Effects of Quinidine Sulfate on the Balance Among Active and Passive Cellular Properties That Comprise the Electrophysiologic Matrix and Determine Excitability in Sheep Purkinje Fibers

Morton F. Arnsdorf and George J. Sawicki

Quinidine is the most commonly used drug for the chronic treatment of ventricular arrhythmias, but it may be arrhythmogenic. Much information exists concerning quinidine's effects on active properties in cardiac tissues, but virtually nothing is known of its effects on passive properties. We studied the effects of quinidine, in a clinically relevant concentration, on the balance among active and passive cellular properties that comprise the electrophysiologic matrix that determines cardiac excitability. The multiple microelectrode method of intracellular-current application and transmembrane voltage recording was used in sheep Purkinje fibers to determine strength-duration and constant current-voltage relations as well as cable properties. A rapid, on-line computerized data analysis system tracked in time the alterations in the active and passive properties relevant to excitability. In normal fibers at \([K^+]_0 = 5.4\text{ mM}\), quinidine increased cardiac excitability as manifested by a decrease in the current required to attain threshold and/or a downward shift in strength- and charge-duration relations by altering passive properties despite a depressed sodium system and a slowed conduction velocity. During washout, excitability and passive properties remained altered despite a return of descriptive action potential parameters such as the resting potential, the maximum rate of rise of phase 0, overshoot, and the action potential duration to or nearly to normal. At \([K^+]_0 = 8.0\text{ mM}\), quinidine could either increase or decrease excitability; net excitability depends on the balance between altered passive properties and the depressed sodium system. The results explain, in part, the antiarrhythmic actions and arrhythmogenic potential of quinidine. The data for quinidine and other antiarrhythmic drugs are interpreted in terms of the electrophysiologic matrix, which we believe has important advantages over traditional hierarchical classifications. (Circulation Research 1987;61:244-255)

Normal cardiac excitability arises from a highly organized control of ionic flow through pores in the cardiac membrane, myoplasm, gap junctions between cells, and extracellular space. \(^1\) We have suggested that a matrix of active and passive cellular electrophysiologic properties determines normal and abnormal cardiac excitability. \(^2,3\) Active properties include the liminal length and the voltage- and time-dependent membrane ionic conductances responsible for regenerative depolarization and repolarization. Passive properties include the determinants of the resting potential, chord and slope conductances in the subthreshold range, and cable properties. Propagation of the action potential depends on both active and passive properties. \(^1,4,5\) The configuration of the matrix and, in turn, net excitability depend on the balance among these active and passive determinants.

Quinidine is the most commonly used drug for the chronic treatment of ventricular arrhythmias. Its arrhythmogenic potential, as well as its antiarrhythmic effect, has long been recognized. There is no literature regarding quinidine’s effect on cable properties or other passive properties relevant to excitability. Studies to date have examined quinidine’s actions on active cellular properties. Quinidine depresses the maximal rate of rise of phase 0 of the action potential \((V_{\text{m}})\), which has been used as an indirect index of the sodium current, alters the voltage-, frequency-, and state-dependency of \(V_{\text{m}}\) under a variety of experimental conditions, and has a particular affinity for the open or active channel with recovery from channel inhibition occurring relatively slowly. \(^6,7\) In the range of the plateau potential, quinidine shifts the current-voltage relation in the outward direction in sheep Purkinje fibers, \(^8,9\) perhaps inhibits the steady-state sodium “window” current, \(^10,11\) alters inward rectification in rabbit Purkinje fibers, \(^12,13\) and can produce triggered sustained rhythmic activity. \(^14\) Recently, Salata and Wasserstrom \(^15\) observed that quinidine in single canine myocytes reduced steady-state outward current (presumably \(i_{\text{K}}\)), the slow inward current (\(i_{\text{s}}\)), and both the sodium (tetrodotoxin-sensitive) and calcium (tetrodotoxin-insensitive) window currents. The complexity of
mechanisms in the range of the plateau potential may explain the differing observations on the action potential duration that may lengthen or shorten depending on the species, conditions, and drug concentration.27-32

