Effects of Lidocaine, Propranolol, and Sotalol on Ouabain-Induced Changes in Transmembrane Potential of Canine Purkinje Fibers

By Barry J. Koerpel and Larry D. Davis

ABSTRACT

Isolated canine papillary muscle-false tendon preparations stimulated at 95/min were perfused with Tyrode's solution containing ouabain, $2.1 \times 10^{-5}$M. Action potentials of Purkinje fibers were recorded. Initially ouabain increased the slope of phase-4 depolarization. Subsequently it decreased the maximum diastolic potential and the rising velocity of phase 0, the amplitude, and the duration of the action potential. The slope of phase-4 depolarization increased progressively, and eventually the configuration of the action potential changed to resemble that of sinoatrial node fibers. Onset of enhanced phase-4 depolarization was delayed significantly by treatment before exposure to ouabain with lidocaine, $3.7 \times 10^{-5}$M, or propranolol, $2.1 \times 10^{-5}$M, but not with sotalol, $3.2 \times 10^{-4}$M. Enhanced phase-4 depolarization produced by exposure to ouabain was reduced in slope by subsequent treatment with lidocaine or propranolol but not sotalol. Application of lidocaine or propranolol to fibers with action potentials in the configuration characteristic of sinoatrial node fibers returned the contour of the action potentials toward normal; sotalol was not effective in this regard. These results, coupled with the relative effectiveness of these drugs in intact animals with digitalis arrhythmias, support the hypothesis that enhanced phase-4 depolarization of Purkinje fibers is a factor in the production of digitalis-induced ventricular arrhythmias.

KEY WORDS action potentials phase-4 depolarization antiarrhythmic drugs cardiac glycosides pacemaker potentials cardiac electrophysiology adrenergic blocking agents

Ventricular arrhythmias often accompany digitalis intoxication, but the precise mechanisms responsible for their occurrence are not known. One approach to studying these problems experimentally has been to determine the effects of cardiac glycosides on the transmembrane potentials of cardiac fibers, especially those of the His-Purkinje system. Such experiments have been done with Purkinje fibers from sheep (1, 2) and dog (3-5) hearts. Commonly observed effects include decreases in the maximum diastolic potential and in the rising velocity, amplitude, and duration of the action potential; also, phase-4 depolarization increases in both rate and magnitude.

Vassalle et al. (5) provided a quantitative comparison of the effects of ouabain on ventricular muscle and Purkinje fibers isolated from the dog heart. They demonstrated that, when these tissues were exposed simultaneously to ouabain, changes occurred much earlier in Purkinje fibers than they did in ventricular fibers. Only in Purkinje fibers was there an increase in phase-4 depolarization. Since this is the characteristic electrical feature imparting automaticity to cardiac fibers, it was
suggested that ouabain-induced ventricular arrhythmias might result from enhancement of phase-4 depolarization and consequent development of ectopic foci.

One possible test of this hypothesis might be to determine the effects of different antiarrhythmic drugs on phase-4 depolarization of Purkinje fibers exposed to ouabain. In the present study this was done using lidocaine, propranolol, and sotalol. Lidocaine and propranolol effectively prevent or terminate digitalis-induced arrhythmias in the dog (6–10). Therefore one would predict that they should prevent or attenuate ouabain enhancement of phase-4 depolarization. Sotalol is not effective against digitalis-induced arrhythmias in dogs (11–13), although like the former antiarrhythmic drugs it antagonizes catecholamine arrhythmias (12). Thus one could speculate that sotalol would fail to prevent the effects of ouabain. The results presented here bear out these predictions and thus support the idea that enhanced phase-4 depolarization of Purkinje fibers is a factor in the production of digitalis-induced ventricular arrhythmias.

**Methods**

Papillary muscle-false tendon tissue preparations were obtained from the hearts of dogs anesthetized with sodium pentobarbital, 30 mg/kg, iv. For study a preparation was mounted in a tissue bath perfused with oxygenated Tyrode's solution at 37.5–38.0°C. Contractions at 95/min were produced by electrical stimulation. Glass microelectrodes were used to record the transmembrane potential of Purkinje fibers. Detailed description of these methods can be found in an earlier publication (14).

