-test for comparing means of independent samples was used. A $P$ value of 0.05 or less was considered significant.

**Results**

**Effects of Lidocaine on Purkinje Fiber Transmembrane Potentials**

**Normal Preparations**

Prior to drug superfusion, differences were observed in the normal preparations between the Purkinje fiber action potentials recorded from the proximal site on the anterior papillary muscle and at the distal site towards the apex of the heart (Table 1 and Fig. 2). Although the resting membrane potential and the action potential amplitude of cells at both sites were not statistically different ($P > 0.05$), the maximum rate of depolarization recorded at the proximal site was significantly higher than the value recorded distally ($P < 0.05$) (Table 1). The action potential durations at 50% and 100% repolarization were significantly longer at the proximal site than at the distal site ($P < 0.01$).

The subendocardial Purkinje fibers at the two sites in the normal preparations responded differently to $2 \times 10^{-5} \text{ M}$ lidocaine (Table 1 and Fig. 2). At the proximal site, the action potential duration at 50% and at 100% repolarization decreased significantly ($P < 0.001$). In contrast, at the distal site, $2 \times 10^{-5} \text{ M}$ lidocaine did not significantly shorten the action potential duration to 50% or 100% repolarization ($P < 0.05$). Despite this difference in response, action potential duration at the proximal site remained longer than at the distal site. Lidocaine caused no significant change in resting membrane potential at either site. Although $V_{\text{max}}$ decreased by 6.5% at the proximal site and 6.3% at the distal site, these decreases were not statistically significant. Action potential amplitude decreased slightly and by a similar amount at each site, but this decrease was only significant in the distal region (Table 1).

**Infarcted Preparations**

The proximal recording sites on the anterior papillary muscle in all the infarcted preparations were outside the infarcted region (Fig. 1). Before drug superfusion, resting membrane potential, action potential amplitude, maximum rate of depolarization, and action potential duration to 50% and 100%

| TABLE 1  Effects of Lidocaine on Resting and Action Potentials of Subendocardial Purkinje Fibers in Noninfarcted Preparations and in Noninfarcted Areas of Infarcted Preparations |
|----------------|--------|--------|--------|
| **Proximal site** | **(noninfarcted preparations)** | **No. of preparations** | **MDP (mV)** | **APA (mV)** | **$V_{\text{max}}$ (V/sec)** | **APD$_{50\text{ms}}$ (msec)** | **APD$_{100\text{ms}}$ (msec)** |
| Control | 11 | 82.0 ± 0.9 | 117.6 ± 1.2 | 437.2 ± 30.6 | 206.0 ± 4.7 | 326.6 ± 7.1 |
| Lidocaine ($2 \times 10^{-5} \text{ M}$) | 82.4 ± 1.2 | 115.3 ± 2.0 | 408.2 ± 23.2 | 190.9 ± 4.4* | 302.2 ± 4.9* |
| **Proximal site** | **(24-hour infarcts)** | **No. of preparations** | **MDP (mV)** | **APA (mV)** | **$V_{\text{max}}$ (V/sec)** | **APD$_{50\text{ms}}$ (msec)** | **APD$_{100\text{ms}}$ (msec)** |
| Control | 11 | 84.3 ± 1.1 | 119.3 ± 2.0 | 435.5 ± 34.3 | 226.8 ± 7.6 | 339.6 ± 8.1 |
| Lidocaine ($2 \times 10^{-5} \text{ M}$) | 82.6 ± 1.0 | 114.0 ± 1.9† | 388.8 ± 22.6 | 170.3 ± 4.5* | 305.9 ± 4.5* |
| **Distal site** | **(noninfarcted preparations)** | **No. of preparations** | **MDP (mV)** | **APA (mV)** | **$V_{\text{max}}$ (V/sec)** | **APD$_{50\text{ms}}$ (msec)** | **APD$_{100\text{ms}}$ (msec)** |
| Control | 11 | 80.1 ± 1.1 | 116.5 ± 1.7 | 333.3 ± 21.3 | 160.0 ± 4.5 | 279.6 ± 4.7 |
| Lidocaine ($2 \times 10^{-5} \text{ M}$) | 79.7 ± 1.0 | 113.8 ± 1.5† | 312.4 ± 15.8 | 151.3 ± 4.0 | 272.8 ± 5.0 |

