Frequency-Dependent Effects of Quinidine on the Ventricular Action Potential and QRS Duration in Humans

Koonlawee Nademanee, MD, William G. Stevenson, MD,
James N. Weiss, MD, Virginia B. Frame, PhD, Michael G. Antimisiaris, MD,
Taworn Suithichaiyakul, MD, and Clara M. Pruitt, RN

We studied the frequency-dependent effects of quinidine on the right ventricular action potential and QRS duration in 10 patients (nine men and one woman; mean age, 57±14 years) undergoing electrophysiologic studies for clinical indications. The right ventricular monophasic action potential, electrocardiographic, and conventional intracardiac electrical signals from various sites were recorded at different pacing cycle lengths from 30 seconds to 1 minute before and after a 10-mg/kg i.v. quinidine infusion. We used the extrastimulus technique to determine the effects of quinidine on ventricular refractory periods at different pacing cycle lengths and on the abrupt changes of the action potential duration. The action potential duration progressively decreased as the ventricular pacing rate increased at baseline and after quinidine infusion. Quinidine significantly increased the action potential duration from that of control by 25 msec (p<0.02) at the relatively slow pacing cycle lengths of 600, 500, and 400 msec. Quinidine's effect on the action potential duration was attenuated at the pacing cycle length of 350 msec and became negligible at 300 msec. In contrast, quinidine progressively lengthened the QRS duration as the pacing rate increased (20, 18, 37, 46, and 34 msec at pacing cycle lengths of 600, 500, 400, 350, and 300 msec, respectively; p<0.05). There were no rate-dependent changes in the QRS duration during the control period. The relation between the ventricular refractory periods and the action potential duration at different pacing cycle lengths was also determined before and after quinidine infusion. Quinidine uniformly increased the ventricular refractory periods by about 9–11% above the control values regardless of the pacing cycle lengths and the action potential durations. Although quinidine generally had no effect on the ratio of ventricular effective refractory period to the action potential duration, a strong trend emerged showing that quinidine increased the ratio as the pacing cycle lengths shortened (p=0.07). Our data demonstrate that at slower heart rates quinidine has a significant effect on the action potential duration, repolarization, and voltage-dependent refractory period. As the heart rate increased, quinidine's effect on these variables diminished, but its effect on the time-dependent refractory period became more pronounced. In contrast to quinidine's effect on the action potential duration, the drug prolonged the QRS duration in a use-dependent manner. (Circulation 1990;81:790–796)

Changes in heart rate affect many facets of cardiac electrical activity.1 In particular, the repolarization phase of the cardiac action potential is quite responsive to heart rate fluctuation.2,3 Although the cycle length–dependent changes in the action potential duration (APD) are well known,1–4 several aspects of the complex ionic mechanisms underlying these changes remain poorly understood. Nevertheless, two main mechanisms are believed to govern these changes1: first, the incomplete recovery of inward currents or incomplete decay of the time-dependent potassium current between one action potential and the next, and second, alterations in intracellular and extracellular ionic concentrations. Fast rates increase extracellular potassium concentration, which augments the out-
ward repolarizing potassium current (I_{K1}) and leads to more rapid repolarization.\textsuperscript{5,6} The intracellular accumulation of sodium ions stimulates the electrogenic sodium pump, generating an outward current that also hastens repolarization.\textsuperscript{7,8} In addition, when diastole is abbreviated, the fast heart rate prevents the complete recovery of inward currents that are important in supporting the action potential plateau.\textsuperscript{1} All of these factors shorten APD at faster heart rates.

The effect of antiarrhythmic agents on these ionic currents adds another layer of complexity to the repolarization process. For example, the rate at which antiarrhythmic agents bind and unbind to the specific ion channels for the inward currents varies according to membrane potential and to different conductance states of the channels (activated, inactivated, and resting).\textsuperscript{9} As the heart rate increases, the binding of the drug to the channel will be modified and so will the drug’s channel-blocking effect.\textsuperscript{9,10} In turn, the magnitude of the antiarrhythmic action on the inward sodium current is altered in a use-dependent manner characteristic of class I antiarrhythmic agents.

