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A graphic method for the study of alternation in cardiac action potentials

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NOLASCO, J. B., AND ROGER W. DAHLEN. *A graphic method for the study of alternation in cardiac action potentials.* J. Appl. Physiol. 25(2): 191–196. 1968.—The cardiac action-potential duration (A) is influenced by the preceding diastolic interval (D_0) and inversely affects the next diastolic interval (D_1). Action potentials were recorded through microelectrodes impaled into frog ventricular muscle strips driven electrically to produce alternation. The graph of $A = f(D_0)$ during the steady state was plotted and the relationship $D_1 = f(A)$ was drawn. The point of intersection of these two curves describes the action-potential duration and diastolic interval in the steady state. When stimulus frequency is altered, the plots of action potentials immediately following the rate change deviated from the steady-state curve. The action-potential behavior in this nonsteady state was explicable by a functional curve, the slope of which determined the occurrence of alternans. Transient alternation appeared and lasted longer as this slope increased and at a driving rate where the slope was +1, persistent alternans occurred. The existence of more than one amplitude of alternation at a given rate was also deduced from the graphs and demonstrated experimentally.

rate effect on intracellular cardiac action potentials; negative feedback; cardiac electrical alternans; arrhythmias; homeostasis; nonsteady-state behavior; diastolic interval

ALTERNATION IN THE ACTION POTENTIALS of isolated animal cardiac tissues and in the electrocardiogram in man and animals has been reported in diverse conditions (1, 2, 5, 7–9, 11–14, 18). The alternation consists of reciprocal variation in the voltage, duration, and shape of adjacent electrical complexes during a regular rhythm. Ordinarily, during regular rhythmic activity, the transmembrane action potentials in cardiac tissues are remarkably constant. Variations appear when the rate is changed and even if only one cycle length is altered (3, 4, 8, 11, 12, 17, 21). This rate effect has been implicated in the genesis of alternation (8, 12, 18) but except for the observation that alternation is prevalent in tachycardias and may be precipitated by an abrupt cycle length change (5, 12, 18, 20), the relation between alternation and rate has not been explicitly defined.

By considering cardiac alternation analogous to the oscillation in electrical circuits and utilizing mathematical principles already established for the latter, we devised a graphic model which permitted prediction of the duration of the action potentials elicited after a change in rate. With this model, the behavior of the action potentials which follow different degrees of acceleration was charted and from the charts, postulates defining the conditions leading to alternans were formulated.

In this communication we aim to explain the theoretical basis for the graphic model, including the model's construction and operation, and to present the postulates, the experimental observations supporting these postulates, and some perspectives about cardiac alternation suggested by this approach.

ANALOGY TO AN ELECTRICAL FEEDBACK SYSTEM AND IDENTITY OF TRANSFER FUNCTIONS

In a simple electrical negative feedback system where an independent signal (X) is a part of the input (I) and following amplification (G) a fraction (F) of the output (O) is fed back to the input, the equations defining the relationship between I and O as elements in the feedback loop may be used to solve for the steady-state value of O at any given value of X (19). The transfer functions $O = G(I)$ and $I = X - F(O)$ may be plotted on common coordinates and the intersection of the graphs provides a simultaneous solution for the two equations and yields the steady-state or set-point values of O and I at a given X.

By relating the action-potential duration to the diastolic interval rather than to the stimulus interval, a similar feedback loop may be shown to exist in the cardiac tissue that is driven regularly. The stimulus interval (S) represents the signal partially contributing to the input which, in this case, is the diastolic interval (D_0). D_0 influences the duration of the following action potential (A) and the latter inversely affects the next diastolic interval (D_1). The transfer functions for the cardiac tissue are: $A = f(D_0)$ and $D_1 = f(A) = S - A$. The parallelism between electrical system and cardiac tissue is clearly apparent in the feedback loops and equations shown in Fig. 1.