Values represent the mean ± sem obtained from 10 consecutive impalements before and after drug in each of 11 preparations. MDP = maximum diastolic potential; APA = action potential amplitude; $V_{\text{max}}$ = maximum rate of depolarization; APD$_{50\text{ms}}$ and APD$_{100\text{ms}}$ = action potential duration at repolarization to 50% and 100% of the amplitude of depolarization.

In each group of preparations, the statistical significance of the difference between the results after lidocaine and those in the control period is indicated as follows:

* $P < 0.001$.
† $P < 0.05$. 

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FIGURE 2 Effects of lidocaine on subendocardial Purkinje fiber action potentials. In each panel, the top trace is the 0 reference potential; the middle trace is the transmembrane potential, and the bottom trace (left and center panels) is the differentiated action potential upstroke preceded by a 200 V/sec calibration. This is inverted in C. A shows recordings from a proximal fiber in a normal preparation, B shows recordings from a distal fiber in a normal preparation, and C shows recordings from a distal fiber (group I) in a 24-hour-old infarcted preparation. The left panels are control tracings and the middle panels are records taken after exposure to $2 \times 10^{-5} \text{M}$ lidocaine for 30 minutes. In the right panels, the action potentials recorded after lidocaine (solid lines) are superimposed on the control action potentials (interrupted lines). In these experiments, action potentials were recorded from the same fiber during control and during lidocaine superfusion. In A, the predominant effect of lidocaine was to reduce action potential duration. $V_{\text{max}}$ was also decreased. In B, lidocaine did not decrease action potential duration and $V_{\text{max}}$ decreased. In C, lidocaine decreased action potential duration and $V_{\text{max}}$.

TABLE 2 Effects of Lidocaine on the Resting and Action Potentials of Purkinje Fibers in Group I Surviving at the Distal Site in the Infarcted Areas

<table>
<thead>
<tr>
<th></th>
<th>No. of preparations</th>
<th>MDP (mV)</th>
<th>APA (mV)</th>
<th>$V_{\text{max}}$ (V/sec)</th>
<th>APD$_{50%}$ (msec)</th>
<th>APD$_{100%}$ (msec)</th>
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<tr>
<td>24-Hour infarcts</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>78.1 ± 1.0</td>
<td>113.8 ± 1.4</td>
<td>353.0 ± 27.0</td>
<td>246.8 ± 9.5</td>
<td>445.6 ± 8.7</td>
</tr>
<tr>
<td>Lidocaine (2 $\times 10^{-5}$ M)</td>
<td>14</td>
<td>76.7 ± 1.3</td>
<td>107.2 ± 2.4*</td>
<td>253.7 ± 19.6†</td>
<td>204.6 ± 6.1†</td>
<td>418.8 ± 9.3††</td>
</tr>
<tr>
<td>72-Hour infarcts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>80.1 ± 0.7</td>
<td>110.5 ± 1.5</td>
<td>296.8 ± 24.3</td>
<td>207.5 ± 15.1</td>
<td>444.6 ± 33.1</td>
</tr>
<tr>
<td>Lidocaine (2 $\times 10^{-5}$ M)</td>
<td>13</td>
<td>77.6 ± 1.0</td>
<td>105.2 ± 2.9</td>
<td>223.8 ± 25.1†</td>
<td>157.0 ± 8.1†</td>
<td>424.5 ± 32.7†</td>
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</tbody>
</table>

Values represent the mean ± SEM obtained from 10 consecutive impalements before and after drug in each preparation. MDP = maximum diastolic potential; APA = action potential amplitude; $V_{\text{max}}$ = maximum rate of depolarization; APD$_{50\%}$ and APD$_{100\%}$ = action potential duration at repolarization to 50% and 100% of the amplitude of depolarization.

