Mechanisms underlying the antiarrhythmic and arrhythmogenic actions of quinidine in a Purkinje fiber–ischemic gap preparation of reflected reentry

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ABSTRACT The effects of therapeutic levels of quinidine were studied in an ischemic gap preparation of reflected reentry. The preparation consisted of a Purkinje fiber mounted in a three-compartment chamber. A narrow central compartment was perfused with a solution prepared to mimic the extracellular milieu at a site of ischemia. Quinidine in concentrations that exert little effect on normal Purkinje tissue, 1 to 2 μg/ml, greatly impaired conduction and markedly prolonged refractoriness across the ischemic gap. The drug effected these changes by (1) extending the inexcitable zone within the depressed region, (2) decreasing the amplitude of the input signal entering this zone, and (3) decreasing the excitability of the tissue beyond the depressed zone (evaluated by current clamp techniques). These actions of the drug produced both antiarrhythmic and proarrhythmic effects. When the initial level of conduction impairment was high, quinidine totally suppressed reflected reentry at all frequencies by precipitating complete anterograde conduction block. At intermediate levels of block, the drug generally caused a prominent shift of the frequency dependence of reentrant activity to lower stimulation rates. Finally, when conduction was relatively less impaired, quinidine created the conditions for reflected reentry to occur. Our results suggest that the heart rate dependence of reentrant arrhythmias might be of prognostic value in the administration of antiarrhythmic drugs.

Circulation 73, No. 6, 1342–1353, 1986.

THE MECHANISMS of action of quinidine, a commonly used antiarrhythmic drug, have generally been inferred from changes in electrophysiologic membrane properties observed in cardiac tissues that with few exceptions have been exposed to toxic concentrations of the drug.

This study was designed to assess the effects of therapeutic concentrations of quinidine on reflected reentry generated in an “ischemic gap” preparation recently developed in our laboratory1 and to evaluate the electrophysiologic changes underlying the alterations of impulse conduction and manifestation of arrhythmia.

The study provides a set of criteria, based on the heart rate dependence of premature beat manifestation, that may be of prognostic value in the administration of quinidine.

Methods Free-running false tendons, excised from hearts removed from dogs anesthetized with sodium pentobarbital (35 mg/kg iv), were mounted in a three-compartment tissue bath. The fibers were threaded through holes preformed in the thin latex partitions separating the three compartments of the tissue bath. During a 1 hr equilibration period, all compartments were perfused independently with normal Tyrode’s solution containing (mM) 129 NaCl, 3 to 4 KCl, 0.9 NaH2PO4, 20 NaHCO3, 1.8 CaCl2, and 0.5 MgSO4 (pH 7.4). The solution was bubbled with a 95% O2/5% CO2 mixture and temperature was maintained at 37° ± 0.5° C.

Ischemic gap preparation. The experimental preparation was similar to that described previously.1 The central compartment (gap) was 1.5 to 2.0 mm wide. Stimuli were applied to the proximal segment through thin silver electrodes insulated except at the tips. In some experiments stimuli were applied simultaneously to both proximal and distal segments during basic drive. Transmembrane recordings were obtained from the proximal, gap, and distal segments by glass microelectrodes filled with 2.7M KCl connected to a high-input impedance amplification system. The amplified signals were displayed on Tektronix oscilloscopes, photographed with a Grass kymographic camera and recorded on an eight-channel FM tape recorder.

If all three segments displayed normal electrical activity after 1 hr of equilibration, the gap was perfused with a simulated
“ischemic” solution consisting of Tyrode’s containing 15 to 22 mM KCl and 10 mM lactic acid (pH = 6.8) bubbled with a 95% N2/5% CO2 mixture. No correction for isotonicity was made in the modified Tyrode’s solution. Starting with a KCl concentration of 15 mM, we carefully titrated the [K+]o until the desired level of conduction impairment was achieved.

Conduction curves relating the impulse conduction time across the gap to the prematurity of responses elicited at the proximal site were obtained by scanning the basic cycle with single stimuli delivered once after every tenth or fifteenth cycle. Frequency scans were performed by increasing the driving basic cycle length in 10 or 20 msec steps every 30 sec.

