Modulation of Procainamide’s Effect on Cardiac Conduction in Dogs by Extracellular Potassium Concentration
A Quantitative Analysis
Christine Villemaire, MScA; Stanley Nattel, MD

Background Antiarrhythmic drugs are known to have state-dependent interactions with cardiac sodium channels, and these have potentially important implications for drug effects on cardiac conduction, particularly in situations of changed resting potential and heart rate. Recent advances in theoretical approaches permit beat-to-beat changes in sodium channel block to be inferred from conduction changes in vivo and allow for an analysis of state-dependence drug action from conduction changes occurring on the onset of pacing at different rates. The purpose of the present study was to use this method to analyze the interaction between hyperkalemia and procainamide’s sodium channel-blocking action in terms of resulting changes in left ventricular conduction.

Methods and Results Epicardial mapping with a 56-electrode array was used to assess ventricular conduction in open chest, anesthetized mongrel dogs with Formalin-induced atrioventricular block. Procainamide was infused as a series of loading and maintenance infusions until at least 20% conduction slowing was obtained at the shortest basic cycle length (300 milliseconds). Results in a control set of normokalemic dogs were compared with results in dogs with moderate hyperkalemia produced by a loading and maintenance infusion of potassium chloride. Plasma procainamide concentration was measured by high-performance liquid chromatography, and the constancy of serum potassium concentration was verified with ion-sensitive electrode measurement. Although hyperkalemia itself (mean±SEM potassium concentration, 6.64±0.66 mmol/L) did not alter conduction, it resulted in substantially increased conduction slowing by procainamide despite substantially lower plasma drug concentrations (102±10 μmol/L) compared with normokalemic dogs (potassium concentration, 3.87±0.24 mmol/L; procainamide concentration, 277±16 μmol/L). The onset of conduction slowing and block followed basic molecular theory, with an exponential time constant that was faster at longer cycle lengths and total block that increased as cycle length decreased. Piecewise exponential analysis of block during the rested and depolarized phases of the action potential showed that the enhancement of procainamide’s action by hyperkalemia was due almost exclusively to increased rested-phase block. Hyperkalemia produced a bradycardia-dependent and slight reduction in action potential duration and antagonized the action potential-prolonging effect of procainamide, particularly at shorter cycle lengths.

Conclusions Hyperkalemia strongly enhances procainamide-induced conduction slowing by increasing the interaction between the drug and sodium channels during the rested phase of the cardiac cycle. These results indicate the applicability of basic molecular theories of antiarrhythmic drug action to understanding drug-induced changes in conduction velocity in vivo and highlight the potential importance of heterogeneous magnification of sodium channel-blocking drug action by the spatially variable hyperkalemia that occurs with acute myocardial ischemia. The latter could play an important role in the known proarrhythmic potential of sodium channel-blocking drugs in patients with coronary artery disease.

Key Words • electrocardiography • arrhythmia • sodium channels • antiarrhythmics

It has long been known that serum potassium concentration can modulate the action of antiarrhythmic drugs. Increases in extracellular potassium concentration ([K+]) are an important consequence of acute myocardial ischemia and contribute significantly to the associated abnormalities of ventricular conduction and cardiac rhythm. The effects of antiarrhythmic drugs on conduction in ischemic ventricular muscle are likely to be influenced by these changes in [K+].

Cascio et al have shown that extracellular hyperkalemia enhances rate-dependent conduction slowing by procainamide. The presumed mechanism underlying their findings was enhancement of state-dependent sodium channel blockade by depolarization caused by hyperkalemia. Quantitative approaches have been developed to analyze state-dependent channel blockade and have been used to derive kinetic parameters characterizing quinidine’s interaction with sodium channels in isolated Purkinje fiber preparations studied in vitro. We have shown that interval-dependent conduction changes produced by sodium channel blockers are consistent with a squared relation between conduction velocity and indexes of sodium current. This allows for the estimation of drug-induced sodium channel blockade based on conduction changes in vivo. We have recently used such in vivo estimates of procainamide-induced block to derive binding and unbinding rate constants for the sodium channel and found them to be in the same range as values obtained from more direct estimates in vitro.
Although qualitative enhancement of procainamide’s conduction-slowing effect by hyperkalemia has been shown to occur in vivo,6 there has been no quantitative assessment of underlying state-dependent changes in drug action. The present experiments were designed to analyze in a quantitative fashion the ways in which hyperkalemia modifies procainamide’s effects on ventricular conduction in vivo.

