Enhancement of procainamide-induced rate-dependent conduction slowing by elevated myocardial extracellular potassium concentration in vivo

WAYNE E. CASCIO, M.D., JAMES R. FOSTER, M.D., JACK W. BUCHANAN JR., M.D., TIMOTHY A. JOHNSON, PH.D, AND LEONARD S. GETTES, M.D.

With the technical assistance of Connie L. Engle, A.A.S.

ABSTRACT  Procainamide, a type 1A antiarrhythmic drug, blocks sodium channels and reduces the maximum rate of rise of the cardiac action potential (Vmax) in a rate-dependent fashion. In vitro, the magnitude of this rate-dependent reduction in Vmax is greater in tissue that is partially depolarized at rest than in tissue with a normal resting potential. Reductions in Vmax produced by drugs that block sodium channels are also directly related to the reductions in longitudinal conduction velocity of action potential propagation in papillary muscle preparations. We therefore sought to determine whether the rate-dependent conduction slowing induced by procainamide in the intact canine heart is enhanced in myocardial tissue abnormally depolarized by an elevated myocardial extracellular potassium concentration, \([K^+]_o\). QRS duration and epicardial activation times were measured as indexes of myocardial conduction. QRS duration and epicardial activation times were measured at control (4.0 mM) and at intermediate (6.5 mM) and high (9.2 mM) myocardial \([K^+]_o\) in the presence or absence of a clinically relevant procainamide concentration (12.2 ± 2.6 g/ml) at the longest obtainable interstimulus interval of 440 msec and at 330, 280, and 250 msec. Intermediate and high myocardial \([K^+]_o\) alone induced rate-dependent conduction slowing as the frequency of stimulation increased (cycle length 440 msec to 330, 280, and 250 msec). In the presence of procainamide, rate-dependent conduction slowing was observed at all levels of myocardial \([K^+]_o\), and the amount of rate-dependent change in conduction time increased as the myocardial \([K^+]_o\) was increased. In addition, the magnitude of the difference between the rate-dependent changes in conduction time produced by high myocardial \([K^+]_o\) in the presence of procainamide compared with high \([K^+]_o\) alone was significantly greater than the difference at control myocardial \([K^+]_o\). This observation shows enhancement of procainamide-induced rate-dependent conduction slowing by high \([K^+]_o\). Therefore, as predicted by studies of longitudinal conduction velocity and Vmax in papillary muscle preparations, rate-dependent conduction slowing in the presence of a clinically relevant concentration of procainamide is enhanced by high myocardial \([K^+]_o\) depolarization. This effect of elevated myocardial \([K^+]_o\), may be important to the antiarrhythmic actions of procainamide in abnormal myocardium, especially in situations such as acute ischemia in which the distribution of high \([K^+]_o\) and resting depolarization are inhomogeneous.


MOST UNDERSTANDING OF the electrophysiologic action of antiarrhythmic drugs is based on their effects in normal myocardial tissue with normal resting membrane potential. However, the abnormal myocardium, including acutely ischemic myocardium in which life-threatening arrhythmias originate, often contains hyperkalemic and acidic tissue with resting membrane depolarization. For this reason, the effects of antiarrhythmic drugs on depolarized tissue may be important to the antiarrhythmic actions of these drugs. It is known that antiarrhythmic drugs produce more sodium-channel blockade and more reduction of maximum rate of rise in cardiac action potential (Vmax) in depolarized tissue than in normal tissue. It is also known that the effects of antiarrhythmic drugs are rate dependent, with more sodium-channel
blockade and more reduction of Vmax at rapid rates than at slow rates, and that this rate dependence is greater in potassium-depolarized tissue.

However, the greater rate-dependent effects of anti-arrhythmic drugs in potassium-depolarized tissue in vitro have not been shown to occur in the hyperkalemic intact heart. We therefore hypothesized that procainamide would cause more rate-dependent conduction slowing, as a consequence of its effect on sodium conductance and Vmax, in hearts with high extracellular myocardial potassium concentration, [K+]o, than in hearts with a normal [K+]o. We studied rate-dependent conduction slowing during ventricular pacing in intact dog hearts using intramyocardial ion-selective potassium electrodes to monitor myocardial [K+]o online during hyperkalemia produced by potassium infusion and measuring QRS duration and epicardial conduction times as indexes of myocardial conduction.