The purpose of the present investigation was to study the effect of quinidine sulfate, in a concentration equivalent to clinically effective antiarrhythmic plasma levels, on important active and passive cellular properties within the electrophysiologic matrix that determines cardiac excitability. The multiple microelectrode method of applying constant current intracellularly while recording transmembrane voltage (V_m) controls numerous electrophysiological variables and permits the determination of strength-duration and current-voltage relations as well as cable analysis, thereby allowing assessment of individual passive as well as active determinants of excitability. Over the years, we have used these and similar techniques to study the effects of antiarrhythmic drugs in the steady state.33-36 More recently, we have developed a rapid, on-line, computerized data analysis system that enables us to track the determinants of excitability in time. We have demonstrated with this approach that arrhythmicogenic interventions and antiarrhythmic drugs may have a complex and changing effect on excitability in time, the net effect due to an altered balance between active and passive properties.37-39

In the present study, quinidine was found to have a complex effect on excitability in time, the overall effect being determined by the balance between altered active and passive cellular properties. The major and somewhat surprising finding was that under the conditions of the present experiments, quinidine increased cardiac excitability despite a depressed sodium system and slowed conduction velocity, an action mediated by changes in passive properties. Important changes in cardiac excitability and cellular electrophysiologic properties were observed to persist even after descriptive parameters of the action potential appeared to have returned to normal. Our findings provide new information regarding the proarrhythmic as well as the antiarrhythmic actions of quinidine. The findings are discussed in terms of our recently proposed electrophysiologic matrix.3

**Materials and Methods**

**Experimental Arrangement**

Sheep hearts were obtained at a local slaughterhouse. After sacrifice, the heart was removed, placed in cooled Tyrode's solution, and transported to the laboratory where Purkinje fiber preparations were dissected. The methods for stimulation and recording have been described in detail.17 Briefly, rectangular constant current pulses were passed intracellularly through 1
microelectrode placed near the cut or ligated end of a long (>3 length constants) Purkinje fiber that appeared to be unbranched grossly under a dissecting microscope. The transmembrane voltage ($V_m$) was recorded by 2 or more additional microelectrodes placed at various points along the length of the fiber. Interelectrode distances and the dimensions of the Purkinje fiber were measured by a dissecting microscope equipped with an ocular micrometer. The tissue bath was kept at virtual ground by an operational amplifier that also produced a voltage signal proportional to the current collected by the Ag-AgCl ground. The signals were displayed on a dual beam oscilloscope and were photographed. A Norland 3001 waveform analysis system converted the analog signals to digital format that, in turn, was fed into a MINC 11/23 computer and was stored on magnetic discs. This system permitted rapid, on-line data analysis.

The composition of the Tyrode’s solution was (in mM): NaCl 125, NaHCO$_3$ 22, NaH$_2$PO$_4$ 2.4, MgCl$_2$ 1.05, CaCl$_2$ 1.8, dextrose 11, and KCl 5.4 or 8.0. The Tyrode’s solution was equilibrated with 95% O$_2$-5% CO$_2$. The volume of the tissue bath was 2 ml, the perfusion rate was 10 ml/min, the bath temperature was maintained at 35–36° C, and the pH was 7.30–7.34. Quinidine sulfate was used in a concentration of 4.0 mg/l (5 μM), a concentration thought equal to clinically relevant antiarrhythmic plasma levels.

**Experimental Procedures**

Our methods of performing and interpreting cable analysis, current-voltage relations, strength-duration curves, charge-duration curves and the limitations of point stimulation for transmembrane voltage control have been described in detail. Briefly, for cable analysis, small hyperpolarizing constant currents of 100-msec duration were applied intracellularly that produced a 4–8 mV change in $V_m$ at a microelectrode located within 100 μm of the stimulating microelectrode. The transmembrane current collected by the bath ground was termed $I_0$. The $V_m$ at the site of stimulus application ($V_s$), the length constant ($\lambda$), the specific membrane resistance ($R_m$), the specific longitudinal resistance ($R_e$), the membrane time constant ($\tau_m$), and the membrane capacitance ($C_m$) were determined according to the method of Weidmann. The limitations of such cable theory have been discussed previously, but the successful and useful description of experimental results using such theory has been demonstrated in physiologic, pharmacologic, and other intervention studies. Threshold voltage ($V_{th}$) was defined as the maximal just-subthreshold $V_m$ response recorded by a microelectrode located within 100 μm of the stimulating microelectrode. Although a change in $\lambda$ after an intervention introduces some error in the determination of $V_m$, the close proximity of the stimulating and recording microelectrodes would limit this error to less than 0.5 mV.