Moreover, class IA antiarrhythmic agents, such as quinidine, also prolong the APD of ventricular muscle and Purkinje fibers.\textsuperscript{11-13} In vitro studies in several species\textsuperscript{14-17} have shown that quinidine prolongs APD by inhibiting the delayed outward potassium current (I_{Kd}),\textsuperscript{14,15} the transient outward current (I_{to}),\textsuperscript{16} and the inward rectifier potassium current (I_{Kr}).\textsuperscript{15} Roden et al\textsuperscript{14} demonstrated that quinidine inhibits I_{Kr} much more effectively in the presence of a long diastolic interval. Thus, in theory, quinidine should lengthen repolarization by inhibiting I_{Kr} more readily at slow heart rates. This, indeed, has been demonstrated in animal experiments,\textsuperscript{17,18} but whether this phenomena occurs in humans is not yet known. The introduction of the Ag-AgCl electrode catheter\textsuperscript{19} enabled us to investigate the frequency-dependent effect of quinidine on APD, refractoriness, and conduction of normal ventricular muscle in humans.

**Methods**

**Patient Population**

Table 1 lists patient characteristics. We enrolled 10 patients (nine men and one woman; mean age, 57±14 years) who underwent electrophysiological studies for the following indications: malignant ventricular tachycardia (six patients), syncope (one), and supraventricular tachycardia (three). Two patients also had atrioventricular nodal ablation for refractory supraventricular tachyarrhythmias. Of these patients, eight had coronary artery disease, and two had cardiomyopathy.

**Electrophysiologic Study Protocol**

The Ag-AgCl bipolar electrode catheter, furnished by the Webster Laboratory (Altadena, California), was used to record the monophasic action potential (MAP) of the right ventricular apex. Conventional quadripolar catheters were used for intracardiac recordings and stimulation. Patients underwent the studies after their regimens of antiarrhythmic agents (including β-blockers) had been discontinued for at least five half-lives. In addition to the conventional stimulation protocol used for arrhythmia induction, we also performed the stimulation protocols outlined below.

**Rapid Ventricular Pacing**

Right ventricular steady-state pacing was performed at cycle lengths of 600, 500, 400, 350, and 300 msec for at least 30 seconds. The duration of pacing, which was performed at twice the diastolic threshold, was increased to 1 minute during the relatively slow (500 and 600 msec) pacing rates. Pacing at faster rates was not possible because angina or hemodynamically compromised symptoms could develop. However, the protocol required the same duration of
pacing in each patient before and after quinidine infusion at a given cycle length.

**Abrupt Changes**

We also determined the effect of premature extra stimulus (S1S2) on APD and the ventricular effective refractory period (VERP). The extra stimulus was delivered after at least eight driven beats (S1S1); the interval of S1S2 during baseline and after quinidine infusion was always the same, either 600 or 500 msec. A long coupling interval (S1S2 of at least 2 seconds) was delivered whenever possible to obtain data on the electrical restitution curve of the APD. However, this was possible only in the two patients who had atrioventricular nodal ablation; the other patients’ escape interval was shorter than 2 seconds.

**Quinidine Infusion**

All patients received a 10-mg/kg i.v. dose of quinidine gluconate during a 15–20-minute period. The infusion was terminated when systolic blood pressure fell below 90 mm Hg. Repeat electrophysiological studies were performed 5 minutes after the end of the infusion; a blood sample was obtained at the completion of the study for the assay of quinidine concentration. As shown in Table 1, quinidine blood levels were determined in most patients.

**Measurements**

We measured the amplitude of the MAP from diastolic baseline to crest of the plateau. APD90 was measured from the initial upstroke to the point when repolarization was 90% completed. The diastolic interval was measured from the point corresponding to APD90 of the preceding beat to the rapid upstroke of the depolarization of the subsequent beat. The test APD is the APD provoked by extra stimulus. We plotted the test APD as a function of diastolic interval, the electrical restitution curve.20 The VERPs were measured by a standard technique with a single S1S2 at various pacing cycle lengths of S1S1 intervals. The VERP was defined as the longest S1S2 interval at which S2 did not capture the ventricle.