Drugs were prepared for use by dissolving the crystalline powder in distilled water. Aliquots of these stock solutions were added to a reservoir of oxygenated Tyrode's solution to achieve a given concentration just prior to an experiment. The concentration of each drug was: ouabain, \(2.1 \times 10^{-5}\)M, lidocaine-HCl, \(3.7 \times 10^{-5}\)M, propranolol-HCl, \(2.1 \times 10^{-5}\)M, and sotalol-HCl, \(3.2 \times 10^{-4}\)M.

Initial experiments were performed to establish the characteristic effects of ouabain under our laboratory conditions. Perfusion with ouabain was initiated and continued until the Purkinje fibers became inexcitable. Records were taken at intervals throughout the treatment. Particular attention was given to the time required to produce a 10-mv increase in the magnitude of phase-4 depolarization. These data were used for comparison with those obtained in experiments with the antiarrhythmic drugs.

Three types of experiments were performed to study the actions of the test drugs. In one set of experiments the antiarrhythmic drug was administered 10 minutes before ouabain was added to the drug perfusate. The time required for a 10-mv increase in the magnitude of phase-4 depolarization was noted. In a second group of experiments the preparation was treated with ouabain until the magnitude of phase-4 depolarization increased to 10 mv, control solution was then perfused for 10 minutes to remove ouabain from the bath, and finally the test drug was administered. In all of four control experiments, ouabain-enhanced diastolic depolarization normally persisted, undiminished in magnitude, for at least 30 minutes after removal of ouabain. In the third type of experiment treatment with ouabain was initiated and continued until the contour of the action potential changed to resemble that normally recorded from fibers of the sinoatrial node (Fig. 1F) (15). At this point the test drug alone was administered.

A number of different features of the transmembrane potential of Purkinje fibers were measured using methods which have been described previously (14). Data from some experiments were analyzed statistically using Student's t-test for unpaired data. An experiment was not used for statistical purposes if the microelectrode was dislodged from the cell and a new impalement with the same microelectrode was not accomplished within 1 minute. Other experiments were excluded because of spontaneous extra beats which occurred early during exposure to ouabain. The increased number of responses in such experiments would have changed the time of onset and the magnitude of the response (5).

**Results**

**EFFECTS OF OUABAIN ON PURKINJE FIBERS**

Preliminary experiments were performed to determine the effects of ouabain under the existing experimental conditions; and 42 cells from 20 hearts were exposed to ouabain, \(2.1 \times 10^{-5}\)M. Data from 12 of these experiments are summarized in Table 1, and typical records from one experiment are shown in Figure 1. The effects of ouabain were progressive, and a steady state was not reached before the fiber became inexcitable. Therefore measurements of membrane potential were made during control perfusion and...
Table 1

Effects of Ouabain, 2.1 × 10⁻⁷M, on the Transmembrane Potentials of Purkinje Fibers

<table>
<thead>
<tr>
<th></th>
<th>Control Tyrode's</th>
<th>Ouabain Tyrode's</th>
<th>Ouabain Tyrode's*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diastolic potential (mv)</td>
<td>92.14±1.40</td>
<td>93.00±2.82</td>
<td>73.25±3.27</td>
</tr>
<tr>
<td>Overshoot (mv)</td>
<td>21.71±1.18</td>
<td>20.50±2.46</td>
<td>17.25±2.13</td>
</tr>
<tr>
<td>Magnitude of action potential (mv)</td>
<td>113.86±1.92</td>
<td>113.30±4.17</td>
<td>90.50±3.88</td>
</tr>
<tr>
<td>Rate of phase-4 depolarization (mv/sec)</td>
<td>11.45±2.88</td>
<td>35.03±3.48</td>
<td>63.12±6.78</td>
</tr>
<tr>
<td>Magnitude of phase-4 depolarization (mv)</td>
<td>1.4±0.67</td>
<td>9.6±2.66</td>
<td>18.5±3.50</td>
</tr>
<tr>
<td>Duration of action potential (msec)</td>
<td>324.86±6.79</td>
<td>336.50±12.54</td>
<td>310.75±11.98</td>
</tr>
<tr>
<td>Maximum rate of rise of upstroke (v/sec)</td>
<td>568.33±61.45</td>
<td>511.43±55.60</td>
<td>360.00±44.49</td>
</tr>
</tbody>
</table>

Values are means ± SE.