Methods

Experiments were performed on 14 mongrel dogs of either sex weighing 15 to 20 kg that were anesthetized with morphine (2 mg/kg IM) and α-chloralose (100 mg/kg IV). A Harvard Apparatus respirator provided mechanical ventilation through an endotracheal tube at a rate of 10 breaths per minute. Arterial blood gases and pH were monitored routinely and maintained in the normal range (pH 7.35 to 7.45, SaO2 >90%) by adjusting the ventilator. Body temperature was maintained constant (37 to 38°C) with a heating blanket. A right thoracotomy was performed at the fifth or sixth intercostal space. Complete ativoventricular block was created by the injection of Formalin,20 and the heart was stimulated with a bipolar Teflon-coated stainless-steel electrode inserted intramurally into the right ventricle. Constant-current pacing stimuli were delivered with a programmable stimulator (model BERS D/A, Digital Cardiovascular Instruments) and a stimulator isolator to provide 4-millisecond square-wave pulses at twice diastolic threshold.

The six standard surface ECG leads, blood pressure, a ventricular electrogram, a right ventricular monophasic action potential (MAP), and stimulus artifacts were monitored and recorded with a computer (Astromed 9600) at a paper speed of 200 mm/s. MAP signals were obtained from the right ventricular endocardial surface using a bipolar contact catheter electrode (EP Technologies Inc) introduced via the right jugular vein. MAP duration was measured at 90% repolarization as previously described.17 The right ventricle was paced at a frequency of 1 Hz, except when specific pacing protocols were used for evaluation of frequency-dependent drug action.

Activation Mapping

A multiple-electrode grid, composed of 56 bipolar electrodes spaced 6 mm apart and aligned in a plaque of 10 rows by six columns, was fixed on the right ventricle. The plaque was sewn to the right ventricular surface with the long axis parallel and adjacent to the left anterior descending coronary artery. Each signal was filtered with a band-pass of 30 to 400 Hz, digitized with 12-bit resolution and a 1-kHz sampling rate, and transmitted via duplex fiberoptic cables into a microcomputer (model 286, Compaq Computer). Software routines were used to amplify, display, and analyze each electrogram signal as well as to generate maps showing activation times at each electrode site. Each electrogram was analyzed by computer-determined peak-amplitude criteria and reviewed manually to exclude low-amplitude signals with indiscernible electrograms. The accuracy of activation time measurements was ±0.5 millisecond. The data were downloaded on high-density (1.2 Mbyte) diskettes for subsequent off-line analysis. Activation maps for each test activation were recorded with an IBM inkjet printer. Hardware and software for the mapping systems were obtained from Biomedical Instrumentation Inc (Markham).

Conduction time was calculated as the time elapsed between activation at the site adjacent to the stimulating electrode and activation at the last epicardial site activated. Conduction velocity was calculated from the time required for activation to travel 1.2 cm (the distance between three consecutive bipolar electrodes) in the direction parallel to fiber orientation. Constancy of the activation pattern was evaluated by observation of isochronal activation (qualitative) and, subsequently, by computation of the relative conduction times to each electrode site for different activations as previously described.16,17

Drug Administration

Loading and maintenance-dose infusion regimens were applied as in previous reports17 to produce a series of stable procainamide concentrations. As many as three loading doses of 50 mg/kg IV were given, followed by maintenance dosages of 12, 24, and 36 mg·kg⁻¹·h⁻¹ after 1, 2, or 3 loading doses, respectively. Electrophysiological studies were begun 20 minutes after the onset of each maintenance infusion. If conduction time at a cycle length of 300 milliseconds was prolonged by at least 20% relative to control, the entire study was performed during that maintenance infusion. On the other hand, if drug-induced conduction slowing was <20%, the next loading dose was administered. This procedure was repeated until a dose was found that increased conduction time by >20%. Blood samples for procainamide concentration measurement by high-performance liquid chromatography16 were drawn before and after electrophysiological studies for confirmation of the stability of drug concentrations.

Experiments were performed in seven normokalemic control dogs and in seven dogs with hyperkalemia produced by systemic infusion of potassium chloride. Stable hyperkalemia with approximately twice control serum potassium concentration was produced by a loading dose of 1 mEq/kg administered as a 0.6 to 0.8 mEq/min IV infusion over 25 minutes, followed by a maintenance dose of 0.3 to 0.5 mEq/min IV. Serum potassium concentration was measured periodically during the study with an ion-sensitive electrode on a multichannel analysis system (Astra-8, Beacham Inc), and values were stable over time (Fig 1).

