Mechanisms of Depressed Conduction From Long-term Amiodarone Therapy in Canine Myocardium

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Amiodarone therapy leads to a significant impairment in myocardial conduction, yet it causes only a modest decrease in the maximum rate of depolarization of the action potential (dV/dT). To determine whether the decrease in dV/dT solely accounts for the impaired myocardial conduction or whether passive membrane properties may also be involved, we studied 21 ventricular epicardial tissues from 14 beagles; six dogs received long-term treatment (3–6 weeks) of amiodarone orally, and the remaining dogs served as controls. Amiodarone therapy was associated with a decrease in conduction velocity (0.41±0.15 vs. 0.56±0.05 m/sec; p<0.01). There was a trend toward a decrease in dV/dT and a significant decrease in the space constant (0.69±0.27 vs. 1.05±0.25 mm; p=0.01), of which the latter correlated closely with the decrease in conduction velocity measured in the amiodarone-treated tissues (r=0.85, p<0.05). These data indicate that the decrease in myocardial conduction velocity caused by amiodarone is primarily due to effects on overall resistance to passive current flow rather than effects on the inward sodium current. (Circulation 1988;78:684–691)

Amiodarone is singularly effective in the treatment of malignant ventricular tachyarrhythmias. In patients with ventricular tachycardia refractory to other antiarrhythmics, there is a 50–80% response rate to amiodarone.1–11 The mechanism of amiodarone’s antiarrhythmic action is unknown. Ventricular tachycardia likely results from reentrant circuits that rely on critical interactions between the conduction characteristics and refractoriness of the myocardium. Pharmacological alterations of these interactions effect an antiarrhythmic (or proarrhythmic) response. Amiodarone prolongs action potential duration and myocardial refractoriness.12–17 Recent evidence also indicates that amiodarone binds to sodium channels that are in the inactivated state and, hence, amiodarone may also affect myocardial conduction.13–15 According to recent work, amiodarone reduces conduction velocity in human myocardium and Purkinje tissue.18–20 Although sodium channel blockade may be an important determinant of slow conduction in amiodarone-treated tissues, amiodarone may also affect passive membrane properties that, in turn, may contribute to slowed conduction velocity. Alterations of passive membrane properties by amiodarone may be particularly relevant in light of recent data that suggest amiodarone is accumulated and concentrated in many tissues, including myocardium.21,22 If amiodarone deposits in and around myocardial cells, there may be alterations in overall resistance (intracellular and extracellular) to current flow and hence to conduction velocity.

The purpose of the present experiments was to demonstrate a depressant effect of amiodarone on conduction velocity in canine ventricular myocardium and to document that the decrement in conduction was due, at least in part, to a decrease in the tissue space constant.

Materials and Methods

Experiments were performed in 21 tissues removed from 14 beagles weighing 8–20 kg. The
animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg body wt), and their chests were opened by a left lateral thoracotomy. The hearts were excised and ventricular epicardial tissues 1–3 mm thick, 2–3 cm long, and 2 cm wide were removed so that their long axis was parallel to the observed superficial fiber orientation. We have previously subjected tissues obtained in a similar manner to histological examination to confirm our ability to obtain parallel fiber orientation over the length of the tissues.23 Nine tissues were removed from six animals that had received amiodarone (400 mg/day orally for 2 weeks, followed by 200 mg/day) for a total of 3–6 weeks. Twelve tissues from eight normal, control animals were removed in the same manner. The tissues were placed in a 100-ml tissue bath and were superfused with standard oxygenated Tyrode’s solution. The tissues were paced at a cycle length of 1,000 msec with bipolar stimulating electrodes consisting of two Teflon-coated silver wires and were allowed to equilibrate for 30 minutes. Constant-current rectangular pulses of 2-msec duration and twice diastolic threshold intensity were used. Our techniques have been described in detail previously.23,24 Thin epicardial tissues such as those used in these studies can be maintained for up to 5 hours without a significant decrement in their electrophysiological variables, indicating that perfusion and oxygenation are adequate in the superficial cell layers sampled.

Transmembrane action potentials were recorded from the superficial cell layers with standard 3M potassium-filled microelectrodes. The transmembrane potentials, as well as their electronically differentiated signals (dV/dT), were displayed on an oscilloscope and photographed on 35-mm film. Action potential variables (action potential amplitude, resting potential, action potential duration at 100% repolarization) were measured by projecting the 35-mm film onto a GTCO manual digitizer (Rockville, Maryland) interfaced with a Hewlett-Packard 9836 computer (Palo Alto, California). The first 10 mV of the action potential foot was digitized, and its time constant was determined from a semilogarithmic plot of voltage and time.