**Data and Statistical Analysis**

We measured APD90 either manually with off-line recordings at a 100-mm/sec paper speed or digitally with Sigma Scan software (Jandel Scientific, Sausalito, California). MAP recordings were considered unacceptable when the MAP amplitude was less than 7 mV or was interrupted by ectopic beats.

Paired t tests and Wilcoxon’s signed-rank test were used for comparisons between quinidine and control values of QRS duration and of APD at each pacing cycle length separately. Most subjects had a very linear increase in APD90 when cycle lengths were increased from 350 to 600 msec. Thus, linear regression was used to determine the rate of APD90 change (as the slope) in this pacing range for each patient during the control period and after quinidine infusion. The Wilcoxon’s signed-rank test was used for comparisons between quinidine and control rates of APD90 change.

Percent change in the quinidine APD from the control APD was compared with the percent change in the quinidine VERP from the control VERP as a function of cycle length by the use of the repeated measures analysis of variance with the Greenhouse-Geisser correction for within-subject correlations.21

**Results**

**Frequency-Dependent Effect of Quinidine on APD90 and QRS Duration During Steady-State Ventricular Pacing**

As the pacing cycle length decreased, APD90 shortened during control and after quinidine infusion.
Quinidine uniformly lengthened the APD90 by about 25 msec \((p<0.02)\) compared with control values at the pacing cycle lengths of 600, 500, and 400 msec. The change in APD90 was less marked at the 350-msec cycle length, and there was no difference between the control APD90 and the quinidine APD90 \((p=0.88)\) at the 300-msec cycle length. The Wilcoxon signed-rank test established that the change in APD90 is indeed rate dependent \((p=0.04)\), for the magnitude of quinidine’s effect on APD is greater at the longer pacing cycle lengths.

Quinidine’s effect on the QRS duration is diametrically opposite to its effect on APD90 (Figure 1). The QRS duration, which is a rough measurement of ventricular conduction time, was lengthened by quinidine at all cycle lengths, but the drug’s effect on QRS was much more pronounced during faster pacing rates \((p<0.02)\). The mean increases in the QRS duration were 20, 18, 37, 46, and 34 msec for pacing cycle lengths of 600, 500, 400, 350, and 300 msec, respectively. There were no rate-dependent changes in the QRS duration during the control period.

Figure 2 shows the effect of different pacing cycle lengths on the QRS duration and APD90 before and after quinidine infusion in one patient. Quinidine substantially increased the APD90 from 280 msec during the control period to 310 msec at the 600-msec pacing cycle length. It also slightly increased the QRS duration from 140 to 160 msec. However, the drug did not have the same effect on APD90 during the 300-msec stimulation. In fact, APD90 was slightly shorter after quinidine infusion at this rate than during the control period. Conversely, the QRS duration was markedly prolonged at this rate (210 msec compared with 140 msec during the control period and 160 msec during quinidine infusion at 600-msec pacing cycle length). This emphasizes the use-dependent effect of quinidine on conduction in ventricular muscle.

**Electrical Restitution of APD**

Figure 3 shows the effect of abrupt changes of cycle length on APD90 in a patient with a relatively prolonged ventricular escape interval due to an existing complete atrioventricular block. Similar to previously described in vitro studies, the test APD90 shortened biexponentially as the diastolic interval progressively decreased; this confirms the integrity of our MAP recordings.