*This series of 12 measurements was taken after ouabain had enhanced the magnitude of diastolic depolarization 7–10 mv (25 ± 1 minutes).

†This series of ten measurements was taken 6 minutes after the initial measurements in ouabain treated Tyrode's solution.

||P < 0.005.

§P < 0.025.

||P < 0.01.

during treatment with ouabain at the time when the magnitude of diastolic depolarization had increased to approximately 10 mv (25 ± 1 minutes) and 6 minutes after this first set of measurements.

Treatment with ouabain produced consistent changes in several features of the membrane potential. In all experiments the first detectable change was an increase in the rate and the magnitude of phase-4 depolarization (Fig. 1B). After 25 ± 1 minutes of exposure to ouabain the magnitude of diastolic depolarization had increased to about 10 mv (Fig. 1C). This effect occurred in the absence of any other significant change in membrane potential, as shown in Table 1. After 30–35 minutes of treatment a further increase in phase-4 depolarization had occurred. In addition significant decreases were noted in the maximum diastolic potential and in the rising velocity of the upstroke. The latter effect probably was, in part, a consequence of the enhanced diastolic depolarization, which reduced the level of membrane potential at the onset of phase 0 (16). After approximately 40 minutes of perfusion with ouabain, the duration of the action potential had decreased significantly. The above changes intensified with increasing time of exposure and after 45–50 minutes the contour of the action potential became similar to that normally recorded from fibers of the sinoatrial node (Fig. 1F) (15). Finally after 50–55 minutes of treatment with ouabain, the fibers ceased to respond to the driving stimulus.

In ten preparations treatment with ouabain resulted in spontaneously depolarizing cells which responded at a rate faster than that of the driving stimulus (95/min). The initial sequence of changes produced by ouabain was as described above. Subsequently the cells began to discharge spontaneously at a rate faster than that of the driving stimulus (Fig. 5C). The transition from phase-4 depolarization to the rapid depolarization of the upstroke was smooth and gradual, which is
FIGURE 1

Effect of ouabain, \(2.1 \times 10^{-7}M\), on the action potential of a Purkinje fiber. A: Control. B, C, D, E, and F were recorded 26, 33, 40, 41, and 45 minutes, respectively, after addition of ouabain to the perfusate. The progressive changes described in the text are apparent. The time calibration in this and subsequent figures applies to action potential traces only. The lowest trace is recorded at a sweep speed 10 times that of action potentials and shows small biphasic deflections preceding a large spike. These represent stimulus artifacts and a differentiated record of the action potential upstroke, respectively. Magnitude of the large spike is proportional to the maximum rising velocity of the upstroke. In this and subsequent figures time and voltage calibrations are shown by two parallel horizontal black lines. The vertical distance between the lines equals 100 mv for all figures. The spikes on the top line show an interval of 200 msec for this figure. The magnitude of the vertical bar on the lower line equals a rising velocity of 300 v/sec for all figures.

characteristic of true pacemaker cells (15). After 7–12 minutes of spontaneous activity such preparations ceased to beat and were unresponsive to the driving stimulus.

In four experiments the microelectrode was withdrawn from the Purkinje fiber after the action potential had acquired the configuration characteristic of sinoatrial node fibers and was inserted into a ventricular muscle fiber. The contour of the ventricular action potential closely resembled that observed during control perfusion, showing that ouabain had not affected the electrical characteristics of the ventricular cells to the same degree as it had those of the Purkinje cells. This finding and those outlined above for Purkinje fibers agree with the results of Vassalle et al. (5).

In 11 preparations a transient arrhythmic effect was observed relatively early during treatment with ouabain. These arrhythmias occurred after the increase in diastolic depolarization was evident but before the more profound changes in membrane potential had occurred. In such experiments the cell discharged prior to the occurrence of the driving stimulus. Occasionally a coupled arrhythmia was observed in which spontaneous excitations occurred with the proper timing so that each subsequent driving stimulus elicited a response during phase 3 of the spontaneous beat. Such arrhythmias were steady for periods of up to 1 minute. Usually these early arrhythmias spontaneously terminated, and the usual sequence of changes described above then occurred.

