The Effects of Lidocaine and Quinidine on Impulse Propagation across the Canine Purkinje-Muscle Junction during Combined Hyperkalemia, Hypoxia, and Acidosis

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SUMMARY. During ischemia, lidocaine or quinidine may prevent arrhythmias by blocking conduction without suppressing abnormal automaticity. The purpose of this study was to determine whether lidocaine or quinidine (5 µg/ml) produced Purkinje fiber-papillary muscle block during superfusion in vitro with an altered Tyrode’s solution containing some components of ischemia: 6 mM potassium, Po2 < 40, pH = 6.8. Unbranched canine Purkinje fibers connected to papillary muscle at one end were threaded through a three-chamber bath with Purkinje fiber-papillary muscle in the left chamber and Purkinje fiber alone in the middle and right chambers. Action potentials were recorded using microelectrodes from Purkinje fiber, papillary muscle, and cells at the Purkinje fiber-papillary muscle junction. Purkinje fiber or papillary muscle was stimulated at 1.5-4 Hz. Perfusion of the left chamber with altered Tyrode’s solution decreased resting membrane potential, action potential amplitude, and the maximum rate of rise of phase 0 of the action potential of Purkinje fiber, papillary muscle, and junctional cells, and prolonged activation times of junctional cells and papillary muscle; but action potentials propagated from Purkinje fiber to papillary muscle, and from papillary muscle to Purkinje fiber. Lidocaine or quinidine plus altered Tyrode’s solution further decreased action potential amplitude and the maximum rate of rise of phase 0 of the action potential of Purkinje fiber, papillary muscle, and junctional cells, and prolonged activation of junctional cells and papillary muscle, inducing bidirectional block only at the Purkinje fiber-papillary muscle junction. Lidocaine or quinidine plus normal Tyrode’s solution and each component of altered Tyrode’s solution alone did not produce block. Perfusion of the right chamber with 0.25 mM barium induced Purkinje fiber automaticity that: propagated to papillary muscle during perfusion of the left chamber with normal Tyrode’s or altered Tyrode’s solution; blocked at the Purkinje fiber-papillary muscle junction during perfusion of the left chamber with altered Tyrode’s solution plus lidocaine; and was not suppressed during perfusion of the right chamber with lidocaine. Thus, lidocaine or quinidine may produce bidirectional block at the Purkinje fiber-papillary muscle junction and interrupt a potential limb of a reentrant circuit without suppressing automatic arrhythmogenic foci. (Circ Res 55: 185-196, 1984)

THE efficacy of lidocaine and quinidine in treating ventricular arrhythmias is well established, yet their precise mechanism of antiarrhythmic action remains unclear. Both agents are thought to be capable of suppressing automatic and reentrant arrhythmias, since they modify refractoriness, slow conduction, and suppress automaticity in normal Purkinje and ventricular muscle cells. Their depressant effects on conduction are exaggerated in abnormal cardiac tissue and in normal fibers exposed to abnormal extracellular environments (Singh et al., 1971; Hondegem et al., 1974; Kupersmith et al., 1975; Obayashi et al., 1975; Allen et al., 1978; Lazzara et al., 1978; Grant et al., 1980; Cardinal et al., 1981; Nattel et al., 1981; Grant et al., 1982).

Although several in vitro studies of lidocaine and quinidine have been conducted on homogeneous Purkinje fibers or ventricular muscle, the effects of these agents on impulse propagation at the Purkinje-ventricular muscle junction have not been studied in detail. The margin of safety for antegrade conduction at the Purkinje-ventricular muscle junction is low (Mendez et al., 1970), and retrograde conduction may be preserved under conditions that produce antegrade block, such as during changes in the extracellular environment that accompany myocardial ischemia (Mendez et al., 1970; Gilmour et al., 1982, in press) and during premature stimulation (Sasyniuk and Mendez, 1971). Unidirectional antegrade block at the Purkinje-muscle could be conducive to the development of reentry, and an intervention that created bidirectional block would be antiarrhythmic (Rosen and Hoffman, 1973).
In addition, most myocardial injuries associated with cardiac arrhythmias produce cellular depolarization that may lead to conduction disturbances and abnormal automaticity. Since lidocaine and quinidine would not be expected to suppress automaticity arising from significantly reduced membrane potentials (Grant and Katzung, 1975; Brennan et al., 1978; Imanishi et al., 1978), it is possible that the anti-arrhythmic action of these drugs in depolarized myocardium may be due to suppression of conduction from an automatic focus rather than suppression of automaticity in the focus itself (Aravindakshan et al., 1977). Drug-induced exit block might be more likely to occur at the site of a “weak link” in the conducting system, such as the Purkinje-muscle junction.