CONSTRUCTION AND OPERATION OF GRAPHIC MODEL

Plotting the two transfer functions on common coordinates with A on the ordinate and D on the abscissa creates a graphic model from which the durations of successive action potentials and diastolic intervals following a change in rate may be mapped out. The graph of $A = f(D_0)$, which will be termed the A curve, is drawn from measurements of action-potential durations and diastolic intervals in the steady state at different driving rates. At constant conduction velocity, $D_1 = S - A$ and, if S is maintained constant at the new rate, $dD_1/dA = -1$. Hence, for any regular rate, the plot of $D_1 = f(A) = S - A$ is

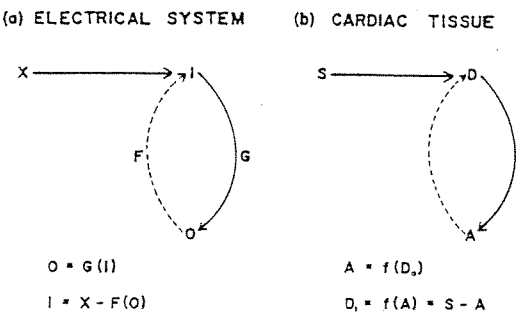

FIG. 1. Feedback loops and equations for an electrical system and the cardiac tissue. X = signal, I = input, G = gain, O = output, F = fraction of O fed back to input, S = stimulus interval, D_0 = diastolic interval preceding, D_1 = diastolic interval following, A = action-potential duration.

a straight line with X and Y intercepts equal to S. This plot will be termed the D line.

To obtain the values of successive A's and D's after a rate change, the D line for the basic rate is drawn first. Its intersection with the A curve corresponds to the steady-state A at the basic rate. The D line for the final frequency is drawn next. If the change in stimulus rate is instantaneous, that is, there are no cycle lengths intermediate between the basic cycle and the final cycle lengths, a horizontal line is drawn from the basic A to the D line of the final rate. Its intersection with the D line gives the magnitude of the first D at the new rate. From this point, a vertical line projected to the A curve yields the first A at the new rate. This procedure of projecting from D line to A curve and vice versa is continued to yield the successive values of D's and A's until a projection line hits the intersection of the A curve and the D line. The point represents the steady state or set point for the new rate.

If the change in stimulus frequency is not instantaneous and a cycle of intermediate length is interposed between the basic cycles and the desired final stimulus cycle, this transition cycle may be disregarded and the D of that cycle which is the first to attain a constant length at the new rate is measured from the experimental record and utilized as the starting point for the projection process.

POSTULATES ON OCCURRENCE AND PERSISTENCE OF ALTERNATION

Using a pilot model with a hypothetical A curve and D lines, the projections lines may be charted to predict the behavior of the action potentials at different rate changes. Such a pilot model is shown in Fig. 7 where five different D lines have been drawn. Each D line represents a different final stimulus rate and the closer the D line to the origin, the faster the rate it represents. The small circle on each D line stands for the first D following the rate change and, for projections 1, 2, 3, and 4, it would be the initial D at the new rate if the basic A is that indicated by the intersection of the horizontal dotted line and the A curve at its extreme right.