Conduction velocity was determined from multiple microelectrode recordings made parallel to fiber orientation. Beginning approximately 2 mm from the stimulating electrode, sequential transmembrane recordings were made approximately every 0.5 mm for a total of 4–10 mm. Distances between recording sites were measured with an optical micrometer (resolution, 0.08 mm). The activation time of each point was determined as the time difference between the pacing stimulus artifact and the time of maximum rate of depolarization of the action potential recorded with the roving microelectrode.

Conduction velocity was determined from a plot of activation time and distance, and it was equal to the slope of the linear regression. These methods provided an average conduction velocity between the multiple points. Because the slope of the regression is used, the value obtained for conduction velocity is independent of stimulus latency. An r value of 0.97 or greater for the regression was considered acceptable and indicated uniform conduction in the area of interest. In these tissues, an extracellular unipolar electrogram was also recorded to confirm nondiscontinuous conduction.25 Tissues exhibiting nonuniform conduction (r<0.97 or notches in the unipolar electrogram) were excluded from the analyses.

Space constants were recorded by a previously described technique.24,26,27 A silver–silver chloride extracellular contact electrode catheter was positioned at one end of the tissue so that a monophasic action potential was recorded, indicating partial access to the intracellular space. Subthreshold rectangular-wave pulses (10–30 μA, 80 msec duration) were delivered by a constant current source between the silver–silver chloride electrode at the catheter tip and a distant bath ground. Four to 10 sequential transmembrane potentials were sampled at distances up to 2 mm from the wall of the contact electrode catheter. The signals were amplified by a differential electrometer (World Precision Instruments, New Haven, Connecticut) that measured the difference between the roving microelectrode and a reference microelectrode positioned in the bath within 1.0 mm of the recording microelectrode. During space-constant determinations, the tissues were paced at a cycle length of 1 second, and the current pulses were delivered after the impaled cell had undergone repolarization after the conducted beat. The electrotonic potentials were displayed on an oscilloscope, photographed on 35-mm film, and the amplitude of the potential was measured to the nearest 0.1 mV. The distance of the impulse from the contact electrode was determined with an optical micrometer (resolution, 0.08 mm). The space constant was calculated from a semilogarithmic plot of the steady-state electrotonic potential amplitude and distance, assuming an infinitely linear cable, and was defined as the distance at which the potential at the site of injection (V0) fell to a value of V0/e.

As in all multicellular preparations in which cable analysis has been applied, certain assumptions must be made, and therefore, any analysis provides only an approximation. In approaching cardiac muscle, a method that can deliver current to a large number of cells is important. The theoretical basis and justification for our method of space-constant determination has been described and is based upon the normal anisotropy of ventricular muscle.24–29 Clerc29 found a 9:1 difference in internal resistance between the longitudinal and transverse directions. He and others have attributed the anisotropy to more junctions per distance in the direction perpendicular to fiber orientation. Similarly, conduction from the superficial to deep fibers in our tissue preparations is transverse to fiber orientation.
In the present experiments, the large diameter of the contact electrode relative to fiber dimension ensured a uniform distribution of intracellular current among a large population of cells, and the anisotropic nature of the preparation offered a preferential pathway for current flow in one spatial dimension. Because all space-constant determinations were performed parallel to fiber orientation, the preferential path for current flow resulting from anisotropy may have accounted for the exponential falloff of voltage with distance and may provide a basis for assuming a one-dimensional cable in approximating the space constant. The finding that the space-constant determinations are little influenced by the absolute amount of subthreshold current injected is further support for the validity of the technique.27 Similarly, that the results of these, as well as previous experiments, fit the predicted analytical relations expected from cable analysis between the space constant, conduction velocity, and the action potential foot further suggest that these methods are justified in approximating determinants of conduction.24,27

A limitation to this method of determining the space constant lies in the inability to determine the exact ratio of intracellular to extracellular current to be delivered. The input resistance cannot be measured and therefore cannot be used to determine membrane resistance. Another problem is that the depolarizing responses used to measure the space constant may be associated with voltage-dependent active components, rectification of steady-state outward currents, and voltage-dependent, steady-state inward currents that may contribute to the subthreshold response. These factors will tend to cause a deviation from a purely exponential voltage drop with distance of the subthreshold response. Unfortunately, hyperpolarizing pulses are frequently accompanied by regenerative activation of the tissue at the current source and hence are not optimal to evaluate passive membrane properties either. Because of these issues, as well as the fact that the tissues from amiodarone-treated animals may be less sensitive to these factors because of their decreased excitability (due to the amiodarone), control tissue space constants were measured in tissues in which depolarizing or hyperpolarizing pulses were delivered. The results with these two techniques were not significantly different from each other, and hence, the data are presented together. Depolarizing pulses were used in the amiodarone-treated tissues. The required correlation coefficient