In current-voltage studies, the current duration was 100 msec. Strength-duration curves were analyzed in nonnormalized form where the recorded current required to attain threshold ($I_{th}$) was plotted as a function of the current duration ($t$) and in a normalized form as $I_{th}/I_{th}$ vs. $t$ where $I_{th}$ is the rheobasic current. $I_{th}$ is the smallest current, regardless of duration, required to produce a regenerative response. Operationally $I_{th}$ was defined as $I_{th}$ at 100 msec to avoid the confounding problem of extracellular K$^+$ accumulation. Charge-duration curves were also assessed in both a nonnormalized form ($Q_{th}/I_{th}$ vs. $t$ where $Q_{th}$ is the charge threshold) and a normalized form ($Q_{th}/I_{th}$ vs. $t$). Normalization of the curves minimizes the differences in the shape of the curves caused by altered passive properties, particularly $R_m$ and other properties dependent on $R_e$, but does not obscure changes in active generator properties. Presumably, $R_m$ and properties dependent on $R_e$ are factored out for long duration stimuli by such normalization, but changes in the sodium system would be unaffected. At short-duration stimuli, the charge is so great that the other determinants of the liminal length become essentially negligible. The Lapicque equation is known to describe the strength-duration curve for long Purkinje fibers, but its calculation depends on the extrapolation of charge threshold to time zero, and this extrapolation may be in error twofold in either direction. The possibility of this large error prevents the use of the
Table 1. The Effect of Quinidine Sulfate on Active Cellular Properties at [K⁺]₀ = 5.4 mM in Sheep Purkinje Fibers

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<th>Vₚₑ (mV)</th>
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<th>OS (mV)</th>
<th>APD₉₀ (mV)</th>
<th>APD₃₀ (msec)</th>
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<td>&lt;0.01</td>
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<td>&lt;0.01</td>
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| QS, quinidine sulfate; other abbreviations as in “Table of Abbreviations.” p, level of significance for comparisons between experiment conditions described within parentheses.

Lapicque equation to compare data obtained during the control and intervention periods.

Unless otherwise indicated, preparations were driven at a cycle length of 750 msec through a pair of extracellular electrodes. Vₚₚₚ, the maximal rate of rise of phase 0, was determined from electronic differentiation. The value of Vₚₚₚ in Table 1 is that for a propagated action potential induced by extracellular tissue stimulation. The conduction velocity (θ) of a propagated action potential induced by extracellular tissue stimulation was determined from the conduction time between 2 microelectrodes and the interelectrode distance measured with an ocular micrometer. Values for descriptive parameters such as Vₚₚₚ, the maximal diastolic potential (Vₑ), the action potential duration at 50% and 90% repolarization (APD₉₀ and APD₃₀, respectively), the voltage at APD₉₀ and APD₃₀, and overshoot (OS) were obtained from the average of 25
Table 2. The Effect of Quinidine Sulfate on Cable Properties at [K⁺]₀ = 5.4 mM in Sheep Purkinje Fibers

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<th>V₀ (mV)</th>
<th>Vₜ₁₀₀ (kΩ)</th>
<th>λ (mm)</th>
<th>Rₑ (Ωcm²)</th>
<th>Rₗ (Ωcm)</th>
<th>rₑ (msec)</th>
<th>Cₑ (μF/cm²)</th>
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Mean (±SD)

| Control      | -75.6  | 125.7   | 1.94       | 994    | 105       | 16.7     | 18.1     | 1,150      |
| QS           | -73.9  | 167.4   | 2.45       | 1,640  | 111       | 23.1     | 15.9     | 701        |
| Washout      | -74.8  | 157.9   | 2.39       | 1,543  | 108       | 23.3     | 17.6     | 782        |

p (Control−QS)  <0.05  <0.01  <0.01  <0.01  NS  <0.01  NS  <0.01

% Change       -2.2    33.2   26.3    65.0    5.7    38.2    -12.2   -39.0

p (QS−washout)  NS  NS  NS  NS  NS  NS  NS  NS

% Change       1.2    -5.7   -2.4    -5.9   -2.8   0.9    10.7    11.6

p (Control−washout) <0.01  <0.01  <0.01  <0.01  NS  <0.01  NS  <0.01

% Change       -1.1    14.0   23.2    55.2    2.9    39.5    -2.7    -32.0

QS, quinidine sulfate; other abbreviations as in "Table of Abbreviations." p, level of significance for comparisons between experiment conditions described within parentheses.

consecutive beats of a train once the action potential morphology had stabilized.