In view of the above considerations, the overall goal of our study was to investigate the effects of lidocaine and quinidine on conduction at the Purkinje-muscle junction. Our specific aims were to test two hypotheses: first, that lidocaine or quinidine could produce bidirectional block at the Purkinje-muscle junction during exposure to selected metabolic alterations that accompany myocardial ischemia (acidosis, hyperkalemia, and hypoxia), and thereby interrupt a potential limb of a reentrant circuit, and, second, that these drugs could block propagation of Purkinje fiber automaticity at the Purkinje-muscle junction, without suppressing Purkinje fiber automaticity.

**Methods**

**General**

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg, iv), and their hearts were rapidly excised and placed in oxygenated Tyrode’s solution at room temperature. Long unbranched false tendons dissected free from muscle at one end and attached to a 3-cm crescent of papillary muscle at the other end were excised from either ventricle. The preparation was threaded through a three-chamber tissue bath with Purkinje fiber and ventricular muscle in the left chamber and Purkinje fiber alone in the middle and right chambers. The chambers were separated by perforated rubber membranes and were perfused independently. The width of the center chamber was 2 mm.

Initially, preparations were superfused at a rate of 5 ml/min with normal Tyrode’s solution gassed with 95% O₂ and 5% CO₂. Composition of the Tyrode’s solution (mM) was: MgCl₂, 0.3; NaH₂PO₄, 0.9; CaCl₂, 2.0; NaCl, 137.0; NaHCO₃, 5.54; and NaCl, 150.0 mM, and was gassed with 95% N₂ and 5% CO₂, resulting in a pH of 6.85 ± 0.05 and a PO₂ < 40 mm Hg. These changes in KCl, pH, and PO₂ were similar to those reported to occur during the early stages of acute myocardial ischemia (Downar et al., 1977; Hill and Gettes, 1977).

To determine the effects of repeated exposures to altered Tyrode’s solution alone on impulse transmission across the Purkinje-muscle junction, three preparations were subjected to four consecutive exposures to altered Tyrode’s solution for 15 minutes each. Each 15-minute exposure to altered Tyrode’s solution was followed by a 30-minute washout with normal Tyrode’s solution. Throughout the experiment, the middle and right chambers were perfused with normal Tyrode’s solution. External pacing stimuli were applied to the false tendon in either the right or left chamber of the bath to study antegrade impulse propagation, and were applied to the papillary muscle tip to study retrograde impulse propagation. During each exposure to altered Tyrode’s solution, the following pacing protocol was used: for the first 9 minutes, the false tendon was stimulated at a BCL of 500 or 600 msec; at 10 minutes the BCL was decreased to 450 msec; 11 minutes, 400 msec; 12 minutes, 350 msec; 13
Tyrode’s solution was 90 minutes before the final exposure to altered Tyrode’s solution. Lidocaine was added to the altered Tyrode’s superfusate during the third exposure.

After 60–120 minutes of equilibration in normal Tyrode’s solution, preparations of false tendon attached to papillary muscle \( (n = 13) \) were superfused with the previously described multiple exposure protocol for both lidocaine \( (n = 7) \) and quinidine \( (n = 6) \). External pacing stimuli were applied to the false tendon in the right or left chamber at a BCL of 500 msec for the entire protocol. At 1-minute intervals during each exposure, action potentials were recorded and resting membrane potential (RMP), action potential amplitude (APA), action potential duration at 90% of repolarization (APD90), the maximum rate of rise of phase 0 (dV/dmax), and the activation time from stimulus artifact to dV/dt were measured. Activation times of junctional cells were measured from the dV/dt of simultaneously recorded Purkinje cells to the first junctional cell dV/dt, and from the first to second junctional cell dV/dt. APD90 of junctional cells was not measured, since it was difficult to determine accurately the onset of the junctional cell action potential. Recordings made at the time of Purkinje-muscle block or after 15 minutes of superfusion with altered Tyrode’s solution plus quinidine or lidocaine then were compared to the corresponding time during superfusion with altered Tyrode’s solution alone.