Methods

Experimental preparation. Mongrel dogs weighing 22.6 ± 4.1 kg (range 15 to 28 kg) were anesthetized with 30 mg/kg sodium thiamylal. Anesthesia was maintained with α-chloralose, 25 to 50 mg/kg/hr, and the animals were ventilated by a Harvard respirator via a cuffed endotracheal tube. The respiratory rate and oxygen content of the inspired air were adjusted to maintain arterial pH at 7.40 ± 0.05 and the arterial oxygen saturation at greater than 90%. The heart was exposed through a midline thoracotomy and suspended in a pericardial cradle. Epicardial and core temperature were maintained between 36° and 38° C. The sinus node was crushed and the heart wasstimulated with a bipolar epicardial plaque electrode. The epicardial stimulating electrode consisted of two silver–silver chloride electrodes, each 1 mm in diameter, embedded 2 mm apart in a methacrylate plaque. A cyanoacrylate adhesive was used to attach the stimulating electrode to the surface of the left ventricle near the left anterior descending coronary artery. The experimental preparation is shown in figure 1. Two pairs of stainless steel bipolar recording electrodes were positioned in the subepicardium along the long axis of the epicardial fibers that extended in parallel from the stimulating electrodes to the apex. The proximal pair of electrodes was placed approximately 5 mm from the stimulating electrode. The distal electrode pair was placed approximately 15 mm from the proximal electrode. In three experiments, monophasic action potentials were recorded from the epicardial surface of the left ventricle by a contact pressure electrode similar to that described by Franz et al. The monophasic action potentials, epicardial electrograms, scalar electrocardiographic leads II and aVR, a precordial lead, and the stimulus were continuously displayed on an oscillographic monitor and recorded photographically (Electronics for Medicine VR-12) at a paper speed of 250 mm/sec, as shown in figure 2.

Measurement of intramyocardial conduction. We assessed ventricular conduction by two methods, one local and the other global, to eliminate experiments in which significant changes in conduction pathway may have contributed to our results. Local conduction, the epicardial activation time (EAT), was determined by measurement of the interval in milliseconds between the first high-frequency component of each epicardial electrogram (figure 2). The results are expressed as conduction time rather than conduction velocity because the interelectrode dis-

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tance was difficult to measure precisely in the beating heart, and cardiac dilatation associated with asystole at the termination of the experiment prevented measurement that would indicate inter-electrode distance before death. Our estimates of conduction velocity determined by dividing the approximate measurement of interelectrode distance by the conduction time were in the range of 0.4 to 0.7 m/sec. These velocities are similar to those observed by others who have measured the influence of myocardial [K⁺]₀, pH, or ischemia on conduction of intact heart preparations.³–⁷

Global conduction was determined by measurement of the interval from the stimulus artifact to the end of the QRS complex. The end of the QRS complex was defined as the intersection of tangents to the ST segment and to the major terminal deflection of the QRS complex. To minimize the effect of latency, the interval measured from the stimulus artifact to the first high-frequency component of the proximal electrogram was subtracted from the total QRS duration, yielding the adjusted QRS duration (QRSₐ), which was then used at the measure of global conduction time.

In all experiments accepted for analysis in the study we required that there be no change in QRS morphology in any of the three monitored electrocardiographic leads and that the correlation coefficient between the changes in conduction induced by our interventions and recorded by these two methods be equal to or greater than .9. Monitoring of myocardial [K⁺]₀. Myocardial [K⁺]₀ was monitored by miniature potassium ion-selective plunge electrodes designed, tested, and calibrated as those described previously from our laboratory.¹⁹ The response characteristics of the electrodes in vitro and in vivo were similar to those reported previously.² Five plunge electrodes were positioned in the midmyocardium of the left ventricular wall. A sixth miniature potassium ion-selective electrode was positioned in the thoracic aorta. The direct-current voltages from the electrodes were recorded on a Grass 7 polygraph. Data were accepted only from electrodes that demonstrated a 57 to 61 mV change per decade potassium change during calibration and an appropriate response to a 1 meq potassium chloride intravenous bolus in vivo. Serum arterial potassium concentrations were verified by flame photometry and are used as the precise values of [K⁺]₀, presented in table 1.

