EFFECTS OF DISOPYRAMIDE ON THE MAXIMUM RATE OF RISE OF ACTION POTENTIAL (Vmax) IN GUINEA-PIG PAPILLARY MUSCLES

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Abstract—The correlation between the steady state and non-steady state depression of Vmax by 50 μM disopyramide was investigated in 2.7, 5.4 and 8.1 mM [K+]o using isolated guinea-pig papillary muscles. An elevation of [K+]o from 2.7 to 8.1 mM strengthened the depressant action of the drug on Vmax (steady state) at 1 to 5 Hz, but attenuated this action at 0.05 and 0.1 Hz. The Vmax-membrane potential (Vm) relationship (steady state) was examined at stimulation rates of 0.1 and 1 Hz by increasing [K+]o from 2.7 to 19 mM. The drug shifted the normalized Vmax-Vm curve at 1 Hz in a hyperpolarizing direction, but shifted the curve at 0.1 Hz upward at Vm, between −90 and −65 mV without a shift along the Vm axis. The recovery process of Vmax (non-steady state) was examined by introducing premature stimuli or by interrupting the basic stimulus of 1 Hz for a certain period. The control recovery processes in three [K+]o were approximated by a triple exponential function (the earliest, intermediate and latest components). The drug slowed the intermediate component, but accelerated the latest one (the earliest component was situated within the refractory period) when [K+]o was elevated from 2.7 to 8.1 mM. The finding that the elevation of [K+]o attenuated the depressant action of disopyramide on the Vmax at 0.05 and 0.1 Hz and accelerated the recovery process of Vmax at long diastolic intervals of more than 10 sec was quite unique.

Disopyramide is an antiarrhythmic drug which is effective in controlling a variety of experimental and clinical arrhythmias (1–3). It is generally accepted that the action of antiarrhythmic drugs on Vmax (the maximum rate of rise of action potential) is one of the important requisites for the antiarrhythmic action (4, 5). Recent electrophysiological studies of these agents, however, have revealed that because the effects of these agents on Vmax are actually time- and [K+]o (voltage)-dependent, the findings on these effects obtained at a particular stimulation rate or [K+]o are not sufficient for an adequate characterization of each drug (6–9). Further, it has been proposed that there is a close interrelationship between the effects of drugs on Vmax in a non-steady state (the Vmax in the recovery process during diastole) and on Vmax in a steady state (the Vmax at a constant stimulation rate): the drug slowing the recovery process of Vmax strengthens a rate-dependent reduction of Vmax (7–9).

It was previously elucidated that 20 μM disopyramide produced more depressant action on Vmax at the stimulation rates of 0.5 to 5 Hz (10), but less depressant action at the rate of 0.1 Hz (unpublished data) in
8.1 mM [K⁺]₀ than in 2.7 mM [K⁺]₀. These results suggest that when [K⁺]₀ is elevated from 2.7 to 8.1 mM, the drug slows the recovery process of \( \dot{V}_{\text{max}} \) at diastolic intervals of shorter than 2 sec, but accelerates the process at diastolic intervals of longer than 10 sec. Although the former property of the drug was observed with lidocaine (6, 9), the latter one has not been reported for any antiarrhythmic drugs. Therefore, the present study was made to confirm these unique properties with respect to the effects of 50 \( \mu \)M disopyramide on the \( \dot{V}_{\text{max}} \) at stimulation rates of 0.05 to 5 Hz as well as on the recovery process of \( \dot{V}_{\text{max}} \) at diastolic intervals of up to 10 min in 2.7, 5.4 and 8.1 mM [K⁺]₀.

**MATERIALS AND METHODS**

Preparation of the papillary muscle: After male guinea-pigs (300–500 g) were stunned by a blow on the head, the hearts were rapidly removed and transferred to an oxygenated, modified Tyrode solution of the following composition (mM): NaCl, 136.9; KCl, 5.4; CaCl₂, 1.8; MgCl₂, 1.05; NaH₂PO₄, 0.42; NaHCO₃, 11.9; glucose, 10.0. The papillary muscle dissected from the right ventricle was pinned to the silicone rubber bottom of a 3-ml tissue chamber and superfused at a constant flow rate of 3–5 ml/min with the Tyrode solution saturated with a mixture of 95% O₂–5% CO₂ (pH = 7.3–7.4). The temperature of the superfusion chamber was kept at 36.5 ± 0.5°C.