### Table 1. Action Potential Variables for Tissues From Control and Amiodarone-treated dogs

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Resting potential (mV)</th>
<th>Action potential amplitude (mV)</th>
<th>dV/dT (V/sec)</th>
<th>Action potential duration (msec)</th>
<th>Conduction velocity (m/sec)</th>
<th>Space constant (mm)</th>
<th>Tt (msec)</th>
</tr>
</thead>
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<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
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<td>97.7</td>
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<td>196.8</td>
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</tr>
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<td>226.3</td>
<td>0.50</td>
<td>1.45</td>
<td>1.21</td>
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<td>82.9</td>
<td>135.7</td>
<td>179.7</td>
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<td>...</td>
<td>1.11</td>
</tr>
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<td>102.2</td>
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<td>111.4</td>
<td>150.6</td>
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<td>0.61</td>
<td>1.00</td>
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<tr>
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<td>109.0</td>
<td>174.8</td>
<td>...</td>
<td>0.54</td>
<td>1.18</td>
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<tr>
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<td>113.3</td>
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<td>183.7</td>
<td>0.55</td>
<td>1.32</td>
<td>1.10</td>
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<td>181.5</td>
<td>0.60</td>
<td>1.06</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>91.2 ± 8.8</td>
<td>104.6 ± 10.3</td>
<td>152.2 ± 15.6</td>
<td>191.2 ± 21.3</td>
<td>0.56 ± 0.05</td>
<td>1.05 ± 0.25</td>
<td>0.98 ± 0.18</td>
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<tr>
<td>Amiodarone</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>87.5</td>
<td>94.8</td>
<td>164.9</td>
<td>160.8</td>
<td>0.49</td>
<td>0.87</td>
<td>1.16</td>
</tr>
<tr>
<td>2</td>
<td>80.8</td>
<td>98.9</td>
<td>182.5</td>
<td>174.8</td>
<td>0.45</td>
<td>0.85</td>
<td>0.94</td>
</tr>
<tr>
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<td>87.2</td>
<td>98.0</td>
<td>154.2</td>
<td>175.4</td>
<td>0.43</td>
<td>0.52</td>
<td>1.25</td>
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<tr>
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<td>92.6</td>
<td>125.0</td>
<td>256.8</td>
<td>0.68</td>
<td>1.16</td>
<td>1.22</td>
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<td>90.0</td>
<td>267.6</td>
<td>0.21</td>
<td>0.56</td>
<td>1.67</td>
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<tr>
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<td>96.6</td>
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<td>225.4</td>
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<tr>
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<td>89.0</td>
<td>100.0</td>
<td>242.2</td>
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<td>8</td>
<td>93.3</td>
<td>101.2</td>
<td>82.2</td>
<td>292.0</td>
<td>0.35</td>
<td>0.76</td>
<td>1.66</td>
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<tr>
<td>9</td>
<td>78.8</td>
<td>77.3</td>
<td>97.8</td>
<td>299.0</td>
<td>0.52</td>
<td>...</td>
<td>1.49</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>88.0 ± 8.7</td>
<td>91.7 ± 9.1</td>
<td>131.8 ± 41.8</td>
<td>232.7 ± 52.0</td>
<td>0.41 ± 0.15</td>
<td>0.69 ± 0.27</td>
<td>1.38 ± 0.25</td>
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<tr>
<td>p = NS</td>
<td>p &lt; 0.01</td>
<td>p = NS</td>
<td>p = 0.05</td>
<td>p &lt; 0.01</td>
<td>p = 0.01</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>
for the regression of the exponential voltage drop with distance was 0.9 or greater to ensure that any error introduced by these factors was small. Nevertheless, our measurements can yield only an approximation of the tissue space constant.

**Statistical Methods**

All tabular data are expressed as mean±SD. Variable means were compared by unpaired *t* tests. Linear fits were made with linear regression techniques. Exponential fits were made by linear regression of the logarithmic transform of the data. A *p* value less than or equal to 0.05 was considered significant for these determinations.

