SINGLE FIBER RECORDING OF THE EFFECTS OF QUINIDINE AT ATRIAL AND PACEMAKER SITES IN THE ISOLATED RIGHT ATRIUM OF THE RABBIT[1]

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The means by which quinidine affects excitability, conduction and refractoriness in myocardial fibers has not been explored satisfactorily. The studies of Weidmann (1955), Johnson and associates (1956, 1957a and 1957b) and of Vaughan Williams (1958) have emphasized the depressant influence of quinidine on the depolarization process in cardiac muscle. All have concluded that the primary action of quinidine is to decrease the rate of depolarization. Relatively little attention has been given to possible effects of the drug on the repolarization process.

The observation that quinidine is capable of exerting a marked effect on the rate of repolarization, and thus on the duration of the action potential, has been made consistently in our laboratory, but usually in spontaneously beating preparations (West, 1955) and at a bath temperature of 30°C. Therefore, a study was undertaken in which both repolarization and depolarization could be observed at 37°C, in rabbit atrial preparations driven electrically, and in those dominated by the sinus rate. Recent experiments (West *et al.*, 1959) have suggested the desirability of studying changes in action potential configuration at various selected heart rates. Accordingly, in the study reported here, preparations were driven electrically at a wide range of stimulation frequencies, from as low as 0.1 per second to the maximal follow rate (usually about 10 per second on control preparations). Quantitative expressions of action potential configuration as a function of frequency were then derived under both control and experimental conditions. The result of this study has been to clarify our understanding of the effects of quinidine on both the rising and falling phases of the atrial action potential. The data indicate that the adequacy of the depolarization process is secondary to the effect of quinidine on the processes of repolarization and recovery.

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METHODS. Albino rabbits of either sex were stunned by a blow to the head, the neck vessels cut and the thorax rapidly opened. The entire heart was removed and placed in Ringer's solution of the following composition in mmol per liter: NaCl, 154; KCl, 5.4; $CaCl_2$, 2.2; $NaHCO_3$, 5.9; and dextrose, 5.0. The atria were dissected from the ventricles and then the right atrium was separated from the left. The left atrium was discarded. For the atrial experiments in which a wide range of stimulation frequency was to be employed the sinoatrial node was excised and an atrial segment extending from the atrial appendage to the area of severance from the SA node was mounted, pericardial side uppermost, in a plastic chamber of 30-ml capacity. The tissue chamber was contained in a larger warming bath in which the temperature was controlled, so that the final temperature of the muscle chamber was 37°C. The opposite end of the segment was attached by means of a thread to a strain gauge transducer. For those experiments in which it was desired to preserve the spontaneous beat, the right atrium with SA node was mounted similarly. An alternative mounting consisted of only the isolated SA node.

The nutrient medium was that used by Holland and his associates (Klein and Holland, 1959; Holland and Klein, 1958) gassed with pure oxygen. The pH of this solution was shown to be 8.4 at 37°C. This value was not altered by the subsequent addition of quinidine sulfate. The pattern of response to quinidine was shown not to be altered in solutions of lower pH. The medium was constantly infused through the tissue chamber by gravity. Both the reservoir and the tissue chamber were oxygenated. When drugs were administered, they were dissolved in the Ringer's solution and perfused through the bath from an auxiliary reservoir.

Quinidine sulfate was employed in the con-

centration of 6 μg per ml, approximating the mean therapeutic concentration reported by Sokolov and Ball (1956) for control of clinical arrhythmias.

Electrical stimulation was provided by a Tektronix assembly in which frequency, pulse duration and pulse intensity could be varied. An isolation transformer was necessarily employed, resulting in distortion of the square pulse delivered by the stimulator. A pulse duration of 5 milliseconds was used throughout all experiments. Stimulus intensity was set at five times the threshold voltage determined at the onset of the experiment in order to prepare for a possible increase in threshold. In all experiments on driven preparations, the tissue was stimulated at the standard frequency of 2 per second from the moment it was placed in the bath except when the standard frequency was replaced by the range of experimental frequencies. Experimentally, a series of varied frequencies was used. The convention was adopted that the series always would would begin at the lowest frequency and progress upward. The frequencies are expressed in the reported data in reciprocal form as the interstimulation interval (ISI). The series used, in duration of milliseconds, was as follows: 10,000; 5,000; 2,500; 1,000; 500; 250; 160; 100. After selection of each frequency, a period of at least 90 seconds was allowed for stabilization of action potential configuration. Records in which a series was applied during the continual impalement of one cell were selected for analysis. Data from 10 separate experiments, with from 10 to 20 analyzed stimulation series for each control and experimental condition, are presented under RESULTS.

After the tissue had been mounted, at least 1 hour was allowed for equilibration before recordings were attempted. Control observations were made over a variable period of 3 hours. Analytical results of the effects of quinidine have been compiled from measured records taken between 1 and 2 hours after starting the administration of the drug.

Single fiber recording was accomplished by means of the glass capillary microelectrode technique reported in a previous communication (Cervoni *et al.*, 1956). A dual-beam cathode ray oscillograph was used for display of the observed phenomena. In order to maintain adequate frequency response in the input circuit, electrodes in which the resistance measured more than 30 megohms were discarded.

Action potentials were analyzed by the method shown schematically in figure 1. Depolarization rate is expressed as rise time. Action potential duration (APD) measured at three levels of repolarization provides a representative profile of the characteristics of repolarization.