EFFECTS OF THE ANTIARRHYTHMIC DRUGS

One set of experiments was done in which the preparation was perfused with the test drug for 10 minutes before ouabain was added to the test solution. The effects of propranolol were studied in ten experiments, lidocaine was studied in ten, and sotalol was studied in six. In each experiment the time required for ouabain to induce an increase in phase-4 depolarization of about 10 mv was noted. The results of all experiments are summarized and compared in Table 2. Both propranolol and lidocaine significantly delayed the development of ouabain-enhanced phase-4 depolarization. Sotalol, on the other hand, had no significant effect in this regard. The sequence of changes observed during treatment with the combination of sotalol and ouabain was

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Effect of Treatment with the Antiarrhythmic Agents on the Onset of Ouabain-Enhanced Diastolic Depolarization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (M)</td>
<td>Time* (minutes)</td>
</tr>
<tr>
<td>Ouabain, control</td>
<td>2.1 \times 10^{-7}</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>3.7 \times 10^{-4}</td>
</tr>
<tr>
<td>Propranolol</td>
<td>2.1 \times 10^{-5}</td>
</tr>
<tr>
<td>Sotalol</td>
<td>3.2 \times 10^{-4}</td>
</tr>
</tbody>
</table>

Number of experiments is indicated in parentheses. *
Time required after infusion of ouabain for the magnitude of diastolic depolarization to increase 7–10 mv. Values are means \(\pm SE\).

\dagger P < 0.01 compared to the control experiment with ouabain alone.

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almost identical to that seen in experiments in which ouabain alone was administered.

In another group of experiments exposure to ouabain was made until diastolic depolarization increased to about 10 mv. Then the perfusate was changed to one containing only the test drug. Propranolol (six experiments) and lidocaine (five experiments) had identical effects: both drugs reduced the rate and magnitude of diastolic depolarization toward control levels within 10 minutes. Records from one of the experiments with lidocaine are shown in Figure 2. Sotalol was tested in a similar manner in four experiments. In no instance was a decrease in ouabain-enhanced diastolic depolarization noted on application of this drug. Additional experiments were done in which sotalol was applied initially to fibers with ouabain-enhanced phase-4 depolarization; again the drug was ineffective in reducing the slope. Subsequent treatment with propranolol caused a prompt reduction in the magnitude of diastolic depolarization. Figure 3 presents records from one of these experiments.

In a final series of experiments Purkinje fibers were exposed to ouabain until their action potentials resembled those recorded from fibers of the sinoatrial node under normal conditions. At this point perfusion with a solution containing only the antiarrhythmic agent was started. In 15 experiments the effects of propranolol were studied.

![Figure 3](http://circres.ahajournals.org/)
*Effect of sotalol followed by propranolol on a moderate degree of ouabain-enhanced phase-4 depolarization. A: Control. B: After 26 minutes in ouabain solution. At this time ouabain perfusion was stopped and perfusion with sotalol was started. C: After 15 minutes in sotalol, 3.2 × 10⁻⁵M. Sotalol had no discernible effect on phase-4 depolarization. Treatment with propranolol then was initiated. D: After 8 minutes in propranolol, 2.1 × 10⁻⁵M. Time calibration equals 200 msec.*

![Figure 4](http://circres.ahajournals.org/)
*Effect of propranolol, 2.1 × 10⁻⁵M, on the action potentials of a Purkinje fiber after prolonged exposure to ouabain. Records A–F show the usual effects of ouabain as depicted in Figure 1. Records G, H, and I were recorded 5, 6, and 8 minutes after perfusion with propranolol was started. See text for discussion. Time calibration equals 200 msec.*

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Records from a typical experiment are shown in Figure 4. Figure 4A was recorded during control perfusion and B–F were recorded from the same cell during perfusion with ouabain. The previously described sequence of changes in membrane potential occurred. When the action potential converted to a configuration characteristic of fibers in the sinoatrial node (F) ouabain treatment was stopped and perfusion with propranolol was started. Figure 4G, H, and I were recorded 5, 6, and 8 minutes, respectively, after instituting treatment with propranolol. As shown in C the rate and magnitude of diastolic depolarization decreased. Probably as a result of the reduced diastolic depolarization, the level of membrane potential at the onset of phase 0 of the action potential was increased, resulting in good recovery of the maximum rising velocity of the upstroke of the action potential. Subsequently, the contour of the action potential assumed a more normal configuration.