Experimental Protocol and Kinetic Analysis

The kinetics and magnitude of procainamide-induced conduction slowing were assessed with the use of experimental protocols and analysis techniques described in detail previously.17 Briefly, pacing was initiated at a selected cycle length after a prolonged pause that averaged 7.2±0.4 seconds. An 8-second window of activation data was recorded, along with MAPs over the same interval. Conduction times and velocities were determined subsequently from activation maps constructed off-line.

To estimate procainamide association (k) and dissociation (l) constants during the depolarized (kₐ, lₐ) and resting (kᵢ, lᵢ) phases of the action potential, we determined characterizing
TABLE 1. Potassium and Procainamide Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Normokalemic Dogs</th>
<th>Hyperkalemic Dogs</th>
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<tbody>
<tr>
<td>Serum potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before K⁺ infusion</td>
<td>3.54±0.36</td>
<td>3.87±0.24</td>
</tr>
<tr>
<td>After K⁺ infusion</td>
<td></td>
<td>6.64±0.66</td>
</tr>
<tr>
<td>Plasma procainamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration, μmol/L</td>
<td>277±16</td>
<td>102±10</td>
</tr>
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</table>

Variables from a piecewise exponential analysis of beat-to-beat sodium channel block. Sodium channel block was estimated from changes in conduction, assuming a squared relation between \( I_{Na} \) and conduction velocity.

Statistical Analysis

Group data are given as mean±SEM. Comparisons between two groups were performed by paired or unpaired Student's t test, as appropriate. A value of \( P<.05 \) was taken to indicate a statistically significant difference.

Results

The infusion of potassium chloride caused an approximate doubling in serum potassium concentration (Table 1), with concentrations remaining constant through the study period (Fig 1). The first loading dose (50 mg/kg) was sufficient to produce >20% conduction slowing in all hyperkalemic dogs, whereas in normokalemic dogs, two doses (total of 100 mg/kg) were required in five dogs and three doses (150 mg/kg) were required in the other two. Correspondingly, lower procainamide concentrations were required to produce perceptible degrees of conduction slowing in the presence of hyperkalemia (Table 1). Despite these lower plasma drug concentrations, conduction was considerably more slowed in the presence of hyperkalemia (Fig 2). Although conduction times were not significantly altered by hyperkalemia per se (Fig 2), procainamide increased conduction time to a much greater extent in the presence of elevated potassium concentration.

A key step in the estimation of kinetic interactions with the sodium channel is the observation of the onset of block following a pause permitting drug unbinding. The onset of procainamide-induced conduction slowing in one normokalemic dog. Changes in conduction time, as measured from the first to the last point activated in the electrode array, are shown at the upper left (Fig 3A). Changes in longitudinal conduction velocity, as measured from the activation of three consecutive electrodes along the line of rapid propagation, are shown in Fig 3B. Fig 3C and 3D show the onset of sodium channel block, as calculated based on changes in conduction time (Fig 3C) and conduction velocity (Fig 3D), respectively. Fig 4 shows corresponding data obtained in the presence of hyperkalemia. The onset of block is well fit by a single exponential relation, with a rate constant (\( \lambda^* \)) that decreases with decreasing cycle length, as predicted by theoretical analysis. The level of steady-state block (\( b_n \), value of \( b_n \) at steady state) increases with decreased cycle length, as expected for a use-dependent channel blocker. Overall, drug-induced changes are substantially greater in the hyperkalemic dog.

There was close agreement between analyses based on conduction time and those based on conduction velocity. Because the conduction velocity determination was based on activation at three points separated by 1.2 cm and the precision of activation measurements with the mapping system was ±0.5 millisecond, small drug-induced conduction velocity changes (as occurred at long cycle lengths in normokalemic dogs) could not be determined with sufficient precision to calculate underlying kinetic variables in some dogs. Because the conduction time measurement was based on more widely separated points, it could be determined with greater accuracy. Therefore, in calculating blocking kinetics, we routinely used estimates of sodium channel block obtained from changes in overall conduction time, as in our previous work.

Fig 5 shows values for \( b_n \) in all normokalemic and hyperkalemic dogs. Block in the presence of hyperkalemia exceeded that in the presence of normokalemia. For both normokalemia and hyperkalemia, block increased with decreasing cycle length. The relative difference between drug-induced block among hyperkalemic versus normokalemic dogs was greatest at long cycle lengths. For example, at a cycle length of 1000 milliseconds, \( b_n \) in hyperkalemic dogs was an average of 84% greater than in normokalemic dogs, compared with a difference of 30% at a cycle length of 300 milliseconds.

