The effects of procainamide on conduction in anisotropic canine ventricular myocardium

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ABSTRACT  Although conduction velocity in cardiac tissue is dependent on fiber orientation, the influence of commonly used antiarrhythmic agents on conduction longitudinal and transverse to such fibers is unknown. We evaluated the effects of procainamide on conduction velocity and intracellular potentials in vitro during conduction longitudinal and transverse to fiber orientation in epicardial strips obtained from areas of uniform fiber orientation from 15 adult mongrel dogs. Ventricular epicardial strips demonstrated marked anisotropy. At a pacing cycle length of 1000 msec, mean conduction velocity longitudinal to fiber orientation averaged 0.602 ± 0.051 m/sec and mean conduction velocity transverse to fiber orientation was 0.186 ± 0.024 m/sec, resulting in a ratio of longitudinal to transverse conduction velocities of (0L/T) 3.27 ± 0.38. After the addition of procainamide, conduction velocity decreased to 0.532 ± 0.062 m/sec longitudinal to fiber orientation and to 0.174 ± 0.023 m/sec transverse to fiber orientation resulting in a decrease of 0L/T to 3.09 ± 0.37 (p < .05 vs control).

Before the addition of procainamide, when pacing at progressively shorter cycle lengths, conduction velocity longitudinal to fiber orientation was relatively unchanged, whereas conduction velocity transverse to fiber orientation decreased resulting in an increase in 0L/T. After the addition of procainamide, conduction velocity at shorter pacing cycle lengths decreased both longitudinal and transverse to fiber orientation demonstrating the well-known use-dependent effect of procainamide. However, in contrast to control conditions, conduction velocity longitudinal to fiber orientation was slowed by a greater extent than the conduction transverse to fiber orientation, resulting in an even greater decrease in 0L/T. To investigate the effect of differences in drug binding during propagation in different directions, we examined conduction velocity during alternations in pacing direction and compared it with velocity during steady-state pacing. At a pacing cycle length of 1000 msec, no difference was observed between the initial conduction velocity after changing pacing directions and the steady-state conduction velocity. At pacing cycle lengths shorter than 1000 msec, when changing from transverse to longitudinal conduction, there was an initial drop in normalized conduction velocity that was present on the first beat of longitudinal conduction; however, with continued pacing in a longitudinal direction there was a further decrease in conduction velocity. We conclude from the above findings that: (1) procainamide has nonhomogeneous effects on conduction in anisotropic ventricular muscle; conduction velocity longitudinal to fiber orientation is depressed by a greater extent than transverse to it; and (2) differences in drug binding depending on propagation direction and/or an effect of procainamide on junctional resistivity may be responsible for the directional differences in the effects of procainamide we observed.

associated with such conduction. If anisotropic conduction is important in contributing to the anatomic basis for arrhythmia generation, as suggested by Spach et al.\textsuperscript{12} in atrial muscle and Dillon et al.\textsuperscript{14} in canine infarction, the effects of procainamide on such conduction may be crucial in understanding its mechanism of action.

**Methods**

**Tissue preparation.** Fifteen adult mongrel dogs weighing 9 to 16 kg were used for experiments. They were anesthetized with intravenous sodium pentobarbital (30 mg/kg iv) and the chest was opened via a lateral sternotomy. Tissues approximately 2 cm × 1.5 cm × 2 mm thick were shaven from the epicardial surface of either the left or right ventricle. They were removed so that the fiber orientation was parallel to the long axis of cut tissue. We avoided areas of epicardial fat, large epicardial blood vessels, or irregularities in fiber orientation. We have previously subjected tissues obtained in a similar way to histologic examination to confirm our ability to obtain parallel fiber orientation over the length of the tissues.\textsuperscript{15}

Immediately after removal, the slices were placed in a tissue bath with the epicardial surface up. Tissues were superfused with 95% oxygen and 5% carbon dioxide in 37°C. Tissues were stimulated with one or more bipolar electrode(s) consisting of Teflon-coated silver wires. Constant current rectangular pulses, 2 msec in duration and twice diastolic threshold, were delivered at cycle lengths of 300 to 1000 msec.