Electrophysiologic techniques: Cathodal stimuli (1 msec duration; 10–40% above the threshold voltage, usually 0.5–3.0 V) were delivered by a stimulator (Nihon Kohden, SEN-7103)-stimulus isolation unit (Nihon Kohden, SS-102J) and applied to the surface of the preparation through a capillary glass electrode filled with the superfusate. After an equilibration period of at least one hour, the transmembrane potential was recorded by means of a conventional microelectrode filled with 3 M KCl (8–20 MΩ). The microelectrode was connected to a high input impedance, capacitance-neutralizing amplifier (WP Instruments, M-707) via an Ag-AgCl half cell (WP Instruments, EH-1R). Both the transmembrane action potential and its first derivative obtained by a CR differentiator (time constant = 50 μsec) were displayed on a dual beam cathode ray oscilloscope (Nihon Kohden, VC-9) and photographed on 35 mm film using an oscilloscopic camera (Nihon Kohden, RLG-6101).

Electrophysiologic parameters: We measured the following action potential parameters by projecting the film onto graph paper: resting membrane potential (RMP), \( \dot{V}_{\text{max}} \), and action potential duration to 90% repolarization (APD₉₀).

When effects of rate changes on the action potential parameters were observed, the stimulation rate was changed either from 1 to 0.05 Hz in some preparations or from 1 to 5 Hz in others (stimulation periods: 5 min for 0.05 to 1 Hz and 3 min for the others). Steady state values at each stimulation rate were determined immediately before switching from one rate to the next one. When effects of [K⁺]₀ on the action potential parameters and the following recovery process of \( \dot{V}_{\text{max}} \) were studied, [K⁺]₀ in the superfusate was changed from 5.4 (normal concentration) to either 2.7 or 8.1 mM without correcting the resultant small change in osmolarity.

The recovery process of \( \dot{V}_{\text{max}} \) was examined in the following two ways: (i) the process within the basic stimulation interval of 1 sec (premature recovery) was studied by introducing premature test stimuli (2–3 times the intensity of the basic stimulus) in every 8–10 basic stimuli, (ii) the process beyond the basic stimulation interval (post-interruption recovery) was studied by assessing \( \dot{V}_{\text{max}} \) in the first response after interruption of the basic stimuli for various periods (2 sec to
10 min). The term "diastolic interval" is defined as the interval from the 90% repolarization time of the conditioning action potential to the onset of the test action potential.

The recovery time course of $V_{\text{max}}$ in the presence and absence of disopyramide was studied by taking mean values of the difference between the $V_{\text{max}}$ in either the premature action potential or the first action potential on the resumption of the stimulation ($V_{\text{max}}$)$_{\text{pre}}$ and the $V_{\text{max}}$ in the conditioning action potential ($V_{\text{max}}$)$_{\text{cond}}$. An attempt to fit the time course to an exponential function was made using a computer program, SALS (Statistical Analysis with Least Squares Fitting made by T. Nakagawa and Y. Koyanagi: Tokyo University Computer Center Program Library). The FACOM-190 computer at Kyushu University was used for this purpose.

**Drug:** The disopyramide base was first dissolved in an adequate amount of 0.2 N HCl and then neutralized to pH 7.0 by adding 0.5 N NaOH solution.

**Data analysis:** All records reported here were obtained from the continuous impalement of a single cell during both control and drug superfusion. Data were analyzed using the Student's paired t-test, unless otherwise indicated. A probability (P) value of less than 0.05 was the criterion for assigning a significant difference. "n" in the text indicates the number of preparations.

