The Effects of Antiarrhythmic Drugs, Stimulation Frequency, and Potassium-Induced Resting Membrane Potential Changes on Conduction Velocity and $dV/dt_{\text{max}}$ in Guinea Pig Myocardium

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SUMMARY. For one-dimensional propagation, a nonlinear relationship between $V_{\text{max}}$ and conduction velocity is predicted by cable theory, and, under experimental conditions, $V_{\text{max}}$ and conduction velocity may change in opposite directions. Using standard microelectrode techniques, we have measured $V_{\text{max}}$ and conduction velocity in guinea pig papillary muscles exposed to tetrodotoxin and low sodium (agents expected primarily to decrease, directly, the rapid inward current), increased extracellular potassium (an agent which decreases the rapid inward current at least partially by inactivation mediated by depolarization of the resting membrane potential), and, over a wide range of stimulation frequencies, the antiarrhythmic drugs, quinidine, lidocaine, and procainamide. In all cases, except for the region of potassium-induced "supernormal conduction" between 5.4 and 9 mM, $V_{\text{max}}$ and conduction velocity varied as predicted by one-dimensional cable theory; that is, changes in $V_{\text{max}}$ were always proportional to changes in the square of conduction velocity. We conclude that the relationship between $V_{\text{max}}$ and conduction velocity predicted by cable theory occurs experimentally in guinea pig papillary muscle subjected to commonly used antiarrhythmic drugs and other interventions expected to reduce the sodium inward current. This relationship may be useful in applying known effects of drugs on $V_{\text{max}}$ to action potential propagation. (Circ Res 56: 696-703, 1985)

A MAJOR factor affecting the propagation of the cardiac impulse is the magnitude of the rapid sodium-dependent inward current. A decrease in this current would be expected to decrease both the maximum rate of rise of the action potential upstroke ($V_{\text{max}}$) and conduction velocity. Because $V_{\text{max}}$ can be measured under conditions of action potential propagation, models for the effects of agents modifying the sodium current have been constructed which utilize the known effects of these agents on $V_{\text{max}}$. In addition, it has been assumed that the effects of antiarrhythmic drugs on conduction correlate directly with their effects on $V_{\text{max}}$. In spite of these assumptions, it appears likely that neither the relationship between the sodium current and $V_{\text{max}}$ (Cohen and Strichartz, 1977; Bean et al., 1982, 1983; Cohen et al., 1984) nor the relationship between $V_{\text{max}}$ and conduction velocity (Hunter et al., 1975, Buchanan et al., 1982; Walton and Fozzard, 1983a, 1983b) is linear. There are even examples of conduction velocity increases in the presence of a decrease in $V_{\text{max}}$ (Dominguez and Fozzard, 1970; Spear and Moore, 1974; Peon et al., 1978; Saito et al., 1978).

The cable equation for constant conduction velocity is $a^2 \frac{d^2 V}{2R \theta^2 dt^2} = C \frac{dV}{dt} + I_e$.

where $a$ is the radius, $R$ is the specific resistivity of the intracellular fluid, $\theta$ is conduction velocity, $V$ is the membrane potential, $C$ is the membrane capacitance per unit area, $I_e$ represents the sum of the instantaneous ionic currents per unit area of membrane, and $t$ represents time. Although this equation must generally be solved numerically, a number of investigators have found that $dV/dt$ varies approximately as $\theta^2$, particularly for mathematical simulations which result in variations of the rapid sodium inward current (Hunter et al., 1975; Jack et al., 1975; Walton and Fozzard, 1983b).

The purpose of the present study was to determine whether commonly used antiarrhythmic drugs altered $V_{\text{max}}$ and conduction velocity in ventricular muscle in a predictable fashion. To be more certain that the observed changes in $V_{\text{max}}$ and conduction velocity were mediated by changes in the sodium inward current, and were not just a fortuitous combination of other factors, we varied the sodium current by other well-established mechanisms, including blockade with tetrodotoxin, changing the chemical gradient for sodium by decreasing extracellular sodium concentration, and changing the electrical driving force for the rapid sodium-dependent inward current by depolarization with potassium.

We utilized guinea pig papillary muscles because suitably selected preparations have demonstrated one-dimensional propagation (Weidmann, 1970;
Sodium (substituted with tetramethylammonium chloride) greater than 30 minutes. In separate experiments, the measurement of interelectrode distance. Pilot studies showed that 10-15 minutes of exposure were necessary to obtain steady state conditions. Thus, all data reported in abstract form (Saito et al., 1978; Buchanan et al., 1982; Buchanan and Gettes, 1983).