**Intracellular and extracellular potential recording.** Electrogrograms were recorded with one to three bipolar Teflon-coated silver electrodes and intracellular potentials were recorded with standard 3M potassium-filled microelectrodes. The recordings were displayed on a multiple-channel oscilloscope and photographed on 35 mm film. Multiple intracellular and extracellular potentials were recorded at a single time to facilitate measurement of conduction intervals. Intracellular potentials were also recorded after further amplification and instantaneous analog differentiation. After the experiment, all variables were manually measured to the nearest millivolt and 0.1 msec, with a Hewlett-Packard 9836 computer and digitizing system. Distances between electrodes were measured with a two-dimensional optical micrometer that was visually calibrated and had a resolution of 0.10 mm. Activation times for extracellular electrograms or the activation sequence occurred, the results were discarded. Impalements were made in the most superficial layer of cells on the epicardial surface.

Action potential variables measured included action potential amplitude, action potential duration at 100% of repolarization, and maximum rate of depolarization determined by instantaneous differentiation of the analog signal (Vmax). Activation times for intracellular recording were determined at the point of Vmax.\textsuperscript{16} Resting membrane potential was obtained from a DC amplified action potential signal (total 100X) and stored on a memory oscilloscope. If resting membrane potential deviated by more than 5 mV, the experiment was not used for the determination of action potential variables so we noted some variability in Vmax. However, if successful impalement could be accomplished in the same cell, the experimental protocol was continued for the determination of conduction velocity. Conduction velocity was calculated by dividing the measured distance between two recording sites by their difference in activation times.

**Experimental protocol.** Tissues were placed in a bath, and conduction across the preparation was monitored continuously to verify its stability. After conduction velocity had remained stable for more than 20 min, experiments were performed in one of two ways. Protocol A: In three tissues (figure 1), pacing at a basic cycle length of 1000 msec was instituted in one corner of the preparation, greater than 2 mm from the cut edge. A single...
roving extracellular electrode was positioned at 25 to 40 points throughout the tissue so that isochronal activation maps could be constructed. Interpoint distances averaged 2 mm. These experiments were performed to verify uniform anisotropic conduction and confirm the absence of irregularities in activation after the addition of procainamide. Protocol B: In 10 tissues (figure 2), two pacing electrodes were placed in opposite corners of the preparation and a microelectrode impalement was made in the third corner so that by changing the pacing site from SL to ST, the direction of the wavefront approaching the microelectrode would change from being oriented longitudinal to being oriented transverse to the direction of the myocardial fibers. In addition, extracellular electrodes were positioned along each axis so that conduction times could be determined between two recording electrodes (extracellular-intracellular) in each pacing direction. Extracellular electrodes were placed at least 1 mm from the pacing electrodes to ensure that uniform conduction had been established in the area over which conduction velocity was determined. Control measurements, drug addition, stabilization of conduction, and repeat experiments required an average of 45 min. The majority of our experiments were performed with protocol B, since this enabled us to obtain precise measurements of intracellular variables and ensured that changes in impalement position did not affect determinations of conduction velocity. Also, we routinely performed multiple additional impalements before and after the addition of procainamide to verify that uniform conduction was still present, but such data were not obtained for dynamic changes involved during the initiation of pacing, changes in pacing cycle length, and changes in pacing direction. To evaluate the effect of cycle length on procainamide’s action, five tissues were paced at several cycle lengths between 300 to 1000 msec with protocol B. Pacing was continued for at least 30 sec from a single electrode pair before conduction velocity was determined.

After measurements were made in the control state, Tyrode’s solution containing 20 μg/ml procainamide was perfused through the tissue bath and serial measurements were repeated. Throughout all experimental procedures, the relationship between the activation sequence of all recorded electrograms and the morphology of extracellular electrograms were closely observed. If a change in the activation sequence or the morphology of electrograms was noted, the preparation was discarded. To be certain that the effects we observed were attributable to procainamide, we continually measured longitudinal and transverse conduction velocities in three control preparations over 3 hr. Although small decreases in conduction velocity (less than 10%) were present over time, there was no change in ΔL/T — the ratio of longitudinal to transverse conduction velocities (less than 2% variability).

Data analysis. Although pacing from a single site produces wavefronts that progress in various directions relative to myocardial fiber orientation, we were able to analyze areas showing preferential longitudinal or transverse conduction by selecting only recording sites with appropriate orientation relative to the pacing site and fiber direction. In protocol A this involved selecting several recordings such as those shown in row b of figure 1 for longitudinal conduction and in column 6 for transverse conduction. In protocol B (figure 2) the same result was accomplished by changing the location of the pacing site relative to fixed longitudinal and transverse recording sites.