**Results**

**Action Potential Characteristics**

Table 1 contains the action potential variables for tissues from control and amiodarone-treated dogs. During pacing at a cycle length of 1,000 msec, amiodarone treatment was associated with a significant reduction in mean action potential amplitude (91.7±9.1 vs. 104.6±10.3 mV, *p*<0.01) and a significant prolongation of action potential duration (232.7±52.0 vs. 191.2±21.3 msec, *p*<0.05). In contrast, the trend toward a reduction in dV/dT was not significant (131.8±41.8 vs. 152±15.6 V/sec). Similarly, there was no difference in resting membrane potential between tissues from amiodarone-treated or control dogs (88.7±8.7 vs. 91.2±8.8 mV).

Conduction velocity was reduced in tissues from amiodarone-treated dogs. Figure 1 shows examples of conduction velocity plots for a tissue from control and a tissue from an amiodarone-treated animal. Note that the relation between activation time and distance was linear in each case (*r*²=0.99), which indicates uniform conduction over the distance sampled. Conduction velocity, determined as the slope of the best fit linear regression of activation time and distance from the stimulating electrodes, was lower in the tissue from the amiodarone-treated animal (0.21 vs. 0.61 m/sec). The measured conduction velocities for each tissue are shown in Table 1. There was a significant difference in mean conduction velocity in tissues from the amiodarone-treated animals compared with that measured in normal, control tissues (0.41±0.15 vs. 0.56±0.05 m/sec, *p*<0.01).

Figure 2 shows semilogarithmic plots of the steady-state amplitude of the subthreshold depolarization and distance for tissues from an amiodarone-treated and a control dog. The falloff of amplitude with distance of the subthreshold depolarization was greater in the tissue from the amiodarone-treated animals compared with tissue from control animals. The measured space constant in the amiodarone-treated tissue was 0.52 mm, whereas the space constant in the normal tissue was 0.93 mm. Table 1 contains the space constants from 11 normal and eight amiodarone-treated tissues. The mean space constant measured in the amiodarone-treated tissues was significantly less than that measured in control tissues (0.69±0.27 vs. 1.05±0.26 mm; *p*<0.01).

**Determinants of Slow Conduction**

To examine the determinants of slow conduction in amiodarone-treated tissues, the statistical relations demonstrated in earlier studies, as well as those relations predicted with one-dimensional cable models between conduction velocity and action potential variables, or the space constant, were studied, Equation 1 is the relation developed by Tasaki and Hagiwara:30


\[ \theta = \lambda \left( T_{\text{foot}} T_{\text{m}} \right)^{1/2} \]  

(1)

where \( \theta \) is conduction velocity, \( \lambda \) is space constant, \( T_{\text{foot}} \) is time constant of the action potential foot, and \( T_{\text{m}} \) is membrane time constant. This equation predicts a linear relation between conduction velocity and the space constant. Similarly, Equation 2 is the approximation of Hunter et al\(^1\):

\[ \theta = \left( \frac{a}{C_{\text{m}} R_{\text{i}}} \right) \left( \frac{V_{\text{max}}}{V_{\text{p}}} \right) \]  

(2)

where \( \theta \) is conduction velocity, \( a \) is fiber radius, \( C_{\text{m}} \) is specific capacitance of the membrane, \( R_{\text{i}} \) is specific internal axial resistance, \( V_{\text{max}} \) is maximal rate of rise of the action potential upstroke, and \( V_{\text{p}} \) is actional potential amplitude. This equation predicts a linear relation between conduction velocity and the square root of the maximal rate of depolarization of the action potential upstroke and the inverse of the square root of the action potential amplitude. These relations, which are predicted from one-dimensional cable theory, have been demonstrated also in earlier experiments with multicellular myocardial preparations such as those used in these experiments.\(^{24,27,32}\)

Although there was a wide range for the measured space constant in the amiodarone-treated tissues, there was a significant linear relation between the space constant and conduction velocity (Figure 3). The equation for this regression was

\[ \theta = 0.06 + 0.49 \lambda \]  

(3)

\( r = 0.85, \ p < 0.01 \): where \( \theta \) is conduction velocity, and \( \lambda \) is space constant. Conversely, no relation was found between conduction velocity and the square root of the maximal rate of upstroke velocity or between conduction velocity and the inverse of the square root of action potential amplitude.

