Combined Effects of Rate, Membrane Potential, and Drugs on Maximum Rate of Rise ($V_{max}$) of Action Potential Upstroke of Guinea Pig Papillary Muscle

CHIA-MAOU CHEN, M.D., LEONARD S. GETTES, M.D.

SUMMARY We studied the effect of increasing the rate of stimulation on the maximum rate of rise of the action potential upstroke ($V_{max}$) in guinea pig papillary muscles at various resting membrane potentials and after the addition of quinidine and lidocaine to the perfusate. Increasing rate caused a decrease in $V_{max}$ due to interaction of three factors: (1) a metabolic factor, presumably resetting of the Na-K pump, which caused a decrease in $V_{max}$ at all levels of resting potential between -90 and -60 mV, (2) a transient decrease in resting potential which influenced $V_{max}$ when the resting potential was less negative than approximately -80 mV, and (3) the recovery characteristics of $V_{max}$, which contributed to the decrease in this variable when rate was faster than 5/sec. As a result of these factors the steady state curve relating membrane potential to $V_{max}$ was itself rate-dependent. Lidocaine and quinidine exaggerated the rate-dependent decrease in $V_{max}$; however, their effects differed. The effect of quinidine was consistent with its known depressant effect on the Na-K pump. The lidocaine effect was consistent with a slowing of recovery of $V_{max}$. Our results help to explain the effects of an increase in rate on $V_{max}$ and conduction velocity in normal, partially depolarized, and drug-treated fibers.

AN INCREASE in driving rate causes a slight decrease in the maximum rate of rise ($V_{max}$) of the action potential upstroke of sinus node, atrial, Purkinje, and ventricular fibers. This rate-dependent effect has been attributed to some* to a decrease in resting potential, and by others to incomplete reactivation of the sodium system or to a resetting of the sodium-potassium pump. It also has been shown that quinidine and lidocaine exaggerate the rate-dependent decrease in upstroke velocity. However, the mechanisms underlying the drug effects have not been clarified. Previous studies indicated that the time constant of recovery of $V_{max}$ was voltage-dependent and became progressively longer as the resting membrane potential was decreased. This result suggested to us that the magnitude of the rate-dependent decrease in $V_{max}$ might depend on the resting membrane potential. In addition, we recently have shown that quinidine did not alter, whereas lidocaine prolonged, the recovery characteristics of $V_{max}$. This result suggested that the influence of quinidine and lidocaine on the rate-dependent change might differ. We regarded these possibilities as of more than academic importance because of the known relationship between $V_{max}$ and conduction velocity and the importance of slow conduction in the pathogenesis of reentrant arrhythmias.

This study was designed to explore these possibilities and to gain a clearer understanding of the contribution of the various postulated factors to a rate-induced change in $V_{max}$.

Methods

The methods used for this study have been described recently. Transmembrane action potentials were recorded through standard 3 M KCl-filled microelectrodes from guinea pig right ventricular papillary muscles mounted in a three-compartmented bath. The proximal (test) and distal compartments were perfused with Tyrode's solution gassed with 95% O$_2$ and 5% CO$_2$ and having the following composition (mM): NaCl, 137; KCl, 5.4; CaCl$_2$, 1.8; MgCl$_2$, 1.05; NaHCO$_3$, 11.9; NaH$_2$PO$_4$, 0.42; and glucose, 5. The middle compartment was perfused with oxygenated (100% O$_2$) isotonic sucrose solution which prevented contraction of the muscle in the middle chamber and enabled us to maintain the electrode in the muscle extending to the proximal chamber for several hours. To determine whether the use of the isotonic sucrose solution altered the results, we performed several experiments for which the middle chamber also was perfused with the Tyrode's solution. The results obtained were the same when we used either sucrose or Tyrode's solution.

The maximum rate of rise of the action potential was determined by electronic differentiation using an RC circuit with a time constant of 50 μsec. The differentiator was linear within the range of 10–1000 V/sec. The preparation was stimulated by rectangular pulses of 4-msec duration and approximately 1.5 times diastolic threshold strength. Resting membrane potential was altered by adding small quantities of 500 mM KCl to the solution perfusing the test compartment. The maximal concentration of KCl in the test compartment usually was less than 15 mM.