The mathematical approach to estimating kinetic variables is described in detail in previous theoretical and experimental articles and will not be repeated here. The overall approach is illustrated in Fig 6. The cell is conceived of as cycling between two drug affinity states: a high-affinity state following activation and designated a (in the case of procainamide, corresponding to the period of channel inactivation during the action potential plateau), and a low-affinity state designated r when the cell is not activated. These correspond to the depolarized and rested phases of the cardiac electrical cycle, respectively. Interaction with the high-affinity state is characterized by a rate constant of \( \lambda_a \), whereas interaction with the low-affinity state has a rate constant of \( \lambda_r \). If cells were continuously activated, block would approach a steady-state level of block \( a \) with a time constant of \( 1/\lambda_a \). On the other hand,
if after activation cells were maintained at rest indefinitely, block would decrease to a steady-state level \(r_s\) with a time constant of \(1/\lambda_s\). Because cells in the beating heart are neither continuously activated nor continuously at rest, the degree of block will depend on the relative amount of time in the high-affinity and low-affinity states during each cycle and the steady-state levels of block for each state at a particular drug concentration. The rate constants \(\lambda_s\) and \(\lambda_a\) are, in turn, dependent on the binding \(k_a, k_r\) and unbinding \(l_a, l_r\) constants of the drug-channel interaction for each state and the drug concentration (D) as shown in the figure. Analysis of the onset of block at different cycle lengths allows for the calculation of \(\lambda_s, \lambda_a, k_a, k_r, l_a, l_r, a_s, a_r\) and \(r_s\) as previously described.\(^{12-14,17}\)

The kinetic variables calculated for procainamide from conduction time changes in the present experiments are shown in Table 2. Although maximal steady-state block in the high-affinity state \((a_s)\) is increased by 20% in the presence of hyperkalemia, steady-state block during electrical diastole \((r_s)\) is increased by more than 170% (despite lower drug concentrations in the presence of hyperkalemia). This increase in steady-state diastolic block is due predominantly to an almost four-fold increase in the forward rate constant for diastolic block \((k_r)\).

Based on the calculated kinetic constants and proportion of time in the rested and depolarized phases of the cardiac cycle, it is possible to estimate the fraction of channel block at any rate that is due to interaction during each phase. For each, block will be proportional to the product of the rate constant for block onset, the time during each cycle occupied by that phase, and the corresponding steady-state block (ie, \(a_s\) and \(r_s\)). Fig 7 shows the results of this analysis. As shown on the left, hyperkalemia did not substantially alter the plateau-phase block \((b_p)\) caused by procainamide. In contrast, hyperkalemia substantially increased the rested-phase block \((b_r, middle)\). Hyperkalemia-induced increases in rested-phase block were greatest at long cycle lengths, at which depolarized-phase block is the least. Consequently, the result of hyperkalemia is to increase the proportion of total block due to association with the rested phase. Fig 7 (right) shows the ratio of rested- to depolarized-phase block \((b_r/b_p)\) in hyperkalemia and normokalemic dogs as a function of cycle length. In normokalemic dogs, rested-phase block is much smaller than depolarized-phase block at all cycle lengths. Hyperkalemia significantly increases the importance of rested-phase block at all cycle lengths, with the relative importance of rested-phase block increasing substantially with increasing cycle length to the point that resting-phase block contributes almost as much as depolarized-phase block at a cycle length of 1000 milliseconds.

Table 2 shows that hyperkalemia produces a small, but statistically significant, increase in maximal steady-state plateau block \((a_s)\) due to procainamide. One