Tabular data are expressed as means ± SDs. Experiments 1 through 10 were derived from protocol B and 11 through 13 from protocol A.

Conduction velocity and action potential variables were compared before and after procainamide with a paired t test. Changes at different cycle lengths were analyzed by two-way analysis of variance. A probability of less than .05 indicated significance.

Results

Characteristics of the tissues. Epicardial ventricular strips exhibited marked anisotropy in the control state. An example of such conduction at a basic cycle length of 1000 msec is presented in figure 1, A. Regular spacing of isochrones is evident, demonstrating uniform conduction throughout the preparation. Conduction velocities for each preparation measured in areas having propagation either longitudinal or transverse to fiber orientation are shown in the left side of table 1. Mean conduction longitudinal to fiber axis was 3.2 times more rapid than transverse to it (table 1). Action potential variables for the first six preparations obtained at a pacing cycle length of 1000 msec was presented in table 2. Vmax was significantly higher at the same site during conduction transverse as opposed to longitudinal to fiber orientation. Spach et al. described similar results and hypothesized that this difference is caused by discontinuities in conduction on a microscopic level that are more prominent during transverse propagation.

Effect of procainamide. Procainamide reduced con-
TABLE 1
Conduction velocities longitudinal and transverse to fiber orientation at a pacing cycle length of 1000 msec before and after the addition of procainamide

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\theta_z$,PRE (m/sec)</th>
<th>$\theta_y$,PRE (m/sec)</th>
<th>$\theta_L/T$,PRE</th>
<th>$\theta_z$,POST (m/sec)</th>
<th>$\theta_y$,POST</th>
<th>$\theta_L/T$,POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.163</td>
<td>0.574</td>
<td>3.515</td>
<td>0.155</td>
<td>0.537</td>
<td>3.463</td>
</tr>
<tr>
<td>2</td>
<td>0.194</td>
<td>0.511</td>
<td>2.628</td>
<td>0.173</td>
<td>0.428</td>
<td>2.470</td>
</tr>
<tr>
<td>3</td>
<td>0.194</td>
<td>0.644</td>
<td>3.973</td>
<td>0.155</td>
<td>0.590</td>
<td>3.808</td>
</tr>
<tr>
<td>4</td>
<td>0.158</td>
<td>0.549</td>
<td>3.475</td>
<td>0.154</td>
<td>0.477</td>
<td>3.097</td>
</tr>
<tr>
<td>5</td>
<td>0.212</td>
<td>0.628</td>
<td>2.965</td>
<td>0.206</td>
<td>0.592</td>
<td>2.872</td>
</tr>
<tr>
<td>6</td>
<td>0.200</td>
<td>0.596</td>
<td>2.980</td>
<td>0.195</td>
<td>0.546</td>
<td>2.798</td>
</tr>
<tr>
<td>7</td>
<td>0.232</td>
<td>0.686</td>
<td>2.962</td>
<td>0.221</td>
<td>0.640</td>
<td>2.897</td>
</tr>
<tr>
<td>8</td>
<td>0.168</td>
<td>0.552</td>
<td>3.290</td>
<td>0.149</td>
<td>0.495</td>
<td>3.320</td>
</tr>
<tr>
<td>9</td>
<td>0.218</td>
<td>0.609</td>
<td>2.794</td>
<td>0.186</td>
<td>0.495</td>
<td>2.598</td>
</tr>
<tr>
<td>10</td>
<td>0.182</td>
<td>0.652</td>
<td>3.581</td>
<td>0.174</td>
<td>0.594</td>
<td>3.412</td>
</tr>
<tr>
<td>11</td>
<td>0.164</td>
<td>0.576</td>
<td>3.510</td>
<td>0.149</td>
<td>0.495</td>
<td>3.320</td>
</tr>
<tr>
<td>12</td>
<td>0.194</td>
<td>0.665</td>
<td>3.430</td>
<td>0.179</td>
<td>0.560</td>
<td>3.120</td>
</tr>
<tr>
<td>13</td>
<td>0.172</td>
<td>0.588</td>
<td>3.420</td>
<td>0.161</td>
<td>0.476</td>
<td>2.957</td>
</tr>
<tr>
<td>Mean±</td>
<td>0.186±0.024</td>
<td>0.602±0.051</td>
<td>3.271±0.377</td>
<td>0.174±0.023</td>
<td>0.532±0.062</td>
<td>3.087±0.374</td>
</tr>
</tbody>
</table>

$\theta_z$ = conduction velocity transverse to fiber orientation; $\theta_y$ = conduction velocity longitudinal to fiber orientation; PRE = control; POST = after procainamide; $\theta_L/T$ = ratio of longitudinal to transverse conduction velocity.