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The combined effects of changes in the membrane potential and rate were studied in two ways: (1) by keeping the resting membrane potential constant at each of several levels between -90 and -60 mV and then increasing the rate in sequential steps from 0.1 to 2.0/sec; and (2) by keeping the rate constant at various frequencies between 0.2 and 7.0/sec and then altering the resting membrane potential. In the former group of experiments, the rate change was initiated 20 minutes after changing the membrane potential, and measurements of $V_{max}$ were made within 3 minutes after the increase in rate. In the latter group, the changes in membrane potential and the determination of the relationship between membrane potential and $V_{max}$ were made 20 minutes after each change in rate. The effects of lidocaine HCl, 6–8 µg/ml (1.15–1.54 x 10^{-5} M), or quinidine gluconate, 6–8 µg/ml (2.52–3.42 x 10^{-5} M), were studied in these experiments. In all experiments the microelectrode was maintained in the same cell before and after addition of the drugs to the perfusate. The data describing drug effects were obtained 30 minutes after the addition of the drug to the perfusate.

Results

EFFECT OF RATE INCREASE ON $V_{max}$

In the initial experiments, the driving rate was increased after the desired membrane potential had been achieved by adding KCl to the perfusate. Figures 1 and 2 illustrate the results of these experiments. An increase in driving rate from 0.1 to 2.0/sec resulted in a decrease in $V_{max}$ which was less than 10% when the membrane potential prior to the rate increase was more negative than -80 mV (K$^+$ = 5.4 mM); the magnitude of this change increased to approximately 30% at membrane potentials of approximately -65 mV (K$^+$ = 10 mM). This result could be attributed to one of the following mechanisms: (1) the increase in rate caused a change in resting potential with no change in the relationship of membrane potential to $V_{max}$; (2) the rate increase caused a change in this relationship but no change in the resting membrane potential; (3) the rate increase caused a change in both resting potential and the relationship of membrane potential to $V_{max}$.

To determine the effect of an increase in rate on resting potential, we recorded action potentials at an expanded voltage scale and slow sweep speed and studied the effects of changes in rate from 0.1 to 0.5/sec, 0.5 to 1.0/sec, 1.0 to 2.0/sec, 0.1 to 1.0/sec, and 0.1 to 2.0/sec. The results of these experiments are shown in Figure 3 and in Table 1. In each experiment the resting potential began to decrease immediately after the rate was increased and the change achieved its maximal value within 30 seconds to 1 minute. Thereafter the resting potential returned toward the original value (Fig. 3). In some experiments the resting potential was completely restored within 3 minutes after the rate change. In others, a slight decrease in resting potential persisted for at least 15 minutes after the rate increase. The maximal decrease in resting potential was dependent on the magnitude of the rate increase (Table 1) but was independent of the resting potential prior to the rate increase. The top panel of Figure 1 illustrates that even in the absence of a change in resting potential, $V_{max}$ was decreased at the more rapid rate. The results of these experiments indicated that the rate increase caused a transient change in resting potential and a steady state change in the membrane potential-$V_{max}$ relationship. To characterize further this latter effect, we studied the membrane potential-$V_{max}$ relationship at rates of 0.2–7.0/sec. In these experiments the rate was increased before membrane potential was changed. An increase in rate from 0.2 to 2.0/sec resulted in a decrease of 6–10% in $V_{max}$ at all membrane potential levels between -90 and -60 mV (10 experiments). Thus, although the curve describing this relationship was depressed, it was not shifted along the voltage axis. As the rate was further increased to 5.0/sec, $V_{max}$ progressively decreased by an amount that was equal at all levels of membrane potential. At rates greater than 5.0/sec, a greater decrease in $V_{max}$ occurred at membrane potentials less negative than -70 mV than at the more negative membrane potentials; this resulted in a shift as well as in a depression of the membrane potential-$V_{max}$ relationship.
ship (Fig. 4). The results of these experiments indicated that the steady state resting membrane potential-\(V_{\text{max}}\) relationship was itself rate-dependent. Similar results were obtained in two other experiments in which the relationship was determined at rates greater than 5.0/sec.