Methods

Guinea pig right ventricular papillary muscles were placed in a 3-ml chamber and superfused (2.5-3.0 ml/min) with control Tyrode’s solution containing (mm) NaCl, 137; KCl, 5.4; CaCl2, 1.8; MgCl2, 1.05; NaHCO3, 24.0; NaH2PO4, 0.42; and glucose, 5.0. The solution was gassed with 95% O2 and 5% CO2, the pH maintained between 7.35 and 7.4, and the bath temperature maintained at 37° ± 0.5°C. Suitable fibers were characterized by a lack of visible branching, by a diameter of 1.5 mm or less, and by a length at least 5 times the diameter. In most experiments, bipolar silver/silver chloride electrodes were used to stimulate the preparation at the cut end. In a few experiments, stimulation was obtained with a bipolar KCl-filled glass macroelectrode constructed by fusing two pieces of 1-mm glass tubing, pulled slightly by hand over a flame. A silver wire then was inserted into the shank of each pole of the electrode and chlorided. The type of stimulation electrode used appeared to have no effect on the results. Two separate microelectrode impalements were made in a line along the long axis of the preparation, and a common reference electrode was used. The signals obtained were amplified by negative capacitance compensation amplifiers (WP Instruments M-707 or Transidyne MPA-6), displayed on a storage oscilloscope (Tektronix 5113), and photographed by a Polaroid camera. Capacitance compensation was adjusted to provide the best reproduction of a 10-mV square wave attached to the input with the electrodes in the bath. In most cases, this corresponded to the maximum compensation which could be obtained without inducing oscillation. The signals were also sent to identical electronic differentiators which corresponded to the maximum compensation which could be obtained without inducing oscillation. The signals were also sent to identical electronic differentiators which produced a linear response to beyond 500 V/sec. Conduction rate was defined as the time between the peaks of the differentiated upstroke signals. We required that both impalements be maintained throughout an intervention and its control, in order to avoid inaccuracies in the measurement of interelectrode distance. Pilot studies showed that 10-15 minutes of exposure were necessary to obtain steady state conditions. Thus, all data reported were obtained at least 20 minutes after any change of the superfusing solution. In most cases, the time interval was greater than 30 minutes. In separate experiments, the following interventions were made: (1) various concentrations of tetrodotoxin (n = 5), (2) decreased extracellular sodium (substituted with tetramethylammonium chloride) (n = 2), (3) varying extracellular potassium (n = 16), (4) various concentrations of lidocaine (n = 6), (5) various concentrations of quinidine (n = 4), and (6) various concentrations of procainamide (n = 3).

The potassium variation was obtained by adding measured amounts from a 500 mM KCl/Tyrode’s stock solution to the perfusate. Osmotic compensation was not attempted. In two quinidine experiments, in two lidocaine experiments, and in two procainamide experiments, the stimulation frequency was varied between 0.1 and either 5 or 8 Hz at each drug concentration. In the experiments in which stimulation frequency was not varied, the driving rate was 0.5 Hz.

Presentation of Data and Statistics

For each experiment and group of experiments, Vmax and the square of conduction velocity were normalized to their values at the slowest stimulation frequency tested during perfusion with the control solution. In each figure, the solid line represents the relationship that would be obtained were Vmax proportional to the square of conduction velocity. The normalized results were plotted and a linear regression was performed. In addition, a t-test was performed to test the confidence with which each set of points actually describes the regression line obtained. Although Figures 6–8 show multiple panels for clarity, linear
Results
Effects of Tetrodotoxin and Decreased Extracellular Sodium Concentration on $V_{\text{max}}$ and Conduction Velocity

Figure 1 shows the effect of various concentrations of the sodium channel blocker, tetrodotoxin, on $V_{\text{max}}$ and conduction. In panel A, $V_{\text{max}}$ is plotted against conduction velocity, obtained by dividing the interelectrode spacing in millimeters by the conduction time in milliseconds. In panel B, and in subsequent figures, $V_{\text{max}}$ and conduction velocity are normalized to the values obtained under control conditions, and the square of conduction velocity is plotted on the abscissa. In this and the following figures, the solid line represents the relationship which would be obtained if $V_{\text{max}}$ were proportional to the square of conduction velocity. The figure shows that tetrodotoxin induces changes in $V_{\text{max}}$ which are proportional to the square of the changes in conduction velocity. Similar results were obtained in three other experiments.