### RESULTS

**Steady state effects of disopyramide on $V_{\text{max}}$ at different stimulation rates:** Steady state effects of 50 nM disopyramide on $V_{\text{max}}$ at different stimulation rates were studied in the superfusate containing 2.7, 5.4 and 8.1 mM [K+]o. The stimulation rate was changed either from 1 to 0.05 Hz in some preparations (series A) or from 1 to 5 Hz in the others (series B) before and 30–45 min after the onset of drug superfusion. The results of these experiments are shown in Fig. 1. Data were expressed as the means

![Fig. 1. Steady state effects of 50 nM disopyramide on action potential characteristics at different stimulation rates. The rate changes from 1 to 0.05 Hz (Series A) and from 1 to 5 Hz (Series B) were determined in different preparations. In each series, P values for % change were calculated using the Student’s paired t-test between the values at 1 Hz (underlined) and those at other rates: *P<0.05, **P<0.01.](image-url)
±S.E. (the bar of S.E. for RMP was smaller than the symbols). The term "% change" means percent change from the control $V_{max}$ values at the corresponding rates (S.E. is not shown).

When $[K^+]_o$ was elevated from 2.7 to 8.1 mM, drug-induced mean percent reductions of $V_{max}$ at 0.05 and 0.1 Hz decreased from 23–24% to 12–18%, those at 0.2 Hz remained fairly constant at 21–27%, and those at 1 to 5 Hz increased from 20–25% to 37–50%. Similar $[K^+]_o$- and rate-dependent results on $V_{max}$ were obtained at 20 $\mu$M disopyramide in the previous paper (10).

These results indicate that the elevation of $[K^+]_o$ attenuated the depressant action of disopyramide on $V_{max}$ at 0.1 Hz and lower, but strengthened this action at 1 Hz and higher.

Effects of disopyramide on $V_{max}$–$V_m$ (membrane potential) relationship at the stimulation rates of 0.1 and 1 Hz: The results in the above section suggest that the $V_{max}$–$V_m$ relationship in the presence of 50 $\mu$M disopyramide must be different at low and high stimulation rates. This possibility was examined at the rates of 0.1 and 1 Hz before and 30–45 min after the onset of drug superfusion. $[K^+]_o$ in the superfusate was elevated from 2.7 to 19 mM. The representative data obtained from a single cell are shown in Fig. 2 in which the $V_{max}$ values were plotted against the membrane potential.

![Fig. 2](image-url)

**Fig. 2.** The $V_{max}$–$V_m$ relationship before and during superfusion with 50 $\mu$M disopyramide at the stimulation rates of 1 Hz (A) and 0.1 Hz (B). The absolute $V_{max}$ values (left) and the ones normalized to the value at -100mV (right) were plotted against the membrane potential ($V_m$). The lines in A were drawn according to the equation given in the text.
Control $V_{\text{max}} - V_m$ curves in absolute values at both stimulation rates were superimposable.

At 1 Hz (Fig. 2A), the $V_{\text{max}}$ in the presence of the drug was gradually reduced with depolarization of the resting membrane. When these $V_{\text{max}}$ values were normalized to the $V_{\text{max}}$ value at $-100$ mV, the normalized curve shifted in a hyperpolarizing direction: the membrane potential at half-maximal $V_{\text{max}}$ ($V_h$) in the presence of the drug ($-66.3 \pm 1.4$ mV) was significantly different from that for the controls ($-61.8 \pm 0.7$ mV) ($P < 0.01$, $n = 5$), but the slope factor(s) was unchanged before and after the onset of drug superfusion (control: $5.5 \pm 0.4$ mV; drug: $7.1 \pm 0.9$ mV, $P > 0.05$, $n = 5$). The values for $V_h$ and $s$ were calculated from the equation: $V_{\text{max}}/(V_{\text{max}})_{-100mV}=1/[1+\exp(V_m-V_h)/s]$ (11).

At 0.1 Hz (Fig. 2B), the $V_{\text{max}}$ in the presence of the drug was first increased by $7.8 \pm 0.9$ V/sec ($n = 5$) with depolarization of the resting membrane from $-102$ to $-80$ mV, but then decreased gradually with further depolarization of the resting membrane. When these $V_{\text{max}}$ values were normalized as in the case of 1 Hz, the normalized curve shifted upward at $V_m$ between $-90$ and $-65$ mV without a shift along the $V_m$ axis. The values for $V_h$ and $s$ at 0.1 Hz were not determined because the $V_{\text{max}} - V_m$ curves were not of a typical sigmoid shape.