In a single representative experiment, the duration between the stimulus artifact and the onset of depolarization was measured for the several frequencies of stimulation employed. The duration is here termed "conduction time," although it is realized that the term is not strictly applicable since latency also is involved in the measured value.

Approximate control and experimental maximal follow rates are shown in the graphic data presented in the RESULTS. In three experiments, recovery of excitability was determined at a pulse duration of 5 milliseconds. In these strength-interval data, the values for threshold of excitability were measured as voltage, rather than current. Therefore, the absolute values for threshold may not be meaningful, although the relative changes in threshold with changing stimulation frequency are valid.

RESULTS. *Effects of quinidine on frequency-dependent phenomena in the driven atrium.* Steady state-phenomena—control: Under control conditions, action potential configuration varies markedly as a function of stimulation frequency, as shown in figure 2. The rate of early repolarization (as represented by APD10 and APD50 is most responsive to atrial rate alteration, whereas terminal repolarization (APD90) is least altered. Contraction amplitude displays the frequency-dependent characteristics described by Blinks.[2]

Depolarization rise time also is a function of frequency, as shown in figure 3 (A-1 and A-2). Rise time is not greatly changed until the interstimulus interval approaches 250 milliseconds or less under the conditions of these experiments. When the frequency is further increased, rise time increases rapidly as the absolutely refractory period is approached.

Action potential amplitude (table 1) is frequency-dependent. Amplitude is reduced at both extremes of the experimental stimulation frequency range. At high frequency, a part of the reduction in amplitude occurs possibly because succeeding beats occur before full repolarization has been achieved.

As can be seen from figures 2 and 5, the conduction time is constant throughout the ISI range from 10,000 to 250 milliseconds, increasing rapidly with further increase in stimulation frequency.

[2] Pharmacologist **1:** no. 2, p. 49, 1959.

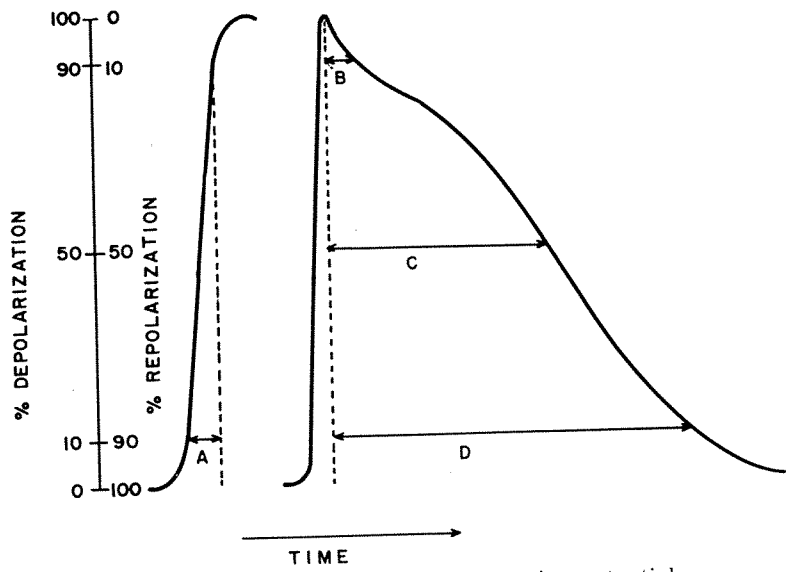

FIG. 1. Method of analyzing membrane action potentials.
On the schematic depolarization limb, A shows the rise time measurement, the elapsed time between 10 and 90% of peak depolarization. B, C and D are the respective times for 10, 50 and 90% of full repolarization.

The combined results of the parameters discussed above are presented in figures 4 and 5, represented by the open circles. The results have been plotted on log-log coordinates for convenience in condensing the graphs.

Data related to recovery of excitability are presented in table 2. In three experiments it is seen that the mean absolutely refractory period for the control is less than 100 milliseconds when determined by this method.

Steady-state phenomena—quinidine: The effect of quinidine becomes manifest within 15 to 20 minutes when employed at the concentration of 6 μg per ml. The effect is essentially maximal for this concentration after 60 minutes of exposure to quinidine, progressing little more during the succeeding hour. Therefore, data taken during 60 to 120 minutes after the start of drug perfusion have been used for comparison with predrug values.

Figure 6A shows the progressive change in action potential configuration during the continual impalement of one cell throughout the first hour of exposure to quinidine. The constant standard stimulation frequency of 2 per second was provided during that time. The change in action potential duration and in conduction time can be noted. Figures 3B and 6B show the change in depolarization rise time as a function of stimulation frequency. Figure 6C illustrates the quinidine effect on repolarization and on conduction time throughout the experimental frequency range.

Action potential amplitude at the higher stimulation rates is lowered by quinidine, according to the data presented in table 1. The tabular data represent only one experiment, so chosen to represent the complete stimulation frequency range possible for predrug and postdrug conditions. Mean data for all measured action potentials agree with the pattern of change shown in table 1.