The actions of lidocaine were studied similarly in 19 experiments. Figure 5 illustrates typical results from one experiment. After 45 minutes of exposure to ouabain, the cell escaped from the influence of the driving stimulus and discharged spontaneously (Fig. 5C). At this point lidocaine perfusion was initiated and the changes shown in D and E occurred. The rate and magnitude of diastolic depolarization decreased, the spontaneous rate slowed, and finally the fiber regained a more normal contour and began to respond to the driving stimulus.

The effects of sotalol were studied in seven experiments. In all experiments application of sotalol caused no change in the contour of the action potential or the rate and the magnitude of diastolic depolarization induced by ouabain. Figure 6 shows the records from one experiment. Figure 6B shows the maximal effect of ouabain just prior to application of sotalol. Figure 6C was recorded after 14 minutes of exposure to sotalol. It is apparent that the drug was without significant effect. Subsequently lidocaine was applied and resulted in marked recovery of the membrane potential within 8 minutes (Fig. 6D).

**Discussion**

One of the consistently observed electrophysiological effects of cardiac glycosides is an increase in the slope of phase-4 depolarization (1-5). In our experiments this was the initial effect observed in Purkinje fibers on exposure to ouabain, and the slope continued to increase with increasing duration of treatment. Since phase-4 depolarization is the

![Figure 5](https://example.com/figure5.png)

**FIGURE 5**

Effect of lidocaine, $3.7 \times 10^{-5} M$, on the action potential of a Purkinje fiber after prolonged exposure to ouabain. A: Control. B and C were recorded 24 and 45 minutes after exposure to ouabain. D and E were recorded 5 and 8 minutes after perfusion with lidocaine was started. See text for discussion. Time calibration equals 200 msec.

![Figure 6](https://example.com/figure6.png)

**FIGURE 6**

Effect of sotalol followed by lidocaine on ouabain-enhanced spontaneous discharge of a Purkinje cell. A: Control. B: Spontaneous discharge observed after 43 minutes in ouabain solution. C: After 14 minutes of perfusion with sotalol, $3.2 \times 10^{-5} M$. D: After 8 minutes of treatment with lidocaine, $3.7 \times 10^{-5} M$. See text for discussion. Time calibration equals 300 msec for A and D and 400 msec for B and C.
electrophysiological correlate of pacemaker activity, this particular action of ouabain could account for the occurrence of ventricular arrhythmias as suggested by Vassalle et al. (5). The ways in which enhanced phase-4 depolarization might produce arrhythmias have been considered in detail by others (17, 18) and only a brief summary will be given here.

Sufficient enhancement of phase-4 depolarization in Purkinje fibers could result in spontaneous discharge of action potentials with consequent development of ectopic foci. Ventricular arrhythmias such as premature excitation, tachycardia, and fibrillation could result depending on the frequency of discharge and the number of active foci. In this study we occasionally observed spontaneous discharge of Purkinje fibers in the presence of ouabain, as have others (2–5). In such fibers the slope of phase-4 depolarization was steep and the transition into phase 0 was smooth and gradual, which is characteristic of true pacemaker cells (15). These observations were made in small tissue preparations which contained only a fraction of the total Purkinje tissue of the ventricles. The chances for spontaneous excitation by single fibers in the intact heart exposed to ouabain would seem to be much greater.

A second mechanism for the production of arrhythmias by enhanced phase-4 depolarization involves an indirect effect on the velocity of impulse conduction. One of the major determinants of conduction velocity is the rising velocity of phase 0, which in turn is dependent on the level of membrane potential at the time of excitation (16). An increase in the slope of phase-4 depolarization carries the membrane potential to a lower level at the time of excitation, resulting in reduced rising velocity and conduction velocity. Slowed velocity of conduction along Purkinje fibers, especially if it occurs to a different degree among the fibers, seems likely to interfere with the organized spread of excitation through the ventricles. Experimental evidence for this concept was provided by Singer et al. (19), using isolated preparations of canine Purkinje fibers. An increase in rate of phase-4 depolarization produced by a variety of means, including application of ouabain, was accompanied by slowed conduction velocity, local block of conduction, and unidirectional block of conduction. These conditions are favorable for reentry of excitation (17, 18). In the present experiments the increased slope of phase-4 depolarization and the decline in maximum diastolic potential resulted in action potentials with very low rising velocity, no overshoot, and low amplitude. These changes would be expected to reduce conduction velocity although no direct measurements were made.