*p < .05 vs control.

Production velocity during propagation both longitudinal and transverse to fiber orientation. Figure 1 shows isochronal maps of activation before (A) and after (B) procainamide, demonstrating that such slowing of conduction was uniform and was not caused by areas of block. In table 1 it can be seen that for all tissues there was a relatively greater decrease in conduction velocity of the wavefronts moving longitudinal to fiber orientation, resulting in a significant decrease in the ratio $\theta_L/T$. An example of the time course of onset of the effect of procainamide is shown in figure 3. Decreases in conduction velocity began 3 to 5 min after procainamide was added and conduction stabilized after 15 to 20 min. The effects of procainamide on action potential variables in tissues 1 to 6 (those in which impalements could be kept throughout the experiment) are shown in table 2.

Before addition of procainamide, conduction velocity transverse to fiber orientation decreased with decreasing pacing cycle length (figure 4, A). This resulted in an increase in $\theta_L/T$ with more rapid pacing (figure 4, B). Spach et al.8 also observed this result in similar preparations and postulated that a short-term increase in junctional resistivity potentially caused by increased intracellular calcium concentration was responsible. Since junctional resistances are encountered more frequently during conduction over a given distance in the transverse direction, propagation in such a

TABLE 2
Action potential variables from six tissues at a pacing cycle length of 1000 msec before and after the addition of procainamide

<table>
<thead>
<tr>
<th>Action potential amplitude (mV)</th>
<th>Action potential duration (msec)</th>
<th>Vmax (V/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>TV PRE</td>
<td>LG PRE</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>1</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
<td>90</td>
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<tr>
<td>3</td>
<td>92</td>
<td>87</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>Mean±</td>
<td>96.2±6.5</td>
<td>89.3±6.4</td>
</tr>
</tbody>
</table>

TV = transverse; LG = longitudinal; PRE = control; POST = after procainamide.

*p < .05 vs control; **p < .05 vs TV.
from transverse to longitudinal conduction in the area around the recording electrode, conduction velocity (normalized to the drug-free state) should decrease gradually from its level during transverse propagation and stabilize at a new lower level.

We examined normalized conduction velocity in the presence of procainamide in five tissues in the beats preceding and following sudden shifts in the pacing site, which altered the propagation direction around our recording electrodes. After pacing tissues for 5 min from one site and verifying that conduction velocity

direction should be slowed to a greater extent by an increase in junctional resistance.

After the addition of procainamide, we observed the expected frequency-dependent decrease in conduction velocity that has been described with procainamide and similar antiarrhythmic agents. However, in contrast to control conditions, conduction longitudinal to fiber orientation was depressed to a greater extent than conduction transverse to it, resulting in a decrease in $0LT$. Data from one such experiment are shown in figure 4 and pooled data from five tissues are presented in figure 5. During pacing, $0LT$ decreased progressively with increased pacing time (figure 6). The majority of the decrease in conduction velocity occurred during the first 5 sec of more rapid pacing and more than 95% of the total effect was present by 30 sec.

**Effects of dynamic changes in propagation direction on conduction with procainamide.** Conduction velocities reported in the previous series of experiments were determined after at least 30 sec of pacing from one of the pacing electrode pairs (SL or ST of figure 2). One possibility for the greater depression of conduction longitudinal to fiber orientation by procainamide is greater drug binding during such propagation. If this were so, one would expect a difference in conduction velocity during alternation in propagation direction in a given area of tissue. For example, after changing

![Graph 3](https://example.com/graph3.png)

**FIGURE 3.** Change in conduction velocity over time after the addition of 20 µg/ml procainamide at time 0. Data are from a single preparation. Most of the decrease in conduction velocity both longitudinal and transverse to fiber orientation occurred within the first 15 min with only small changes thereafter. Changes in the ratio of longitudinal to transverse conduction velocity $0LT$ over time after the addition of procainamide are shown at the top. Despite a larger absolute decrease in longitudinal conduction velocity, the relative decrease in conduction velocity was larger transverse to fiber orientation, resulting in a decrease in the ratio $0LT$ from 3.58 to 3.41.