The functional refractory period (FRP) of the system is defined in this study as the shortest attainable D1-D2 interval, where D1 is the distal action potential resulting from transmission of a basic proximal response (P1) across the gap and D2 is the distal response to a premature proximal beat (P2) transmitted across the gap. The effective refractory period (ERP) is defined as the longest P1-P2 interval at which P2 fails to propagate across the gap.

Current clamp method. Standard current clamp techniques were used.2 The central compartment of a three-compartment bath was perfused with a solution consisting of purified sucrose (300 mM) and dextrose (5 mM) dissolved in deionized water equilibrated with 100% oxygen; CaCl2 (0.1 mM) was added to the sucrose solution to prevent cellular uncoupling. The proximal segment was inactivated by superfusion with Tyrode’s solution containing 20 to 30 mM KCl, and the distal compartment, which contained the test segment, was perfused with normal Tyrode’s solution. A constant current unit, under computer control (designed by Dr. Elharrar, Indianapolis), delivered 0.1 to 20 μA of current through Ag-AgCl electrodes placed in the two outer compartments. Transmembrane potentials were recorded differentially from the test segment and the applied current was measured as the voltage drop across a 10 kΩ resistor placed in series with the negative output of the constant current unit.

Basic drive was applied to the test segment through bipolar electrodes. Current pulses of 200 msec duration were applied during a brief pause introduced after each train of 15 to 20 basic beats. The threshold current requirement (Ith) was obtained by careful titration of the current intensity. A strength-interval relationship was obtained by repeating Ith measurement at different delay intervals. The current-voltage (I-V) relationship was obtained by measuring the responses to depolarizing and hyperpolarizing current pulses of varying intensity at one or more intervals during diastole.

Drugs. Quinidine HCl (Mallinckrodt) was prepared fresh daily by dissolving in water to yield a stock solution of 1 mg/ml.

Results

The characteristics of impulse conduction in the ischemic gap preparation are illustrated in figure 1. Each panel is a composite of two sweeps of the oscilloscope depicting transmembrane activity recorded from (bottom to top) the proximal, central (gap), and distal segments of the three-compartment preparation. The first beat is the last of a train of 15 beats elicited by stimulation of both proximal and distal segments at a basic cycle length (BCL) of 300 msec. Each train was followed by an 800 msec pause during which a premature stimulus was delivered to the proximal segment only. Each panel consists of two superimposed sweeps showing the latest impulse that failed to conduct across the gap and the earliest that succeeded. The gap segment was superfused with a simulated ischemic solution containing 19 mM K+ and 10 mM lactic acid.

FIGURE 1. Effect of quinidine on refractoriness and conduction in an ischemic gap-Purkinje fiber preparation. The bottom, middle, and top traces in each panel represent intracellular recordings from the proximal (P), central, and distal (D) segments, respectively. Premature stimuli were applied to the proximal segment at progressively earlier intervals, once after every train of 15 beats elicited by stimulation of both proximal and distal segments. Each panel consists of two superimposed sweeps showing the earliest propagated premature beat (FRP) and the latest that failed to propagate across the gap (ERP). A, Control; B, recorded 90 min after quinidine (1 μg/ml) was added to the gap perfusate; C, recorded 90 min after the concentration of quinidine in the gap perfusate was increased to 2 μg/ml.

When stimulation was applied to the proximal segment late enough to permit transgap propagation, the transmembrane potentials recorded from the gap showed a two-component upstroke; the first occurred shortly after the initiation of proximal activity and the second after the upstroke of the distal action potential. Earlier studies1,3 have shown these characteristics to
be consistent with electrotonically mediated impulse transmission, indicating the presence of a short inexcitable cable at the recording site within the gap. Under these conditions, the local circuit current generated by the proximal action potential decays as it flows through the intercellular connections of the inexcitable region. This electrotonic current, when of sufficient intensity upon reaching excitable tissue beyond the depressed zone, gradually depolarizes the distal tissue to its threshold level. Propagation therefore stops and then resumes after a step delay.

In the absence of drug, the ERP and FRP of the preparation shown in figure 1, A, were 185 and 225 msec, respectively. Panel B shows activity recorded 90 min after the addition of quinidine (1 μg/ml) to the gap perfusate; ERP increased to 225 msec and FRP to 270 msec. The refractory periods were further prolonged after an additional 90 min exposure to 2 μg/ml quinidine (panel C; ERP = 340 msec, FRP = 385 msec). Postrepolarization refractoriness, a common feature of this system, was extended well into diastole.