In a multivariate model, including each of the three independent variables, that is, the space constant \( \lambda \), the square root of the maximal rate of upstroke velocity \( (V_{\text{max}}) \), and the square root of action potential amplitude \( (V_{\text{p}}) \), conduction velocity was appropriately predicted. The equation for this regression was

\[ \theta = 0.34 + 0.23 \left( V_{\text{max}} \right)^{1/2} - 4.99 \left( V_{\text{p}} \right)^{-1/2} + 0.45 \lambda \]  

(4)

\( F = 8.24; \ r = 0.93; \ p < 0.05 \). This partial multivariate analysis confirmed that the only independent predictor of conduction velocity was the space constant \( (p < 0.02) \). In contrast, changes in conduction velocity in these experiments were independent of changes in the maximal rate of upstroke velocity \( (p = 0.24) \) and in action potential amplitude \( (p = 0.57) \). These data suggest that the decrement in conduction in the amiodarone-treated tissues was largely due to the decreased space constant. The small decreases in action potential amplitude and the maximal rate of upstroke velocity (probably reflecting changes in sodium channel activity) did not play a significant role in the decreased conduction velocity.

**Discussion**

The major finding in this study is that long-term amiodarone administration is associated with a depression of the space constant. This decrease in the space constant accounted in large part for the measured decrease in conduction velocity. In contrast, only minor changes in action potential amplitude and the maximal rate of upstroke velocity were noted.

Amiodarone has been shown to exert several electrophysiological effects. It has long been known that amiodarone treatment leads to prolongation of repolarization.\(^12\) Amiodarone administration has been associated with prolongation of action potential duration in vitro and of the QT interval and monophasic action potential duration in vivo. The antiarrhythmic effects of amiodarone were originally attributed to these alterations in repolarization. Recently, it has been demonstrated that amiodarone has effects on myocardial conduction as well.\(^18\) Amiodarone’s depression of conduction velocity has been attributed to sodium channel blockage.\(^13\) The reductions in both action potential amplitude and maximal rate of upstroke velocity are consistent with amiodarone-induced sodium channel blockade (Table 1). The amiodarone-induced reduction of the maximal rate of upstroke velocity measured, however, was not statistically significant in our nonischemic preparations that were paced at a cycle length of 1,000 msec. The analysis was limited, however, by small sample size and the large variance in the determinations; the \( \beta \) error was 0.36. Conversely, if the reductions in measured conduction velocity were due entirely to the decrease in the maximal rate of upstroke velocity, then Equation 2 predicts that the mean value of the maximal rate of upstroke velocity would be 81 V/sec. Given 1) the assumption that the control group mean is representative, 2) that the pooled variance is 878, and 3) that the significance level (\( \alpha \)
is 0.05, the power or probability of detecting a difference in dV/dT that would be physiologically significant (i.e., a change from control to the predicted mean of 81 V/sec) is greater than 0.9999. Hence, it is highly unlikely even given our small sample size to have missed an amiodarone-induced change in the maximal rate of upstroke velocity large enough to account for the reduction in conduction velocity ($\beta$ error < 0.0001). Furthermore, in the univariate and multivariate analyses of the determinants of conduction in the amiodarone-treated tissues, neither the maximal rate of upstroke velocity nor action potential amplitude was an independent predictor of conduction velocity. Thus, even if the amiodarone-induced trend toward the reduction in the maximal rate of upstroke velocity had reached statistical significance, it would be highly unlikely to account for the decrease in the measured conduction velocity. These data imply, therefore, that although sodium channel blockade may be important in explaining some of the use-dependent properties of amiodarone\textsuperscript{13–15} as well as effects in injured or ischemic myocardium, sodium channel blockade does not explain the depression in conduction velocity during resting, stable conditions.

Myocardial conduction velocity is determined, in part, by passive membrane properties. Alterations in these properties may therefore account for changes in conduction velocity. We could not directly measure the membrane time constant in our experiments; however, the increase in time constant of the foot of the action potential may reflect an effect of amiodarone on that variable. Though we could not measure membrane resistance or axial resistance, we could, however, estimate the overall effectiveness of cell coupling by measuring the falloff of voltage with distance of a subthreshold potential and by calculating the tissue space constant (Figure 2). The space constant in the amiodarone-treated tissues was significantly decreased compared with that in the normal, control tissues (Table 1).

As predicted from one-dimensional cable theory, the decline in conduction velocity was closely correlated with that of the space constant (Figure 3). In addition, in the multivariate analysis, only the space constant proved to be an independent predictor of conduction velocity. Thus, the depression in conduction velocity in our tissues was accounted for by changes in the space constant and not by the relatively small changes in sodium channel–mediated action potential amplitude and maximal rate of upstroke velocity.