The statistical significance of the results is indicated as follows:
* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.
LIDOCAINE ON PURKINJE FIBERS AFTER INFARCTION/Allen et al. 475

TABLE 3  Effects of Lidocaine on the Electrophysiological Properties of Subendocardial Purkinje Fibers in Group II Surviving at the Distal Site over the Infarcted Area

<table>
<thead>
<tr>
<th>No. of preparations</th>
<th>MDP (mV)</th>
<th>APA (mV)</th>
<th>Vmax (V/sec)</th>
<th>APD50 (msec)</th>
<th>APD100 (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72-Hour infarcts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>64.7 ± 2.2</td>
<td>77.4 ± 9.1</td>
<td>111.3 ± 31.5</td>
<td>172.1 ± 21.7</td>
</tr>
<tr>
<td>Lidocaine (2 x 10^-5 M)</td>
<td>64.3 ± 2.5</td>
<td>60.4 ± 11.0*</td>
<td>44.1 ± 17.8*</td>
<td>174.4 ± 19.9</td>
<td>560.3 ± 42.9</td>
</tr>
</tbody>
</table>

Values represent the mean ± SEM obtained from 10 consecutive impalements before and after drug in each preparation. MDP = maximum diastolic potential; APA = action potential amplitude; Vmax = maximum rate of depolarization; APD50 and APD100 = action potential duration at repolarization to 50% and 100% of the amplitude of depolarization. *P < 0.05.

The effects of lidocaine on distal Purkinje fibers in group I (not severely depressed) in both 24- and 72-hour-old infarcts were somewhat different from its effects on distal fibers in noninfarcted preparations. Lidocaine did not alter resting membrane potential but significantly reduced action potential amplitude of these cells. Vmax of phase 0 also was significantly reduced by 60% (Table 3 and Fig. 3). Lidocaine did not significantly decrease action potential duration at 50% or 100% repolarization (Table 3).

In two of these preparations we recorded transmembrane potentials from regions into which conduction was presumably blocked. Resting membrane potential was less than -70 mV, and the response in the distal region which followed excitation of the preparation proximally resembled a nonregenerative, electrotonic response (Fig. 3). Li-
docaine did not alter membrane potential or restore conduction into these areas.

Effects of Lidocaine on Purkinje Fiber Pacemaker Activity

Sites of pacemaker activity were located in the Purkinje fibers which survived on the endocardial surface of four infarcted preparations studied 24 hours after ligation of the coronary artery. In the absence of electrical stimulation, this pacemaker activity was monitored for at least 30 minutes (after the 2-hour equilibration period) and determined to be stable before the effects of superfusion with lidocaine were studied. During this time, electrical activity in the pacemaker area was characterized by spontaneous diastolic depolarization which resulted in the generation of a slow-rising action potential before the onset of electrical activity in adjacent cells (Fig. 4). Spontaneous activity in one of the preparations stopped after superfusion with $2 \times 10^{-5}$ M lidocaine for 1 hour. Spontaneous activity in the other three preparations slowed from 73 ± 7 to 59 ± 11 per minute. Although this was not statistically significant for the group ($P > 0.05$), substantial slowing did occur in each preparation. Two of these preparations were also superfused with lidocaine, $4 \times 10^{-5}$ M, for an additional hour. Pacemaker activity continued in both preparations, although the rate was further reduced in one preparation from 71 per minute after $2 \times 10^{-5}$ M lidocaine to 63 per minute, and in the other from 49 per minute to 38 per minute.