Figure 2 illustrates the slow time course of drug action in three experiments similar to that shown in figure 1. Under control conditions, the FRP remained stable (265 msec) for a period of 60 min. The addition of quinidine (1 μg/ml) to the gap perfusate resulted in a slow progressive increase of the FRP, reaching a value of 295 msec after 90 min of exposure. Increasing the drug concentration to 2 μg/ml caused a further prolongation of the FRP that approached a plateau phase (353 to 360 msec) after 90 to 120 min. The changes in ERP paralleled those of the FRP.

In seven experiments we extended the control period to 3.0 to 3.5 hr. When conduction characteristics and refractoriness remained stable during the initial hour (five of seven experiments), no significant changes were observed in the succeeding hours. In two cases, deterioration of conduction occurred continuously and was accompanied by progressive depolarization of one or both of the outer segments. Preparations that failed to exhibit stable conduction characteristics during the initial hour were excluded from drug study.

The predrug level of conduction impairment greatly influenced the drug-induced alteration of refractoriness and conduction, as illustrated in figure 3. The conduction curves summarize data derived from two experiments similar in design to that illustrated in figure 1. The conduction time of each premature beat (P2-D2) is plotted as a function of the prematurity of the impulse (P1-P2) elicited with a stimulus delivered to the proximal segment during a pause introduced after each train of 15 beats (simultaneous proximal and distal stimulation; BCL = 300 msec).

When the predrug level of conduction impairment was relatively low, quinidine produced a small shift of the conduction curve upward and to right (figure 3, A).
However, when the initial level of block was more severe, the drug-induced shift was substantially greater and generally occurred more rapidly (panel B).

The occurrence of high-degree block after quinidine was common when predrug impairment of conduction was at a high level. In 15 experiments, low concentrations of quinidine (2 μg/ml) induced high-grade or complete block. In all cases the briefest P₂-D, conduction time during control runs was longer than 20 msec.

Reflection. When anterograde conduction across the gap is sufficiently delayed, retrograde transmission may occur in time to reexcite the proximal tissue, thus generating reflections. Because transgap conduction is time and frequency dependent, the incidence of reflected reentry is a sensitive function of the stimulation rate. Figure 4 illustrates these characteristics of the preparation.

Under control conditions, at a BCL of 600 msec, proximal to distal conduction was 5:2. Every second stimulated beat conducted across the gap and every other distal response conducted in the retrograde direction in time to reexcite the proximal segment, thus generating reflected reentry in a pattern of concealed trigeminy. At a BCL of 700 msec, the impulses elicited by stimulation of the proximal segment were transmitted across the gap with delays long enough to permit a reflection after each stimulated response; this pattern is one of bigeminy. When the BCL was increased to 1000 msec, proximal-to-distal conduction time was greatly abbreviated. Because the distal response occurred during the refractory period of the proximal segment, no reentrant activity was possible. The records shown in figure 4, B, were obtained 60 min after the addition of quinidine (2 μg/ml) to the gap perfusate. At BCLs of 600 and 700 msec, reflected reentry was abolished because of the drug-induced precipitation of complete anterograde conduction block. However, at the slower driving rate (BCL = 1000 msec) the drug exerted an arrhythmogenic effect; conduction across the gap succeeded but with delays long enough to permit reflection of each propagated beat, generating a pattern of bigeminy. Thus quinidine’s actions on the manifestation of reflected reentry clearly depend on frequency.

The drug-induced effect on conduction and arrhythmias was generally apparent within 15 min and approached a steady state after 90 min of drug exposure. Although the major part of the effect occurred within 60 min, significant further changes developed in the ensuing 30 min period.

The results of complete frequency scans performed in the experiment illustrated in figure 4 are summarized in figure 5. The graphs plot the percentage of conducted beats (top) and the incidence of reflected beats as a function of the driven cycle length. Under control conditions, progressive abbreviation of the BCL was attended by prolongation of anterograde conduction time until, at a BCL of 800 msec, reflections were manifest. Further shortening of the cycle length led to an increase in the incidence of reflected beats.