Figure 2 shows the results of substituting tetramethylammonium chloride (Walton and Fozzard, 1983a), mole for mole for extracellular sodium, in order to decrease the sodium current by changing the transmembrane concentration gradient for sodium. Similar results were obtained in one other experiment. Also shown is our plot of mean data obtained by Walton and Fozzard (1983a, 1983b) when several similar experiments were performed with sheep Purkinje fibers. The data for each intervention are well represented by the relationship that changes in $V_{\text{max}}$ are proportional to the square of changes in conduction velocity.

**Effects of Variations in Extracellular Potassium on $V_{\text{max}}$ and Conduction Velocity**

Table 1 shows the average results of 16 experiments in which $V_{\text{max}}$ and conduction velocity were measured as extracellular potassium was raised in steps from 5.4 to 15 mM, and lowered to 2.0 mM. Figure 3 shows the results from a typical experiment. In panel A, data are normalized to 5.4 mM potassium. Increasing potassium first speeds, then slows, conduction, in spite of a consistent decrease in $V_{\text{max}}$. In panel B, when the data are normalized to the point of maximum conduction velocity (8 mM potassium), values obtained from 8 to 15 mM are in excellent agreement with the relationship of $V_{\text{max}}$ proportional to the square of conduction velocity. As has been shown previously (Gettes et al., 1985), similar results are seen when the average data from all 16 experiments are used (intercept 0.016, slope 1.03, $r = 0.958$, $P < 0.001$). In the experiment shown in Figure 4, conduction velocity and $V_{\text{max}}$ were first measured

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Effects of Potassium on $V_{\text{max}}$ and Conduction Velocity in Guinea Pig Papillary Muscles</strong></td>
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<tr>
<th>Potassium (mM)</th>
<th>$n$</th>
<th>RMP (mV)</th>
<th>$V_{\text{max}}$ (V/sec)</th>
<th>$V_{\text{max}}$ (%)</th>
<th>Conduction velocity (%)</th>
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<tbody>
<tr>
<td>2.0</td>
<td>4</td>
<td>$-99.6\pm 2.3$</td>
<td>273.0$\pm 29.6$</td>
<td>$98.7\pm 1.5$</td>
<td>88.0$\pm 3.1$</td>
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<tr>
<td>5.4</td>
<td>16</td>
<td>$-86.2\pm 1.8$</td>
<td>277.5$\pm 35.0$</td>
<td>100</td>
<td>100</td>
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<tr>
<td>7</td>
<td>7</td>
<td>$-80.4\pm 2.1$</td>
<td>276.7$\pm 27.6$</td>
<td>99.7$\pm 2.1$</td>
<td>105.9$\pm 5.5$</td>
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<tr>
<td>8</td>
<td>5</td>
<td>$-76.7\pm 2.4$</td>
<td>248.2$\pm 45.0$</td>
<td>89.4$\pm 3.3$</td>
<td>113.7$\pm 6.8$</td>
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<tr>
<td>9</td>
<td>7</td>
<td>$-72.8\pm 1.9$</td>
<td>247.4$\pm 22.3$</td>
<td>89.2$\pm 5.0$</td>
<td>107.5$\pm 5.1$</td>
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<tr>
<td>10</td>
<td>7</td>
<td>$-71.1\pm 3.0$</td>
<td>233.0$\pm 46.9$</td>
<td>80.3$\pm 6.8$</td>
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<td>3</td>
<td>$-57.1\pm 1.9$</td>
<td>65.2$\pm 16.8$</td>
<td>23.5$\pm 1.4$</td>
<td>66.1$\pm 9.7$</td>
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at six potassium levels between 5.4 and 15 mM. The extracellular potassium was then maintained at 10 mM, and six concentrations of tetrodotoxin were added to the test solution (points (B–G). The figure shows that the changes in $V_{\text{max}}$ and conduction velocity fit the predicted relationship in both situations.

**Effects of Various Concentrations of Antiarrhythmic Drugs on $V_{\text{max}}$ and Conduction Velocity**

Figure 5 shows the effects of various concentrations of quinidine and lidocaine on $V_{\text{max}}$ and conduction velocity at a constant stimulation frequency of 0.5 Hz. Within the range tested, increasing concentrations of these drugs produce changes in $V_{\text{max}}$ and conduction velocity which fit the predicted relationship.