Effects of Lidocaine on Conduction and Refractoriness in the Subendocardial Purkinje Fiber Network

Noninfarcted Preparations

In noninfarcted preparations, the conduction time of the basic drive impulses from the proximal to the distal recording site was 11.5 ± 3.8 msec (mean ± se for seven preparations) during the control period, and this was not changed by $2 \times 10^{-5}$ M lidocaine. The interelectrode distance in these preparations was 3.1 ± 0.5 cm.

Premature impulses conducted rapidly from the proximal to distal recording sites, and conduction delay did not increase markedly as the coupling interval of the premature stimulus was progressively decreased (Figs. 5 and 6). The maximum conduction delay obtained for propagation of early premature impulses in all preparations was 23.0 ± 1.9 msec. The failure of premature impulses to

![Figure 4](image_url)  
**Figure 4** Effects of lidocaine on a pacemaker cell in a 24-hour infarct. The top trace in each panel is the zero reference potential and the bottom trace is the transmembrane potential. Recordings from the same fiber were obtained throughout this experiment. During the control, the spontaneous rate of the pacemaker cell was 77 per minute. The rate decreased to 71 per minute after superfusion with $2 \times 10^{-5}$ M lidocaine for 1 hour and to 63 per minute after superfusion with $4 \times 10^{-5}$ M lidocaine for an additional hour.

![Figure 5](image_url)  
**Figure 5** Effects of lidocaine on conduction of premature impulses in the subendocardial Purkinje fiber network of a representative 24-hour infarcted preparation and a normal preparation. In each panel the conduction time of the premature impulse between the proximal and distal electrode is plotted on the ordinate and the coupling interval of premature impulses elicited at the proximal site ($P_1 - P_2$) is on the abscissa. In the infarcted preparation (left panel) during the control (filled circles), conduction time increased as the premature coupling interval decreased. After $2 \times 10^{-5}$ M lidocaine (unfilled circles), premature impulses could be elicited at shorter coupling intervals and they conducted with increased delays. In the normal preparation (right panel), conduction time of premature impulses increased only slightly during control (filled circles) and was not significantly increased after $2 \times 10^{-5}$ M lidocaine, even though earlier premature impulses could be elicited.
The effects of lidocaine on refractory periods of the subendocardial Purkinje fiber network in a representative 24-hour infarct (panel A) and a normal heart (panel B). In both panels, the interval between basic and premature responses at the distal site (D1-D2) is plotted on the ordinate and the coupling interval of premature impulses elicited at the proximal site (P1-P2) is on the abscissa. In the normal preparation (B) during the control (filled circles), D1-D2 decreased as P1-P2 decreased, indicating that early premature impulses did not undergo marked conduction delays. The shortest D1-D2 interval is the functional refractory period (FRP) and the shortest P1-P2 interval is the effective refractory period (ERP). After $2 \times 10^{-5}$ M lidocaine, both the FRP and the ERP decreased; the decrease in FRP is indicated by the striped area on the ordinate; the decrease in ERP is indicated by the cross-hatched area on the abscissa. In the 24-hour infarct preparation (A) during control (filled circles), as P1-P2 decreases, D1-D2 decreases (but less than the decrease in P1-P2) and then begins to increase, indicating marked conduction delays of premature impulses. After $2 \times 10^{-5}$ M lidocaine, premature impulses with shorter coupling intervals are induced because of the decrease in ERP indicated by the cross-hatched area on the abscissa. These earlier premature impulses conduct more slowly than premature impulses induced during control, as indicated by the marked increases in the D1-D2 intervals. The functional refractory period is slightly decreased in this experiment as shown by the striped area on the ordinate.

Undergo long conduction delay presumably was due to the fact that action potential duration was longer at the proximal than at the distal site, and so a premature response elicited proximally encountered more fully repolarized and, therefore, less refractory tissue as it propagated distally. For the same reason, when conduction block of early premature impulses occurred, it resulted from failure to excite the proximal cell when it was stimulated early during repolarization. The effective refractory period for conduction between the sites ($257.0 \pm 8.6$ msec) was, therefore, the same as the effective refractory period of the Purkinje fibers at the proximal site. The functional refractory period ($263.0 \pm 5.3$ msec) was similar to the effective refractory period (Fig. 6).