**FIGURE 4.** Effects of quinidine on reflected reentry generated in an ischemic gap preparation ([K⁺]₀ of the gap perfusate was 18.5 mM). From top to bottom, the traces shown are recordings from the proximal (P), middle, and distal (D) segments of the preparation. A, Control, at BCLs of 600, 700, and 1000 msec; proximal to distal conduction was 5:2 (trigeminy), 2:1 (bigeminy), and 1:1 (no reflection), respectively. B, After 60 min of exposure of the middle segment to quinidine (2 μg/ml), reflections (bigeminy) appeared at the slower frequency (BCL = 1000) but were suppressed at the faster frequencies (BCLs of 600 and 700 msec). Both antiarrhythmic and proarrhythmic actions were in large part caused by the drug-induced impairment of anterograde conduction across the area of depressed conductivity.
which reached a maximum at a BCL of 700 msec and thereafter declined gradually.

After 60 min of exposure to quinidine, as the level of block progressed, no conducted beats were observed at BCLs briefer than 700 msec and the percentage of conducted beats was reduced at all cycle lengths briefer than 1200 msec. The reflection zone (i.e., the range of frequencies manifesting reflected reentry) shifted to higher BCLs, peaking at a level of 50% (bigeminy) when the BCL was within a range of 1000 to 1100 msec. Further deterioration of conduction accompanied by a further shift of the reflection zone to still longer BCLs occurred after 90 min of drug exposure. We obtained qualitatively similar results in three different preparations.

In four other experiments, the addition of quinidine to the gap perfusate resulted in complete suppression of reentrant activity at all frequencies. In these cases, conduction under control conditions was considerably more impaired than in the preceding example. Figure 6 presents the results of a complete frequency scan performed in one such preparation. Conduction across the gap was 1:1 only at BCLs greater than 1900 msec. A 2:1 zone extending from a BCL of 1400 to 1900 msec was attended by bigeminal activity throughout. With further acceleration of the driving rate, conduction block progressed to higher levels and the incidence of reflections gradually diminished. Within 15 min of the introduction of quinidine (2 μg/ml) to the gap perfusate, complete anterograde conduction block occurred at all frequencies and reflected activity was abolished.

Since quinidine's actions on proximal and distal tissues (exposed to normal Tyrode's solution) must also contribute to its overall influence on refractoriness, conduction, and reflection, in a series of five experiments we assessed the actions of the drug on the two outer segments.

The extent of the quinidine-induced effect depended on the electrophysiologic state and length of the tissue segment within the proximal and distal compartments. Because of depolarizing electrotropic influence from the gap, the degree of depolarization of the outer segments is in large part a function of their length.2 Figure 7 presents the results of an experiment conducted in a preparation with a long proximal segment (4.3 mm) but a short distal segment (1.4 mm). Panels A to C of figure 7 each show two superimposed sweeps recorded from the three respective segments showing the ERP and FRP of the system. The first beat (P1) is the last of a train of 10 elicited by proximal stimulation at a BCL of 1000 msec. As expected, the morphology of the action potentials recorded from the two outer segments differ

FIGURE 5. Summary of the results of complete frequency scans performed in the experiment from figure 4. The percentage of conducted beats are plotted as a function of the stimulation cycle length (BCL) and represents the number of reflected responses as a fraction of the total number of proximal beats occurring in a given period once steady state was achieved (i.e., 50% = bigeminy and 33% = trigeminy). The percentage of conducted beats represents the number of proximal beats that succeeded in propagating across the gap as a fraction of the total number of proximal responses. Scans were performed before drug and 60 and 90 min after the addition of quinidine (2 μg/ml) to the gap perfusate. Bi = bigeminy; Tri = trigeminy; Penta = pentageminy.
greatly, the distal response having a lesser resting potential and amplitude than the proximal response. Before drug (panel A), the ERP and FRP were 320 and 370 msec. Panel B was recorded 90 min after the addition of 2 μg/ml quinidine to the proximal perfusate; the refractory periods remained unchanged. Exposure of the depolarized distal segment to drug for the same length of time, however, effected a prolongation of the ERP and FRP to 340 and 400 msec, respectively (proximal exposure to drug was continued during this period). Panel D summarizes the results of a complete scan. Quinidine, although it did not affect conduction

**FIGURE 6.** Effect of quinidine on conduction and reflected reentry in an ischemic gap preparation manifesting a high level of predrug conduction impairment. Results of complete frequency scans performed before and after drug are shown in the graphs. Axes as in figure 5. Within 15 min, quinidine produced anterograde conduction block at all frequencies and completely suppressed reentrant activity. Insets, Transmembrane activity recorded from the three segments of a preparation stimulated at a BCL of 1500 msec before and 15 min after the addition of quinidine (2 μg/ml) to the gap perfusate. Abbreviations as in figure 5.