Figures 6, 7, and 8 show the effects of several concentrations of lidocaine, quinidine, and procainamide, respectively, on $V_{\text{max}}$ and the square of conduction velocity over a wide range of stimulation frequencies. Within each figure, all data are normalized to 0.1 Hz without drug. Each concentration of drug is displayed in a separate panel for clarity. The figures show that the changes in $V_{\text{max}}$ are proportional to the square of changes in conduction velocity for all drugs at all tested stimulation frequencies. Similar results were obtained in each of two other experiments, for lidocaine and quinidine, and in one other experiment for procainamide, where both stimulation frequency and drug concentration were varied.

**Discussion**

It is generally accepted that, in tissues in which the rapid sodium inward current predominates, a decrease in this current will lead to some decrease in the maximum rate of rise of the action potential upstroke ($V_{\text{max}}$), and, although this relationship may not be linear (Cohen and Strichartz, 1977; Bean et al., 1982, 1983, 1984), the effects on $V_{\text{max}}$ of agents that block the sodium inward current have been used to construct models of drug action (Hondeghem and Katzung, 1977, 1980). Whereas there has been a tacit assumption that decreases in $V_{\text{max}}$ relate to decreases in conduction velocity, this relationship also need not be linear, and, in fact, experimental evidence (Walton and Fozzard 1983a, 1983b), as well as conventional cable theory (Hunter et al., 1975; Jack et al., 1975), predict that it is not. In addition, effects such as "supernormal conduction," which has been observed in the presence of a decrease in $V_{\text{max}}$ (Dominguez and Fozzard, 1970; Spear and Moore, 1974), demonstrate that, under some circumstances, there is not a direct relationship between $V_{\text{max}}$ and conduction velocity.

One-dimensional cable theory predicts that $V_{\text{max}}$ should be approximately proportional to the square of conduction velocity (Hunter et al., 1975; Walton
FIGURE 5. Effects of four concentrations of quinidine and three concentrations of lidocaine on \(V_{max}\) and conduction velocity measured at a stimulation frequency of 0.5 Hz. Note that changes in \(V_{max}\) and conduction velocity are consistent with the predicted relationship for quinidine: intercept -0.06, slope 1.08, \(r = 0.991\), \(P < 0.001\); for lidocaine: intercept -0.11, slope 1.13, \(r = 0.978\), \(P < 0.001\).

FIGURE 6. Stimulus frequency-dependent effects of three concentrations of lidocaine on \(V_{max}\) and conduction velocity. All panels are normalized to 0.1 Hz without drug. Although both frequency-dependent and steady state effects of lidocaine are seen, all changes are consistent with the prediction that \(V_{max}\) is proportional to the square of conduction velocity (intercept 0.020, slope 0.968, \(r = 0.984\), \(P < 0.001\)).

FIGURE 7. Stimulus frequency-dependent effects of four concentrations of quinidine on \(V_{max}\) and conduction velocity. All panels are normalized to 0.1 Hz without drug, and the control is shown in the inset. Note that both steady state and stimulus frequency-dependent changes in \(V_{max}\) and conduction velocity are consistent with the predicted relationship (intercept -0.023, slope 1.02, \(r = 0.996\), \(P < 0.001\)).

and Fozzard, 1983b). Using a ventricular muscle preparation which can be considered to show one-dimensional propagation (Weidmann, 1970; Spach et al., 1981; Buchanan, et al., 1983; Veenstra et al., 1984), we found the decrease in \(V_{max}\) to be proportional to the square of the decrease in conduction velocity in the presence of tetrodotoxin, a known sodium channel-blocking agent. Varying the sodium current by a different mechanism (i.e., modification of the driving force for sodium by decreasing its extracellular concentration) causes changes in \(V_{max}\) and conduction which also fit the theoretical relationship, not only in muscle, but also in Purkinje fibers (Walton and Fozzard, 1983b).

We confirmed the biphasic relationship of increasing extracellular potassium to first accelerate and then slow conduction velocity in spite of a constant decrease in \(V_{max}\) (Kagiyama et al., 1982). However, beyond the point of maximum velocity, the cable theory-predicted relationship between \(V_{max}\) and con-
To determine, in addition, whether the effects of potassium above the region of supernormal conduction are consistent with a decrease in the sodium inward current, we compared the effects of potassium depolarization on \( V_{\text{max}} \) and conduction with those induced by tetrodotoxin, administered at the potassium level that showed the maximum conduction speeding. Under these conditions, the administration of either more potassium or TTX produced results consistent with the predicted relationship between \( V_{\text{max}} \) and conduction velocity.