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Potassium (mM)</th>
<th>Procaainamide (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control [K⁺]₀ (n = 21)</td>
<td>4.0 ± 0.1</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Control [K⁺]₀ and PCA (n = 7)</td>
<td>3.8 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Intermediate [K⁺]₀ (n = 12)</td>
<td>6.4 ± 0.2</td>
<td>6.5 ± 0.2</td>
</tr>
<tr>
<td>Intermediate [K⁺]₀ and PCA (n = 15)</td>
<td>6.4 ± 0.2</td>
<td>6.5 ± 0.2</td>
</tr>
<tr>
<td>High [K⁺]₀ (n = 13)</td>
<td>9.1 ± 0.2</td>
<td>9.2 ± 0.2</td>
</tr>
<tr>
<td>High [K⁺]₀ and PCA (n = 16)</td>
<td>9.2 ± 0.2</td>
<td>9.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. PCA = procainamide.

Experimental protocols. The ventricle was stimulated by a square-wave bipolar pulse of 4 msec at the threshold current for each of the experimental conditions. The characteristics of this stimulator have been reported previously.²⁰ The changes in ventricular rate were accomplished by increases in the stimulus frequency in steps by 0.5 Hz until 2:1 capture occurred. The shortest interstimulus interval included in our analysis, 250 msec, was at least 10 msec greater than that causing 2:1 capture. The heart was paced for 25 beats at each rate and allowed to beat spontaneously or was driven at the slowest pacing rate between each increment in ventricular rate. The slowest rate used was that capable of overdriving the spontaneous escape supraventricular pacemaker and was usually 2 to 2.5 Hz (100 to 150/min). The first beat of the 25 beat pacing train was coupled to the last spontaneous beat or slowly paced beat by the same interstimulus interval as that present during the 25 beat pacing train.

Infusion of potassium and procainamide. Myocardial [K⁺]₀ concentration was raised by the infusion of potassium chloride solution at a constant rate in the range of 0.25 to 1.0 meq/min with a mechanical infusion pump. The miniature potassium ion-selective electrodes were used to guide the potassium chloride infusion rate. When the myocardial [K⁺]₀ reached the intermediate level, i.e., approximately 6 mM, the infusion rate was adjusted to maintain a stable myocardial [K⁺]₀. Equilibration of arterial and myocardial [K⁺]₀ required 15 to 20 min. The pacing protocol was performed 5 to 10 min after equilibration. Myocardial [K⁺]₀ was then elevated to the high concentration, i.e., approximately 9 mM, by adjustment of the infusion rate, and maintained at that level for 25 to 30 min before the rapid pacing protocol was repeated. The potassium infusion was then discontinued.

It was our intent to allow the myocardial [K⁺]₀ concentration to return to the initial concentration, i.e., control [K⁺]₀, before the administration of procainamide. However, the new baseline was always significantly greater than the control [K⁺]₀. Therefore, it was necessary to use two protocols to determine the effects of procainamide at each of the three potassium levels. The first protocol, protocol A, was carried out in 14 animals. Activation times for various frequencies of left ventricular stimulation were determined in the presence of control, intermediate, and high myocardial [K⁺]₀. The myocardial [K⁺]₀, was then allowed to return to the intermediate [K⁺]₀. Procainamide was then administered and left ventricular stimulation was repeated at the intermediate and high myocardial [K⁺]₀.

The effect of procainamide in the presence of control [K⁺]₀, was addressed by protocol B. Activation times were determined at the control myocardial [K⁺]₀, both before and after the administration of procainamide. Rapid ventricular stimulation was then repeated in the presence of procainamide at the intermediate and high myocardial [K⁺]₀. Protocol B was carried out in seven animals. In both protocols arterial serum potassium concentrations were obtained immediately before and after ventricular stimulation for each experimental condition and are reported in table 1.

In each protocol, procainamide hydrochloride was administered by an intravenous bolus of 20 mg/kg over 20 min followed by a constant infusion of 3 mg/min. The pacing protocol commenced 40 min after the constant infusion had begun. Serum procainamide concentrations were determined by an enzymatic immunoassay (Emit procainamide assay) of the arterial blood drawn immediately before and after ventricular stimulation at each myocardial [K⁺]₀ level. This dosing protocol resulted in steady-state procainamide concentrations of 12.2 ± 2.6 g/ml (range 7.7 to 16.5 g/ml). The mean concentrations of procainamide at each potassium concentration are illustrated in table 1. Neither the potassium nor procainamide concentration dif-
ferred significantly in protocol A and protocol B. Therefore, the potassium and procainamide concentrations from the two protocols are combined in table 1.