Slow process of postexcitation recovery—transitional phenomena: From the foregoing results it is clear that action potential configuration is related to frequency of excitation. However, when the rate of stimulation is reduced step-wise, a value is reached beyond which further change in action potential configuration fails to occur. This value, in the control experiments reported here, is approximately 0.1 per second. From the data presented, each interstimulation interval in the range between 10 seconds and the absolutely refractory period yields a characteristic steady state action potential configuration. Thus, following excitation, a slow recovery process is

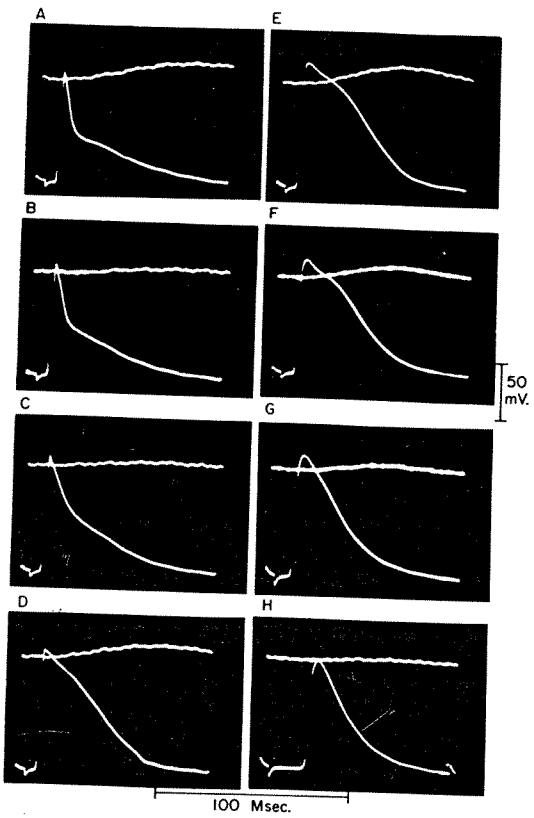

FIG. 2. Alteration in atrial action potential configuration and in total contraction as a function of interstimulation interval.

Contraction base line set at zero membrane potential. Control preparation. Interstimulation interval, in milliseconds, as follows: A—10,000; B—5,000; C—2,500; D—1,000; E—500; F—250; G—160, and H—100. All records taken from one stimulation series in the same cell.

operative during a period of at least 10 seconds, and which influences configuration of an action potential appearing during that period. At interstimulation intervals longer than the total refractory period, the influence of the recovery process is manifest primarily in the repolarization limb of the action potential. During the relatively refractory period depolarization also is affected. The slow recovery process is here termed the period of *complete recovery* from excitation.

Some insight into the nature of complete recovery can be learned when the atrial action potentials are observed during the transition from one driving frequency to another. Figure 7, taken from one representative experiment, illustrates this phenomenon. Under control

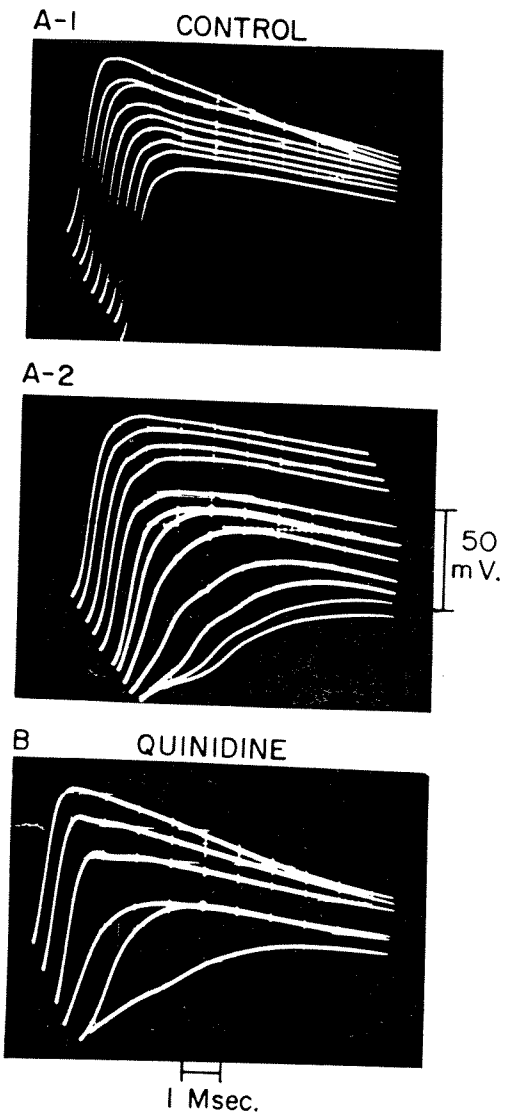

FIG. 3. Depolarization characteristics of atrial action potentials as a function of stimulation rate.

Position of beam varied on oscilloscope face to facilitate display. Sweep triggered by upstroke of action potential.

Panel A: Control recordings from one cell during an expanded stimulation series. Interstimulation interval in milliseconds as follows from top to bottom: A-1—10,000; 5,000; 4,000; 3,200; 2,500; 2,000; 1,600; 1,300; 1,000. A-2—1,000; 800; 630; 500; 400; 320; 250; 200; 160; and 130 (three alternating traces).

Panel B: Another cell 1 hour after quinidine, 6 μg/ml. Interstimulation interval in milliseconds, from top to bottom: 10,000; 5,000; 2,500; 1,000; and 500 (two alternating traces).

TABLE 1

Influence of quinidine (6 μg per ml) on action potential amplitude in right atrial segment driven at several stimulation rates

Data from one representative experiment.