Means, standard deviations, and the t test for paired samples were determined by usual statistical methods.46

Results

Experiments at [K⁺]₀ = 5.4 mM

Iₑ, Vₑ, and Vₜ₁₀₀ at t = 100 msec was most commonly used as the index of excitability since it could be rapidly repeated and tracked using the rapid data analysis system. Iₑ at t = 100 msec occurs on the relatively flat portion of the strength-duration curve and is used often as an estimate of Iₑₐ (for example, see Figure 2). The product of current and time, Qₑ, can also be used as an index. Increased excitability is defined as a decrease in Iₑₐ; decreased excitability is defined as an increase in Iₑₐ.

Our approach to the definition of excitability is illustrated in Figure 1. The current and Vₑ traces are at the top and bottom, respectively, of each panel. Note the increase in excitability following quinidine as evidenced by Iₑₐ decreasing from 78 nA in the con-
control situation to 67 nA 30 minutes after exposure to quinidine. \( V_n \) and \( V_r \) did not change significantly in this experiment. Quinidine depressed the sodium system compared with control as evidenced by a decrease both in \( V_{ma} \) from 511 to 310 V/sec and in the overshoot from 37 to 25 mV. In this experiment, \( \theta \) decreased from 2.79 m/sec in the control to 1.97 m/sec after quinidine. \( R_m \) increased from 617 to 1.018 \( \Omega \) cm\(^2\), and \( \lambda \) increased from 1.33 to 1.74 mm after the drug as compared with control.

At \([K+]_o = 5.4 \) mM (Tables 1 and 2), a statistically significant increase in excitability as manifested by a decrease in \( I_n \) (\( -18.7\% \), \( p<0.01 \)) was seen for the 8 experiments. \( V_s \) was 2.2% less negative (\( p<0.01 \)) after quinidine, but \( V_a \) was unchanged. On washout of 60 minutes, excitability remained decreased despite a return to control values of \( V_n \), overshoot, and \( \theta \) and to near control of \( V_s \) and \( V_{ma} \).

**Strength- and Charge-Duration Curves.** Strength- and charge-duration relations are more powerful indexes of excitability than \( I_n \) since normalization gives an indication as to whether active or passive properties are primarily responsible for the shift. Figures 2A and 3A are complete strength-duration relations at \([K+]_o = 5.4 \) mM and 8.0 mM, respectively. These relations have not been normalized and show quinidine to increase excitability as evidenced by the downward shift in the curves. The normalized strength-duration relations (Figures 2B and 3B) showed the curves to be virtually superimposable except for very short-duration stimuli. As discussed in "Materials and Methods," this suggests that changes in passive membrane properties, particularly \( R_m \) and those dependent on \( R_m \), were primarily responsible for the observed net increase in excitability despite depression of the sodium system.

To permit comparison between normalized strength-duration curves for stimuli of short and long duration, points were chosen at \( t/t_m = 0.5 \) and 5, respectively. At \([K+]_o = 5.4 \) mM, significant changes were seen in the normalized strength-duration curves after quinidine, which diverged at \( t/t_m = 0.5 \) (\( p<0.01 \)) but were virtually superimposable at 5.0. As mentioned above, normalization of the strength-duration curve minimizes the differences caused by altered passive properties but does not obscure those caused by altered active generator properties. The data obtained at \( t/t_m = 0.5 \) and 5 suggest that altered passive properties were important in determining total excitability at long current durations but were less important at very short durations. As expected from the strength-duration curves, nonnormalized charge-duration relations (\( Q_a \) vs. \( t \)) revealed a decreased charge requirement for threshold over a wide range of current durations. Normalization (\( Q_a/I_{nma} \) vs. \( t/t_m \)) showed the relation for the control and quinidine curves to be identical over essentially the same range as for the normalized strength-duration curve.

**Current-Voltage Relations.** The curves in Figure 4 reflect increased excitability after quinidine superfusion in the same experiment shown earlier (L3). Membrane slope resistance can be approximated by the relation \( dV_r/dI \). In all 8 experiments at \([K+]_o = 5.4 \) mM, \( I_{na} \) decreased as compared with the control, \( V_{ma} \) remained near the control value, and both slope resistance and \( R_m \) increased. Note that the nonlinearities in the subthreshold portion of the current-voltage relation changed after the drug. Data obtained after a 1 hour washout showed the relation not to have returned to its control, a phenomenon seen in all our experiments.