If enhanced phase-4 depolarization is a fundamental feature of ventricular arrhythmias induced by ouabain, then those agents capable of antagonizing the arrhythmias should attenuate this action. The specific antiarrhythmic drugs studied here were chosen because of their effects on digitalis arrhythmias in intact dogs and also because the electrophysiological effects of each drug on canine Purkinje fibers is known (20–24). Propranolol, a drug which blocks beta receptors (25), is effective in the treatment of several types of cardiac arrhythmias including those caused by cardiac glycosides (7–10). Lidocaine, a well-known local anesthetic agent, has a spectrum of antiarrhythmic action similar to that of propranolol (26). It too terminates ouabain-induced arrhythmias in dogs (6, 8). Sotalol, which also blocks beta receptors (27) and prevents catecholamine-induced arrhythmias (12), has not been found effective in suppressing digitalis-induced arrhythmias in dogs (11–13).

In our studies propranolol and lidocaine were found to attenuate the effects of ouabain on phase-4 depolarization. Treatment with either drug before exposure of the preparation to ouabain produced a significant delay in the enhancement of phase-4 depolarization. It also was shown that these drugs could reduce the slope of phase-4 depolarization which resulted from prior exposure to ouabain. The most dramatic illustration of this effect was in experiments in which the contour of the action potentials in the ouabain-exposed fibers was compared with that in control fibers. The results of these experiments are illustrated in Figure 1. The original action potentials were characterized by low rising velocity, no overshoot, and low amplitude. Following exposure to ouabain, the action potentials showed a marked increase in rate of phase-4 depolarization which resulted in reduced rising velocity and conduction velocity. Treatment with propranolol or lidocaine before exposure to ouabain produced a significant delay in the enhancement of phase-4 depolarization and a reduction in the slope of phase-4 depolarization. These results are illustrated in Figure 1 and are consistent with the hypothesis that enhanced phase-4 depolarization is a fundamental feature of ventricular arrhythmias induced by ouabain.
potential had changed to a configuration characteristic of the sinoatrial node. Application of propranolol or lidocaine decreased the slope of phase-4 depolarization and restored the rising velocity, amplitude, and overshoot of the action potential toward normal. In experiments in which the cell discharged spontaneously at rates in excess of the driving stimulus, the drugs slowed the spontaneous rate to the point that the driving stimulus regained control of the preparation. These effects are correlated with the observation that in intact animals lidocaine or propranolol terminates ventricular tachycardia caused by digitalis. Sotalol, on the other hand, when tested in identical experiments had none of these effects. The lack of effect is consistent with the failure of this drug to terminate ouabain-induced arrhythmias in dogs. Thus these experimental results support the hypothesis that enhanced phase-4 polarization of Purkinje fibers plays a role in production of ventricular arrhythmias induced by digitalis.

One hypothesis advanced to explain the mode of action of antiarrhythmic drugs holds that a reduction in the rising velocity of phase 0 is the basis for their effects (28, 29). This concept is based largely on the fact that several proven antiarrhythmic drugs cause a reduction in the velocity of phase 0 of different cardiac fibers. Propranolol has this basic effect (20, 30, 31) and so does lidocaine if the concentration is adequate (21, 22) or if certain experimental conditions are provided (32). Yet in our experiments both lidocaine and propranolol improved the rising velocity in Purkinje fibers in which this feature had been depressed by ouabain. This effect apparently was secondary to the reduction in the slope of phase-4 depolarization. Thus the basic mode of antiarrhythmic action for ventricular arrhythmias produced by digitalis compounds might be a decrease in the slope of phase-4 depolarization of Purkinje fibers. Recently Rosen and Gelband (33) appraised the action of several different antiarrhythmic drugs. They concluded that the ideal antiarrhythmic drug would decrease the slope of phase-4 depolarization and either have no effect on maximum rising velocity or else improve this feature in depressed fibers. As shown here lidocaine and propranolol have both these effects on Purkinje fibers exposed to toxic concentrations of ouabain.

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doi: 10.1161/01.RES.30.6.681

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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