**EFFECT OF QUINIDINE AND LIDOCAINE ON RATE-DEPENDENT CHANGES IN \(V_{\text{max}}\)**

Both drugs exaggerated the rate-dependent effect observed when the rate was increased from 0.1 to 2.0/sec (Fig. 5), and neither drug altered the transient change in membrane potential associated with a rate increase. However, the drugs differed in their effects in two ways: (1) Quinidine caused a progressive decrease in \(V_{\text{max}}\) for each increment in rate from 0.1 to 2.0/sec (0.2, 0.5, 1.0, 2.0/sec). Lidocaine decreased \(V_{\text{max}}\) when the rate was 0.1/sec, an action consistent with its effect on the steady state curve relating membrane potentials to \(V_{\text{max}}\) but did not cause a further decrease in \(V_{\text{max}}\) which was greater than control until the rate was increased to more than 1.0/sec. This difference is illustrated in Figure 6. (2) The quinidine-induced depression in \(V_{\text{max}}\) was constant at all membrane potential levels until, as in the control, the driving rate exceeded 5.0/sec (Fig. 7). Lidocaine, however, caused a shift in this relationship along the voltage axis when the driving rate was increased from 0.2 to 2.0/sec and a greater shift at a driving rate of 6.0/sec (Fig. 8). This progressive rate-dependent shift in the curve was observed in three additional experiments.

**Discussion**

The results of this study suggest that resetting of the sodium-potassium pump, a decrease in membrane potential, and incomplete reactivation of the sodium system may each have contributed to the decrease in \(V_{\text{max}}\) which followed an increase in driving rate.

**TABLE 1**  
*Effect of Rate Increase on the Maximum Decrease of Resting Membrane Potential*

<table>
<thead>
<tr>
<th>Rate Increase</th>
<th>0.1 - 0.5/sec (22)</th>
<th>0.5 - 1.0/sec (17)</th>
<th>1.0 - 2.0/sec (19)</th>
<th>0.1 - 1.0/sec (11)</th>
<th>0.1 - 2.0/sec (32)</th>
</tr>
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<td>Maximum decrease in RP ± SD (mV)</td>
<td>1.1 ± 0.67</td>
<td>1.2 ± 0.68</td>
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Number in parentheses = number of experiments; RP = resting potential; NS = not statistically significant (\(P > 0.05\)).
made. When the resting potential prior to the rate change is less negative than -80 mV, the slope of the S-shaped curve describing the relationship between membrane potential and \( V_{\text{max}} \) is steep, and a small change in resting potential will induce a significant change in \( V_{\text{max}} \). This factor explains the exaggerated rate-induced decrease in \( V_{\text{max}} \) associated with a decrease of 1-2 mV in resting membrane potential when, as shown in the bottom panel of Figure 1 and in Figure 2, the resting potential prior to the rate increase was between -80 and -65 mV.

The time at which \( V_{\text{max}} \) is measured is important because of the transient nature of the decrease in membrane potential. We never observed the hyperpolarization which has been reported for Purkinje fibers.

**INCOMPLETE REACTIVATION OF THE SODIUM SYSTEM**

The recovery characteristics of \( V_{\text{max}} \) depends on the interval from the end of the action potential to the onset of the following action potential (diastolic interval). The time constant of recovery of \( V_{\text{max}} \) in ventricular fibers of guinea pig, sheep, calf, and pig is less than 20 msec when the resting potential is more negative than -80 mV but increases to approximately 100 msec when the resting potential is decreased to approximately -60 mV. Thus, the rate at which this mechanism becomes operative depends on the resting potential. At resting potentials of -60 to -70 mV, the effect is manifest when the diastolic interval shortens to approximately 100 msec (rate of approximately 5.0/sec). As a result, the membrane potential-\( V_{\text{max}} \) relationship changes at rates greater than 5.0/sec (Fig. 4). If the recovery of \( V_{\text{max}} \) is prolonged, the curve defining this relationship will be shifted at diastolic intervals of longer than 100 msec (rates slower than 5.0/sec). Lidocaine causes a dose-dependent prolongation of the recovery of \( V_{\text{max}} \). The lidocaine-induced decrease in \( V_{\text{max}} \) which occurred as the driving rate was increased from 1.0 to 2.0/sec (Fig. 6), i.e., as the diastolic interval shortened to approximately 300 msec, and the progressive rate-dependent shift in the membrane potential-\( V_{\text{max}} \) curve observed at faster rates (Fig. 8) can be attributed to this prolongation. Quinidine does not prolong the recovery of \( V_{\text{max}} \) and thus this mechanism did not contribute to its effect on \( V_{\text{max}} \) at rates below 6.0/sec.