With the projection technique described above it could be established that: *a*) When the D line crosses the A curve where the latter's slope is zero (no. 2 in Fig. 7) the steady-state action-potential duration is instantly attained, no oscillation of the action-potential duration may be expected at this stimulus rate. *b*) When the D line intersects the A curve where the slope is between zero and +1 (no. 3 in Fig. 7) the projection lines course centripetally around the set point before eventually ending on it. The corners formed by the lines on the A curve represent the action-potential durations and diastolic intervals whose values oscillate about the steady-state value. The steeper the slope of the A curve, the more the number of turns it takes to reach the steady point. This implies that the alternans, though transient, persist longer on acceleration to faster rates than to slower rates. *c*) If the intersection is where the slope is +1 (no. 4 in Fig. 7) the projection lines form a square and fail to converge on the set point and persistent or sustained alternans result. The size of the square is an index of the amplitude or degree of alternation. *d*) If concomitant with *condition c* above, a sizeable segment of the A curve lies symmetrically on each side of the D line, it is possible to draw several separate squares each representing a different amplitude of alternans (no. 5 in Fig. 7). Since each square originates from a different initial value of D, persistent alternans of different amplitudes may be induced at the same stimulus rate if the initial D is varied. *e*) When the D line crosses the A curve where the latter's slope is negative (no. 1 in Fig. 7) the projection lines course toward the set point in a stairlike manner suggesting that after the change in rate, the action potential durations approach the steady-state value in direct steps without oscillating. *f*) If the stimulus rate is so rapid that its D line cuts the A curve at a slope greater than +1, the projection lines pursue a centrifugal course and veer away from the left limit of the A curve (no. 6 in Fig. 7). Failure to respond to subsequent stimuli is implied.

Experimental observations supporting *postulates a–d* are given below. Attention is particularly invited to the induction of different degrees of alternation at the same alternans-inducing rate as predicted by postulate *d*.

METHODS

Endocardial strips of muscle from the ventricle of pithed frogs (*Rana catesbiana*) were perfused with a solution containing: NaCl, 110 mM; NaH_2PO_4, 12 mM; $NaHCO_3$, 0.4 mM; KCl, 2.7 mM; $CaCl_2$, 1.8 mM; $MgCl_2$, 2.1 mM; glucose, 5.5 mM. This solution was gassed with a mixture of 95% oxygen and 5% carbon dioxide and maintained at constant temperature between 26 and 28 C.

The tissue was stimulated through a glass electrode in which the bathing fluid bridged the gap between the tissue and a chlorided silver wire connected to the cathode of a model S-8 Grass stimulator through a stimulus isolation unit. A similar glass electrode in the bath near the first one was connected to the anode. Stimulus current was not measured. The rectangular pulses ranged from 5 to 15 v (20–100% over threshold) and were 5 msec in duration. Driving pace began at about 12/min and was increased in steps of 12 until the tissue failed to respond to every stimulus. To minimize variations in stimulus intervals during the change in rate, a relay switch and a second stimulator were employed. The relay switch was triggered by the stimulator initially pacing the tissue and it effected instantaneous shifting from the preset frequency of the first stimulator to the preset frequency of the second stimulator. Only one stimulator always supplied the stimulus to the tissue, the second stimulator merely driving the first. At any setting of the frequency dial of either stimulator, stimulus intervals varied not more than 1% and when switched from one rate to another, the transitional cycle did not vary more than 3% from the basic cycle.

The tissue was impaled with glass microelectrodes filled with 3 M KCl solution and with resistances ranging from 20 to 60 megohms. A high-impedance electrometer connected the elec-

trode to an oscilloscope. The push-pull output from the preamplifier was tapped and led to a tape recorder. A time pulse of 20 cycles/sec was simultaneously recorded on another channel of the tape. Taped records were reproduced on photographic paper by means of an Electronics for Medicine recorder (model DR-8) at speeds of 10 and 75 mm/sec. Occasional photographs of the tracings on the oscilloscope screen were used to check the accuracy of the tape system.

Action-potential duration was measured at 90% repolarization and the interval extending from this point to the beginning of the next action potential was considered the diastolic interval.

The experimental procedure usually consisted of pacing the preparation at a certain rate, recording three to seven action potentials for the control and switching to the desired frequency of driving while recording was continued for another 10–15 cycles. Longer records were taken when necessary, otherwise recording was temporarily suspended. After a few minutes, the procedure was repeated with the driving rate either restored to the original rate or changed to another level. Tracings at the start of each recording prior to the change in rate were regarded as representative of the steady state. Uninterrupted recording while continuously increasing the stimulus rate was also done.

For plots of the A curve in any one muscle preparation, only records obtained while the microelectrode remained undislocated were used.

