The effect of quinidine and mexiletine on the adaptation of ventricular refractoriness to an increase in rate

The purpose of this study was to determine the effects of quinidine and mexiletine on the adaptation of ventricular refractoriness to a change in heart rate. The ventricular effective refractory period was measured at a basic drive cycle length of 500 msec with basic drive train durations of two beats, eight beats, 20 beats and 3 minutes. The ventricular refractory periods were measured in the baseline state and after oral treatment with quinidine or mexiletine in 20 subjects each. In the baseline state, there was progressive shortening of the ventricular refractory period as the drive train duration increased from two beats to 3 minutes. Quinidine prolonged refractoriness by 5% ($p < 0.001$) at each drive train duration. Mexiletine did not affect the ventricular effective refractory period at any of the drive train durations. In a control group of 20 subjects, there were no significant differences between two determinations of refractoriness at each basic drive train duration. In conclusion, neither quinidine nor mexiletine affect the adaptation of ventricular refractoriness to an increase in rate. Although the ventricular effective refractory period measured with a conventional basic drive train duration of eight beats is often more than 20 msec longer than the actual ventricular effective refractory period measured with a drive train duration of 3 minutes, the effects of quinidine and mexiletine on the conventionally measured ventricular effective refractory period accurately reflect the effects of these drugs on the actual ventricular effective refractory period. (Am Heart J 1991;121:512.)

Shimon Rosenheck, MD, Stephen Schmaltz, MPH, Alan H. Kadish, MD, Joni Summitt, DO, and Fred Morady, MD. *Ann Arbor, Mich.*

Ventricular refractoriness progressively shortens when there is an abrupt increase in heart rate, and several minutes at the higher heart rate may be necessary before the maximum shortening of ventricular refractoriness is attained.[1-8] However, in the clinical electrophysiology laboratory, ventricular refractoriness has been conventionally measured by scanning diastole with an extrastimulus introduced after a basic drive train that is only eight beats in duration,[9-12] and this method often yields a ventricular effective refractory period that is 10 to 30 msec longer than the actual ventricular effective refractory period.[1, 13, 14] In clinical electrophysiology studies, the effects of antiarrhythmic drugs on ventricular refractoriness have also been measured with a basic drive train duration of eight beats[15-19]; therefore, the effects of antiarrhythmic drugs on the actual ventricular effective refractory period are not known. Depending on the effect of an antiarrhythmic drug on the adaptation of ventricular refractoriness to an increase in rate, the conventionally measured ventricular effective refractory period may or may not accurately reflect the effect of the drug on the actual ventricular effective refractory period.

The purpose of this study was to determine the effects of quinidine and mexiletine on the adaptation of ventricular refractoriness to an increase in heart rate. Quinidine and mexiletine were selected for this study because they are commonly used representatives of class IA and IB antiarrhythmic drugs.[20] Our aim was to determine whether the effects of these drugs on the conventionally measured effective refractory period accurately reflect their effects on the actual ventricular effective refractory period.

METHODS

Subjects of study. The subjects of this study were 54 patients who underwent clinically indicated electrophysiology tests for evaluation of ventricular tachycardia, unexplained syncope, or paroxysmal supraventricular tachycardia. There were 48 men and 6 women, and their mean age

From the Division of Cardiology and the Clinical Research Center, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan.

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Reprint requests: Fred Morady, MD, Division of Cardiology, B1 F245 Box 0022, University of Michigan Medical Center, Ann Arbor, MI 48109.

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was 61 ± 12 years (± standard deviation). Forty patients had coronary artery disease, six patients had cardiomyopathy, and eight patients had no structural heart disease. The mean left ventricular ejection fraction determined by echocardiography or contrast or radionucleide ventriculography was 0.43 ± 0.14. Thirty-four of these subjects had sustained monomorphic ventricular tachycardia that was inducible by programmed stimulation, and they underwent drug testing; the effects of quinidine and mexiletine were assessed in 20 electrophysiology tests each. An additional 20 subjects served as a control group. Patients were not selected as subjects for this study if they were not in sinus rhythm at a cycle length longer than 600 msec, if ventricular tachycardia or paroxysmal supraventricular tachycardia was inducible with a single ventricular extrastimulus, or if 3 minutes of ventricular pacing at a cycle length of 500 msec was not hemodynamically tolerated.