**Relation and Comparison of Effect of Quinidine on APD and VERP**

The relation between APD90 and VERP could be determined at pacing cycle lengths of 600, 500, 400,
and 350 msec before and after quinidine infusion in seven patients. Quinidine increased the VERP and APD at each ventricular pacing cycle length, but the quinidine-induced increase in APD$_{90}$ was less at shorter pacing cycle lengths. The percent increases in the quinidine APD$_{90}$ over the control APD$_{90}$ for pacing cycle lengths of 350, 400, 500, and 600 msec were 6.9%, 8.9%, 13.5%, and 15.2%, respectively (Figure 4). Unlike quinidine's effect on APD$_{90}$, its effect on the VERP was not dependent on the pacing cycle length. The change in the VERP was relatively flat when plotted against the pacing cycle lengths (Figure 4). The percent changes of the quinidine VERP over the control VERP for pacing cycle lengths of 350, 400, 500, and 600 msec were 10.9%, 10.4%, 8.8%, and 11.9%, respectively. Using the repeated-measures analysis of variance with the Greenhouse-Geisser correction for within-subject correlations, we compared the percent change in the quinidine APD from the control APD with the percent change in the quinidine VERP from the control VERP as a function of cycle length. A clear trend emerged (Figure 4), which showed that the difference between the percent change of APD and that of the VERP at each pacing cycle length resulted in relations having opposite directions when fast and slow pacing cycle lengths were compared ($p=0.09$).

Similarly, the VERP/APD ratio increased after the quinidine infusion as the cycle length decreased ($p=0.07$). After the quinidine infusion, the VERP/APD ratio increased 0.04±0.03 and 0.01±0.02 msec at the 350- and 400-msec cycle lengths, respectively. In contrast, the VERP/APD ratio decreased 0.04±0.02 and 0.03±0.03 msec at the 500- and 600-msec cycle lengths, respectively. This emphasizes that the effect of quinidine on the VERP at the fast rate is not dependent on the change in APD.

**Discussion**

**Divergence in Frequency-Dependent Effect of Quinidine on Conduction and Repolarization**

Quinidine blocks the fast inward sodium current and decreases the $V_{\text{max}}$ of the action potential upstroke, which is a major determinant of conduction velocity.$^{11,13}$ This effect is much more pronounced at faster heart rates because of quinidine's greater binding affinity for activated sodium channels than for inactivated or resting ones.$^{17,22-26}$ Faster heart rates allow sodium channels to spend a greater percentage of time in the activated state, potentiating the sodium current block by quinidine. Consistent with these observations, quinidine markedly prolonged the QRS duration in our patients at faster pacing rates irrespective of the progressive decrease in APD.

Unlike its effect on depolarization, quinidine's action on repolarization is more complex. In rabbit Purkinje fibers$^{17}$ and guinea pig ventricular myocytes,$^{14}$ quinidine has been shown to lengthen APD by blocking $I_K$. These effects are enhanced during slow heart rates, as described by Nattel and Zeng,$^{18}$ who found that sustained increases in frequency attenuated the effect of quinidine on APD in canine cardiac Purkinje fibers. Our data in humans are consistent with these in vitro observations. Quinidine significantly increased APD at different heart rates (Figure 1). However, the faster the heart rate,

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** Plot of effects of quinidine on the action potential duration restitution curve in one of our patients. APD$_{90}$, action potential duration at 90% repolarization.

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Plot of percent change of action potential duration at 90% repolarization (APD$_{90}$) and ventricular effective refractory period (VERP) from control before and after quinidine infusion as a function of pacing cycle length. The bar graph shows the difference between the percent change of APD$_{90}$ and the percent change of VERP.
the less was quinidine’s effect on APD; at 300-msec cycle length, quinidine had a negligible effect on APD.

Although our observations on the frequency dependence of quinidine on APD are consistent with the drug’s known pharmacologic effect on Ik, it should be pointed out that many other factors contribute to changes in APD when there is a change in heart rate. We cannot exclude the possibility that quinidine may have a significant effect on other processes responsible for repolarization changes.