RESULTS

A curves. The steady-state A curves of six preparations are shown in Fig. 2. The curves were drawn from averaged values of A and D at each rate. Over a wide range of rate, the change in action potential duration was minimal. At rapid rates, the slope of the A curve became increasingly steep and some curves, in addition, exhibited a downward trend at very slow rates.

Plots of cycles after a rate change did not coincide with these steady-state curves. If a nonsteady state supervenes after a rate change, it may be assumed that the earlier cycles would show greater evidence of this state than the later ones. Accordingly, the first two cycles immediately following a rate change were plotted. The existence of the nonsteady state on either accelerating or decelerating the rate became evident. Values in acceleration (points joined by line A_a in Fig. 3) were observed to lie above, while those in deceleration (A_d) fell below the steady-state values (A_s). The larger the rate change, the greater the deviation from the steady-state value. The nonsteady-state curve, therefore, is not a single curve but a family of curves which approach the steady-state curve the longer the time interval elapsing after the rate change. The tissue follows a composite functional nonsteady-state A curve before settling down to the steady state.

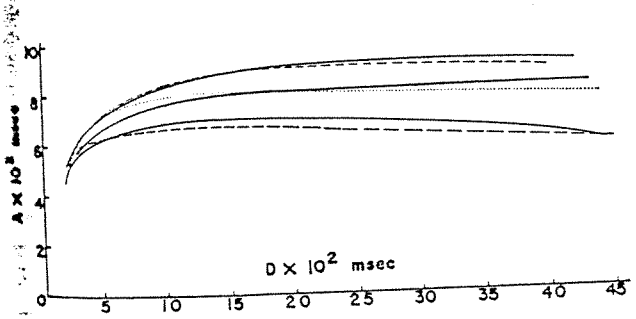

FIG. 2. Steady-state A curves in six preparations. A = action-potential duration, D = preceding diastolic interval. Scale in hundred milliseconds.

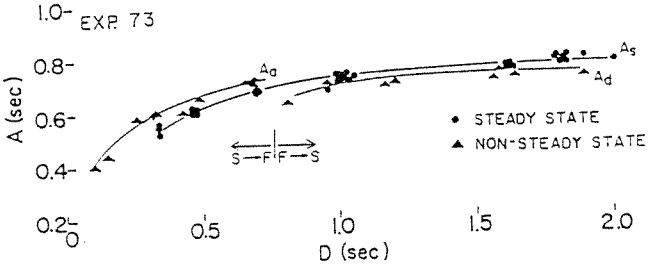

FIG. 3. Deviation of the nonsteady state from steady state. Steady-state values were obtained after action potentials had stabilized following a change in rate. Nonsteady-state values were from the first two cycles immediately following the rate change. Triangles to the left of the vertical bar (A_a) represent values after a slow rate (S) was changed to a fast rate (F); those to the right (A_d) followed deceleration from a fast rate (F → S).

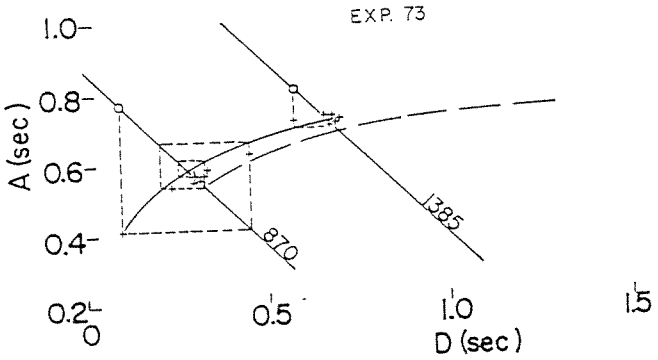

FIG. 4. Plots of an experiment without alternation and another with transient altenans. Initial S = 2,500 msec in both. Curves A_s and A_a as in Fig. 3. Diagonal lines are D lines after rate was changed to S = 1,385 msec and S = 870 msec. Circle on each D line was the initial diastolic interval shortened by the rate change. Crosses represent action-potential durations of successive cycles traced by the vertical and horizontal broken lines.