**FIGURE 7.** Effects of quinidine on conduction when added to the proximal and distal superfusates of a preparation with a long proximal segment (4.3 mm) and a short distal segment (1.4 mm). The preparation was driven at a BCL of 1000 msec; gap [K+]o was 20 mM. Panels A to C are each composed of two superimposed sweeps showing the ERP and FRP of the system (as in figure 1). A, Control; B, recorded 90 min after addition of quinidine (2 μg/ml) to proximal perfusate; C, recorded 90 min after addition of quinidine (2 μg/ml) to distal perfusate; D, summary of complete scans. The conduction time of each test response (P2-D2) is plotted as a function if its prematurity (P1-P2).
when applied to the proximal side, significantly altered conduction characteristics when applied to the distal end, shifting the conduction curve upward and to the right. Steady-state (during basic stimulation of 1000 msec) transgap conduction time increased from 5 to 17 msec (see last portion of curve, panel D).

Figure 8 illustrates an example of quinidine’s actions on conduction and reflection when added to the outer compartments of a preparation in which the geometric asymmetry was reversed. Each panel shows traces recorded from the three segments of a preparation with a short (1.4 mm) proximal segment but a relatively long (5.5 mm) distal segment. Under control conditions (panel A), at a BCL of 500 msec, conduction across the gap approached 1:1 with only occasional beats blocked. Panel B, recorded 30 min after the addition of quinidine (2 \( \mu \)g/ml) to the distal perfusate, shows a slight improvement of conduction characteristics. Although the conduction ratio remained unchanged, conduction time across the ischemic gap was slightly abbreviated. In contrast, the addition of quinidine to the proximal perfusate produced marked depression of the already depolarized proximal response within 15 min, engendering long delays in conduction attended by reflected reentry.

In five similar experiments, when the outer segments were long and well polarized, quinidine exerted little or no effect. However, when these segments were short (<2.5 mm) or otherwise depolarized, the drug produced relatively greater effects on refactoriness, conduction, and reflection.

Excitability. Quinidine-induced changes in excitability at the distal end of the preparation are likely to contribute to the drug’s effects on conduction and reentrant activity. To assess the extent of such a contribution, we examined quinidine’s actions on threshold current requirements (\( I_{th} \)) and the steady-state current voltage (I-V) relationship in seven experiments. Standard current clamp techniques were applied with use of a three-compartment sucrose gap–Purkinje fiber preparation.

Figure 9 illustrates the results of an experiment in which the test (distal) segment was superfused with Tyrode’s solution containing 10 mM K+ and 10 mM lactic acid (the proximal segment was inactivated with high \([K^+]_b\)). We used this combination in an attempt to approximate the conditions that would exist at the distal border of the ischemic gap, where distal activation is likely to be effected. The first 2 beats of each inset in figure 9, A, are the last of a train of 16 beats stimulated at a BCL of 500 msec (recorded from the test segment). Current pulses of 200 msec duration were applied during the ensuing 1300 msec pause. Each picture shows two superimposed sweeps of activity elicited with just subthreshold and suprathreshold current pulses. The strength-interval relationships are graphed below. Under these conditions, quinidine (2 \( \mu \)g/ml, 60 min) added to the test segment perfusate produced an upward shift of the strength-interval plot (figure 9, A). The maximum diastolic potential and \( V_{th} \) were unaffected, although the amplitude and rate of rise of the action potential were clearly decreased (inset). The I-V plot (figure 9, B) shows that quinidine decreased the voltage response to depolarizing pulses (upper right quadrant) but caused no change in the membrane response to hyperpolarizing pulses. We obtained similar results in two other experiments of this type. Similar changes in excitability were also observed in one “spontaneously” depolarized preparation.