**Cable Analysis.** Cable analysis was performed in 8 Purkinje fibers (Table 2) at \([K+]_o = 5.4 \) mM. A 2.2% change in \( V_s \) was observed that was sufficiently small to permit comparison of cable values in each group. Quinidine, as mentioned, increased excitability as manifested by a decrease in \( I_n \) (\( p<0.01 \)) at which time a statistically significant increase in \( V_{ma} \), overshoot, and \( \theta \) (\( p<0.01 \)). After 1 hour of washout, these measurements were significantly different from control. \( R_m \) and \( C_m \) did not change significantly.

**Descriptive Action Potential Parameters and Conduction Velocity.** The data at \([K+]_o = 5.4 \) mM is summarized in Table 1. After exposure to quinidine, \( V_n \) and \( V_{ma} \) became less negative (\( p<0.05 \) and 0.01, respectively), and progressive, statistically significant decreases were observed in \( V_{ma} \), overshoot, \( APD_{0} \) and \( APD_{\infty} \), and \( \theta \) (\( p<0.01 \)). After 1 hour of washout, overshoot, \( APD_{0} \) and \( APD_{\infty} \), and \( \theta \) returned to the control values. \( V_n \) and \( V_{ma} \) had returned to within 1 and 7% of the control values, respectively.

**Interval Dependency.** Because of the interval dependency in which quinidine is postulated to bind more avidly to open channels and would have more of an effect on sodium channels at more rapid heart rates, we postulated that there might be a crossover in excitability in which increased excitability seen at a stimulated cycle length of 750 msec might be replaced by decreased excitability at shorter cycle lengths because of further suppression of the sodium system. This was not observed in 4 experiments at \([K+]_o = 5.4 \) mM and 3 experiments at \([K+]_o = 8.0 \) mM with CL as short as 500 msec. While \( V_{ma} \) decreased, \( V_n \) became less negative at the faster driving rates without much change in \( V_a \) and \( I_n \) either was not changed or actually decreased.

**Experiments at \([K+]_o = 8.0 \) mM**

We postulated that at \([K+]_o = 8.0 \) mM, voltage-dependent inactivation of the sodium system might be sufficient to depress excitability despite alterations in passive properties that would tend to increase excitability. Indeed, we observed that at \([K+]_o = 8.0 \) mM, excitability could increase as it had at \([K+]_o = 5.4 \) mM or it could decrease. In the 4 experiments in which excitability increased, the percent change and the mean (± SD) control values as compared with the values during drug infusion were, respectively: \( I_n \), −17.9% from 81.0 (±31.6) to 66.5 (±26.2) nA; \( V_{ma} \), −7.1% from −49.0 (±4.9) to −45.5 (±2.4) mV; and \( V_n \), −2.2% from −68.3 (±1.7) to −66.8 (±0.9) mV. A strength-duration relation from such a preparation is
shown in Figure 3. In the 2 experiments in which excitability decreased, the percent change and the mean control (± SD) values as compared with the values during drug infusion were, respectively: \( I_{\text{ax}} \), +20% from \( 70.0 (± 8.5) \) to \( 84 (± 16.9) \) nA; \( V_{\text{ax}} \), -24% from \( -44 (± 12.7) \) to \( -33 (± 3.7) \) mV; and \( V_r \), -1.4% from \( -70.5 (± 0.7) \) to \( -69.5 (± 0.7) \) mV.

Cable analysis was performed in the same 6 Purkinje fibers at \([K^+]_o = 8.0\) mM, and the change in cable properties was similar for all the preparations regardless of whether excitability increased or decreased. Quinidine produced statistically significant changes in the same parameters as at a \([K^+]_o = 5.4\) mM; only \( R_m \) and \( C_m \) did not change. The mean (± SD) values during the control and drug infusion periods were, respectively: \( V_{\text{m}}/L_m \), 143.6 (± 66.7) and 168.8 (± 74.4) kΩ (+17.5%, \( p<0.01 \)); \( \lambda_1 \), 1.65 (± 0.44) and 1.86 (± 0.95) mm (+13%, \( p<0.01 \)); \( R_m \), 913 (± 618) and 1,220 (± 798) Ω cm² (+34%, \( p<0.01 \)); \( \tau_m \), 9.6 (± 2.7) and 14.2 (± 5.3) msec (+48%, \( p<0.01 \)); \( g_m \), 1,358 (± 488) and 997 (± 345) mS/cm² (-27%, \( p<0.01 \)); and \( V_r \), 69.8 (± 1.1) and -68.5 (± 1.9) mV (-1.9%, \( p<0.05 \)).