Although we have shown that the space constant is reduced in amiodarone-treated tissues, we have not delineated a mechanism. Equation 5 shows the relation between the space constant and internal cellular, membrane, and extracellular resistance:

$$\lambda^2 = r_m / (r_i + r_o)$$

where $\lambda$ is space constant, $r_m$ is membrane resistance, $r_i$ is internal axial resistance, and $r_o$ is resistance of the extracellular space. A decrease in the space constant could be due to a decrease in membrane resistance or to an increase in internal axial resistance and resistance of the extracellular space. Unfortunately, we were unable to measure the input resistance in our experiments and, therefore, could not determine which of these factors contributed to the reduced space constant. In addition, resistance of the extracellular space may be increased by amiodarone deposition in the interstitial space. Finally, amiodarone may become incorporated into the cell membrane and affect passive current flow.

Other factors, such as voltage-dependent active components, rectification of steady-state inward currents, and voltage-dependent outward currents may also contribute to subthreshold responses. These factors tend to cause a deviation from the purely exponential relation between voltage drop and distance of the subthreshold response. That the correlation coefficients for the exponential relation between voltage drop and distance were close to unity ($r\geq 0.90$) suggests that these factors were of minor significance. Similarly, complex interactions caused by changes in intercellular resistance in anisotropic myocardium must also be considered in evaluating the factors relating the space constant and conduction velocity in our tissues.

The findings of this study are clinically relevant. Reentrant tachyarrhythmias are dependent upon a myocardial substrate that exhibits areas of slow conduction and block. Slow conduction in ischemic, sublethally ischemic, or recently infarcted myocardium stems not only from a depression in action potential amplitude and maximum rate of upstroke velocity (sodium channel–mediated phenomena) but also from cell-to-cell electrical uncoupling.\textsuperscript{24,27,33} Under these circumstances, agents affecting myocardial conduction through either sodium channel blockade or cell-to-cell coupling may be effective antiarrhythmics because affecting either abnormal mechanism should lead to more pronounced slowing of conduction. Conventional antiarrhythmic agents, which are often effective clinically in the setting of acute infarction or infarction, further depress conduction through sodium channel blockade, and, thereby, may interrupt reentry by this effect. Most of these agents, however, are relatively ineffective in managing severe, life-threatening ventricular tachyarrhythmias that arise from a substrate of chronic scar.

Recent experimental studies indicate a basis for this relative resistance of tachyarrhythmias in chronic infarction to conventional sodium channel blockers. As canine infarcts age, action potential characteristics (sodium channel–mediated phenomena) have been shown to normalize even though slow inhomogeneous conduction and fractionated electrograms persist.\textsuperscript{34} The slow conduction in these
experimental infarcts has been attributed to cell-to-cell electrical uncoupling due to the interposition of collagen between islands of surviving, normal myocardium.27 If slow conduction and reentrant tachyarrhythmias are dependent upon a myocardial substrate that exhibits abnormal cell-to-cell coupling but normal sodium channel-mediated characteristics (action potential amplitude and maximum rate of upstroke velocity), it follows that agents aimed at the “weak link” of conduction (cell-to-cell coupling) may be more effective antiarrhythmic agents. Our experiments demonstrate that one of amiodarone’s primary mechanisms is to depress overall axial resistance as indexed by a reduced space constant. This hypothesis, therefore, is consistent with the clinical findings of relative efficacy of sodium channel blockers in patients with acute ischemic syndromes. More importantly, this hypothesis helps to explain not only the relative inefficacy of conventional antiarrhythmic agents but also the marked effects of amiodarone in the treatment of clinical tachyarrhythmias in patients with chronic myocardial scar.

It should be noted, however, that the effect on the space constant described in this study is not the only potential mechanism of antiarrhythmic action of amiodarone. For example, at faster heart rates, amiodarone-induced sodium channel blockade and, hence, depression of myocardial conduction will likely be enhanced. In addition, amiodarone also affects myocardial refractoriness. Furthermore, as noted, the presence of acute or subacute ischemia may be associated with action potential changes as well as changes in overall axial resistance. Thus, the interactions of the drug and myocardial substrate are likely complex, and all may influence the efficacy of the agent. Nevertheless, that long-term amiodarone therapy leads to a decrease in the space constant may explain its unique antiarrhythmic effects in patients with refractory ventricular arrhythmia arising from a substrate of chronically scarred myocardium.

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