**FIGURE 8.** Effect of quinidine on conduction and reflection when added to the proximal and distal perfusates of a preparation with a short proximal segment (1.4 mm) and a long distal segment (5.5 mm). Each panel shows transmembrane activity recorded from the proximal (P), gap, and distal (D) segments. Gap \([K^+]_b\) was 21 mM; BCL was 500 msec. A, Control; B, recorded 30 min after addition of quinidine (2 \( \mu \)g/ml) to distal perfusate; C, recorded 15 min after addition of quinidine (2 \( \mu \)g/ml) to proximal perfusate.
Discussion

Previous studies have reported quinidine’s ability to reduce action potential amplitude and rate of rise, to prolong action potential duration, and to suppress spontaneous activity in mammalian Purkinje fibers.\(^5\) Similar effects have been described in atrial and ventricular muscle preparation.\(^6,\)\(^7\)

More recent studies have focused on the differential effects of quinidine on hypoxic, ischemic, and normal tissues of the heart.\(^8,\)\(^9\) Voltage clamp studies in multicellular and single-cell preparations have further delineated the ionic mechanisms of drug action demonstrating quinidine-induced inhibition of the fast inward current (\(i_{Na}\)), delayed rectifier current (\(i_{Na},i_K\)), pacemaker current (\(i_F\), \(i_K\)), slow channel current (\(i_S\)), and steady-state or “window” sodium current.\(^10\)\(^-\)\(^13\)

Although many studies have inferred an antiarrhythmic mechanism based on the depressant effects of the drug on membrane currents, membrane responsiveness, excitability, automaticity, conduction, and refractoriness observed in isolated tissues,\(^14\)\(^-\)\(^17\) to our knowledge none has demonstrated a direct antiarrhythmic action of quinidine with microelectrode recordings in vitro.

With few exceptions, most studies of quinidine action in isolated tissues have used drug concentrations of 4 to 16 \(\mu\)g/ml. Plasma quinidine concentrations in patients receiving therapeutic doses rarely exceed 7 \(\mu\)g/ml and usually range between 2 and 6 \(\mu\)g/ml. Because the drug is extensively bound to plasma proteins (\(~70\%\) to \(80\%)\), the therapeutic plasma levels of free-drug range between 0.4 and 1.8 \(\mu\)g/ml.\(^18\)\(^-\)\(^21\) Accurate assessment of the drug’s antiarrhythmic actions requires that electrophysiologic studies of isolated tissues bathed with protein-free perfusates employ quinidine concentrations approaching this range. We therefore chose a concentration range of 1 to 2 \(\mu\)g/ml.

Hypoxia, elevated concentrations of \(K^+\), lactate, and \(H^+\) are some of the identifiable components contributing to the electrophysiologic abnormalities of the early phase of ischemia.\(^22\)\(^-\)\(^23\) These ischemic components were added to the perfusion fluid to create a narrow zone of depressed conductivity in isolated Purkinje fibers. This preparation is similar to other preparations of ischemia in vitro in its ability to mimic many of the characteristics of impaired conduction observed in depressed tissues in situ, but differs in that, once equilibrated, conduction characteristics re-
main stable for long periods of time (>=3 hr). The stability of the preparation, together with the capability to record and test drugs in both normal and ischemic zones simultaneously, has proved valuable in the assessment of drug actions.1, 3, 24

In previous studies we have shown that very slow conduction across the ischemic gap is the result of step delays imposed by the electrotonically mediated transmission of impulses across an inexcitable segment within the gap.1 Continuity of conduction across the inactivated region is maintained by the flow of local circuit current from proximal to distal excitable elements. The gap segment is strongly depolarized by the ischemic solution, but because of steady-state electrotonic interactions, the membrane potential increases gradually with distance from the maximally depolarized central zone toward the normally polarized regions at either end, thus providing zones at the gap borders at which slow or depressed fast responses are possible. Any agent affecting the boundary zones can alter the length of the inexcitable segment and thus affect impulse propagation across the gap.1

Quinidine’s action to markedly depress conduction across the ischemic gap may be largely explained by its ability to diminish inward current intensity (iNa and the steady-state or “window” sodium currents). This action of the drug may serve to (1) render cells within the boundary regions inexcitable and thus broaden the inexcitable zone, (2) diminish the action potential amplitude and rate of rise (Vmax) at the proximal end of the inexcitable cable (source) (figure 8), and (3) depress excitability at the distal end (sink) (figure 9, A). Local circuit current provided to the sink therefore decreases because of a lesser input at the source and a longer distance for the current to decay between source and sink. Moreover, the greater threshold current requirement (Ith) at the sink can render the provided electrotonic current less effective (figure 9).