Plotting cycles showing alternation. Changes in voltage and in duration characterized the action-potential alternation in frog ventricular muscle. The degree of the voltage alternans did not always parallel the magnitude of the duration alternans but persistent voltage and duration alternans occurred at the same rates.

Transient alternation extending over a few cycles often appeared on rate acceleration. The values of A and D of the cycles during this alternation and the D line for the rate at which it was observed were plotted. One experiment, shown in Fig. 4, was done on the same tissue as was used in Fig. 3. The values shown as crosses were not included in the construction of the A curve. Each D line, one for S = 1,385 msec and another for S = 870 msec, represents an increase to the rate indicated from a basic S of 2,500 msec. The broken lines trace the sequence of the cycles from the first diastolic interval (circle), abbreviated by the rate change, and end near the intersection of the D line with the A curve. At S = 1,385 msec only the first action potential varied from the subsequent cycles. At S = 870 msec the first four beats showed distinct oscillatory behavior. None of the points coincided with the steady-state A curve and it was this behavior that directed our attention to the nonsteady state. If the points are considered to belong to a functional A curve, the slope of this curve at any D line intersection may be

calculated by using the two-point formula:

$$T = (A_2 - A_1)/(D_2 - D_1)$$

where T is the slope, A_1 and A_2 are the durations of the first two action potentials after the rate change, and D_1 and D_2 are the diastolic intervals preceding them. In the experiments depicted, at S = 1,385 msec, T = (712-712)/(687-578) = 0, while at S = 870 msec, T = (628-415)/(455-102) = 0.6. These values are less than what the curves suggest and, in fact, the T calculated for the steady-state A curve at S = 1,385 msec is 0.5. The possible explanation for the deviation is presented in the discussion.

In a few experiments, persistent alternation occurred after a random acceleration. Frequently, we looked for it through a systematic stepwise increase in rate.

A case of persistent alternation is plotted in Fig. 5. The dotted lines trace the earlier cycles while the largest square drawn in broken lines charts the later cycles during a uniformly varying persistent alternation. The slope of the functional curve calculated from the data listed in the columns ranged from 0.96 to 1.17 (mean = 1.03). The projection lines joining the short and long diastolic intervals to their corresponding action potential durations form a square and, unlike those in Fig. 4, do not converge on any set point.

When the onset of the rapid stimulation was changed while the intensity and duration of the stimuli were kept constant, a different amplitude of persistent alternation was observed at the same stimulus frequency. The smallest square in the figure links the diastolic intervals and action potential durations measured. The actual tracings showing the amplitudes of alternation are pictured in Fig. 6. Any change in the phase of