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**Table 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>CV (m sec)</th>
<th>BCL (m sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normokalemic</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperkalemic</td>
<td>0.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Fig 3. Plots of beat-to-beat changes in conduction time \((CT; A)\) and conduction velocity \((CV; B)\) in a normokalemic dog. Results were obtained at five basic cycle lengths \((BCLs)\); 300 milliseconds, \(\odot\); 400 milliseconds, \(\circ\); 500 milliseconds, \(\bullet\); 600 milliseconds, \(\triangle\); 800 milliseconds, \(\triangleright\). The onset of drug-induced sodium channel block was estimated from changes in CT \((C)\) and CV \((D)\), assuming a squared relation between CV and sodium current. Results were well fit by single exponential equations (lines shown), with rate constants \((\lambda^2)\) shown. As predicted from underlying theory, the onset of block was more rapid at longer BCLs.
might therefore expect hyperkalemia to augment both plateau and diastolic sodium channel block. Fig 7A shows, however, that plateau sodium channel block was not increased by hyperkalemia. This finding can be explained by three factors. First, hyperkalemia reduced action potential duration (APD) at slower rates (Fig 8, top). Second, hyperkalemia antagonized the APD-prolonging properties of procainamide (Fig 8, bottom), such that APD was increased significantly less by the drug, particularly at shorter cycle lengths, in hyperkalemic dogs than in normokalemic dogs. Consequently, the amount of time available for drug binding to the plateau state was reduced by hyperkalemia. Finally, the estimated rate constant for plateau block ($\lambda_p$) was reduced by hyperkalemia (Table 2), so that for a given plateau duration a smaller percentage of maximal plateau-state block was achieved by the drug.

**Discussion**

We have shown a strong interaction between moderate hyperkalemia and the conduction-slowing properties of procainamide in vivo. Sodium channel blockade, as inferred from conduction changes, was increased in a rate-dependent fashion, primarily because of an increased interaction with channels during the resting phase of the cardiac cycle. The magnitude and dynamic beat-to-beat blocking properties followed the predictions of basic theoretical models.7-14

**Comparison With Previous Studies in the Literature**

Interactions between extracellular potassium concentrations and antiarrhythmic drug action have long been recognized.1 Hyperkalemia is known to enhance the $V_{max}$-suppressant properties of sodium channel-blocking antiarrhythmic drugs2,18,24,25 by voltage-dependent enhancement of state-dependent channel blockade.7-11 Relatively less research has been done to examine the
When an action potential is elicited after a prolonged rest period, a high-affinity state for drug interaction is produced, and block moves toward a steady-state level \( (a_d) \) with a rate constant \( \lambda_s \). Block does not generally reach the steady-state value for the high-affinity state during one action potential, and when repolarization occurs block decreases toward the steady-state value for the resting phase \( (r) \) with a time constant \( \lambda_r \). At the time that the next action potential is initiated, block has not returned to the steady-state value for the resting phase, and additional block occurs as during the first action potential. Block continues to increase until a steady state is achieved, as indicated by \( b_w \). The rate constants for the depolarized and resting phase are related to the forward and reverse affinity constants \( (k_a, k_b, l_a, l_b, i_d, l) \) and the drug concentration \( (D) \) as shown by the equation in the figure. For a detailed description of the methods to determine these rate constants, see References 12 through 14 and 17.

Potentially Important Findings

We have shown that even moderate hyperkalemia strongly enhances the conduction-slowing actions of procainamide. Despite much smaller plasma drug concentrations in hyperkalemic dogs, which averaged 36% of the values in normokalemic animals, procainamide increased conduction times to a much greater extent in the presence of hyperkalemia (Fig 2). We were able to relate the enhancement of procainamide’s action by hyperkalemia to differential changes in interactions between the drug and sodium channels during the rested and depolarized phases of the cardiac cycle. Our results suggest that hyperkalemia increases procainamide’s conduction-slowing action by increasing block during the resting phase of the cardiac cycle. These observations are consistent with the concept that the increased drug action caused by hyperkalemia is due to a reduction in the resting membrane potential, favoring sodium channel inactivation. The latter promotes drug binding to the channel either by promoting a true high-affinity state or by increasing access to, and limiting egress from, the depolarized inactivated state.

TABLE 2. Kinetic Variables for Procainamide–Sodium Channel Interaction

<table>
<thead>
<tr>
<th></th>
<th>Normokalemic Dogs (n=7)</th>
<th>Hyperkalemic Dogs (n=7)</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_r ), maximal steady-state procainamide block during plateau</td>
<td>0.64±0.06</td>
<td>0.77±0.05*</td>
<td>...</td>
</tr>
<tr>
<td>( r_r ), maximal steady-state procainamide block during diastole</td>
<td>0.14±0.04</td>
<td>0.38±0.05*</td>
<td>...</td>
</tr>
<tr>
<td>( k_a ), rate constant for plateau binding</td>
<td>5.62±0.73</td>
<td>5.97±1.17</td>
<td>per mmol/L per second</td>
</tr>
<tr>
<td>( k_b ), rate constant for diastolic binding</td>
<td>0.41±0.11</td>
<td>1.51±0.43*</td>
<td>per mmol/L per second</td>
</tr>
<tr>
<td>( l_a ), rate constant for plateau unbinding</td>
<td>0.79±0.13</td>
<td>0.19±0.02†</td>
<td>per second</td>
</tr>
<tr>
<td>( l_b ), rate constant for diastolic unbinding</td>
<td>0.43±0.05</td>
<td>0.32±0.08</td>
<td>per second</td>
</tr>
<tr>
<td>( \lambda_s ), rate constant for onset of plateau block</td>
<td>2.14±0.22</td>
<td>0.94±0.16†</td>
<td>per second</td>
</tr>
<tr>
<td>( \lambda_r ), rate constant for onset of diastolic block</td>
<td>0.53±0.07</td>
<td>0.50±0.10</td>
<td>per second</td>
</tr>
</tbody>
</table>