Relative Effect of Quinidine on VERP and APD

A comparison of the VERP/APD ratio before and after quinidine infusion demonstrates that the drug increases this ratio at short cycle lengths and decreases it at long cycle lengths, although these differences were not significant (p = 0.07). Thus, at short pacing cycle lengths, an increase in VERP by quinidine cannot be attributed exclusively to a prolongation of APD, that is, an increase in voltage-dependent refractoriness. This finding suggests that at shorter cycle lengths quinidine increases the refractory period by its sodium current blockade that results in depressed excitability. This action is similar to that of other class I antiarrhythmic agents (e.g., lidocaine and mexiletine) that do not prolong APD and that have been shown to increase the VERP/APD ratio in proportion to their depression of Vmax. Conversely, at long cycle lengths, the effect of quinidine on VERP appears to be voltage dependent, that is, mediated through its effect on the lengthening of APD. This finding is in agreement with the in vitro observations of Varro et al and Campbell, who found no increase in the VERP/APD ratio in quinidine-treated canine ventricular muscle.

Effect of Abrupt Changes of APD

Quinidine may interact with a variety of processes that influence APD after a premature beat. We found that after a long diastolic interval quinidine lengthened APD more profoundly than after a short diastolic interval (Figure 3). This finding is in line with that of Nattel and Zeng and supports the theory that the quinidine block of Ik accumulates during long diastolic intervals. In addition, a long diastolic interval may allow the quinidine block of sodium channels to dissipate, augmenting the inward sodium “window” current during the subsequent action potential and tending to prolong its duration.

Study Limitations

Our study was restricted by the hemodynamic and heart rate responses of patients to intravenous quinidine infusion. The ventricular stimulation rate was confined to a narrow range because the drug substantially reduces systemic blood pressure and increases heart rate. Thus, only a few patients could be studied at pacing cycle lengths longer than 600 msec. Similarly, we could perform the study on abrupt changes on APD in only two patients because the escape interval after the premature extrastimulus was substantially shortened after quinidine infusion. This prevented us from evaluating the slow phase of the electrical restitution curve of the APD and from calculating the time constants of the restitution curves in most patients. We cannot rule out the possibility that increased sympathetic tone or the anticholinergic effect of quinidine influenced APD and refractory period measurements. Despite these shortcomings, our findings were generally consistent with the results of in vitro studies in which autonomic tone was not a factor. Thus, it is unlikely that our data were significantly skewed by alterations in autonomic tone.

Clinical Implications

Our observation that quinidine markedly prolonged repolarization during slow heart rates or a long pause may explain the arrhythmogenicity associated with quinidine. In patients who develop torsades de pointes after quinidine administration, it is well known that the arrhythmias, which frequently emerge during bradycardia, can often be suppressed by pacing the heart at a faster rate. Because quinidine depresses repolarizing currents that may allow the partially recovered inward current to depolarize cardiac cells before repolarization is complete, the drug may promote the development of early afterdepolarization that leads to torsades de pointes. Indeed, Roden and Hoffman have shown in Purkinje fibers that after long pauses in the presence of low doses of quinidine, the subsequent beat had a prolonged APD-associated early afterdepolarization that could lead to sustained ventricular tachycardia.

Our observations also shed light on the antiarrhythmic mechanism of quinidine. The effect of quinidine on repolarization may prevent the initiation of reentrant ventricular tachycardia (fast rate), particularly when triggered by a late diastolic premature ventricular contraction. However, once reentrant ventricular tachycardia has started, quinidine probably would not significantly affect repolarization. Under these conditions, the blocking of the sodium current by quinidine, potentiated at faster rates, is probably largely responsible for the antiarrhythmic efficacy of the drug.

Conclusion

Our data offer new insight into the spectrum of quinidine’s electropharmacologic properties in humans. At one end of the spectrum, quinidine has a profound effect on APD and repolarization during slower heart rates. This is consistent with in vitro studies showing that quinidine depresses repolarizing currents more effectively at slow heart rates. Quinidine’s effect on the voltage-dependent refractory period is more marked at slow heart rates. Yet, as the heart rate progressively increases, this effect diminishes. At the other end of the spectrum, quinidine’s effect on the time-dependent refractory period is more marked during faster rates. The frequency dependence of quinidine’s electrophysio-
logical effect should be borne in mind so as to maximize the drug’s efficacy and to avoid toxicity.

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