Effect of Superfusion with Altered Tyrode’s Solution and Lidocaine on Barium-Induced Automaticity

In five preparations, the false tendon of the right chamber was superfused with 0.25 mM BaCl2 Tyrode’s solution to induce automaticity that propagated throughout the false tendon to papillary muscle. The left chamber was perfused with altered Tyrode’s solution alone for 15 minutes, followed by a 30-minute washout period with normal Tyrode’s solution. Lidocaine then was added to the BaCl2 Tyrode’s perfusate of the right chamber while the left chamber simultaneously was perfused with altered Tyrode’s solution and lidocaine for 15 minutes. The purpose of this combination was to study the effect of lidocaine on barium-induced automaticity at the same time as its effects on impulse transmission across the Purkinje-muscle junction in an ‘ischemic’ extracellular environment were being evaluated. Washout with normal Tyrode’s solution completed these experiments.

Statistics

Statistical analysis was performed using ANOVA with multiple comparisons or the Wilcoxon signed rank test, where appropriate (Winer, 1971). Differences were considered significant for \( P < 0.05 \).

Results

Impulse Propagation across the Purkinje-Muscle Junction

Figure 2 illustrates the effects of altered Tyrode’s solution alone (panel A) and combined with lidocaine (panel B), or quinidine (panel C) on impulse propagation across the Purkinje-muscle junction. The degree of conduction block depended on cycle length and lessened with each exposure to altered Tyrode’s solution. In panel A, Purkinje-pap-

![Figure 1. Top: analog recordings of action potentials (lower recordings) and upstroke velocities (upper recordings) progressing from terminal Purkinje fiber (A), across the Purkinje-muscle junction (B–E) to papillary muscle (F). Note decrease in the amplitude and upstroke velocity of the initial action potential upstroke and increase in the secondary action potential amplitude and upstroke velocity from cells A to E. Vmax for cell F is not seen at this sweep speed. Vertical calibration, 50 mV and 200 V/sec; horizontal calibration, 100 msec and 4 msec. Upstroke velocity traces retouched. Bottom, plot of maximum upstroke velocities (Vmax) and activation times (ACT) of the initial action potential upstroke (filled symbols) and secondary action potential upstrokes (unfilled symbols) for cells A–E. Stars indicate ACT (13 msec) and Vmax values for cell F (papillary muscle). ACT were measured relative to the onset of the stimulus artifact. Note that ACT of the initial upstroke was delayed and ACT of the secondary upstroke was accelerated as the impalement was advanced across the Purkinje-muscle junction.

FIGURE 1.
illary muscle impulse propagation during repeated exposures to altered Tyrode’s solution alone is illustrated. Conduction block increased with the shortest pacing cycle lengths and was most pronounced with the first exposure of the preparation to altered Tyrode’s solution. Block progressively decreased with each subsequent exposure to altered Tyrode’s solution.

A typical experiment illustrating the effect of the combination of altered Tyrode’s solution and lidocaine on impulse propagation is shown in panel B. Once again, shorter pacing cycle lengths increased and repeated exposures to altered Tyrode’s solution decreased the degree of conduction block across the Purkinje-papillary muscle junction. Superfusion of altered Tyrode’s solution, together with lidocaine, increased the degree of conduction block at longer cycle lengths, compared with the degree of conduction block produced by altered Tyrode’s solution alone. On the final exposure to altered Tyrode’s solution alone, the degree of conduction block from Purkinje to muscle always was decreased. Altered Tyrode’s solution combined with quinidine produced qualitatively similar results (panel C). Conduction block increased during superfusion with altered Tyrode’s solution and quinidine, compared with altered Tyrode’s solution alone.

In six experiments in which impulse propagation from papillary muscle to Purkinje fiber was studied, superfusion with lidocaine (n = 4) or quinidine (n = 2) and altered Tyrode’s solution increased the degree of conduction block, compared with the degree of conduction block produced by altered Tyrode’s solution alone. Repeated exposures to altered Tyrode’s solution likewise reduced the degree of conduction block across the Purkinje-papillary muscle junction.

Conduction block did not occur with superfusion of either hyperkalemic, hypoxic, or acidotic Tyrode’s solution alone. Similarly, no conduction block occurred during superfusion with lidocaine or quinidine and normal Tyrode’s solution.