These results indicate that in depolarized cells (up to $-65$ mV), the depressant action of disopyramide on the $V_{\text{max}}$ became greater at 1 Hz and higher, but became smaller at

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Fig. 3. Representative experiments showing the recovery process of $V_{\text{max}}$ before and during superfusion with 50 μM disopyramide in 2.7, 5.4 and 8.1 mM $[K^+]_o$. Note the difference of time scale for the diastolic intervals of 0–900 msec, 1–60 sec and 1.5–10 min.
0.1 Hz and lower.

Effects of disopyramide on the recovery process of $V_{\text{max}}$: The observations described in the foregoing two sections clearly indicate that the changes in the behaviour of the $V_{\text{max}}$ caused by disopyramide are different at low and high stimulation rates. Therefore, the premature and post-interruption recoveries of $V_{\text{max}}$ before and 30–45 min after the onset of drug superfusion were studied in 2.7, 5.4, and 8.1 mM [K+]o at wide ranges of the diastolic interval (0–10 min). Figure 3 shows representative data in which the $V_{\text{max}}$ values were plotted against the diastolic interval before and during superfusion with disopyramide at three levels of [K+]o.

As shown in Fig. 3, the $V_{\text{max}}$ reduced by the drug recovered toward the asymptotic value with extension of the length of the diastolic interval at three [K+]o. The recovery percentages of $V_{\text{max}}$ obtained after the longest interruption period examined (10 min for 2.7 mM [K+]o and 2 min for 5.4 and 8.1 mM [K+]o) were 76.9±2.3, 84.2±2.9 and 97.8±2.5% (n=5) of the control $V_{\text{max}}$ values obtained after the corresponding interruption period in 2.7, 5.4 and 8.1 mM [K+]o, respectively. Similar, but less effective, results on the recovery process of $V_{\text{max}}$ were observed at 20 μM disopyramide (unpublished data).

In Fig. 4, the differences between ($V_{\text{max}})_{\text{test}}$ and ($V_{\text{max}})_{\text{cond}}$ in the absence and presence of the drug were plotted against the diastolic interval. When the bar for S.E. was smaller than the symbols, it was not shown in this figure. The recovery processes of $V_{\text{max}}$ in 2.7, 5.4 and 8.1 mM [K+]o are shown as the difference between ($V_{\text{max}})_{\text{test}}$ and ($V_{\text{max}})_{\text{cond}}$ before and during superfusion with 50 μM disopyramide. Statistically significant differences (unpaired t-test) were seen at *($P<0.05$) and **($P<0.01$). The lines were drawn using the parameters shown in Table 1.
In 2.7 and 5.4 mM [K+]o, these differences (minus values) in the absence and presence of the drug were not significant at any intervals within 1 sec, whereas in 8.1 mM [K+]o, these differences in the presence of the drug were significantly greater than those for the controls at diastolic intervals of 60-275 msec. Figure 4 also shows that in 8.1 mM [K+]o, most of the preparations exposed to the drug failed to elicit responses at diastolic intervals shorter than 60 msec, thereby indicating the prolongation of the refractory period.

On the other hand, these differences (plus values) during the post-interruption recovery in the presence of the drug were significantly greater than those for the controls at diastolic intervals of over 20 sec in 2.7 mM [K+]o and at diastolic intervals of over 5 sec in 5.4 and 8.1 mM [K+]o. It was evident that the higher the [K+]o was, the greater the recovery amount of Vmax was.