![Graph 4](https://example.com/graph4.png)

**FIGURE 4.** Influence of changes in pacing cycle length on conduction longitudinal and transverse to fiber orientation before (A) and after (B) the addition of 20 µg/ml procainamide. Data are from a single experiment. Before addition of drug, conduction velocity was essentially unchanged at different pacing cycle lengths longitudinal to fiber orientation, but that transverse to fiber orientation decreased with shorter cycle lengths. The resulting increase in $0LT$ is shown in B. After procainamide there was a marked depression of conduction velocity longitudinal to fiber orientation at shorter pacing cycle lengths, whereas the effect on transverse conduction velocity was less marked. This resulted in a decrease in $0LT$, which was in sharp contrast to the increase seen in the control state. CTL = control; PCA = procainamide.
and activation sequence were stable, we shifted to pacing from the other site for 30 sec and determined conduction velocity through each beat during the protocol. We subsequently returned to pacing from the initial site and performed such alternations several times in each tissue. The results of one experiment are shown in figure 7. At a pacing cycle length of 1000 msec there was a mean of 5% greater depression of conduction longitudinal than transverse to fiber orientation. After sudden shifts in pacing direction there was a rapid shift in normalized conduction velocity from the higher transverse level to the lower longitudinal level (figure 7, A). There was never more than a 2.8% difference between conduction velocity in the first few beats after a direction change and during steady-state conduction in the same direction. The rapid change in normalized conduction velocity after a direction shift, occurring even on the first beat, suggests that differences in drug binding do not account for the observed differences in the effects of procainamide on conduction velocity at a cycle length of 1000 msec.

When pacing at cycle lengths shorter than 1000 msec, the difference in normalized conduction velocity between longitudinal and transverse conduction also occurred with the first beat after a change in the stimulating electrode site. After the transition from transverse to longitudinal pacing, however, there was a further decrease in conduction velocity with more prolonged pacing in the longitudinal direction. Conduction stabilized after approximately 15 sec of pacing (figure 7, B and C). Thus there was a difference in the effects of procainamide on longitudinal and transverse conduction that was present at all pacing cycle lengths evaluated and was not dependent on propagation direction of the previous beats. In addition, during conduction longitudinal to fiber orientation at short pacing cycle lengths, there was a further decrease in conduction velocity with more prolonged pacing.

**Discussion**

Procainamide has been shown to decrease conduction velocity in cardiac tissue. It has generally been assumed that this effect is mediated through a depression of inward sodium current. There is also evidence in some preparations that procainamide may have effects on passive membrane properties. Arnsdorf and Bigger found a 10% increase in the space constant attributable to an increase in membrane resistance in Purkinje fibers. Buchanan et al. have recently studied the relationship between Vmax and conduction velocity in ventricular papillary muscle and demonstrated that with procainamide as well as with other interventions that decrease the inward sodium current, there is an excellent correlation between Vmax and t0. Our results for conduction longitudinal to fiber orientation are similar (figure 8). Thus the major effect of procainamide on longitudinal conduction in ventricular muscle is attributable to a depression of inward sodium current and thus Vmax.

In addition, we observed in our experiments that...
proacainamide decreased conduction velocity by 11.6% longitudinal to fiber orientation but only 6.4% transverse to fiber orientation. There are several potential explanations for this effect. They include a differential effect of uniform depression of inward sodium current, changes in junctional and/or cytoplasmic resistivity, or differences in drug binding depending on conduction wavefront orientation.

**Uniform depression of membrane properties in anisotropic tissue.** Several investigators have demonstrated anisotropic conduction in canine ventricular muscle. Spach et al. have proposed a model to explain the differences in conduction velocity and action potential properties in anisotropic muscle, which includes an equivalent circuit in which many more junctional resistances per unit distance of impulse conduction are present transverse than longitudinal to fiber orientation. They suggested on the basis of such a model that factors that produce a uniform depression of inward sodium current would produce a uniform depression of conduction velocity. They verified their hypothesis by examining depression of conduction velocity with the introduction of premature beats and found that 0L/T did not change. We obtained similar results in our tissues with the introduction of premature beats, and it therefore seems unlikely that factors that produce a uniform depression of inward sodium current would produce differential effects on conduction longitudinal and transverse to fiber orientation.