The conduction block produced by the combination of lidocaine and altered Tyrode’s solution was bidirectional, as shown in Figure 3. The left side of this figure illustrates intact propagation of action potentials from Purkinje fiber to papillary muscle.
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CONTROL AT+LIDO

PM
PF

Figure 3. Bidirectional block of impulse transmission across the Purkinje-papillary muscle junction produced by altered Tyrode’s solution (AT) and lidocaine (LIDO). During control, action potentials were recorded from Purkinje fiber (PF, lower tracing) and papillary muscle (PM, upper tracing) in the left side of the bath during stimulation of the right-sided PF at a BCL of 600 msec. After 11 minutes of superfusion with AT + LIDO (right panel), action potentials in PF did not propagate to PM. After stimulation of PF is discontinued, direct bipolar stimulation of PM in the left chamber induces action potentials, as indicated by stars, that block in the retrograde direction. Vertical calibration, 50 mV; horizontal calibration, 2 sec. See text for discussion.

during control. The right side of the figure is a demonstration of bidirectional block between Purkinje fiber and papillary muscle after exposure to both lidocaine and altered Tyrode’s solution. In the first half of the right panel, the Purkinje fiber was driven by pacing stimuli applied to the Purkinje fiber in the right chamber of the bath. Propagation occurred to the Purkinje fiber in the left chamber, but failed to propagate to papillary muscle. Direct stimulation of muscle (stars) demonstrates the presence of retrograde block from muscle to Purkinje fiber.

Site of Block

Figures 4–6 demonstrate that altered Tyrode’s solution plus lidocaine or quinidine produced block between Purkinje fiber and muscle by suppressing impulse transmission across the Purkinje-muscle junction. During control, Purkinje fiber action potentials propagated to papillary muscle via junctional cells that had biphasic action potential upstrokes. The initial action potential upstroke in the junctional cell occurred within 1 msec of the action potential upstroke of terminal Purkinje cells. Following a variable delay (2–8 msec), distal papillary muscle was activated, as evidenced by the second upstroke of the junctional cell. The left panel of Figure 4A demonstrates intact action potential propagation from Purkinje fiber in the lower tracing to junctional cell in the upper tracing during control. On exposure to altered Tyrode’s solution alone, as shown in the right panel of Figure 4A, there was a slight delay between the first and second upstrokes of the junctional cell action potential, and a small diminution in action potential amplitude of the Purkinje cell and in the initial upstroke of the junctional cell action potential (Table 1). After washout and return to control (Fig. 4B, left panel), the same preparation was exposed to altered Tyrode’s solution plus lidocaine (Fig. 4B, right panel). Two superimposed action potentials are recorded as block between Purkinje fiber and junctional cell occurred. In the first set of action potentials, there was a marked diminution in Purkinje fiber action potential amplitude and in the initial action potential upstroke of the junctional cell, and a slightly greater delay between the first and second upstrokes of the junctional cell action potential than with altered Tyrode’s superfusion alone (Fig. 4A, right panel; Table 1). In the superimposed next set of action potentials, complete Purkinje-junctional cell conduction block occurred. Failure of the junctional cell to generate an action potential corresponded with shortening of the

Figure 4. Effects of AT alone (panel A), and AT + LIDO (panel B), on action potentials recorded from a Purkinje-papillary muscle junctional cell (JC) and a Purkinje cell (PF) during stimulation of the Purkinje fiber at a BCL of 500 msec. Tracings in each panel are, from top to bottom, JC dV/dt; JC action potential, PF action potential, and PF dV/dt. Two consecutive action potentials are superimposed for AT + LIDO. Vertical calibration: 200 V/sec and 400 V/sec for the JC and PF dV/dt recordings, respectively, and 50 mV for the action potential recordings. Horizontal calibration: 10 msec for the dV/dt recordings, except for AT + LIDO, 20 msec; and 50 msec for the action potential recordings. See text for discussion.
Purkinje fiber action potential secondary to loss of electrotonic interaction. These changes were completely reversed after 5-10 minutes of washout (not shown).