Condition	Interstimulation Interval (ISI) in Milliseconds							
	100	160	250	500	1,000	2,500	5,000	10,000
Control series 1 (mV)	94	107	100	108	105	100	98	98
series 2	90	95	98	98	97	95	95	90
Quinidine (65–90 min exposure)								
series 1	*	*	92	98	98	103	103	105
series 2	*	*	83	90	85	85	93	92

* Did not respond to this frequency of stimulation.

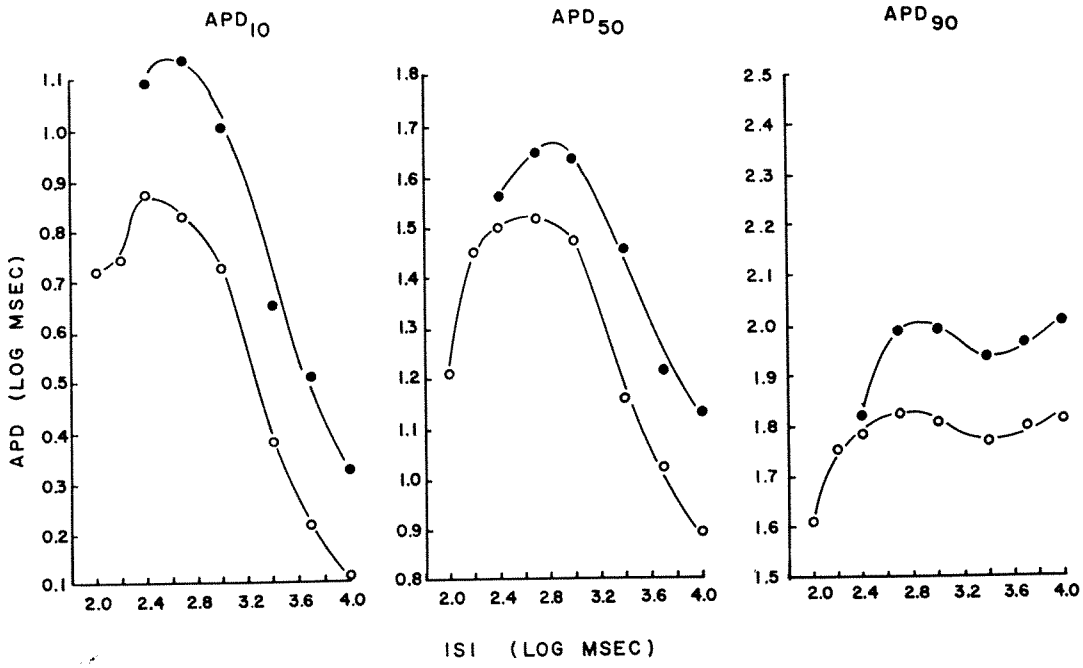

FIG. 4. Mean data from ten experiments to illustrate atrial repolarization characteristics as a function of frequency and of quinidine action.

See text for explanation of APD values. Open circles are controls. Solid circles represent quinidine effects between 60 and 120 minutes following start of drug administration. Differences between control and drug curves statistically significant (P = 0.01 or less) except for APD50 and APD90 when ISI = 250 milliseconds (log 2.4).

conditions, the transition from the steady state configuration at 0.1 per second to that at 1.0 per second is accomplished within seven to eight successive beats. Five to six beats are required upon changing from 0.1 per second to 2.0 per second. The transients pass through replicas of steady state configurations shown in figure 2. The higher the final frequency, the less the number of transitional beats. The same procedures were applied in the presence of quinidine. In addition to the marked changes in action potential duration induced by quinidine, it is clear that the number of beats required to approach the higher frequency steady state is reduced, relative to the controls. Furthermore, in the presence of quinidine, a progressive increase in conduction

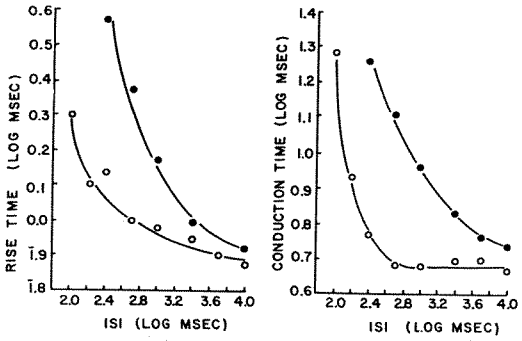

FIG. 5. Atrial depolarization rise time and conduction time as a function of interstimulation interval.

Left panel comprises means from ten experiments. Right panel comprises means from one experiment. Open circles represent control data. Solid circles represent quinidine data between 60 and 120 minutes after start of administration of quininidine, 6 μg/ml. Control and quinidine rise time means not significant for ISI values of 10,000 (log 4.0), 5,000 (log 3.7) and 2,500 (log 3.4). Significant at approximately 5% at ISI of 1,000 (log 3.0). Highly significant throughout remainder of stimulation range. In conduction time curve each point represents three to four observations, with no standard error greater than 1.4 (log 0.15).

TABLE 2

Data concerning recovery of excitability

Threshold voltages at various interstimulation intervals at a constant pulse duration of 5 milliseconds.