Figure 5 representatively shows a semilogarithmic plot of the differences between (Vmax)test and (Vmax)asymp in 2.7 and 8.1 mM [K+]o that were given in Fig. 4 ((Vmax)asymp: the asymptotic value of Vmax). The peeling-off analysis for the data in the absence and presence of disopyramide in three [K+]o showed that the recovery time course was composed of three components: the earliest, intermediate, and latest components. Therefore, a triple exponential function was applied here to the recovery time course of

Fig. 5. The peeling-off analysis for the difference between (Vmax)test and (Vmax)asymp in the presence of 50 μM disopyramide in 2.7 and 8.1 mM [K+]o. In each [K+]o, the time scale for 0-6 sec in right figures was expanded in the left figures. Figures for the time constant of each component were cited from Table 1.
\[ V_{\text{max}} \] using the computer program, SALS. (Here, a value of 2 V/sec was assigned as the measurement error). Table 1 shows the amplitude (the intercept of \( V_{\text{max}} \) at the origin of the diastolic interval, \( t=0 \)), the percentage with respect to the total recovery, and the time constants of three components which were estimated by the computer program. The validity of the parameter values estimated would be limited particularly for the components for which the coefficients of variations were large. In Table 1, therefore, the amplitude and time constants of which the coefficients of variation were over 40% are shown in brackets, as these are considered not to be decisive.

The following conclusions are deduced by analyzing the values in this table: (i) The time constants of the earliest component were not modified by the drug in 2.7 and 5.4 mM \([K^+]_o\), whereas such values in the presence of the drug in 8.1 mM \([K^+]_o\) could not be estimated due to the prolongation of the refractory period. (ii) There were no apparent effects of the drug on the intermediate component in 2.7 and 5.4 mM \([K^+]_o\). In 8.1 mM \([K^+]_o\), however, this component was divided into two in the presence of the drug. The amplitudes of either component and the time constant of the one component were larger than those for the control. (iii) The amplitude of the latest component was increased in the presence of the drug. The time constant of this component in the presence of the drug became smaller when \([K^+]_o\) was elevated.

These results indicate that when \([K^+]_o\) was elevated from 2.7 to 8.1 mM, disopyramide slowed the recovery time course of \( V_{\text{max}} \) at diastolic intervals of shorter than about 10 sec, but accelerated the one at diastolic intervals of longer than about 10 sec.

**DISCUSSION**

Drug concentration, stimulation rates and diastolic intervals: The previous paper (10) and the present results indicate that the steady state and non-steady state effects on \( V_{\text{max}} \) seen at 50 \( \mu \)M disopyramide were qualitatively similar to and were simply more pronounced than the effects seen at 20 \( \mu \)M disopyramide which roughly cor-

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**Table 1.** Amplitude (A), their percentage (%) with respect to the total recovery, and time constant (\( \tau \)) for the recovery process of \( V_{\text{max}} \) before and during superfusion with disopyramide (DSP), estimated by a computer program based on a non-linear regression.

| Component         | 2.7 mM \([K^+]_o\) | 5.4 mM \([K^+]_o\) | 8.1 mM \([K^+]_o\) |
|-------------------|-------------------|-------------------|-------------------|
| \( t=0 \)         | Control           | 50 \( \mu \)M DSP | Control           |
| Amplitude (V/sec) | 17                | 12                | 20                |
| Percentage (%)    | 8                 | 12                | 39                |
| Time constant (msec) | 5                | 4                 | 10                |
| Amplitude (V/sec) | 514               | 679               | 383               |
| Percentage (%)    | 2                 | 2                 | 2                 |
| Time constant (msec) | 249-1227         | 389-2676          | 270-657           |
| Amplitude (V/sec) | 37                | 37                | 47                |
| Percentage (%)    | 23                | 26                | 26                |
| Time constant (msec) | 197              | 197               | 39                |

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\( ^a \) The intercept of \( V_{\text{max}} \) at the origin of the diastolic interval (\( t=0 \)).

\( ^b \) Values in which (S.D.)/A or (S.D.)/\( \tau \) > 0.4 are shown in brackets.

\( ^c \) Ranges of time constants, [1/(1/\( \tau \) + (S.D.))\( \tau \)] - [1/(1/\( \tau \) - (S.D.))\( \tau \)], are shown in parentheses.

\( ^d \) Parameter values could not be estimated due to a prolongation of the refractory period.
responded to the maximum effective (anti-arrhythmic) plasma concentration (12, 13).