The quinidine-induced increase in Ith at the sink and decrease of local circuit current provided to the sink may likewise explain the marked effect of the drug to prolong refractoriness under conditions in which action potential duration is not greatly altered (figure 1). Slow restitution of excitability at the sink under these conditions (figure 9; see also refs. 25 to 27) in large measure accounts for the time and frequency dependence of impulse conduction across the inexcitable gap. Because excitability continues to recover for hundreds of milliseconds after an action potential, postpolarization refractoriness may extend well into diastole.

A quinidine-induced decrease of the iKr (ifK) or pacemaker currents at the sink may further contribute to the effects of the drug on refractoriness by altering the time dependence of restitution of excitability through prolongation of the action potential and suppression of phase 4 depolarization.24

Reflection. The success or failure of reflection depends critically on the magnitude of anterograde and, to a lesser extent, retrograde conduction delays across the gap. Because impulse conduction delay across the inexcitable gap is a sensitive function of time or frequency, the incidence and pattern of reflected reentry depend greatly on the driving frequency.1, 2, 25, 28, 29

It is therefore not surprising that quinidine’s effect on the manifestation of reflected reentry also depends on the rate of stimulation. The drug can cause either antiarrhythmic or arrhythmogenic effects depending on the driving rate (figures 4 and 5). By depressing conduction across the ischemic gap, quinidine produces a shift of the reflection zone to lower frequencies. In the example illustrated in figure 5, the shift after 90 min of drug exposure was such that an antiarrhythmic effect occurred at BCLs of 550 to 800 msec and an arrhythmogenic effect at BCLs of 900 to 1300 msec, with little or no change at a BCL of 850 msec. These results emphasize the importance of considering heart rate in the assessment of antiarrhythmic drug efficacy.

The degree of predrug conduction impairment is another important determinant of quinidine’s influence on manifest reentrant activity. When the initial level of block was low, quinidine further impaired conduction and created the conditions for reflection to occur. When the initial level of block permitted reflected reentry over a wide range of frequencies, the drug caused a shift of the frequency dependence of the arrhythmia to slower rates and usually a broadening of the reflection zone. Finally, when predrug conduction was greatly impaired and reflections were primarily observed at relatively low rates of stimulation, quinidine in therapeutic concentrations completely suppressed the arrhythmia.

The effect of quinidine on manifest reflection depended also on (1) the concentration of drug, (2) the duration of exposure to the drug, and (3) the segment(s) of the preparation exposed to the drug. Because of the strong interdependence among variables, a quantitative assessment of the contribution of any one variable to arrhythmogenic manifestation was not possible. The time course of drug action, for example, depends critically on the initial level of block (among other variables). When the initial level of block was high, complete suppression of the arrhythmia attended by complete anterograde block was effected within 15
min (figure 6). When predrug conduction was somewhat less encumbered, the same concentration of drug continued to influence arrhythmic activity over a 90 min period (figure 5). Moreover, we observed greater depressant effects with 1 μg/ml quinidine in preparations with initially high levels of conduction impairment than we did with 2 μg/ml drug in preparations that displayed less impaired predrug conduction characteristics.

The effects of the drug on the active (outer) segments of the preparation depended on the maximum diastolic potential of those segments. When well polarized, quinidine exerted little or no depressant effect (figure 7) and in some cases produced a slight facilitation of conduction (figure 8). However, when much of the tissue was depolarized (because of steady-state electrotonic interaction with the gap segment), the drug produced major effects on conduction and reflection (figure 7 and 8). These results are consistent with the well-known voltage dependence of quinidine interaction with the sodium channel. The voltage and rate dependence of association and dissociation of quinidine from the sodium channels (modulated receptor hypothesis and guarded receptor hypothesis) must also contribute to the frequency dependence of the drug-induced changes in conduction and reflection.