ISI	Expt. No. and Measured Threshold Voltages					
	6-17		6-25		6-30	
	Control	Quinidine	Control	Quinidine	Control	Quinidine
msec	*V*	*V*	*V*	*V*	*V*	*V*
540	6.0	7.5	—	13.0	—	—
450	6.0	7.5	—	13.0	—	—
370	6.0	7.5	—	13.0	—	—
290	6.0	8.5	8.5	14.5	4.5	5.0
240	6.0	8.5	8.5	50.0	4.5	5.0
200	6.0	10.0	8.5		4.5	5.0
170	6.0	15.0	8.8		4.5	20.0
160	6.0	50.0	9.0		4.5	50.0
140	7.0		9.5		4.5	
110	8.5		12.5		4.5	
100	10.0		—		4.5	
90	50.0*		50.0		12.0	
80					50.0	

* Final value in each column is at minimal ISI at which preparation would respond to the second of a pair of stimuli.

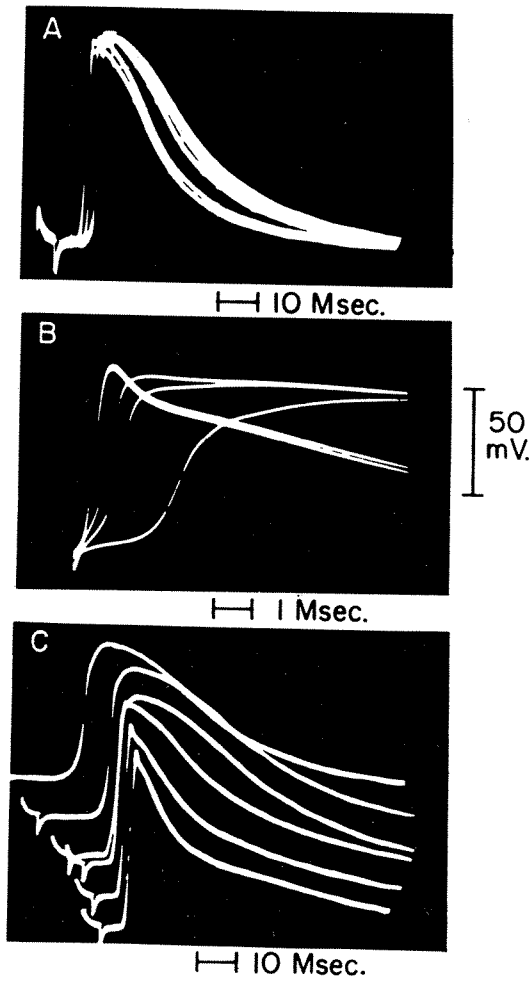

FIG. 6. Effect of quinidine on atrial action potential configuration.

Quinidine concentration is 6 μg/ml in all recordings.

Panel A: Superimposition of progressive quinidine effect in same cell over 1-hour period from start of quinidine perfusion. Recordings made at 10-minute intervals, with control furthest to left. Constant ISI of 500 milliseconds. CR sweep triggered by stimulus artifact. Note progressive shift in position of depolarization and repolarization limbs.

Panel B: Depolarization as a function of frequency 110 minutes after start of quinidine perfusion. Interstimulation interval in milliseconds, from left to right: 10,000; 1,000; 500 and 250. CR sweep triggered by rising limb of action potential.

Panel C: Repolarization as a function of frequency 120 minutes after start of quinidine perfusion. Oscilloscope beam positioned to facilitate display. CR sweep triggered by stimulus artifact. Interstimulation interval in milliseconds, from top to bottom: 250; 500; 1,000; 2,500; 5,000 and 10,000. Note changing conduction time.

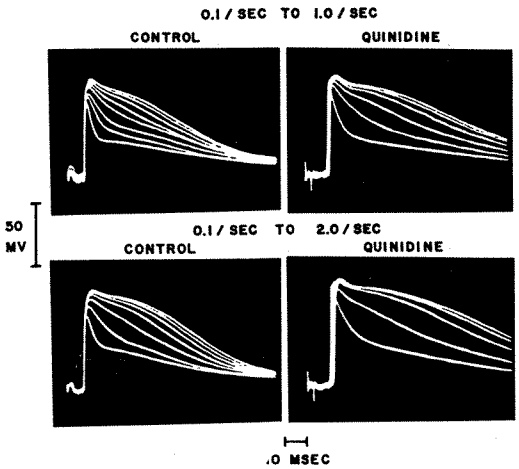

FIG. 7. Transient forms of atrial action potentials observed upon shifting from steady state configuration at one frequency to approximate steady state configuration at a new frequency.

In all panels, the most peaked potential is the final steady state configuration at 0.1 per second prior to an abrupt increase in stimulation rate. Subsequent repolarization limbs are from successive superimposed potentials occurring during the transition. Oscilloscope sweep triggered by stimulation artifact in each case.

Upper panels: Successive sweeps from one atrial cell during control period (left panel) and from another cell (right panel) after 90 minutes exposure to quinidine sulfate, 0.6 μg per ml. Driving frequency changes from 0.1 per second to 1.0 per second in both panels.

Lower panels: Recordings from same experiment as above. Stimulation rate varied from 0.1 per second to 2.0 per second in both panels. Quinidine recording made 5 minutes later than that in the upper right panel.

time is apparent during the transitional period.

The hypothetical basis for these phenomena is described schematically in figure 8. For preparation of the diagram it was assumed that the degree of slow recovery is zero throughout the absolutely refractory period, increasing asymptotically to 100% if the interstimulation interval is not less than 10 seconds. The course of the postulated complete recovery curve is shown in the upper graph as the solid line. The probable alteration of the curve by quinidine is shown as a dotted line. In the lower plot, the transition from a driving frequency of 0.1 per second to 2 per second is illustrated. Because transients are observed during the transition from one steady state to another (as shown in figure 7), it is necessary to postulate that the early rate of slow recovery is altered during the transition period until a steady state which is characteristic of the new frequency is achieved.