As mentioned in Introduction, the depressant action of disopyramide on $V_{\text{max}}$ at low rates and long diastolic intervals was suggested to differ from the action at high rates and short diastolic intervals (10). To confirm this suggestion, we used wide ranges of stimulation rates (0.05–5 Hz) and diastolic intervals (0–10 min). It was necessary to observe the $V_{\text{max}}$ at such long diastolic intervals for the determination of the asymptotic value in the recovery time course of $V_{\text{max}}$.

**Effects of disopyramide on $V_{\text{max}}$ and $V_{\text{max}}$–$V_m$ relationship at different stimulation rates:** The present study demonstrated that disopyramide modified $V_{\text{max}}$ in both $[K^+]_o$- and rate-dependent fashions: a rise in $[K^+]_o$ from 2.7 to 8.1 mM attenuated the depressant action of the drug on $V_{\text{max}}$ at 0.1 Hz and lower, but strengthened this action at 1 Hz and higher. These findings were reconfirmed in the experiments on the $V_{\text{max}}$–$V_m$ relationship which showed that the drug shifted the normalized curves at 0.1 Hz upward at $V_m$ between $-90$ and $-65 \text{ mV}$, but shifted the curve at 1 Hz in a hyperpolarizing direction.

Curves for the normalized $\dot{V}_{\text{max}}$–$V_m$ relationship were not shifted by quinidine (6, 14), but were shifted in the hyperpolarizing direction by lidocaine, both drugs depressing the $V_{\text{max}}$ in cardiac cells (5, 6, 8). In this respect, the effects of disopyramide on this curve at the stimulation rate of 0.1 Hz are quite unique, although the effects seen at 1 Hz have already been observed by Danilo et al. (15), Kus and Sasyniuk (14, 16) and Kojima (10). Kus and Sasyniuk (14) reported that the actions of disopyramide on $V_{\text{max}}$ resembled those of lidocaine rather than quinidine because the former two drugs shifted the normalized $V_{\text{max}}$–$V_m$ curve in a hyperpolarizing direction. However, our present findings clearly indicate that Kus and Sasyniuk's conclusion should be reconsidered from the viewpoint of the stimulation rate used.

**Effects of disopyramide on the recovery process of $V_{\text{max}}$:** The recovery process of $V_{\text{max}}$ may represent not only the reactivation of the sodium system from inactivation (17), but also the functional state of Na/K pump (18) and other changes in active and passive membrane properties. Further, Hondeghem and Katzung's model (7) suggests that there are several routes for the reactivation of the sodium channels from inactivation: one route for inactivated drug-free channels and two routes for inactivated drug-associated channels (For details, see diagram 1 in reference 7). Because the recovery process of $V_{\text{max}}$ may consist of these complicated factors, this process in the absence and presence of disopyramide was analyzed using the computer program, SALS. The three components yielded were termed the earliest, intermediate, and latest components or two intermediate and latest components (discussed later).

**Earliest component:** The time constants of the earliest component (8–13 msec) estimated for the controls in 2.7, 5.4, and 8.1 mM $[K^+]_o$ are of the same order of magnitude reported in previous studies using guinea-pig papillary muscles (6, 8, 9, 17). Disopyramide seems not to change the time constant of this component, although the drug made the estimation of this constant in 8.1 mM $[K^+]_o$ impossible because of the prolongation of the refractory period.

**Intermediate component(s):** In the absence of drugs, the slow recovery of the sodium system with a time constant of several hundred msec has been observed in sheep Purkinje fibers (19, 20) and frog atrial preparations (21). Further, the gradually developing hyperpolarization of the membrane potential during interruption of
the driving stimulation in cardiac tissues has been interpreted as indicating an activation of the Na/K pump (18). Such activation would be expected to produce a time-dependent increase in $V_{\text{max}}$, during the post-interruption period both by decreasing $[\text{Na}^+]_o$ and by increasing the take-off potential. The intermediate and latest components observed for the controls in the present study may reflect such slow reactivation of the sodium system or activation mechanism of the Na/K pump, or both.