\(*P<.05, †P<.01 vs normokalemic dogs.\)
The substantial potentiation of drug-induced conduction slowing caused by hyperkalemia has important potential implications for drug effects during acute myocardial ischemia. Acute myocardial ischemia causes important and progressive increases in \([K^+]_{\text{e}}\).\(^{29,30,33-36}\) The latter are heterogeneously distributed across infarct and border zones\(^{29,30,33-36}\) and contribute to the conduction slowing and genesis of reentrant ventricular arrhythmias during acute ischemia.\(^{37,38}\) In the present study, we have shown that moderate hyperkalemia, as may occur in the border zone of an acute infarction, profoundly enhances procainamide-induced conduction slowing by increasing resting-phase block. More severe degrees of hyperkalemia would be expected to produce even greater enhancement of drug action. The heterogeneous pattern of drug-induced conduction slowing resulting from heterogeneous increases in \([K^+]_{\text{e}}\), would enhance the intensity and dispersion of conduction slowing caused by acute ischemia, contributing to the arrhythmogenic properties of sodium channel-blocking drugs during experimental ischemia\(^{39-41}\) and in patients with chronic coronary artery disease.\(^{42,43}\)

Mathematical models of sodium channel blockers\(^{8,12-14}\) have provided useful insights into potential interactions between antiarrhythmic drugs and the sodium channel at the molecular level. Our previous studies showed that these concepts could be applied to analyze the kinetics of drug effects on ventricular conduction during paired-pulse\(^{16}\) and sustained-pacing\(^{17}\) protocols in anesthetized dogs. The present study extends these observations to the quantitative analysis of drug-induced conduction slowing in the presence of varying \([K^+]_{\text{e}}\), in vivo.

**Study Limitations**

Changes in drug-induced conduction slowing in vivo are, at best, an indirect indicator of varying interactions with sodium channels. We are not proposing that this approach be put forward as a way of analyzing drug-receptor interactions at the molecular level; rather, we show that inferences can be made about such interactions based on in vivo conduction changes and that the conclusions are in agreement with theoretical predictions and with observations at the cellular level. Our findings reinforce the relevance of basic theories about drug action on sodium currents for the detailed understanding of their effects on macroscopic properties like conduction in vivo.
We were not able to cause more severe hyperkalemia while maintaining dogs in a sufficiently stable condition to perform the protocols necessary for detailed quantitative analysis. Our analysis is therefore limited to the moderate hyperkalemia (doubling of $[K^+]_o$) that might occur in the border zone of an acute infarction. The creation of regional hyperkalemia by intracoronary infusion of potassium might be an interesting approach to studying in more detail the interactions among various levels of hyperkalemia, drug-induced conduction changes, and sodium channel–blocking action.

Throughout this article, we have referred to block during the depolarized phase of the action potential as “depolarized-phase block” and to block between depolarizations as “rested-phase block.” The latter should not be equated with rested-state block. Because hyperkalemia results in depolarization, a substantial portion of the block occurring during the resting phase of the cardiac cycle may be due to interaction with inactivated channels.

Conclusions

We have shown that moderate hyperkalemia strongly increases the rate-dependent conduction-slowing action of procainamide. Quantitative analysis suggests that the potentiation of drug action is due predominantly to enhancement of block during the resting phase of the cardiac cycle. This is the first study to apply theoretical models to the analysis of drug–sodium channel interaction underlying drug-induced conduction slowing in the presence of a component of acute myocardial ischemia, extracellular hyperkalemia. It demonstrates the applicability of this type of analysis and suggests its potential relevance to understanding drug action in the presence of derangements of the extracellular milieu and pathological cardiac states.

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