For the remainder of our measurements at \([K^+]_o = 8.0\) mM, the mean (± SD) values in the control and drug periods were: \( V_{\text{m}} \), 70.2 (± 3.1) and 68.7 (± 3.4) mV (-2.1%, \( p<0.02 \)); \( V_{\text{m}} \), 377 (± 95) and 211 (± 80) V/sec (-44.1%, \( p<0.001 \)); overshoot, 22.2 (± 7.4) and 6.5 (± 8.9) mV (-70.7%, \( p<0.001 \)); and APD\(_{\text{m}} \), 190 (± 83) and 157 (± 68) msec (-17.6%, \( p<0.05 \)).

**Discussion**

**Quinidine and the Electrophysiologic Matrix**

Traditional classifications of antiarrhythmic drugs are based on a hierarchy of predominant drug actions. In many classifications, drugs such as quinidine, lidocaine, procainamide, and encainide have been categorized together because of their depressant action on the sodium system in tissues with \( i_N \)-dependent phase 0 action potentials. These are often termed Group I drugs, although more and more, experimental results are forcing a further subdivision as in the widely used classification of Vaughan Williams. Our data cannot be interpreted in terms of the traditional hierarchical classification of Group I drugs, which does not account for changes in passive properties or for multiple changes in both active and passive properties. This present study found that quinidine sulfate in a concentration equal to clinically effective antiarrhythmic plasma levels affected passive as well as active cellular properties and that net excitability after quinidine depended on the balance among these altered properties.

A different theoretic framework must be employed, and our recently proposed concept of the electrophys-
iologic matrix\textsuperscript{2,3} accommodates the data of this study quite comfortably. A simple matrix is depicted by the “normal” hexagon in Figures 5 and 6. Only a few of the active and passive properties that form the matrix and determine excitability are included. These are resting potential ($V_r$), threshold voltage ($V_{th}$), sodium conductance ($g_{Na}$), membrane resistance ($R_m$), length constant ($\lambda$), and, as a measure of overall excitability, liminal length (LL). The liminal length is the amount of membrane that must be raised above threshold to provide local circuit current sufficient to elicit an action potential, depends on both active and passive properties,\textsuperscript{4} and was estimated from $I_A$ at $t = 100$ msec, $V_m$, $\lambda$, and $C_m$. While each of these 6 properties has its own set of determinants, these properties can be depicted readily and represent 1) net changes in the resting potential and its several determining factors, 2) active properties in tissues that depend on the sodium
further depression of primarily from increased Rm, X, and slope resistance despite passive cellular properties that determine transmembrane and posed of active and passive cellular properties relevant to determinants suggest interactions and mutual dependencies.

decrease in quantity: a shift away from center of hexagon that overcame influence of altered passive properties.

FIGURE 5. Effect of quinidine at \([K^+]_o = 5.4\) and 8.0 mM on the electrophysiologic matrix. Simplified "normal" matrix is composed of active and passive cellular properties relevant to cardiac excitability. Determinants selected for this representation include resting potential (\(V_r\)), threshold voltage (\(V_t\)), sodium conductance (\(g_{Na}\)), membrane resistance (\(R_m\)), length constant (\(\lambda\)), and, as a measure of overall excitability, liminal length (LL). Each in turn has its own determinants, but these contain broad descriptions of resting potential and its several determinants, active generator properties and relevant gates, passive cellular properties that determine transmembrane and longitudinal current flow, and net excitability. Bonds between determinants suggest interactions and mutual dependencies. After a perturbation, normal state is depicted by hexagon (interrupted lines). A shift towards center of hexagon indicates decrease in quantity: a shift away from center of hexagon indicates increase in quantity. In all experiments at \([K^+]_o = 5.4\) mM, quinidine increased excitability (leftward path) by increasing \(R_m\), \(\lambda\), and slope resistances while depressing \(g_{Na}\). \(V_r\) changed little, and \(V_t\) was essentially unchanged. Net effect was decrease in LL despite depressed sodium system. Increase in \([K^+]_o = 8.0\) mM made \(V_r\) less negative, decreased \(g_{Na}\) through voltage-dependent inactivation, made \(V_t\) less negative, and decreased both \(R_m\) and \(\lambda\), resulting in a net increase in LL. In this situation, quinidine could either increase or decrease excitability. Increased excitability as manifested by decreased LL resulted primarily from increased \(R_m\), \(\lambda\), and slope resistance despite further depression of \(g_{Na}\). Decreased excitability as manifested by increased LL resulted from further profound depression of \(g_{Na}\) that overcame influence of altered passive properties.