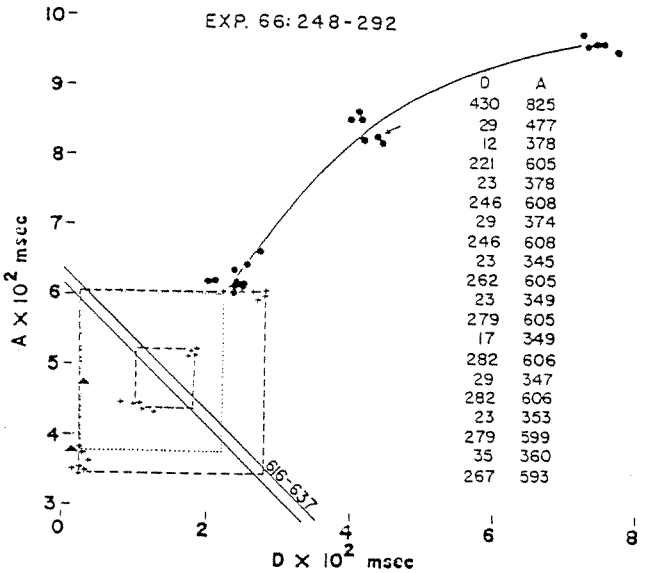

FIG. 5. Plot of persistent alternation. A part of the A_n curve is shown in the upper right quadrant. Arrow points to the last of the basic cycles (also the first pair of numerals in the columns). The two triangles are the transitional cycles introducing the alternans. The dotted lines link the earlier cycles while the largest square links cycles after alternans was firmly established. S = 616-637 msec. The columns give the measurements (msec) of the 19 cycles following the rate change. A change in timing of the onset of rapid stimulation produced the cycles linked by the small square. Scale in hundred milliseconds.

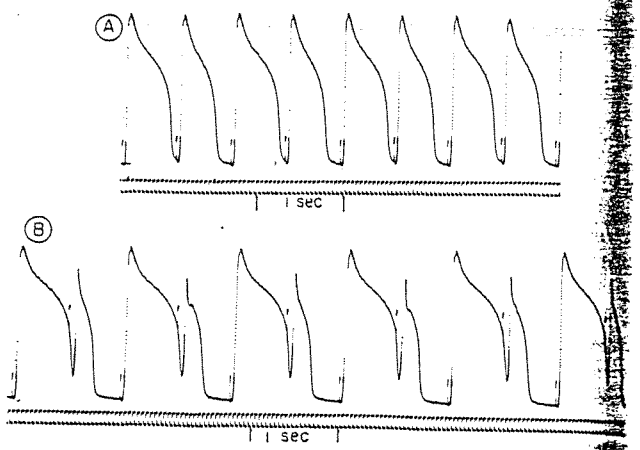

FIG. 6. Action-potential tracings showing the two amplitudes of alternation plotted in Fig. 5. These were obtained in the same preparation with the same rate, intensity, and duration of stimuli, only the timing of the onset of rapid stimulation was different. Stimulus marks precede each action potential.

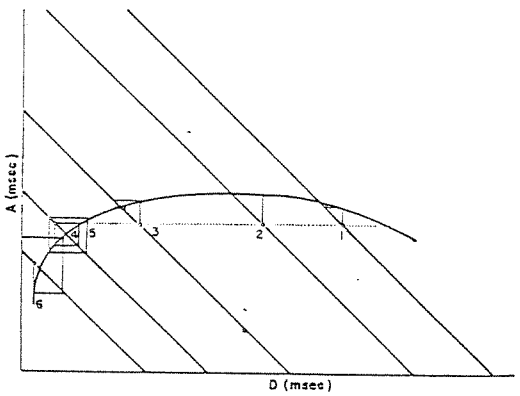

FIG. 7. Model with a hypothetical functional A curve and several D lines to illustrate how the slope of the A curve at its intersection with a D line determines the occurrence of alternation.

the stimulus trains which accentuated the inequality between successive diastolic intervals increased the amplitude of the alternation. The plots show the tendency of the briefer action potentials to lie above the steady-state curve (if this were extended) and of the longer ones to locate below it.

DISCUSSION

Riggs (19) states that the homeostatic index which is the product of the slopes of the graphs of the equations relating the elements of a feedback loop reflects the property of the system to resist changes. The larger the numerical value of this index the more stable the system. Mathematically, the D line has a constant negative slope of −1, hence the sole variable in the D line would be its intercept. Therefore, one is forced to look into the A curve for an explanation to the alternation. According to the theory, the negative slope or flatness of the steady-state A curve at slow rates makes it unlikely for alternation to occur at these rates, whereas the increasing positive slope at rapid rates renders the system more unstable. Our observation that transient alternation persisted longer when the magnitude of the rate increase was greater is in accord with the theory. However, the plots of successive cycles after a rate