**Effects of drug binding.** The binding of antiarrhythmic agents to sodium channels is a dynamic process for which analytical models have been developed. Although controversy exists about whether there are actually several different states of the sodium channel or whether access to such channels is changed, it nevertheless is clear that drug binding differs depending on stimulation frequency. Very little binding of procainamide occurs during the recovered state of the sodium channel. In support of this, Buchanan et al. found no effect of procainamide on conduction velocity in ventricular muscle during stimulation at a rate of 0.1 Hz. The affinity of sodium channel–blocking agents for open and inactivated channels (or guarded states) varies depending on the drug. It is thought that

**FIGURE 7.** Normalized conduction velocity longitudinal and transverse to fiber orientation during pacing at a fixed pacing cycle length while alternating directions. Conduction velocity is normalized to a fraction of that before drug addition. Stimulation from one or the other pacing electrode was performed so that impulse propagation from that electrode to the recording electrode (as shown in figure 2) was either longitudinal (LG) or transverse (TV) to fiber orientations. Stable conduction transverse to fiber orientation was maintained for 5 min before the values were obtained. Changes in pacing direction are indicated. At a cycle length of 1000 msec (A), normalized conduction velocity longitudinal to fiber orientation was slower than that transverse to it and there was no difference between conduction velocity for the first few beats after the change from transverse to longitudinal conduction and that after prolonged pacing longitudinal to fiber orientation. At cycle lengths of 600 and 400 msec (B and C), normalized conduction velocity was also slower longitudinal than transverse to fiber orientation. In addition, after the transition from transverse to longitudinal pacing, conduction velocity continued to decrease over the first few beats. Note that conduction velocity on the first beat of longitudinal conduction was far slower than that for transverse conduction, suggesting that although increased drug binding during conduction longitudinal to fiber orientation may contribute to the further decrease in conduction velocity with prolonged pacing longitudinal to fiber orientation, it is not an adequate explanation for all of the difference between longitudinal and transverse conduction.
proacainamide may have slightly more affinity for in-activated than open channels but binds significantly to both.23

A theoretical model taking into account the differences in the kinetics of the inward sodium current that occur among a propagating action potential, an action potential at a site of collision, and a uniformly depolarizing isolated patch of membrane has been developed by Spach and Kootsey.24, 25 They found that the area under the E_{Na} curve (sodium conductance vs time) is greater during uniform propagation than at a site of collision or in an isolated patch of membrane. They postulated that the area under the E_{Na} curve should represent a good approximation of the sodium channel open time. Since the shape and amplitude of depolarization of a cardiac action potential recorded during transverse propagation is similar to that noted at sites of collision, the authors further postulated that total open time of the sodium channels should be greater when propagation occurs longitudinal to fiber orienta-
tion than when it occurs transverse to fiber orientation. Since procainamide binding is related to sodium channel open time, as noted above, this simulation predicts that procainamide should produce a greater depression of longitudinal conduction velocity.

Since the model proposed by Spach and Kootsey for sodium conductance at site of collision is not exactly identical to transverse propagation, it is impossible to say from their results whether the magnitude of differ-
ence in the effect of procainamide or longitudinal and transverse conduction we found is entirely explicable by differences in drug binding. In addition, the results of the experiments we performed in which the direction of propagation was abruptly changed suggest the possibility that other factors may be operating. If greater drug binding occurs during longitudinal conduction, this effect should require several beats to reach a steady state after a change in pacing site. That is, one would expect that if in a given area of tissue where the wavefronts have been moving transverse to fiber orientation they are suddenly made to move longitudinal to fiber orientation, the conduction velocity of the beats initially traversing this area after the change should be greater than during the steady state after several beats have passed. We found no such differences at a pacing cycle length of 1000 msec. At faster pacing cycle lengths, conduction velocity decreased progressively after the change to longitudinal propagation (figure 7, B and C), suggesting that greater drug binding was in fact occurring during propagation longitudinal to fiber orientation. However, even at these more rapid stimulation frequencies, a clear difference in normalized conduction velocity was always present between the last beat of transverse pacing and the first beat of longitudinal pacing suggesting the possibility that a mechanism other than differences in drug binding was responsible for most of the greater depression of conduction longitudinal to fiber orientation.