current for depolarization and the relevant gates, 3) passive cellular properties that influence ionic flow through the membrane and between cells, and 4) the overall excitability. The bonds between the determinants suggest interactions and mutual dependencies. The normal state is depicted by the hexagon. Changes in the position of properties and of the lengths of the bonds in space were estimated qualitatively based on the percent increase or decrease in the properties after an intervention. This matrix is quite simplified and qualitatively describes only those components that underwent change. Multidimensional analysis cannot be diagrammed easily because it has as many dimensions as it has variables and is essentially a mathematical description. Moreover, these variables are often nonlinear with complicated voltage, use, and time-dependent kinetics. While qualitatively employed in this report, the matrical approach will permit the development of a multidimensional quantitative model.

The major result of the study was surprising — namely, that quinidine increased excitability in normal cardiac Purkinje fibers at \([K^+]_o = 5.4\) mM as manifested by a decrease in \(I_o\) and, in preparations tested, by a downward shift in the nonnormalized strength- and charge-duration curves. Normalized strength- and charge-duration curves suggested that altered passive properties were largely responsible for the increase in excitability. Cable analysis showed that, primarily by increasing \(R_m\), quinidine increased input resistance, the length constant, and the time constant. Constant current–voltage relations revealed that quinidine increased both chord and slope resistance over the subthreshold range. These actions decreased the amount of current and charge required to attain the requirements of liminal length. The increase in excitability occurred despite a drug-induced depression of the sodium system as manifested by a decreased \(V_{max}\) overshoot, and \(V_{th}\), which would tend to increase liminal length and decrease excitability. The decreased conduction velocity we observed is best explained by depression of the sodium system. Additionally, quinidine further depressed \(V_{max}\) at more rapid stimulation rates as predicted by the modulated or guarded receptor hypotheses, but at \([K^+]_o = 5.4\) mM, excitability remained increased at the faster rates because of altered passive properties. The mechanisms postulated by the modulated or guarded receptor hypotheses, of course, would be contained in the \(g_{Na}\) term of the matrix. At a hyperkalemic \([K^+]_o = 8.0\) mM, excitability could increase if the effect of the altered passive properties was predominant, or excitability could decrease if the sodium system were sufficiently depressed because of voltage-dependent inactivation. Net excitability depended on the overall configuration of the electrophysiologic matrix; that is, it depended on the interrelations among the active and passive properties. The manner in which quinidine affects these determinants at \([K^+]_o = 5.4\) and 8.0 mM and deforms the overall matrix so as to increase or decrease excitability is shown diagrammatically in Figure 5.
Quinidine and Cardiac Excitability

Quinidine

Excitability Increases

Normal

Excitability Decreases

Encainide

Procainamide

Lidocaine

Antiarrhythmic drugs should alter the matrix to prevent an arrhythmogenic configuration. However, there is the risk that a drug may produce a matri
cular configuration that gives rise to arrhythmias. The arrhythmog
etrical potential of quinidine has long been recognized and was most commonly thought to be a
result of depression of the speed of conduction with re
sultant reentry and dispersion of refractoriness with QT
interval prolongation. Recently, Roden and Hofman23 per
formed studies in which the dose of quinidine, [K+],
and cycle length were varied in canine Purkinje fibers. At
slow rates of stimulation at [K+]= 2.7 mM, quinidine at low and high concen-
trations produced early afterdepolarizations, suggest-
ing that early afterdepolarizations may be involved in

torsades de pointes induced by quinidine. The present
study adds another brushstroke to this picture by de
monstrating the importance of altered passive prop-
erties in increasing cardiac excitability, a mechanism
that may be proarrhythmic.