Over the ranges tested, both the steady state (constant slow stimulation frequency) and stimulation frequency-dependent effects of lidocaine, quinidine, and procainamide are well fit by the relationship that changes in \( V_{\text{max}} \) are proportional to the square of changes in conduction velocity. Differences in the steady state and time (rate)-dependent characteristics of the individual drugs are seen in our results, and correspond to differences previously reported (Chen and Gettes, 1976; Hondeghem and Katzung, 1980).

As can be seen in the control panels of Figures 6–8, variations in stimulus frequency alone often caused variations in \( V_{\text{max}} \) and conduction velocity that appeared to fit the predicted relationship. Possible mechanisms for this effect include the time dependence of recovery from sodium current inactivation, a change in the electrical gradient due to slight membrane depolarization caused by an extracellular accumulation of potassium at rapid frequencies, or a change in the sodium concentration gradient due to the intracellular accumulation of sodium. In addition, it is quite possible that some of our interventions themselves result in the intracellular accumulation of sodium. All of these mechanisms involve direct modulation of the sodium inward current which would add to any effect of pharmacological channel blockade.

Models describing action potential propagation in one-dimensional cables have been constructed (Cooley and Dodge, 1966; Hunter et al., 1975; Sharp and Joyner, 1980), and progress is being made toward extending these models to realistic situations including three-dimensional propagation (Joyner et al., 1983). Since many of the assumptions inherent in these models have not been tested extensively, and some may be untestable by current experimental techniques, perhaps the results we have presented should be considered only as empirical observations of the effects of specific interventions on \( V_{\text{max}} \) and conduction velocity. On the other hand, even though we varied the sodium current by several different mechanisms, our results are well described by predictions of the most simple of models.

Recently, Walton and Fozzard (1983b) compared three different models for the action potential upstroke to their experimental observations concerning the effects of decreased extracellular sodium on action potential propagation in sheep Purkinje fi-

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**FIGURE 8.** Stimulus frequency-dependent effects of procainamide on \( V_{\text{max}} \) and conduction velocity. All panels are normalized to 0.1 Hz without drug. Note that, in spite of high drug concentrations, compared to the quinidine and lidocaine experiments, no change in \( V_{\text{max}} \) or conduction velocity was seen at the slowest stimulation frequency. Frequency-dependent effects are clearly seen. In all cases, the results are consistent with the relationship that \( V_{\text{max}} \) is proportional to the square of conduction velocity (intercept 0.014, slope 0.977, r 0.990, P < 0.001).
bers. They found that the relationship between $V_{\text{max}}$ and conduction velocity, as well as a number of other relationships, were model independent and arose from the cable theory relationships upon which all the models were based. Their results regarding $V_{\text{max}}$ and conduction velocity are completely consistent with our own. The true complexity needed to adequately describe action potential propagation in various excitable tissues under the influence of important interventions will be determined only by further experimental observations and further mathematical simulations.

In spite of these unresolved theoretical considerations, our results indicate that, at least under the conditions of our experiments, information concerning the effects on action potential propagation in guinea pig papillary muscle of agents which primarily affect the sodium inward current can be inferred from a knowledge of the effects of these agents on $V_{\text{max}}$ provided the squared relationship between the two is approximated. Although the results of Bean et al. (1982, 1983) and Cohen et al. (1984) regarding the nonlinearity of the sodium current/$V_{\text{max}}$ relationship were determined in rabbit Purkinje fibers at non-physiological temperatures, their results, combined with our own, may provide a useful qualitative model of the effect of sodium channel blockade on impulse propagation. If their results are ultimately shown to be correct for guinea pig papillary muscle under physiological conditions, an 80% reduction in available gNa would produce about a 35% reduction in $V_{\text{max}}$ which would be associated with less than a 15% reduction in conduction velocity. An understanding of the $V_{\text{max}}$/conduction velocity relationship, as well as the sodium channel/$V_{\text{max}}$ relationship, may provide a link between models of sodium channel blockade at the cellular level and action potential propagation in cable-like structures and, ultimately, in the intact heart.

References


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