**Data analysis.** We analyzed our data to determine the significance of the following: (1) Differences in conduction slowing induced by changes in myocardial [K⁺]₀ in the absence and presence of procainamide at a constant interstimulus interval of 440 msec. (2) The effect of an increase in myocardial [K⁺]₀ on the magnitude of conduction slowing induced by procainamide at a constant interstimulus interval of 440 msec. (3) Differences in rate-dependent conduction slowing induced by changes in myocardial [K⁺]₀ in the absence and presence of procainamide as the interstimulus interval was decreased from 440 to 330, 280 or 250 msec. (4) The effect of an increase in myocardial [K⁺]₀ on the magnitude of rate-dependent conduction slowing induced by procainamide.

The EAT and QRSₐ were determined as the mean of the individual EAT or QRSₐ durations of the last four complexes at each paced interstimulus interval.

The experience for each condition was summarized with the mean and its standard error. Because the extent of variability for conditions tended to increase as the mean value increased, comparisons were undertaken by applying analysis of variance methods to the ranks of the data for all conditions of all animals. The analysis of variance model included components for animal and condition. Statistical tests for pairwise comparisons between conditions were based on approximate t statistics for corresponding estimated differences in the mean ranks from this analysis of variance model. Comparisons of the magnitude of the procainamide effect among the three myocardial [K⁺]₀ levels were undertaken by use of contrast statements in the analysis of variance model.

**Results**

Conduction times at the longest common interstimulus interval (440 ms). Figure 3 shows the EATs (A) and QRSₐs (B) recorded at the longest interstimulus interval common to each experiment at each myocardial [K⁺]₀ before and after the administration of procainamide. The results obtained from measurements of EAT and QRSₐ were similar. Increasing the myocardial [K⁺]₀ from the control to the intermediate [K⁺]₀ resulted in no significant change in the conduction time. The further increase of myocardial [K⁺]₀ to the high level resulted in a statistically significant prolongation of conduction.

Procainamide caused a small increase in conduction time at the control [K⁺]₀ at a level of significance of p = .14 for EAT and p = .08 for QRSₐ. At both the intermediate and high [K⁺]₀ procainamide significantly increased conduction time.

Although the change in conduction time produced by procainamide at the longest common interstimulus interval increased progressively as the myocardial [K⁺]₀ increased from control to intermediate to high levels, differences reached statistical significance only between intermediate and high [K⁺]₀.

**Rate-dependent effects of potassium and procainamide on conduction times.** The rate-related change in conduction relative to the conduction time at an interstimulus interval of 440 msec for all experiments is shown in figure 4. In the absence of procainamide, at the control myocardial [K⁺]₀, no rate-related change in conduction time was observed as the interstimulus interval was decreased from 440 through 250 msec. An increase in myocardial [K⁺]₀ to the intermediate level resulted in a small rate-dependent change in conduction time for both QRSₐ and EAT at 250 msec. At the high [K⁺]₀, even a slight decrement in the interstimulus interval from 440 to 330 msec resulted in rate-dependent conduction slowing that increased progressively as the rate was increased.

**FIGURE 3.** Steady-state epicardial activation time (A) and QRSₐ (B) obtained at the longest common interstimulus interval (440 msec) at control (C), intermediate (I), and high (H) myocardial [K⁺]₀, before (open bar) and after (hatched bar) procainamide (PCA). The number of experiments performed for each condition are included above each bar. The values represent the mean ± SEM.
After the administration of procainamide, rate-dependent conduction slowing was observed at the control \([K^+]_0\) at an interstimulus interval of 280 and 250 msec. At the intermediate and high myocardial \([K^+]_0\), rate-dependent conduction slowing increased progressively as the interstimulus interval was decreased from 330 through 250 msec.

Comparisons of the rate-dependent change in conduction between various experimental conditions and their corresponding p values for the interstimulus intervals of 280 and 250 msec are shown in table 2.

In general, in the absence of procainamide the rate-dependent conduction slowing induced by high \([K^+]_0\) was greater than that caused by intermediate \([K^+]_0\) or control \([K^+]_0\). For each myocardial \([K^+]_0\) studied administration of procainamide resulted in greater rate-dependent conduction slowing. Furthermore, the magnitude of the rate-dependent change in conduction time at high \([K^+]_0\) was significantly greater than that at the control or intermediate \([K^+]_0\).