The conduction block between Purkinje fiber and papillary muscle produced by quinidine and altered Tyrode's solution also occurred at the junctional area, as shown in Figure 5. During control, impulse propagation from the Purkinje fiber to junctional cell was intact, as demonstrated in the left panel of Figure 5A. On exposure to altered Tyrode's solution alone (right panel, Fig. 5A), there was a decrease in the amplitude of the Purkinje cell action potential and in the initial upstroke of the junctional cell action potential with an increase in the delay between the first and second upstrokes of the junctional cell action potential. After washout and return to control (left panel, Fig. 5B), the preparation was exposed to altered Tyrode's solution and quinidine (right panel, Fig. 5B). Two superimposed action potentials were recorded as block occurred between the Purkinje fiber and junctional cell, as in Figure 4B. In the first set of action potentials, impulse transmission from the Purkinje cell to junctional cell occurred, with marked attenuation of the amplitude of the Purkinje fiber action potential and the initial upstroke of the junctional cell action potential, and with increased delay between the two action potential upstrokes of the junctional cell. As block occurred, as shown in the superimposed action potential tracings, failure of the junctional cell to generate an action potential resulted in shortening of the Purkinje fiber action potential due to loss of electrotonic interaction. With washout, normal impulse propagation resumed (not shown).

Figure 6 demonstrates that failure of the junctional cell to generate an action potential during exposure to altered Tyrode's solution and lidocaine or quinidine resulted in the absence of papillary muscle activation distal to the junction. During control, impulse propagation was intact from the junctional cell in the upper tracing to papillary muscle in the lower tracing (left panel, Fig. 6A). During superfusion with altered Tyrode's solution alone, there was attenuation of the initial upstroke of the junctional cell action potential and the amplitude of the papillary muscle cell action potential with in-

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**Figure 5.** Effects of AT alone (panel A), and AT + QUIN (panel B), on action potentials recorded from a Purkinje-papillary muscle junctional cell (JC) and a Purkinje cell (PF) during stimulation of the Purkinje fiber at a BCL of 500 msec. Tracings in each panel are, from top to bottom, JC dV/dt, JC action potential, PF action potential, and PF dV/dt. Two consecutive action potentials are superimposed for AT + QUIN. Vertical calibration: 200 V/sec and 400 V/sec for the JC and PF dV/dt recordings, respectively, and 50 mV for the action potential recordings. Horizontal calibration: 10 msec for the dV/dt recordings except for AT + QUIN, 20 msec; and 50 msec for the action potential recordings. See text for discussion.

**Figure 6.** Effects of AT alone (panel A), AT + LIDO (panel B), and AT + QUIN (panel C), on action potentials recorded from a Purkinje-papillary muscle junctional cell (JC) and a papillary muscle cell (PM). The preparation was driven by stimuli applied to the Purkinje fiber at a BCL of 500 msec. Tracings in each panel are, from top to bottom, JC dV/dt, JC action potential, PM action potential, and PM dV/dt. Two consecutive action potentials are superimposed for AT + LIDO and AT + QUIN. Vertical calibration: 200 V/sec and 50 mV for the dV/dt and action potential recordings, respectively. Horizontal calibration: 50 msec for action potential recordings and 10 msec for the dV/dt recordings, except for AT + LIDO and AT + QUIN, 20 msec. See text for discussion.
increased delay between the first and second upstrokes of the junctional cell action potential (Tables 1 and 2). The delay in muscle activation corresponded with the delay between the two junctional cell upstrokes. After washout and return to control (left panel, Fig. 6B), the preparation was exposed to lidocaine and altered Tyrode’s solution. Two superimposed action potentials are once again recorded at the time of block of impulse propagation from the junctional cell to papillary muscle (right panel, Fig. 6B). In the first set of action potentials, impulse propagation remained intact from the junctional cell to papillary muscle with marked attenuation of the initial upstroke of the junctional cell action potential, delay between the two junctional cell action potential upstrokes with subsequent delay of papillary muscle activation, and attenuation of the papillary muscle cell action potential amplitude. At the onset of conduction block, failure of the junctional cell to generate an action potential resulted in the absence of papillary muscle activation. In Figure 6C, after washout, return to control, and then exposure of the same two cells to altered Tyrode’s solution and quinidine, similar effects were demonstrated. At the time of conduction block, two action potentials were superimposed (right panel, Fig. 6C). Initially, as was seen with lidocaine, conduction occurred with attenuation of the initial junctional cell action potential upstroke and papillary muscle cell action potential amplitude, and delay between the junctional cell action potential upstrokes, which corresponded to the delay in papillary muscle activation. With failure of impulse propagation and absence of junctional cell activation, there was failure of papillary muscle activation.