Although the quantitative aspects of the diagram in figure 8 may be inexact, it seems clear that the higher the frequency of excitation, the more rapidly the steady state level of the diastolic slow recovery curve is attained, and the more closely that level approaches zero per cent of complete recovery. In addition, if it is assumed that quinidine retards the slope of slow recovery and shifts the hypothetical curve to the right, then it is understandable that inexcitability will be achieved at lower frequencies than were characteristic for the control preparation. Furthermore, it is reasonable that in the presence of quinidine the shift from one frequency to another will be accomplished with a smaller number of transients than were observed under control conditions.

Effect of quinidine on pacemaker action potentials. Because quinidine is known to retard spontaneous heart rate directly, it was of interest to explore this effect by means of direct electrical observation of pacemaker cells. Three experiments were conducted specifically for this purpose. In one, dual recording was employed for simultaneous observation of membrane potentials from both sinoatrial node and from atrium. In the remaining two experiments, the isolated sinoatrial node was used. In one such experiment the quinidine concentration was increased to 10 μg per ml.

Control: The characteristic configuration of pacemaker cell action potentials is shown in figure 9A and 9B. The two recordings were taken at different time bases. Figure 9A shows the simultaneous recording of a pacemaker and an atrial cell before drug administration. The atrial electrode was 5 mm distant from the nodal electrode. Action potential duration for the pacemaker cell was measured as described in figure 1, using the vertical distance between maximal depolarization and maximal repolarization to establish the per cent of repolarization levels. Depolarization characteristics were not quantified for these cells.

Quinidine: The effect of quinidine after 1 hour is shown in figure 9C and 9D. The spontaneous rate decreased from 2 per second to 1.55 per second and stabilized at the latter value. Action potential duration increased at all levels, but particularly at the 50 and 90% levels. These

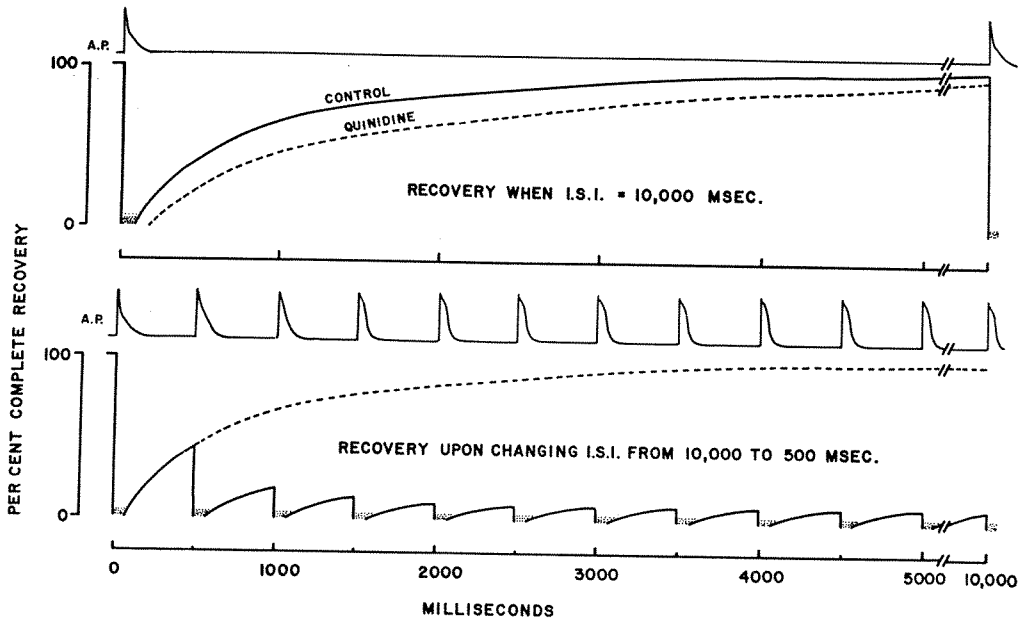

FIG. 8. Schematic diagram to indicate hypothetical time course of complete recovery (see text) from excitation. Data for half-repolarization rate at various driving frequencies used to construct curves.

Upper graph: First line shows schematic membrane potential (A.P.) when driving frequency is set at 0.1 per second. Immediately below, the heavy solid curve indicates per cent of complete recovery during electrical systole and diastole. Shaded area indicates period when depolarization is abolished or depressed. Dotted line shows hypothetical displacement of curve by quinidine.

Lower graph: First line shows schematic membrane potential upon changing from driving frequency of 0.1 per second to 2.0 per second. First potential on left is final steady-state potential at 0.1 per second prior to changing to higher driving rate. Immediately below, the fluctuating solid line indicates transition to new steady state for maximal diastolic recovery. Dotted line indicates predicted course of recovery had the frequency not been altered.

effects are similar to those recently reported for rabbit SA node by Matsumura and Takaori (1959). Figure 10 shows a plot of pacemaker action potential duration against time from the start of quinidine adminstration. The dotted lines represent two-point curves taken from the experiment pictured in figure 9 in which the quinidine concentration was 6 μg per ml. The extreme ends of the lines (at 0 and 60 minutes) represent the means of four control and four experimental impalements. Variation between the values included in the means was extremely slight. The solid lines represent data recorded from the continual impalement of one cell in an isolated pacemaker experiment in which the quinidine concentration was 10 μg per ml. In both experiments the spontaneous rate had decreased to 73% of control by the time of the final observation. The absolute APD values for the two experiments also correspond closely, with respect to control and final experimental observations.