Electrophysiology protocol. Electrophysiologic studies were performed in the fasting, unsedated state and after informed consent was obtained, either at least five half-lives after discontinuation of treatment with antiarrhythmic drugs or after at least 2 days of treatment with quinidine or mexiletine. Two to four quadripolar electrode catheters (1 cm electrode spacing) were inserted into a femoral or subclavian vein and positioned as clinically indicated in the right atrium, His bundle position, coronary sinus, or right ventricle. Electrocardiographic leads V_1, I, and III, and the intracardiac electrograms were recorded on a Siemens Elema Mingograph 7 recorder (Siemens Medical Systems Inc., Iselin, N.J.) at a paper speed of 25 to 100 mm/sec. Bipolar pacing was performed with the distal pair of electrodes with the use of a programmable stimulator (Bloom Associates Ltd., Reading, Pa.). The pacing stimuli were 2 msec in duration and had a current strength twice that of the late diastolic threshold.

Study protocol. The study protocol was approved by the Human Research Committee and was performed on completion of the clinically indicated portion of the electrophysiology test. An electrode catheter was positioned in the right ventricular apex, and a stable position in which the pacing threshold was less than 0.8 mA was obtained with fluoroscopic guidance. The ventricular effective refractory period was measured with a pacing drive cycle length of 500 msec and drive train durations of two beats, eight beats, 20 beats, and 3 minutes. The 3-minute drive train was used because an earlier study demonstrated that this is sufficient to yield the maximum shortening of ventricular refractoriness when the drive train cycle length is 400 to 600 msec.[1] The initial beat of the drive train was synchronized always to occur 500 msec after a sinus beat. If there was ventriculoatrial dissociation, the atrium was paced simultaneously with the ventricle to avoid disruption of the basic drive train by sinus capture beats. The drive trains of two, eight, and 20 beats were separated by an intertrain pause of 3 seconds. When the drive train duration was 3 minutes, the drive train was not interrupted by pauses and the extrastimulus was inserted after every eighth beat of the drive train.

A ventricular extrastimulus was introduced at an initial coupling interval that was shorter than the ventricular effective refractory period. The coupling interval was progressively increased in steps of 2 msec until ventricular capture was elicited, and the ventricular effective refractory period was defined as the longest coupling interval that did not evoke a ventricular response. The ventricular effective refractory period was measured in this fashion because an earlier study demonstrated that this method yields a more accurate ventricular effective refractory period than when the extrastimulus coupling interval is initially longer than the ventricular refractory period and the coupling interval is progressively shortened until ventricular capture is lost.[21]

Ventricular effective refractory periods were measured in the control state and after at least 2 days of oral treatment with a mean of 1.4 ± 0.6 gm/day of quinidine (mean plasma concentration, 2.4 ± 0.7 μg/ml) in 20 subjects, and in the control state and after at least 2 days of oral treatment with a mean of 675 ± 100 mg/day of mexiletine (mean plasma concentration 1.3 ± 0.7 μg/ml) in 20 subjects. In six of these subjects, a single control study was followed by serial testing with mexiletine and quinidine, whereas in 28 subjects a control study was followed by a single drug study with either quinidine or mexiletine.

Control group. The reproducibility of the techniques that were used in this study to determine the adaptation of ventricular refractoriness to an increase in heart rate was assessed in a control group of 20 subjects. In these subjects, ventricular effective refractory periods were measured at the beginning of an electrophysiology test and again 45 to 90 minutes later, on completion of the clinically indicated portion of the electrophysiology test. The electrode catheter that was used to measure the ventricular effective refractory periods was purposely moved out of the right ventricular apex and repositioned in the same general area before the second set of measurements to simulate the catheter repositioning that occurred in the subjects who underwent the control study and a drug study on different days.

Statistics. To determine the effects of the basic drive train duration and the two drugs on ventricular refractoriness, a repeated measures analysis of variance was used.[22] Multiple comparisons were performed using Fisher's least significant difference multiple comparisons procedure.[23] The reproducibility of the baseline measurements of refractoriness was ascertained by calculating a reliability estimate at each basic drive train duration.[24] A p value of less than 0.05 was considered significant.