The increments in conduction time at each myocardial \([K^+]_0\) attributed to procainamide were compared by the use of contrast statements in the analysis of variance model. In general, the increment in the conduction time produced by procainamide increased progressively as myocardial \([K^+]_0\) rose and as the interstimulus interval decreased. Comparison of the rate-dependent increment in conduction time at an interstimulus interval of 250 msec at control compared with high myocardial \([K^+]_0\) indicated a significant difference (p = .0134).

**Relationship between pacing stimulus and repolarization.**
The monophasic action potential from the epicardial surface at the left ventricular apex was obtained in three experiments of protocol A to guarantee that our results were not influenced by the depolarization of incompletely repolarized fibers. Figure 5 demonstrates the effects of procainamide at the high \([K^+]_0\) in one such
TABLE 2

<table>
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<tr>
<th>Interstimulus interval (280 msec)</th>
<th>C</th>
<th>C/PCA</th>
<th>I</th>
<th>I/PCA</th>
<th>H</th>
<th>H/PCA</th>
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<tr>
<td>C</td>
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<td>NS</td>
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<td>.0001</td>
<td>.0001</td>
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<td>.0001</td>
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<tr>
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<td>.0003</td>
<td>.0125</td>
<td>.0001</td>
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<tr>
<td>H</td>
<td>.0001</td>
<td>.034</td>
<td>.0006</td>
<td>NS</td>
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<tr>
<td>H/PCA</td>
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<td>.0001</td>
<td>.0001</td>
<td>.0011</td>
<td>.0010</td>
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<table>
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<th>Interstimulus interval (250 msec)</th>
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<th>I</th>
<th>I/PCA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>.0001</td>
<td>.0023</td>
<td>.0001</td>
<td>.0001</td>
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<tr>
<td>C/PCA</td>
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<td>.0006</td>
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<tr>
<td>I/PCA</td>
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<td>.0001</td>
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<td>.0001</td>
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<td>.178</td>
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<td>.0001</td>
<td>.0001</td>
<td>.0018</td>
<td>.058</td>
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The table lists p values for comparisons for rate-dependent changes in conduction time among experimental conditions. The data show that the rate-dependent changes occur at different intervals and are influenced by various factors such as the interval between stimuli and the presence or absence of drugs. The table provides a detailed analysis of these changes across different conditions.

Discussion

Rate-dependent changes in conduction can be attributed to changes in a variety of active and passive membrane properties, including Vmax, an active membrane property, and cell-to-cell coupling, a passive property. Changes in Vmax can be voltage-dependent and time-dependent. Voltage-dependent changes occur when the membrane potential at the onset of depolarization is made less negative by a reduction in the resting membrane potential, or when the fiber depolarizes before completion of the preceding repolarization. These changes are a function of the inactivation of the sodium current.3 Time-dependent changes occur both in the presence and absence of changes in the membrane potential. These changes are in themselves voltage dependent and reflect the reactivation characteristics of the sodium current.22

Rate-dependent decreases in Vmax of the action potential upstroke and in conduction of responses arising from completely repolarized fibers have been described both in the absence and presence of drugs in cardiac tissue preparations7, 10, 23, 24 and in man.25, 26 In the absence of drugs, these changes can be attributed to rate-dependent changes in the resting potential7 and to the recovery characteristics of the action potential upstroke.22 Both mechanisms can be invoked to explain the rate-dependent conduction slowing observed from high myocardial [K+]o alone. It is also possible that cellular uncoupling may occur at rapid rates of stimulation27 due to the accumulation of sodium28 and intracellular calcium.29 However, there is no reason to expect that cellular uncoupling would be more pronounced at the higher potassium levels.

These mechanisms are also operative in the presence of antiarrhythmic drugs. However, the most important mechanism for drug-induced rate- or use-dependent changes in Vmax and conduction involves the characteristics of the interaction of the drug with the sodium channel and the subsequent effects of this interaction on Vmax and conduction as expressed in the modulated30 or guarded31 receptor hypotheses.

Our study has shown that the rate-dependent changes in conduction induced by procainamide become progressively greater as myocardial [K+]o rises, and there-
fore, when the resting potential is made less negative. This result is consistent with those of Sada et al. who showed that the rate-dependent effects of procainamide on Vmax in guinea pig papillary muscles were greater when the fibers were depolarized with potassium. In their experiments, increasing the stimulation frequency from 2 to 4 Hz at a 10 mM [K+]o in the presence of 0.37 mM procainamide (200 g/ml) was associated with a 10% reduction in Vmax from 60 to 40 V/sec relative to a control Vmax of 200 V/sec.