The influence of the recovery kinetics of \( V_{\text{max}} \) will be greatest for the initial response after a sudden rate change. This is explained by the known relationships between action potential duration and rate and the time required for the ventricular action potential duration to reach a new steady state following a sudden rate increase. The duration of the action potential decreases with increasing rate. As a result, the interval from the end of one action potential to the onset of a subsequent action potential, i.e., the diastolic interval, will be shortest and the influence of recovery kinetics on \( V_{\text{max}} \) will be greatest for the first response following an increase in rate. In addition, considerable time is required before the action potential achieves a new steady duration following an increase in rate. During this period action potential duration will be longer, diastolic interval shorter, and the influence of recovery characteristics

**FIGURE 4** Effect of an increase in rate to 6.0/sec on the relationship between membrane potential and \( V_{\text{max}} \). In the normalized curves shown on the right, 100% represents the \( V_{\text{max}} \), associated with a membrane potential of -87 mV. When the rate is increased from 1.0 to 3.0/sec the percent decrease in \( V_{\text{max}} \) is constant at all levels of membrane potential. Thus, the curves on the right are superimposed. When the rate is 6.0/sec the percent decrease in \( V_{\text{max}} \) is greater at resting potentials less negative than -70 mV than at more negative potentials. Thus, the normalized curve on the right is shifted along the voltage axis in the direction of more negative potentials.

**FIGURE 5** Effect of lidocaine (upper panel) and quinidine (lower panel) on rate-dependent change in \( V_{\text{max}} \). The \( \Delta \) to the right of each row is the percent decrease in \( V_{\text{max}} \) when driving rate is increased from 0.1 to 2.0/sec.
on $V_{\text{max}}$ greater than when the steady state value associated with the faster rate has been achieved. The influence of the transient change in resting potential on $V_{\text{max}}$ also will be greatest for the initial responses following the rate change, and the influence of both factors will be greater on partially depolarized fibers.

These factors suggest additional mechanisms for aberrant ventricular conduction. Such conduction disturbances have been attributed to responses arising either from incompletely repolarized fibers (phase 3 or tachycardia-dependent aberrancy) or from spontaneously depolarizing pacemaker fibers (phase 4 or bradycardia-dependent aberrancy). In both situations the membrane potential at the onset of depolarization will be decreased. The factors which we have identified would be operative in completely repolarized, nonpacemaker fibers. The factors identified in this study also help to explain the postrepolarization refractoriness and rate-dependent decrease in $V_{\text{max}}$ recently observed studies on acutely ischemic, partially depolarized His bundle fibers and the tachycardia-induced slowing of conduction velocity observed in acutely ischemic ventricular myocardium.

Quinidine and lidocaine exaggerate the rate-induced change in $V_{\text{max}}$ by different mechanisms. Quinidine probably depresses the sodium-potassium ATPase system. Its effect is demonstrated after any increase in rate and is independent of the resting potential. The rate-dependent slowing of intraventricular conduction in dogs and man after quinidine is consistent with our results. Lidocaine alters recovery kinetics. Its effect does not become manifest until the rate exceeds a critical level which depends on the resting potential and is slower for fibers with a decreased resting potential than for those with a normal resting potential. Lidocaine’s ability to slow conduction in acutely ischemic (and therefore partially depolarized) areas of dog hearts driven at rates of 2.0–3.0/sec without slowing conduction in adjacent nonischemic areas can be attributed to...
two factors: (1) the shift in the membrane potential-V_{\text{max}} relationship that occurs even at slow rates,\(^{19}\) and (2) the further shift in this relationship induced by rapid rates (Fig. 8). The lidocaine-induced prolongation of the effective refractory period within an ischemic zone but not in the nonischemic area\(^{24}\) is consistent with the marked prolongation of the recovery of V_{\text{max}} induced in partially depolarized fibers by lidocaine.\(^{19}\)

The results of our study indicate that the decrease in V_{\text{max}} of the action potential upstroke associated with an increase in rate is caused by the complex interaction of factors that cause both transient and steady state effects. An appreciation of these factors is essential to an understanding of the various rate-related changes in V_{\text{max}} and conduction velocity which occur in normal fibers as well as in partially depolarized and/or drug-treated fibers.

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