After superfusion with $2 \times 10^{-5}$ M lidocaine, action potential duration at the proximal site still remained longer than at the distal site; all premature responses still propagated successfully and with little delay to the distal site, and lidocaine did not alter conduction time of premature responses elicited at identical coupling intervals before and after drug superfusion (Figs. 5 and 6). Since proximal action potential duration was shortened by lidocaine, the effective refractory period (which still occurred when the proximal cells could not be excited) decreased by $20 \text{ msec}$ to $237 \pm 6.4 \text{ msec}$. Premature impulses could be elicited at shorter coupling intervals after lidocaine but they did not conduct very slowly to the distal site. Therefore, the functional refractory period decreased to $244 \pm 4 \text{ msec}$ (Fig. 6).

**Infarcted Preparations**

We are only reporting the effects of lidocaine on conduction and refractoriness in the subendocardial Purkinje network in 24-hour infarcts. The Purkinje fibers in the preparations from which the data was obtained had resting and action potential characteristics of group I. The conduction time of the impulses elicited at a constant cycle length of 800 msec was $11.7 \pm 1.3$ msec in the 11 preparations during the control period. The value does not differ significantly from the values obtained in normal preparations. Interelectrode distance also was not significantly different from that in noninfarcted preparations.
preparations. As in the normal preparations, this conduction time in the infarcted preparations did not change during exposure to $2 \times 10^{-5}$ M lidocaine.

The characteristics of propagation of premature impulses in the subendocardial Purkinje network of 24-hour infarcts differed markedly from those in noninfarcted preparations. In infarcted preparations, marked conduction delay of the premature impulses occurred during a wide range of coupling intervals (Figs. 5 and 6). The maximum conduction delay of early premature impulses was $82.0 \pm 10.5$ msec, which was significantly greater than maximum conduction delay in noninfarcted preparations ($P < 0.001$). This presumably reflects the fact that action potential duration was longer at the distal site than at the proximal one. Thus, premature responses elicited at the proximal site at sufficiently short coupling intervals encountered tissue which was less repolarized, and therefore more refractory, as they propagated distally.

Despite the longer action potentials at the distal site, premature responses elicited at the proximal site were not blocked before reaching the distal site in any of the preparations. Thus the effective refractory period for the infarcted preparations (269.5 ± 6.4 msec) was similar to that of normal preparations and was determined by the effective refractory period of Purkinje fibers at the noninfarcted proximal site. The marked conduction delay of early premature impulses in 24-hour infarcts, however, resulted in a functional refractory period of 324.5 ± 5.2 msec which was significantly longer than that of normal preparations ($P < 0.001$) (Fig. 6).

After exposure to $2 \times 10^{-5}$ M lidocaine, action potential duration still remained longer at the distal site as described above. Conduction block of premature responses still did not occur between the proximal and distal recording sites. The effective refractory period (which still resulted from failure to excite proximal cells) was shortened by $31.0 \pm 6.3$ msec because the action potential duration of the fibers at the proximal site was similarly shortened. Early premature responses elicited at the proximal site continued to exhibit marked conduction delay. Lidocaine usually did not change the conduction time of premature impulses initiated at coupling intervals similar to the coupling intervals tested before drug (Figs. 5 and 6). For example, during the control period the maximum conduction delay of $82.0 \pm 10.5$ msec occurred at a coupling interval of 269.5 ± 6.4 msec (i.e., at the end of the effective refractory period). During exposure to lidocaine, the conduction delay of premature impulses at the same coupling interval was $93.0 \pm 14.1$ msec, which is not significantly different. However, in two of the preparations, conduction of premature impulses was speeded slightly (Fig. 7). Since lidocaine usually did not alter conduction delay of these premature impulses, the functional refractory period of the subendocardial Purkinje network in all