Because Vmax is related to the square of longitudinal conduction velocity in papillary muscle, the 10% reduction in Vmax observed by Sada et al. would be expected to cause an 18% reduction in conduction velocity. Our results, illustrated in figure 4, demonstrate a 27% and 20% increase in the EAT and QRS, respectively, as the stimulation frequency was increased from 2.3 to 4 Hz at a myocardial [K+]o of 9.2 mM and a procainamide concentration of 12.5 g/ml. The cause of the greater rate-dependent changes in the presence of increased myocardial [K+]o has been attributed to a voltage-dependent effect on the modulated receptor mechanism. Hondeghem and Katzung have listed three explanations for these voltage-dependent changes in the use-dependent effects of the antiarrhythmic drugs on Vmax. These include a greater affinity of depolarized sodium channels for the drug, a slowed recovery from sodium-channel block in depolarized channels, and a drug-induced shift in the relationship between the resting membrane potential and Vmax to more negative potentials. They also considered the possibility that the association and dissociation rate constants themselves might be voltage dependent.

Because the range of frequencies studied corresponds to clinically encountered tachyarrhythmia rates, the enhancement by high myocardial [K+]o of procainamide-induced rate-dependent conduction slowing may have clinical relevance. Recent studies have demonstrated rate-dependent effects of a variety of antiarrhythmic drugs, including procainamide, in man. If resting depolarization and/or elevated myocardial [K+]o were inhomogeneous, as occurs in acute ischemia, one might anticipate significant differences between the effect of the drug on conduction in the center of the ischemic area and in the adjacent marginal and nonischemic areas. Inhomogeneities in conduction may also occur in chronically, but inhomogenously, diseased ventricles. Such inhomogeneities may result in the selective rate-dependent depression of conduction by antiarrhythmic drugs in the areas of depressed myocardium, which could either abolish or create reentry circuits. Further studies are required to characterize the magnitude and consequences of regional differences in conduction slowing induced by the use-dependent effects on antiarrhythmic drugs in ventricles that are acutely or chronically diseased.

Possible limitations of the study. The purpose of this study was to determine the influence of a progressive increase in myocardial [K+]o on the rate-dependent conduction slowing induced by procainamide. We are aware that the determination of conduction time in the intact heart must be carefully performed to eliminate the confounding effect of a change in conduction pathway. Discontinuous propagation of the wavefront may occur as the excitability of the tissue is altered by hyperkalemia and/or antiarrhythmic drugs. Tsuoi et al. showed that noncontinuous propagation occurred during rapid electrical stimulation when the extracellular [K+]o was increased above 10 mM in superfused canine ventricular muscle. However, we believe that the prior work by others with the methods used in this study allows us to interpret our results as indicative of changes in conduction velocity rather than changes in conduction pathway. In particular, Gardner et al. used a microelectrode grid to show uniform propagation of the wavefront in canine epicardium in the presence of 1 g/ml of epinephrine, despite a [K+]o of 16 mM. Physiologic levels of catecholamines not present in the superfused preparation might serve to facilitate conduction and maintain longitudinal conduction in vivo. We also required that no change occur in the morphology of the QRS complex during any of the interventions performed in this study, a criterion used by several groups of investigators to indicate that conduction pathways did not change. Moreover, we required that the correlation coefficient between changes in QRS and EAT during all interventions be equal to or greater than .9 and rejected experiments in which this criterion was not met.

Participation of the Purkinje system was also considered as a potential source of error in the measurement of conduction time. However, Swain and Weidner showed that the conduction time of an impulse propagating along the epicardium as measured between multiple electrodes was not significantly influenced by the Purkinje system until the recording electrode was greater than 20 mm from the stimulation electrode, even in the presence of high [K+]o or quinidine. Because of these observations by Swain and Weidner, we positioned our distal recording electrode no more than 20 mm from the stimulating electrode.

To exclude complexes initiated before the end of a preceding repolarization, which would result in voltage-dependent changes, we restricted our analysis of
beats having an interstimulus interval at least 10 msec longer than that associated with 2:1 conduction at threshold stimulation current. We also determined in three experiments that the onset of the monophasic action potential at the most rapid stimulation rate did not occur before the completion of the preceding repolarization.

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