Impulse propagation between Purkinje fiber and papillary muscle remained intact during marked attenuation of the initial upstroke of the junctional cell until the onset of conduction block between Purkinje and muscle, which frequently was associated with only small changes in the initial upstroke of the junctional cell. In Figure 7, panel A, superfusion with lidocaine and altered Tyrode’s solution produced 3:2 block between Purkinje fiber and a junctional cell. A progressive 1-mV decrease in the initial upstroke of the junctional cell over the course of three stimuli correlated with progressive delay in the onset of the second action potential component of the junctional cell upstroke until conduction block occurred. Conduction resumed with 1-mV increase in the initial upstroke of the junctional cell action potential (last action potential). In a separate experiment (panel B), 2:1 block between a junctional cell and papillary muscle during superfusion with altered Tyrode’s solution and lidocaine was associated with an 8-mV decrease in the initial junctional cell action potential upstroke during the blocked cycle. Superfusion with quinidine and altered Tyrode’s solution produced similar results. In panel C, during a period of 6:1 conduction, a 1.5-mV increase in the

### Table 1

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<th>Characteristics</th>
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<th>JC upstroke (msec)</th>
<th>AT+LIDO (msec)</th>
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Data are reported as mean ± SEM. NM = not measured, n = number of cells, ACT = activation time, APA = action potential amplitude, APD<sub>90</sub> = action potential duration at 90% repolarization, dV/dt<sub>max</sub> = maximum rate of rise of phase 0, JC = junctional cell, PF = Purkinje fiber, RMP = resting membrane potential, and NS = not significant.

* P < 0.05
† P < 0.01
‡ P < 0.001
§ dV/dt<sub>max</sub> and APA of JC refers to 1st upstroke; ( ) = statistical difference between AT and AT+L.
Effects of Altered Tyrode’s Solution (AT) and Altered Tyrode’s Solution with Quinidine (AT+QUIN) on Action Potential Characteristics

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<td>50.0±11.1</td>
<td>NM</td>
<td>67.0±23.6†</td>
<td>10.4±3.0 NS</td>
<td>10.6±3.0 NS</td>
</tr>
<tr>
<td>Control</td>
<td>-86.2±1.6</td>
<td>95.2±5.3</td>
<td>NM</td>
<td>145.5±21.5</td>
<td>6.2±1.1</td>
<td>9.2±2.3</td>
</tr>
<tr>
<td>AT+QUIN</td>
<td>-69.8±1.5</td>
<td>19.2±2.4</td>
<td>NM</td>
<td>14.7±5.6</td>
<td>9.6±2.2 NS</td>
<td>29.2±5.2†</td>
</tr>
<tr>
<td>Papillary muscle (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>-83.3±1.3</td>
<td>110.7±1.1</td>
<td>187.5±3.7</td>
<td>181.0±22.6</td>
<td>16.4±2.8</td>
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<tr>
<td>AT</td>
<td>-69.3±1.2</td>
<td>90.6±2.7</td>
<td>128.0±3.9</td>
<td>122.3±25.4†</td>
<td>18.5±3.0 NS</td>
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<tr>
<td>Control</td>
<td>-83.1±1.6</td>
<td>112.5±2.2</td>
<td>193.2±6.4</td>
<td>181.6±24.4</td>
<td>16.2±2.7</td>
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<tr>
<td>AT+QUIN</td>
<td>-68.5±2.2</td>
<td>86.3±3.1</td>
<td>137.2±6.7 NS</td>
<td>92.6±37.8†</td>
<td>29.8±5.2†</td>
<td></td>
</tr>
</tbody>
</table>

Data are reported as mean ± SEM. Abbreviations same as in Table 1.

* P < 0.05.
† P < 0.01.
‡ P < 0.001.
§ dV/dtmax and APA of JC refers to 1st upstroke; (t) = statistical difference between AT and AT+Q.