![NORMAL INFARCT](https://example.com/image.png)

**Figure 7** Effects of lidocaine on conduction of premature impulses in a normal and a 24-hour infarcted preparation. In each panel, the first action potential at the left recorded at each site results from the basic drive. The second action potential at each site (shaded and unshaded arrows) is the response to a premature stimulus. In the left panels (normal preparation), the upper action potential (unshaded arrow) is recorded from the proximal fiber and the lower action potential (shaded arrow) is recorded from the distal fiber. A shows the earliest obtainable premature response in the proximal fiber under control conditions. This propagated rapidly to the distal site; B shows the earliest response after 30 minutes of superfusion with $2 \times 10^{-5}$ M lidocaine. The premature response occurs at a shorter coupling interval, but conduction time between the two recording sites is only slightly prolonged. In the right panels (24-hour infarcted preparation), the upper action potential (shaded arrow) is recorded from the distal fiber in the infarct and the lower action potential (unshaded arrow) is recorded from the proximal cell in the noninfarcted area. A shows the earliest premature response obtained in the proximal cell during the control. The conduction delay of this response to the distal site was significant. B shows conduction of a premature response elicited at a similar coupling interval to that in A, after superfusion with $2 \times 10^{-5}$ M lidocaine. Conduction time was decreased. In C, conduction of the earliest obtainable premature response after lidocaine is illustrated. Conduction of the proximal premature impulse (unshaded arrow) to the distal site (shaded arrow) was prolonged. Several nondriven responses at the proximal site followed the slowly conducted premature response.
preparations after lidocaine was 319 ± 9 msec, which was not significantly different from control (Fig. 6).

The shortening of the effective refractory period after lidocaine enabled premature responses to be elicited at a range of shorter coupling intervals after drug perfusion than prior to drug perfusion. These earlier premature responses propagated much more slowly than any of the premature responses elicited before drug perfusion (Figs. 5 and 6). The maximum conduction delay of these earlier premature responses was 137.0 ± 12 msec, a value significantly higher than the maximum conduction delay observed during the control period ($P < 0.001$).

Before lidocaine superfusion, the slowly conducting premature responses which occurred as the coupling interval approached the effective refractory period were followed by one or more closely coupled, unstimulated responses, which may have resulted from reentry (see Discussion) in two of the seven preparations. These were not prevented by lidocaine. After lidocaine, the more slowly conducted premature responses which could be elicited because of the shorter effective refractory period were invariably followed by such nonstimulated responses in all the preparations (Fig. 7). Furthermore, the range of coupling intervals over which this phenomenon occurred during lidocaine administration occasionally exceeded the shortening of the effective refractory period; i.e., a premature response, despite being initiated at an identical coupling interval and conducting with similar delay before and during exposure to lidocaine, was followed by a nonstimulated response only during exposure to lidocaine.

**Discussion**

Recent studies indicate that the transmembrane potentials of cardiac cells are altered during pathological conditions and that such alterations may be important in relation to the genesis of cardiac arrhythmias. Antiarrhythmic drugs may exert their therapeutic (or toxic) actions by affecting the transmembrane potentials of these diseased cardiac cells. Nevertheless, most previous studies designed to elucidate the actions of these drugs on transmembrane potentials have been conducted on cardiac tissue from normal hearts. We therefore undertook to study the effects of lidocaine on the electrophysiological properties of the subendocardial Purkinje fiber network surviving in acute myocardial infarcts. It has been reported previously that these fibers have abnormal action potentials and may be the cause of the ventricular arrhythmias which occur between 24 hours and 72 hours after coronary occlusion.