RESULTS

Effects of quinidine. In the baseline state in 20 subjects, the ventricular effective refractory period progressively shortened as the basic drive train duration increased (Fig. 1). Quinidine significantly lengthened the ventricular effective refractory period at each basic drive train duration (Fig. 1). There were no significant differences in the magnitude of quinidine's effects on the ventricular refractory period, either in

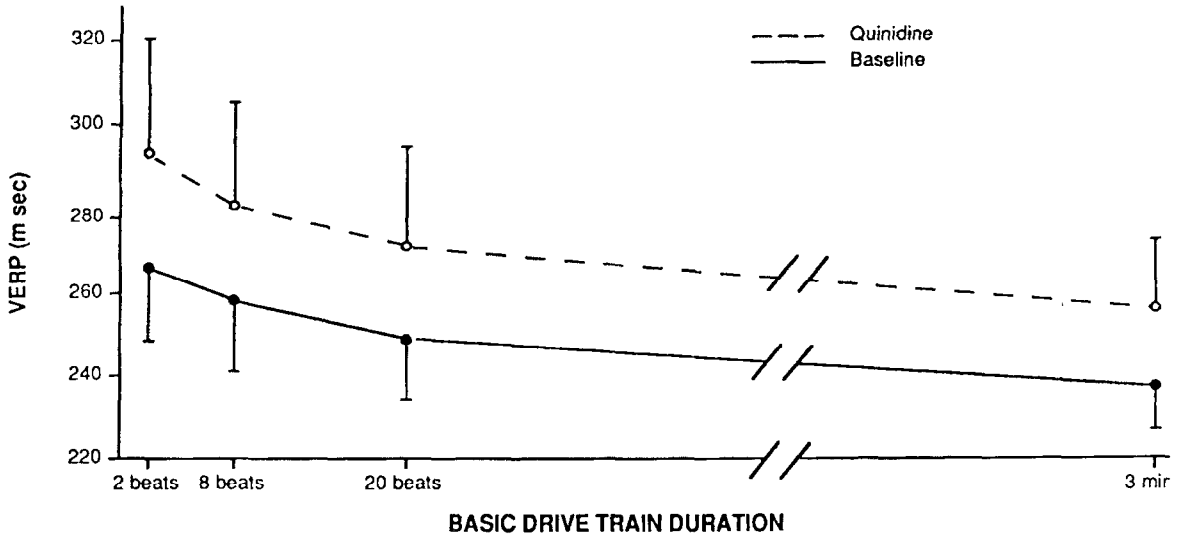

Fig. 1. The effect of quinidine on the adaptation of the ventricular effective refractory period *(VERP)* to an increase in rate. Quinidine significantly lenghened refractoriness at each drive train duration ($p < 0.001$).

Table I. Absolute and percent change in ventricular effective refractory period caused by quinidine in 20 subjects

	Basic drive train duration			
	Two beats	*Eight beats*	*20 Beats*	*3 Minutes*
Absolute change from baseline	29 ± 21*	24 ± 15*	22 ± 17*	21 ± 14*
Percent change from baseline	11 ± 4	9 ± 3	9 ± 4	8 ± 2

Values are expressed as mean ± standard deviation.
There were no significant differences in the absolute or percent changes from the baseline among the various basic drive train durations.
*$p < 0.001$ when compared to baseline.

absolute terms or when expressed as percent change, among the different basic drive train durations (Table I). Quinidine did not significantly change the mean resting sinus cycle length (841 ± 189 msec baseline vs 822 ± 147 msec with quinidine).

Effects of mexiletine. In the baseline state in 20 subjects, the ventricular effective refractory period progressively shortened as the basic drive train duration increased, in a fashion identical to the ventricular effective refractory periods in the baseline studies of the subjects who were treated with quinidine (Fig. 2). Mexiletine did not significantly affect the ventricular effective refractory period at any of the basic drive train durations (Fig. 2). Mexiletine also did not significantly affect the mean resting sinus cycle length (810 ± 157 msec baseline vs 824 ± 149 msec with mexiletine).

Control group. There were no significant differences between the two determinations of ventricular refractoriness at each drive train duration in the 20 subjects in the control group (Table II). The reliability estimate for the measurements of refractoriness ranged from 0.9 for the 3-minute drive train duration to 0.97 for the 20-beat drive train duration.

DISCUSSION

Main findings. In this study, ventricular effective refractory periods were measured in the baseline state with basic drive train durations of two beats, eight beats, 20 beats, and 3 minutes to define the time course of adaptation of ventricular refractoriness to an increase in heart rate. As expected, the ventricular effective refractory period was found to shorten progressively as the duration of the basic drive train increased to 3 minutes. The results of this study demonstrate that neither quinidine nor mexiletine affect the adaptation of ventricular refractoriness to an increase in heart rate. At a drive cycle length of 500 msec, quinidine significantly lengthened the ventricular effective refractory period, and there was no interaction between quinidine's effects and the duration of the basic drive train. Mexiletine had no significant effect on the ventricular effective refractory period, regardless of the duration of the basic drive train. Therefore although quinidine and mexiletine differ in that the former prolongs ventricular refractoriness whereas the latter does not, both drugs are similar in that neither one alters the time course of progressive shortening in the ventricular effective refractory period that occurs as the duration of the basic drive train increases to 3 minutes.