In the presence of disopyramide, there was one intermediate component in 2.7 and 5.4 mM $[\text{K}^+]_o$, but two intermediate components in 8.1 mM $[\text{K}^+]_o$. Since the earliest component in 8.1 mM $[\text{K}^+]_o$ was masked by the prolongation of the refractory period, the reason for the appearance of two intermediate components in this $[\text{K}^+]_o$ is not clearly understood at present.

A delay of recovery in the early part of the recovery process of $V_{\text{max}}$ in 8.1 mM $[\text{K}^+]_o$ has been obtained with 20 $\mu$M disopyramide and has been considered as a cause for the rate-dependent reduction of $V_{\text{max}}$ observed at this concentration (10). Here it is also conceivable that the increments of the time constant and the amplitude of the intermediate component(s), i.e. the delay in the recovery process, in the presence of 50 $\mu$M disopyramide in 8.1 mM $[\text{K}^+]_o$, are responsible for the more prominent reduction of the $V_{\text{max}}$ at 1 to 5 Hz in this $[\text{K}^+]_o$ level. This $[\text{K}^+]_o$-dependent delay by disopyramide was similar to that seen with lidocaine (6, 9). However, lidocaine differed from disopyramide in producing a significant delay of the recovery process even in the lowest $[\text{K}^+]_o$ of 2.7 mM (9).

**Latest component:** The drug decreased the time constant of the latest component from 197 to 28 sec and attenuated the depression of $V_{\text{max}}$ of the latest component when $[\text{K}^+]_o$ was elevated from 2.7 to 8.1 mM. These actions are very opposite to the actions of known antiarrhythmic drugs: when $[\text{K}^+]_o$ was elevated, lidocaine increased (6, 9) or quinidine and procainamide did not change (6, 8) the time constants of the recovery process of $V_{\text{max}}$. Recently, Courtney (22) has reported that in guinea-pig papillary muscle exposed to 4.5 mM $[\text{K}^+]_o$, the $V_{\text{max}}$ in the presence of disopyramide recovered from rate-dependent depression with a recovery half-time of 37 sec. This value is very comparable to the time constant (39 sec) estimated here for the latest component in 5.4 mM $[\text{K}^+]_o$.

Since the drug does not alter the take-off potential in both the premature and the post-interruption responses at each level of $[\text{K}^+]_o$, these slow recovery processes in the presence of disopyramide do not seem to be derived from an effect of the drug on the activation of the Na/K pump. Thus, one possible interpretation of the present findings in terms of the Hondeghem and Katzung's model (7, 8) is that in 8.1 mM $[\text{K}^+]_o$, disopyramide preferentially affected the sodium channels in their inactivated state rather than in their resting state, whereas in 2.7 mM $[\text{K}^+]_o$, the reverse is true. However, the possibility that a time-dependent change in cable properties of the myocardial fibers would affect the $V_{\text{max}}$ in the propagated action potentials (23) cannot be excluded at present.

**Pharmacological significance:** As discussed above, the more depressant action of disopyramide on $V_{\text{max}}$ was demonstrated either at the high rates and short diastolic intervals in higher $[\text{K}^+]_o$ or at the low rates and long diastolic intervals in lower $[\text{K}^+]_o$. Since the $V_{\text{max}}$ is considered to be a valid index of conduction velocity (24, 25), the former action suggests that at a physiological heart rate, (i) disopyramide causes a greater slowing of conduction in depolarized (ischemic) areas than in normopolarized ones, (ii) a change by this drug of a uni-
directional block into a bidirectional one is more possible in the heart with tachycardia than bradycardia, and (iii) disopyramide abolishes early extrasystoles more selectively in depolarized areas than normopolarized ones.

The latter action has never been reported for any antiarrhythmic drugs. However, this action, only evident at extremely low rates, may not be operative in the clinical situation because disopyramide is claimed not to be effective against arrhythmias in hypopotassemia (16, 26).

If structural specificity responsible for each of the actions of the drug is made clear, it would be possible to design a new antiarrhythmic agent which exerts a class 1 action only in hypopotassemia.

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