Previous studies have described the electrophysiological effects of lidocaine on normal canine Purkinje fibers in false tendons. In Purkinje fibers with normal maximum diastolic potentials, action potentials and $V_{\text{max}}$ of phase 0, therapeutic concentrations of the drug have no effects on these parameters when $[K^{+}]_o$ is ≤ 3 mM, and slightly reduce $V_{\text{max}}$ when $[K^{+}]_o$ is ≥ 4 mM. Lidocaine also accelerates repolarization of these normal Purkinje fibers. Our studies on the subendocardial Purkinje fibers in normal regions of noninfarcted and infarcted hearts indicate that fibers toward the papillary muscle tip respond similarly to lidocaine as Purkinje fibers in false tendons. On the other hand, subendocardial Purkinje fibers at the apex of the noninfarcted left ventricle have a very short action potential duration compared to Purkinje fibers in other regions of the heart and, in this area, repolarization is not significantly altered by lidocaine.

The transmembrane potential characteristics of Purkinje fibers in experimental infarcts at both 24 hours and 72 hours after coronary occlusion are markedly altered. In some respects, the effects of lidocaine on these transmembrane potentials were different from its effects on potentials of Purkinje fibers in comparable regions of noninfarcted hearts and, in other respects, they were the same. Lidocaine did not alter the maximum diastolic potential of Purkinje fibers in both 24- and 72-hour infarcts when the maximum diastolic potential was not severely reduced (group I). In 72-hour infarcts, lidocaine also had no significant effect on the very low maximum diastolic potential of cells in group II. Our finding that lidocaine failed to alter maximum diastolic potential when it was markedly reduced is significant in light of some proposed concepts concerning mechanisms of lidocaine's antiarrhythmic action. It has been shown that lidocaine increases potassium conductance in Purkinje fibers from normal hearts and that it increases resting membrane potential when $[K^{+}]_o$ is low. It has been suggested therefore that lidocaine may increase the low resting potential of abnormal cells and thereby abolish conduction block in reentrant pathways. Our study is the first test of this hypothesis on pathological tissue. The failure of the drug to increase the low maximum diastolic potential of the group II Purkinje fibers in 72-hour infarcts or to restore conduction in regions of block indicates that either lidocaine does not increase $K^+$ conductance in these cells, or that the low maximum diastolic potential is not due to a low $K^+$ conductance but to some other cause such as a decrease in $[K^{+}]_o$, which may accompany ischemia.

Concentrations of lidocaine which are considered to be therapeutic have a slight depressant effect on $V_{\text{max}}$ of normal Purkinje fibers although in our study, this effect was not statistically significant. $V_{\text{max}}$ decreased by 20–50 V/sec (by 5–10%), but since $V_{\text{max}}$ is initially high (usually greater than 400 V/sec), this decrease should not slow conduction significantly. Lidocaine had a greater depressant effect on $V_{\text{max}}$ of the Purkinje fibers in group I in
the infarcts, which was statistically significant. However, conduction of basic impulses throughout the entire subendocardial network was not noticeably altered. The decrease in $V_{\text{max}}$ of 25–28% in these fibers might be expected to slow conduction, but such slowing may be confined to localized areas and, therefore, was not detected by our method of measurement. In fibers with a very low $V_{\text{max}}$ (group II), lidocaine significantly depressed it further. This finding is also contrary to the proposal that lidocaine exerts its antiarrhythmic action by increasing $V_{\text{max}}$ in depressed Purkinje fibers.\footnote{14, 18} Although the absolute depression of $V_{\text{max}}$ in these cells may not be greater than in other Purkinje fibers, since these cells initially had a very low $V_{\text{max}}$, the percent depression (60%) was much greater. In three experiments, $V_{\text{max}}$ was decreased by greater than 80%.