change and the slopes calculated at these rates did not coincide with those predicted from the model drawn with steady-state A curves. The deviations may be explained by the features of the nonsteady state and by assuming that on acceleration, the tissue follows a composite functional A curve nearly similar in shape to the steady-state curve but with less positive slope. This decreased slope is expected for two reasons: *1*) the action potential following an abbreviated diastolic interval behaves as if in acceleration while that following a lengthened diastolic interval reacts as if in deceleration, and *2*) an earlier cycle in the series following acceleration would lie farther from the steady-state curve than any succeeding cycle. The first reason is bolstered by the observation that in persistent alternans, the briefer action potentials were above while the longer ones lay below the steady-state curve. The impression is created that while the tissue exhibited a regular irregularity in this situation it never settled into a constant steady state or set point, but alternately swung from accelerative to decelerative behavior and vice versa. The second reason derives from the decay of the nonsteady state with time.

The rate effect emerges as having two components: a fast one immediately evident on changing the rate and a second slow component responsible for the nonsteady state. Carmeliet and Boulpaep (4) have presented support for such a view.

The graphic model described in this paper is based entirely on this rate effect. The direct relation of diastolic interval to action-potential duration and the inverse effect of the latter on the following diastolic interval have been pointed out previously by Hoffman and Suckling (12). In most cardiac tissues, the action-potential duration is a function of the preceding cycle length (3, 11, 12, 17, 21). The shape or position of the A curve may differ with the kind of tissue or the condition to which the latter is subjected but such variation merely alters the level of the alternans-inducing rate or the magnitude of the alternation. The postulates relating the appearance of alternation to the slope of the A curve should still apply. We have used diastolic interval and action-potential duration because their reciprocal relationship can be easily established, but other parameters showing alternation may be similarly graphed. So long as a feedback relationship exists between any pair of parameters and one transfer function is curvilinear, alternation may be predicted by the postulates described. The converse creates an interesting question. If alternation in one parameter results after varying another, can a feedback relationship always be demonstrated in the two? We have mentioned earlier that voltage alternans was observed to occur simultaneously with the duration alternans. There may be a hidden relationship between voltage and some interval within the cardiac cycle or else the action-potential duration may be a function of voltage. Both may give rise to a feedback loop with voltage but the first possibility may explain alternation without any visible change in action-potential duration. We have no answer to this question.

Cole (6) believes that oscillations are connected to the inductive reactance associated with alternating currents. The inductance, according to Hodgkin and Huxley (10) is partly due to the inactivation process and partly to the changes in potassium conductance in the nerve fiber. If so, the rates at which persistent alternation appeared may reflect the natural frequency of the ionic conductances in the membrane. If the system can be thrown into oscillation, it must possess a natural frequency. The greater persistence of the alternation as rate was increased could mean that the stimulus frequency was approaching the natural frequency of the system and when the forced frequency represented by the stimulus rate equaled the natural frequency, sustained or persistent alternans resulted (resonance). The production of different degrees of alternation at the same alternans-inducing rate by simply varying the time of onset of the stimulus trains suggests that the initial diastolic interval and not the stimulus rate itself is the force which determines the amplitude of the alternation. This may explain why a premature beat or an extrasystole has been observed to induce alternation (20). In the lower tracing shown in Fig. 6, it could be argued that the marked changes in the smaller action potentials were due to the different level of the membrane potential from which they started and not because of the short diastolic interval per se. Although the membrane potential may have contributed to the attenuation of the action potentials, we have other experiments showing marked alternation where membrane repolarization is complete and each action potential starts at the same level of transmembrane potential.

Alternation has been reported in a variety of conditions including tachycardia (1, 2, 20), coronary insufficiency (5, 13), pericarditis (16), and after the administration of citrate (7), digitalis (9), epinephrine (15), or thyroid substances (14). It could be that under these conditions the hearts were altered in a manner so that the D line at the prevailing cardiac rate intersected the A curves of the component tissues of the heart where the slope was +1. This could be the common denominator in all of these conditions. A study of the influences of various factors on the A curve of the different cardiac tissues might help in developing an inclusive explanation for electrocardiographic alternation observed in intact hearts under diverse conditions.

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