In the third experiment the response to quinidine was closely similar to be described above.

DISCUSSION. Two distinct phases of the investigation require comment. The first concerns the frequency-dependent characteristics observed for action potential configuration, regardless of the presence or absence of quinidine. The second pertains to the effects of quinidine on action potential configuration, and the functional significance of these effects.

Frequency-dependent phenomena. As a function of frequency the total action potential duration (closely represented by APD90) does not vary greatly, although the *pattern* of repolarization is strongly dependent on stimulation rate, particularly at rates of 0.4 per second or higher. Relatively little change in pattern occurs at lower rates. These observations suggest that a process of finite duration is initiated by depolarization and that it continues well beyond the duration of the observed action potential. The period occupied by this process is assumed to be the

time required for "complete recovery" from a single depolarization.

In order to postulate the nature of the events concerned, certain assumptions, recently summarized in part by Hoffman (1959), are necessary. The assumptions are not indisputable, but serve as a departure point for interpretation of the observed phenomena. It is assumed that the level of membrane potential in atrial fibers is at any instant a reflection of the relative magnitudes of the conductances of each of the two major cations, Na^+ and K^+. The direction of current flow and polarity of the potential differences arising as an effect of each of these conductances are diametrically opposed. Thus, it is assumed that depolarization results from a marked relative increase in Na^+ conductance, and that repolarization in the simplest form results from the re-establishment of a dominant K^+ conductance. The relative contribution of Na^+ and of K^+ conductance during the plateau phase of repolarization is not clear. However, Weidmann (1956a) has suggested that the mechanisms responsible for the plateau phase in Purkinje fibers might involve a decrease in membrane conductance and the participation of metabolic processes (possibly active transport of cations).

In atrial fiber recordings the plateau phase shows a greater slope than that usually reported for ventricular or Purkinje fibers. The atrial plateau will thus be defined as the period of minimal voltage change occurring between maximal depolarization and terminal repolarization. A sequence of steady-state recordings at varying stimulation rates (see figure 2) shows that the time for onset of the plateau is relatively constant, but that it appears at an increasingly lower membrane potential as the stimulation rate is increased. The change in plateau level occurs because the slope of early repolarization is reduced as stimulation frequency is increased. It is possible that a process capable of reducing the conductances of both Na^+ and K^+ during the plateau phase affects Na^+ conductance only until terminal repolarization is attained, but continues to exert a diminishing effect on K^+ conductance well beyond the termination of repolarization. This process is indicated as the heavy line (K^+ conductance) and shaded area (Na^+ and K^+ conductance) in the diagrams shown in figure 8, and is here termed the process of complete recovery from excitation. With increasing stimulation frequency the level of slow recovery approaches zero. Because of diminishing K^+ conductance the slope of early repolarization becomes more shallow. Encroachment of Na^+ conductance results in a depression of excitability and of the rate of depolarization.

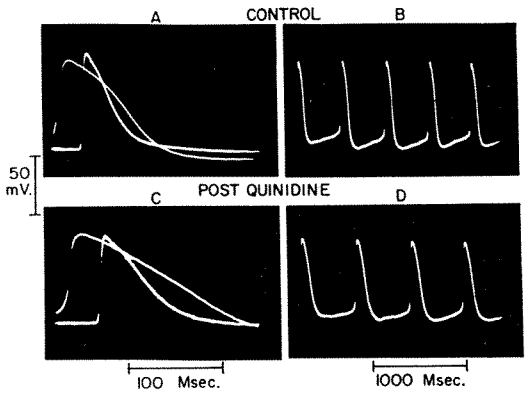

FIG. 9. Effect of quinidine on pacemaker action potential configuration.

Panel A: Control pacemaker recording (slow potential) recorded simultaneously with atrial action potential. Note comparative differences in configuration and timing.

Panel B: Same pacemaker cell as in A, at slower sweep and with atrial recording moved off screen.

Panel C: Another pacemaker cell and atrial cell from areas used for A and B, 60 minutes after start of quinidine (6 μg/ml) perfusion. Note changes in configuration and timing of both action potentials.

Panel D: Same pacemaker cell as in C, with atrial recording removed from screen. Sweep triggered by upstroke of pacemaker action potential in all recordings.

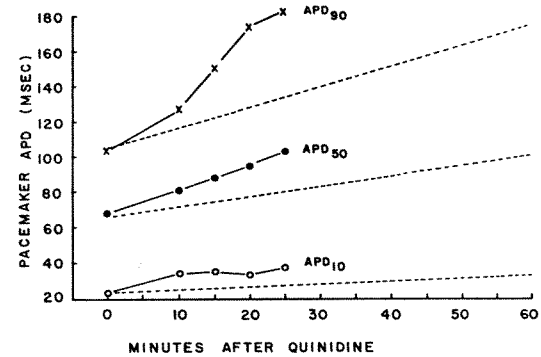

FIG. 10. Effect of quinidine on pacemaker repolarization.

Dotted lines connect control means and experimental means taken from experiment depicted in figure 7. Solid lines represent observations from continual impalement of one cell in an isolated pacemaker preparation in which the quinidine concentration was 10 μg/ml. For further explanation, see text.