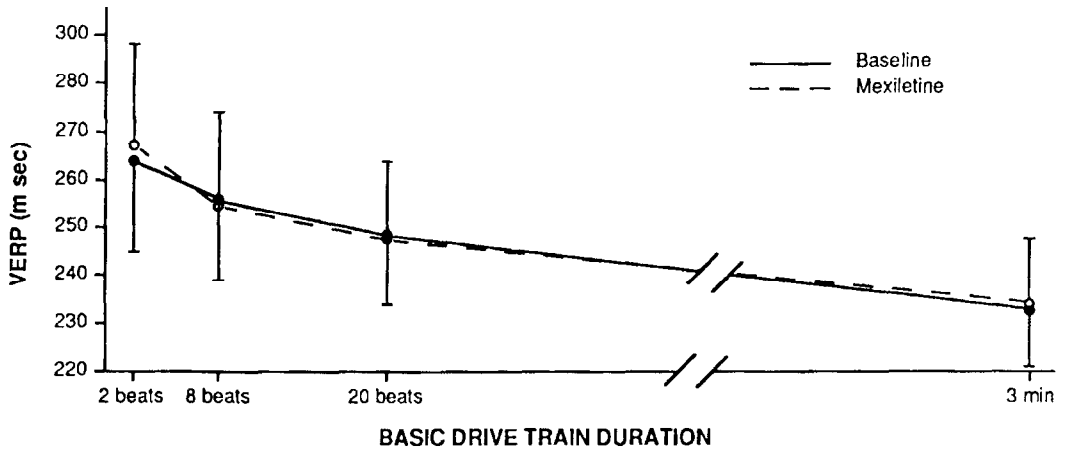

Fig. 2. The effect of mexiletine on the adaptation of the ventricular effective refractory period *(VERP)* to an increase in rate. Mexiletine had no effect on refractoriness at any of the drive train durations.

Reproducibility of measurements. The results that were obtained from the 20 subjects in the control group demonstrated a mean difference of 1 ± 6 msec between two determinations of the ventricular effective refractory period at a given basic drive train duration, and this difference was not significant. These findings provide validation that the lengthening of refractoriness that occurred during treatment with quinidine was in fact attributable to a drug effect and that a systematic drug effect was not present in the subjects who were treated with mexiletine.

Use-dependent effects of quinidine and mexiletine. Experimental studies have demonstrated that the effects of antiarrhythmic drugs that block sodium channels such as quinidine and mexiletine, are use-dependent.[25-29] In concert with the findings of experimental studies, clinical studies have demonstrated that the effects of class I antiarrhythmic drugs and amiodarone on His-Purkinje and intraventricular conduction are also use-dependent.[19, 30-32] In regard to the ventricular effective refractory period, experimental studies have demonstrated that class I drugs, including quinidine and mexiletine, have frequency-dependent effects on the ventricular effective refractory period,[27, 33, 34] and an earlier clinical study demonstrated that procainamide has use-dependent effects on ventricular refractoriness.[35] However, no previous clinical studies have investigated the use-dependent effects of quinidine or mexiletine on the ventricular effective refractory period. Depending on the binding and dissociation kinetics of these drugs, effects on the ventricular effective refractory period might be expected to be less pronounced after a drive train of two beats than after drive trains of eight beats or more. However, because pacing was performed only at a single cycle length of 500 msec, no conclusions can be drawn in regard to the presence or absence of use-dependent effects of quinidine or mexiletine on ventricular refractoriness.

Table II. Two determinations of the ventricular effective refractory period in 20 control subjects

	Basic drive train duration			
	Two beats	*Eight beats*	*20 Beats*	*3 Minutes*
First determination	264 ± 26	253 ± 24*	244 ± 22*	227 ± 13*
Second determination	264 ± 26	253 ± 24*	245 ± 23*	229 ± 15*

Values are expressed as mean ± standard deviation.
There were no significant differences between the two determinations of refractoriness at any of the drive train durations.
*$p < 0.001$ when compared to preceding drive train duration.