Quinidine’s actions in the ischemic gap preparation are qualitatively similar to those of other antiarrhythmics. For example, verapamil, lidocaine, and propranolol (unpublished observation) have been found to exert both antiarrhythmic and arrhythmogenic effects in this preparation through actions very similar to those described for quinidine. These agents share the ability to diminish inward current intensity and thus the capability of suppressing regenerative activity and decreasing excitability in depressed cardiac fibers. This capability serves to impair conduction within the reentrant pathways and appears to be a primary factor common in the mechanism of action of these agents representative of classes I, II, and IV of standard antiarrhythmic classification schemes. All of the drugs prolong refractoriness across the ischemic gap.

However, quinidine’s actions on reentry generated in this preparation are opposite those of milrinone. Milrinone has been shown to exert both antiarrhythmic and arrhythmogenic effects by improving conduction across the zone of impaired conductivity. Milrinone shifts the reflection zone to higher rather than lower frequencies. But like quinidine, its actions on the manifestation of reflected reentry depend on such variables as the initial state of conduction, drug concentration, and frequency. Understandably, milrinone proved to be most effective in suppressing reflected reentry in a situation in which quinidine was least effective (low level of predrug conduction impairment). Conversely, milrinone was least effective under conditions in which quinidine is most effective (high level of predrug conduction impairment).

Clinical implications. It seems clear that quinidine’s effectiveness in influencing conduction and arrhythmias depends on many variables. Chief among these is the initial state of conduction at the arrhythmogenic site; others include heart rate, drug concentration, drug access to specific tissue sites, and the level of membrane potential at these sites. The modulating roles of pH, [K+]o, and hypoxia are also well known. As we have shown, relatively small variations in one or more of these factors may not only alter the antiarrhythmic efficacy of a given concentration of quinidine but also may critically determine whether an antiarrhythmic or proarrhythmic action will result. In light of this, it is perhaps not surprising that in the clinical setting there is a high interpatient variability in response to quinidine and similar agents administered for the treatment of ventricular arrhythmias and that attempts to arrive at an optimal therapeutic serum level at which maximal control of ventricular rhythm disturbances can be expected in all patients have met with failure.

One major concern in the clinical evaluation of any antiarrhythmic agent is marked spontaneous variation in the degree of ventricular ectopy. Our experience with this and similar preparations indicates that mere changes in heart rate may account for some of the “spontaneous” variability in the incidence of reentrant extrasystoles. Relationships between the frequency of ectopic beats and heart rate, similar to those observed in our preparations, have been reported in animal studies and in recent clinical studies. Our results suggest that the heart rate dependence of the arrhythmia might be of prognostic value in the administration of quinidine. The data suggest that patients manifesting reentrant premature beats only at slow rates might respond favorably to low doses of quinidine, whereas those presenting with reentrant extrasystoles principally at rapid rates may experience an overall increase in extrasystolic frequency after low doses of quinidine. The latter group may require higher doses to suppress ventricular ectopy or might benefit more from an agent that facilitates conduction, such as milrinone.

Although we base this hypothesis on data derived largely from models of reflection, there is good reason to believe that reentry caused by reflection and reentry
caused by circums movement are similarly dependent on heart rate and in many instances may respond similarly to agents such as quinidine.

Conclusion. The present study provides, for the first time, some characterization of the effects of therapeutic levels of quinidine on reflected reentry and suggests means by which critical evaluation may be accomplished in the clinic and other systems in vivo. The diagnostic and prognostic value of the relationships presented are clearly amenable to clinical trials.

The study also provides some understanding of the mechanisms responsible for the antiarrhythmic and arrhythmogenic effects of the drug under conditions that predispose to the development of reflected reentry in a simulated ischemic environment. Although it was clearly not within the scope of the study to critically assess the individual effects of pH, [K⁺]₀, voltage, and other variables in modulating quinidine’s actions, the data collected may be helpful in putting into perspective the findings of numerous prior studies that have carefully evaluated these factors.

We thank Dr. Gordon K. Moe for his encouragement and advice and acknowledge the expert technical assistance of Judy Hefferon and Robert Goodrow.

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Circulation. 1986;73:1342-1353
doi: 10.1161/01.CIR.73.6.1342

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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