Effects of Altered Tyrode’s Solution, Alone and in Combination with Lidocaine or Quinidine, on Action Potential Characteristics

The effects of altered Tyrode’s solution alone, and in combination with lidocaine or quinidine, on action potential characteristics of Purkinje, junctional, and papillary muscle cells are summarized in Tables 1 and 2, respectively. APA and dV/dtmax values for junctional cells refer to the initial action potential upstroke. The secondary action potential upstroke amplitude of junctional cells was similar during control (108.8 ± 3.0 mV) to the APA of papillary muscle, and showed similar changes during altered Tyrode’s superfusion (87.2 ± 2.7 mV), or altered Tyrode’s and quinidine (110.2 ± 3.0 to 83.4 ± 3.0 mV) or lidocaine superfusion (107.8 ± 4.0 to 85.0 ± 4.1 mV). Superfusion with altered Tyrode’s solution alone reduced RMP, APA, APD90, and dV/dtmax, and prolonged ACT in all three cell types. Altered Tyrode’s solution also reduced the amplitude of the initial upstroke of the junctional cell action potential and prolonged the delay between the first and second action potential upstrokes.

Superfusion with a combination of altered Tyrode’s solution and lidocaine or quinidine further decreased APA, and dV/dtmax (P < 0.05) and prolonged the activation time of Purkinje fibers and papillary muscle. Lidocaine or quinidine and altered Tyrode’s solution had a more marked effect than altered Tyrode’s alone on decreasing the amplitude of the initial upstroke of the junctional cell action potential (P < 0.05) and on delaying the activation of the second upstroke of the junctional cell action potential (P < 0.05). Lidocaine and altered Tyrode’s solution reduced APD90 of both Purkinje fiber and papillary muscle cells. The effects of quinidine and altered Tyrode’s solution were similar, except APD90 was decreased less.

Effect of Superfusion with Altered Tyrode’s Solution and Lidocaine on Barium-Induced Automaticity

Lidocaine did not suppress barium-induced automaticity but, in combination with altered Tyrode’s solution, produced exit block by interrupting impulse propagation at the Purkinje-muscle junction, as shown in Figure 8. Superfusion of the right chamber with barium produced automatic activity in the Purkinje fiber that propagated to the Purkinje fiber in the left chamber of the bath and then to the papillary muscle (top panel). During superfusion of the left chamber with altered Tyrode’s solution alone, propagation remained intact and the preparation continued to be driven by barium-induced automaticity in the Purkinje fiber located in the right chamber (middle panel). After a washout period,
the preparation in the left chamber was superfused with lidocaine and altered Tyrode’s solution, and the preparation in the right chamber was superfused with Tyrode’s solution containing barium and lidocaine. Automaticity in the Purkinje fiber located in the right chamber persisted and propagated to Purkinje fiber in the left chamber, but antegrade conduction block occurred between Purkinje fiber and papillary muscle (bottom panel).

Discussion
New Observations from This Study
The results of this study demonstrated that lidocaine or quinidine in combination with some components of ischemia (KCl = 6.0 mM, pH = 6.85, and
Po2 < 40 mm Hg) produced bidirectional block of impulse transmission between Purkinje fibers and papillary muscle. The site of block was at the Purkinje-muscle junction and was associated with a reduction in APA and dV/dtmax of Purkinje fiber action potentials and in the initial upstroke of the junctional cell action potential. Lidocaine and quinidine, and altered Tyrode's solution reduced APA, dV/dtmax of Purkinje fiber action potentials, and the initial upstroke of the junctional cell action potential more than altered Tyrode's solution alone. In fact, impulse propagation from Purkinje fiber to papillary muscle improved during repeated exposures to altered Tyrode's solution alone. Lidocaine did not suppress barium-induced automaticity in Purkinje fibers, but combined with altered Tyrode's solution, prevented conduction of barium-generated impulses across the Purkinje-muscle junction.

The mechanisms responsible for Purkinje-muscle block following exposure to lidocaine or quinidine in an altered Tyrode's solution are multifactorial and probably involve changes in both the passive and active membrane properties of cells in the junctional region. For example, hypoxia and acidosis increase the internal resistance of myocardium and Purkinje fibers (De Mello, 1982), and it is likely that these interventions depress cell-to-cell communication and impulse propagation to a greater degree at regions where step delays in conduction occur, such as the Purkinje-muscle junction (Mendez et al., 1970; Gilmour et al., in press). Addition of lidocaine or quinidine to the altered Tyrode's solution may have further reduced passive current flow across the Purkinje-muscle junction, since lidocaine decreases the membrane length and time constants, possibly by increasing K+ conductance (Arnsdorf and Bigger, 1972, 1975). However, hyperkalemia and hypoxia would also be expected to increase K+ permeability (Carmeliet, 1961; Vleugels et al., 1980). Under these conditions, lidocaine and quinidine may not increase K+ permeability further, and their effects on membrane resistance may be attenuated (Lamanna et al., 1982).