Such depression probably decreases conduction velocity in these localized areas. Previous studies have shown that lidocaine significantly decreases partially inactivated Na+ current.\footnote{21, 22}

Previous studies in normal canine Purkinje fibers have shown that lidocaine depresses spontaneous diastolic depolarization.\footnote{14, 15} To produce automaticity in such normal fibers (K$^+$)$_o$ is reduced to 3 mM or below, the fiber is damaged by stretching, or catecholamines or digitalis is added to the superfusate. Lidocaine exerts its antiarrhythmic effect by increasing gK in these fibers.\footnote{20} Some of the subendocardial Purkinje fibers surviving in canine infarcts demonstrate marked spontaneous diastolic depolarization and automatic impulse initiation, even in the presence of a normal (K$^+$)$_o$ (4 mM) and in the absence of mechanical damage or pharmacologic agents.\footnote{3, 4} Spontaneous diastolic depolarization in these fibers may result from alterations in membrane properties caused by prolonged ischemia or other factors associated with the coronary occlusion. Lidocaine slowed the rate of this spontaneous activity, although the slowing was not as marked as reported in the studies on normal fibers. Nevertheless, even a small degree of suppression may sometimes be sufficient to restore the arrhythmic heart to sinus rhythm.

The effects of lidocaine on the action potential duration of Purkinje fibers in infarcts also was of interest. The action potential duration of these distal Purkinje fibers is markedly lengthened after infarction and, as a result, premature impulses arising at the border of the infarct conduct slowly through the subendocardial Purkinje fiber network and sometimes result in reentry.\footnote{11} When we undertook this study, we speculated that lidocaine might shorten the duration of these long action potentials in the infarct toward normal and thereby improve conduction of premature impulses in the infarcted region and prevent reentry.\footnote{22} Lidocaine did shorten action potential duration of Purkinje fibers in both 24- and 72-hour infarcts, and this effect does represent a difference in the action of the drug when compared to its effects on normal distal Purkinje fibers in which it did not affect repolarization. However, action potential duration was not restored to normal, and it remained significantly longer than the action potential duration of Purkinje fibers in the normal region which was also shortened by lidocaine. Premature impulses still conducted with significant delay after lidocaine, and a normal conduction pattern was not restored. Conduction of premature impulses arising throughout most of the basic cycle was not affected, although presumably they were conducting through more repolarized tissue (due to lidocaine’s shortening of action potential duration). That conduction of these premature impulses was usually not speeded, despite the shortening of action potential duration in the infarct, may be due to depression of membrane responsiveness by lidocaine.\footnote{16} although we do not have data to demonstrate this. The nondriven repetitive responses which sometimes followed early premature impulses also were not prevented. Premature impulses could also be initiated at much shorter coupling intervals after lidocaine and they conducted with even greater delays. These premature impulses may have been induced early enough so that they propagated into Purkinje fibers in the infarct earlier during repolarization, when membrane potential was lower. Acceleration of repolarization of Purkinje fibers outside the infarct to a greater extent than Purkinje fibers in the infarct could enable this to occur. Depression of membrane responsiveness also may cause additional conduction delay. These slowly conducting premature impulses were invariably followed by several nondriven repetitive responses which may have resulted from reentry caused by the long conduction delays.\footnote{17} This induction of repetitive activity by lidocaine may be related to clinical observations of lidocaine-induced arrhythmias in some patients after myocardial infarction.

The present study demonstrated that lidocaine has some effects on Purkinje fibers surviving in infarcts which are different from its effects on normal fibers, but it does not clearly demonstrate lidocaine’s antiarrhythmic mechanism. The possible relation between antiarrhythmic activity and depression of spontaneous diastolic depolarization was mentioned previously. Reentry in cardiac tissue may depend on the presence of slow conduction and unidirectional block in sick fibers,\footnote{24} and the marked depression of $V_{\text{max}}$ in some fibers by lidocaine might cause block in reentrant pathways, but such abolition of reentry was not demonstrated. Lidocaine did not abolish reentry caused by conduction delay of premature impulses and therefore might not be effective against this mechanism for arrhythmias in the in situ heart.

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