Other Antiarrhythmic Drugs and the
Electrophysiologic Matrix

Little literature exists concerning the effects of other
antiarrhythmic drugs on the determinants of the normal matrix. Early on, we rec
the importance of the balance of active and passive properties in determi
net excitability in our studies on procainamide and lidocaine.435 Both procainamide and lidocaine shifted
the strength-duration curve upward indicating that the
threshold current requirement and, by implication, the
liminal length increased after exposure to the drug; in
classic terms, such a shift indicates a less-excitable

cell. Although I\textsubscript{Na} was increased by both drugs, pro-
cainamide decreased excitability by making V\textsubscript{Na} less
negative (a term that depends on g\textsubscript{Na}) despite an actual
increase in membrane resistance, while lidocaine little
affected V\textsubscript{Na} but decreased membrane resistance in the
subthreshold range. Cable analysis showed that pro-
cainamide increased and lidocaine decreased the length
constant so that the sink (the passive characteristics of the
aggregate of quiescent cells that are adjacent to and are
influenced by the activated cells) would also be
altered differently by the two drugs. Using such data
retrospectively suggests that procainamide and lido-
caine alter the configuration of the electrophysiologic
to, control values. We previously have observed the
same with encainide48 and LPC.37

FIGURE 6. Deformation of normal electrophysiologic matrix by antiarrhythmic drugs in normal cardiac Purkinje fibers at physiologic
[K+]o. We previously have reported that encainide has multiphasic effect on excitability, and mechanism during stage of increased
excitability was similar to that found in present study for quinidine.44 Our earlier studies indicate that procainamide49 and encainide50
could decrease excitability in normal tissues by decreasing g\textsubscript{Na} and making V\textsubscript{Na} less negative despite increases in R\textsubscript{m}, \lambda, and slope
resistances, resulting in increased LL. Both drugs produced very similar matri
cial deformation. We found lidocaine51 to decrease
excitability quite differently in normal tissues by decreasing R\textsubscript{m}, k, and slope resistances while little affecting g\textsubscript{Na} and V\textsubscript{Na}, resulting
in increased LL.
matrix in normal tissue as depicted in rightward path of Figure 6. At the time of those experiments, however, we did not track the changes in time and may have missed multiphasic drug effects on excitability.

More recently, we tracked in time the effects of encainide on active and passive determinants of excitability with the rapid, on-line, computerized data analysis system used in the present study and noted several states of excitability. Although the changes were not discussed in terms of the matrical concept, it is clear that increased excitability resulted from one matrical configuration, while decreased excitability could result from one of several matrical configurations. As seen in Figure 6, encainide can produce matrical configurations that result in increased (left) or decreased excitability (right). In the matrical configuration responsible for increased excitability, the actions of encainide resembled those of quinidine in the present study in that the increase in membrane and slope resistance predominated over depression of the sodium system. In the configuration responsible for decreased excitability, the reverse held.

Lysophosphatidylcholine (LPC) is a metabolite that accumulates in the ischemic myocardium and appears in the effluent of ischemic tissues. LPC can also increase or decrease excitability in sheep Purkinje fibers by altering passive properties while at the same time depressing the sodium system. Lidocaine’s predominant action depended on the characteristics of the matrix altered by LPC: lidocaine acted during the phase of increased excitability primarily by its effects on passive properties and during the phase of decreased excitability primarily by its effects on active properties. The effects of LPC and lidocaine on the matrix have been discussed and diagrammatically presented.

While the present study shows the importance of quinidine on the passive properties in determining overall excitability in normal Purkinje tissues, other studies on the active properties suggest that the similarities of drugs on the sodium channel may be more apparent than real and further erode the traditional classification of antiarhythmic drugs. Recent investigations suggest that the mechanisms by which drugs affect the sodium channel differ with quinidine and procainamide blocking the sodium channels primarily in their open state, while lidocaine, tocainide, and mexilitene primarily block the sodium channel in their inactive state although there does seem to be some overlap in action. The modulated receptor hypothesis and the more recent guarded receptor hypothesis fit only with difficulty into the traditional hierarchical classification of Group I drugs, but, as mentioned, are easily accommodated by the matrical theory.

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254
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**KEY WORDS**

- active and passive cellular properties
- antiarrhythmic drugs
- arrhythmias
- cardiac excitability
- cardiac Purkinje fibers
- cellular electrophysiology
- electrophysiological matrix
- pharmacology
- quinidine sulfate
- strength-duration and charge-duration relations
Effects of quinidine sulfate on the balance among active and passive cellular properties that comprise the electrophysiologic matrix and determine excitability in sheep Purkinje fibers.

M F Arnsdorf and G J Sawicki

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