Limitations. A limitation of this study is that the adaptation of ventricular refractoriness to an increase in heart rate was determined with only a single pacing cycle length of 500 msec. The results that were obtained at this cycle length may not be applicable to other cycle lengths. A second limitation is that serial measurements of the ventricular effective refractory period in the control group were obtained in the course of a single electrophysiology test, and day-to-day variability in the measurement of the ventricular effective refractory period therefore was not controlled. The third limitation is that the use of a 3-second intertrain pause when the ventricular effective refractory period was measured may have allowed for a cumulative effect of the basic drive trains on the ventricular effective refractory periods; therefore, the ventricular effective refractory periods that were measured during basic drive trains of two, eight, and 20 beats may have been influenced not only by

the number of beats in the drive train but also by the total number of drive trains that preceded the particular drive train that defined the ventricular effective refractory period. Finally, we cannot rule out the possibility that higher plasma drug concentrations than those tested in this study would have yielded different results.

Conclusions. Because ventricular refractoriness adapts to an increase in heart rate in a gradual fashion, the conventional method of determining the ventricular effective refractory period with a basic drive train of eight beats does not yield an accurate measurement of the actual ventricular effective refractory period. When the basic drive train cycle length is 500 msec, the conventionally measured ventricular effective refractory period overestimates the actual ventricular effective refractory period by a mean of more than 20 msec. Nevertheless, because neither quinidine nor mexiletine affects the adaptation of ventricular refractoriness to an increase in heart rate, the effects of these drugs on the conventionally measured ventricular effective refractory period are similar in magnitude to their effects on the actual ventricular effective refractory period. Therefore although conventional measurements of ventricular refractoriness are inaccurate in absolute terms, the change in ventricular effective refractory period that results from treatment with quinidine or mexiletine can be accurately determined regardless of the duration of the basic drive train, at least when the cycle length of the basic drive train is 500 msec.

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Effect of hyperkalemia on experimental myocardial depression by verapamil

Three patients with systemic hypotension and sinus bradycardia that were initially refractory to conventional therapy responded well to intravenous calcium administration. Two-dimensional echocardiography revealed immediate reversal of severe left ventricular dysfunction after intravenous administration of calcium in two instances. Common factors were hyperkalemia and verapamil therapy. This interaction was examined further by evaluation of contractility, heart rate, and arterial blood pressure in anesthetized dogs. Controls (n = 9) received saline infusion, and a second group (n = 10) received saturated potassium chloride (approximately 0.2 ml/min intravenously). In control dogs, administration of verapamil (1195 ± 181 μg/kg intravenously) reduced systemic arterial pressure from 113 ± 7 mm Hg to 74 ± 5 mm Hg, and heart rate from 147 ± 9 beats/min to 86 ± 11 beats/min. Potassium chloride infusion alone increased blood [K^+] from 3.4 ± 0.1 to 6.2 ± 0.2 mEq/L, but was without hemodynamic effects. In hyperkalemic dogs, a significantly lower dose of verapamil (428 ± 42 μg/kg intravenously) reduced systemic arterial pressure from 102 ± 8 mm Hg to 36 ± 4 mm Hg, and heart rate from 150 ± 5 beats/min to 104 ± 15 beats/min. Myocardial contractile function was examined with right ventricular isometric contractile force and left ventricular segment length changes. In normokalemic and hyperkalemic groups, contractility was decreased by verapamil. Effects of verapamil on arterial pressure and contractility could be reversed significantly by administration of calcium, 0.4 mEq/kg intravenously. The present results support the theory that the negative hemodynamic effects of verapamil may be exaggerated to a harmful degree by concomitant hyperkalemia. These adverse events may be reversed by calcium administration. (Am Heart J 1991;121:517.)

Stanley R. Jolly, PhD, Nancy Keaton, MD, Assad Movahed, MD, Gregory C. Rose, MD, and William C. Reeves, MD. *Greenville, N.C.*

Verapamil[1-3] is one of the first calcium channel blockers to be used clinically for the treatment of systemic hypertension, supraventricular tachyarrhythmias, and angina pectoris. High doses of verapamil can produce significant myocardial depression with reduced ventricular contractility, sinus bradycardia, atrioventricular conduction delay, and systemic hypotension.[4, 5] Clinical and experimental studies have suggested when adverse exaggerated responses to verapamil could be expected to occur. For example, intravenous verapamil plus β-adrenergic

From the Cardiology Section, Department of Internal Medicine, East Carolina University School of Medicine, Greenville, N.C.

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Reprint requests: Assad Movahed, MD, Cardiology Section, Department of Medicine, East Carolina University School of Medicine, Greenville, NC 27858-4354.

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