Changes in junctional resistivity. Experimental data and computer simulations8, 12, 25–27 have examined the effects of changes in junction and cytoplasmic resistivity on conduction in anisotropic muscle. Increases in junctional resistivity such as that caused by digitalis-like compounds preferentially depressed conduction transverse to fiber orientation, whereas increases in cytoplasmic resistivity theoretically should have a greater effect on conduction longitudinal to cardiac fibers.8 It is unlikely that major changes in cytoplasmic resistivity occur,8 and data demonstrating a lack of change in cytoplasmic resistivity when intracellular sodium activity was decreased to as low as 25% of control support this notion.28 In the present experiments, we did not directly measure internal resistance, and although cable theory models for calculation of internal resistance are available,5 there may be significant deviations from cable theory behavior during transverse propagation. The application of these models to transverse propagation is therefore uncertain. Nonetheless, a decrease in junctional resistivity caused by procainamide is another potential explanation for our experimental results. How a change in junctional

FIGURE 8. Correlation between measured and calculated maximum rate of depolarization after addition of procainamide. Calculated values were derived from control V_{\text{max}} (LG PRE of table 2) and control conduction velocity (\theta_{\text{PRE}} of table 1) using the relationship \( t^2 = KV_{\text{max}} \) suggested by Buchanan et al.19 Measured values were taken from V_{\text{max}} after procainamide (LG POST of table 2). Excellent agreement between measured and calculated values is apparent (\( r^2 = .97 \)). V_{\text{max}} = maximum rate of depolarization.
resistivity is preferentially manifest transverse to fiber orientation can be explained based on the model proposed by Spach et al.\textsuperscript{8}

Internal resistivity in cardiac muscle can be expressed as a sum of junctional and cytoplasmic resistance. Although cytoplasmic resistance is assumed to be identical longitudinal and transverse to fiber orientation, cell junctions are far more frequent per unit distance an impulse crosses transverse to fiber orientation and thus total internal resistance is higher. Consequently, a small decrease in the resistance of each individual junction will be far more apparent transverse to fiber orientation. Thus a greater decrease in transverse internal resistance caused by procainamide could partially counteract the depression of conduction velocity caused by sodium channel blockade and result in less marked depression of conduction transverse to fiber orientation.

Is there a theoretical basis for the position that procainamide decreases junctional resistance? Sodium channel blockade with a variety of drugs has been shown to decrease internal sodium and internal calcium activity in experimental preparations.\textsuperscript{23} Measurable changes in intracellular calcium activity occur with physiologic concentrations of antiarrhythmic agents. Although a variety of mechanisms, including intracellular pH, intracellular cycle AMP concentrations, and internal calcium, have been shown to affect junctional resistivity,\textsuperscript{29} changes in internal calcium concentration can by themselves modulate junctional resistivity. By blocking sodium channels, procainamide should decrease intracellular sodium and thus calcium concentration decreasing junctional resistance. Such a decrease would explain the relative preservation of transverse conduction velocity.

Thus there are two major factors that may be responsible for the preferential effect of procainamide on longitudinal conduction. A greater sodium channel open time during longitudinal propagation may be responsible for greater drug binding and thus a greater depression of conduction velocity. Our evidence suggests that this effect may be more important at pacing cycle lengths shorter than 1000 msec. In addition, it is possible that a small decrease in the resistance of individual cell-to-cell junctions by procainamide may also be responsible for some of our findings.

Implications. This study has potential implications for understanding the mechanisms of action of antiarrhythmic agents. Many agents that produce sodium channel blockade have use-dependent properties and could exhibit similar directional differences in drug binding as procainamide. In addition, these agents should all have similar effects on internal calcium concentration and thus could possibly have similar effects on junctional resistivity.

The role of fiber orientation in the generation of arrhythmias has only recently been investigated.\textsuperscript{11,14} Under experimental conditions, the anisotropic properties of cardiac muscle may provide both the slow conduction and unidirectional block necessary for the development of arrhythmias in the canine atrium.\textsuperscript{11} Dillon et al.\textsuperscript{14} have shown that directional differences in conduction velocity based on fiber orientation persist in 2-week-old canine myocardial infarctions and that slow conduction transverse to fiber orientation may be an important part of reentrant circuits in such animals. Although the roles of myocardial fiber geometry in clinical arrhythmias remains to be established with certainty, it seems likely that it is a contributing factor to conduction and reentrant arrhythmias in some cases. Differences in antiarrhythmic drug action depending on the direction of conduction relative to the fiber orientation in a particular arrhythmogenic area may be one of the factors responsible for the heterogeneous response to antiarrhythmic agents.

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