Lidocaine also increases the current threshold for excitation, both at normal (Arnsdorf and Bigger, 1975) and at elevated [K+], (Lamanna et al., 1982). Since blockade of the steady state sodium current (Atwell et al., 1979) appears to mediate the effects of lidocaine on excitability during hyperkalemia (Lamanna et al., 1982), changes in junctional cell excitability secondary to suppression of the steady state sodium current may have contributed to Purkinje-muscle block in the presence of altered Tyrode's solution and lidocaine or quinidine. It was not possible, however, to measure directly the current threshold of junctional cells during superfusion with altered Tyrode's solution. The fact that lidocaine combined with altered Tyrode's solution shortened action potential duration more than altered Tyrode's solution alone is indirect evidence that lidocaine further reduced the steady state sodium current (Colatsky, 1982; Carmeliet and Saikawa, 1982). Quinidine did not shorten action potential duration, but this was expected, since the depressant effects of quinidine on the steady state sodium current are counterbalanced by an apparent reduction in the inwardly rectifying K+ current (Colatsky, 1982).

Altered Tyrode's solution alone exerted important effects on active membrane properties, reducing action potential amplitude and maximum upstroke velocity significantly in Purkinje and muscle fibers, and attenuating the initial upstroke of the junctional cell. Both lidocaine and quinidine in altered Tyrode's solution exerted an additional significant depressive effect on these parameters, in agreement with a prior study (Kimura et al., 1982). It is possible that reduced action potential amplitude and upstroke velocity of Purkinje fiber and muscle cells decreased the electrical input into the junctional region, and that this change, along with decreased membrane excitability, contributed to the bidirectional block. Conduction block during lidocaine or quinidine superfusion was greatest at short cycle lengths, suggesting that rate-dependent reductions in maximum upstroke velocity (Carmeliet and Zaman, 1979; Chen and Mettes, 1976; Hondeghem and Katzung, 1980) may have affected impulse transmission across the junction.

Impulse propagation from Purkinje fibers to muscle improved during repeated exposures to altered Tyrode's solution. This finding may be related to our previous observations (Gilmour and Zipes, 1980) that less marked action potential changes occurred in Purkinje fiber and ventricular muscle cells during the second exposure to altered Tyrode's solution than during the first exposure. The mechanism responsible for the increased resistance to the second exposure to altered Tyrode's solution is unknown, but the adaptive response seen in vitro may have an in vivo counterpart. For example, it is well established that the initial occlusion of a coronary artery produces more severe electrophysiological changes than do subsequent occlusions (Scherlag et al., 1974; Ruffy et al., 1979).

Effects of Lidocaine on Automaticity

Lidocaine may suppress both normal (Davis and Temte, 1969; Bigger and Mandel, 1970) and some forms of abnormal automaticity (Allen et al., 1978; Rosen and Danilo, 1980) in Purkinje fibers. In the present study, lidocaine in normal Tyrode's solution did not suppress Purkinje fiber automaticity induced by exposure to BaCl2. However, lidocaine in altered Tyrode's solution prevented propagation of Purkinje fiber automaticity to papillary muscle. If ischemia, or some other event, created Purkinje fiber automaticity that was generated by the slow inward current or another lidocaine-resistant automatic mechanism, it is possible that lidocaine could exert its antiarrhythmic effect by blocking conduction...
from the focus at the Purkinje-muscle junction, without suppressing the focus itself. In addition, if 

an ischemic Purkinje fiber developed triggered ac-
tivity, lidocaine could create entrance block into the 
Purkinje fiber and prevent initiation of the arrhyth-
ma.

The present experiments were devised to de-
monstrate the effect of lidocaine on conduction under 
circumstances where automaticity was maintained. 
Higher concentrations of lidocaine or lidocaine, 
combined with altered Tyrode's solution, might 
have suppressed the automatic focus. Furthermore, it 
is possible that lidocaine might slow the discharge 
rate of the focus and restore propagation to muscle, 
since Purkinje-muscle block was rate dependent. 
Accordingly, application of these concepts to ex-
plaining the effects of lidocaine on ventricular ar-
rhythmias in vivo is speculative.

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INDEX TERMS: Lidocaine • Quinidine • Purkinje-muscle junction • Arrhythmias
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