From the above considerations it might appear that a progressive increase in heart rate should result in an increasingly greater action potential duration, at least during the plateau phase. This is not the case. In fact, at frequencies approaching the maximal follow rate, action potential duration at all levels of measurement is reduced relative to the maximal values observed at slower rates. Action potential configuration at high frequency is similar to that seen at slower rates when the external K^+ concentration has been elevated experimentally. Weidmann (1956b) has shown that a sudden increase in external K^+ concentration shortens the time required for ventricular repolarization in the amphibian ventricle. For the rabbit atrium the possibility is here suggested that (at normal K^+ concentration) high frequency repetitive firing leads to an accumulation of K^+ in, or at the surface of, the cell membrane. This could be responsible in part for the shortening of action potential duration under those conditions. Figure 7 does not take into consideration this possibility.

In summary, on the basis of the argument employed above, the configuration of a given transmembrane action potential depends on the extent to which slow recovery has occurred from an immediately preceding action potential.

Quinidine effects on atrial fibers. Quinidine, in the concentration used, increases the repolarization time at all levels of measurement independently of stimulation frequency within the experimental range.

In contrast, the quinidine effect on the rate of depolarization is directly related to the frequency of depolarization. The functional result of the effect on depolarization is to cause decreased excitability at lower driving rates than were observed under control conditions. The effect on excitability is reflected in the influence of the drug on conduction time, the values of which depart significantly from control values only as the stimulation rate is increased. We believe that the effects of quinidine on depolarization, excitability and conduction are based on the ability of the drug to retard the rate of slow recovery from excitation. The result of this action is manifested in the prolonged plateau phase of the action potential and in the repolarization time measurements throughout the driving frequency range.

The fundamental action quinidine on post-excitation recovery, together with the frequency-dependent effect on depolarization, result in prolongation of the total refractory period and its component parts, and in a reduction of the maximal driving rate to which the preparation will respond.

The finer mechanism of the drug action cannot be determined from the electrical approach. However, certain inferences can be drawn. Retardation of the rate of repolarization could result from a depression of K^+ conductance. Whether the drug affects the cell membrane directly, or indirectly through depression of metabolic reactions associated with the plateau process is not apparent. Radiostope studies have demonstrated the depressant effect of quinidine on K^+ efflux (Holland and Klein, 1958) as well as on Na^+ influx and on the "active transport" of Na^+ and K^+ (Klein *et al.*, 1960). However, it should be noted that the latter authors interpret their data to mean that quinidine acts primarily through depression of Na^+ influx.

Quinidine effects on pacemaker activity. The effect of quinidine on membrane repolarization of cells of the sinoatrial node is generally similar to that observed for atrial cells. Repolarization time is markedly prolonged. Although the rate of systolic depolarization was not measured, the drug effect on this component of the action potential appears to be slight. No attempt was made to drive the node electrically to determine the effect of heart rate on action potential configuration. Simultaneously with retardation of repolarization rate the spontaneous discharge rate from the pacemaker was reduced, although the relative changes in the two parameters were not of identical magnitude. Changes in the action potential associated with reduction of spontaneous rate by quinidine are different from those obtained with acetylcholine or vagal stimulation (Hutter and Trautwein, 1956). In the latter case the slope of repolarization increases and a variable amount of hyperpolarization occurs. This observation is in agreement with the indirectly observed effect of acetylcholine to increase atrial membrane conductance (Trautwein *et al.*, 1956) and the presumed action of quinidine to decrease conductance.

The pattern of effect by quinidine on pacemaker cells simulates in many respects the effect of temperature reduction. That is, the pattern

includes lengthening of action potential duration, reduction in the rate of repolarization and reduction spontaneous discharge rate. A similar comparison can be made for the drug effect on atrial cells. Thus, the possible action of quinidine on metabolic processes is reemphasized.

Importance of heart rate. From these data it is evident that a knowledge of the effects at various stimulation rates is important to a complete description of drug-induced phenomena. For example, were one to investigate quinidine effects at the concentration employed in the present investigation only at a frequency of 0.1 to 0.2 per second, it would be concluded that depolarization is depressed little, if at all, although a definite retardation of repolarization would be evident. However, should the experiments be conducted at the single frequency of 4 per second, the results would point to a predominant effect on the depolarization process. Should only the spontaneous rate be employed, the quinidine-induced slowing of sinus rate would introduce an uncontrolled variable.

Conclusions. Under the experimental conditions, the effects of quinidine are interpreted to result from a primary prolongation of a slow process of postexcitation recovery in cardiac cell membranes. The shorter the time interval between successive spikes, the more prominent is the quinidine effect, and the more pertinent is this mechanism to the control of certain clinical arrhythmias.

SUMMARY

The effects of quinidine were studied in isolated atrial preparations from rabbits. Quinidine was administered in the concentration of 6 μg per ml. The environmental temperature was 37°C. Atrial segments deprived of the normal pacemaker were driven electrically. Action potential configuration was observed over a wide range of stimulation rates, both under control and experimental conditions. Quinidine was shown to depress the rate of repolarization at all frequencies, but depressed the rate of depolarization only at the higher frequencies of the range. In spontaneously beating right atria, or in isolated sinoatrial node preparations, quinidine retarded the rate of repolarization in pacemaker cells and reduced the spontaneous discharge rate of such cells. It was concluded that the effect of quinidine on the depolarization process was secondary to its effect on the processes of repolarization and recovery.

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