PROPAGATED REPOLARIZATION IN HEART MUSCLE*

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ABSTRACT

The effect of current flow on the transmembrane action potential of single fibers of ventricular muscle has been examined. Pulses of repolarizing current applied during the plateau of the action potential displace membrane potential much more than do pulses of depolarizing current. The application of sufficiently strong pulses of repolarizing current initiates sustained repolarization which persists after the end of the pulse. This sustained repolarization appears to propagate throughout the length of the fiber. Demonstration of propagated repolarization is made difficult by appearance of break excitation at the end of the repolarizing pulse. The thresholds for sustained repolarization and break excitation are separated by reducing the concentration of Ca^{++} in the environment of the fiber. In fibers in such an environment it is easier to demonstrate apparently propagated repolarization and also, by further increase of the strength of the repolarizing current, to demonstrate graded break excitation.

INTRODUCTION

Weidmann has shown that passage of repolarizing currents across the membrane of a single Purkinje fiber during the plateau of its action potential evokes all-or-nothing repolarization which is propagated for some distance (1). This propagated repolarization resembles propagated depolarization in at least two respects: it is all-or-none in nature and it has a threshold. There has been no definite evidence to indicate whether or not propagated repolarization occurs in any other tissue and in particular its existence in cardiac muscle has not been demonstrated. There is, however, some reason to suppose that the same phenomenon might take place in ventricular muscle since Biedermann (2, 3) showed long ago that anodal current pulses initiate propagated relaxation in the ventricle of frog and snail hearts. For these reasons we have examined the problem in cardiac muscle (4, 5) and by means of repolarizing current pulses have elicited in papillary muscles of dog and cat hearts repolarization which is regenerative and apparently propagated.

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Methods

Papillary muscles were obtained from the right ventricle of dog or cat hearts and maintained at 38°C. in constantly circulating Tyrode solution. This solution was equilibrated with 95 per cent O_2 and 5 per cent CO_2 and had the following composition in millimoles/liter: NaCl, 140; $NaHCO_3$, 12.5; KCl, 2.7; $CaCl_2$, 2.7; NaH_2PO_4, 3.6; $MgCl_2$, 1.0; glucose, 5.5. In certain experiments the concentration of $CaCl_2$ was reduced to 0.68 mM/liter. Spontaneous activity was usually absent and the muscles were driven at a regular rate by means of surface electrodes. A period of 2 hours usually was allowed to elapse between isolation of the papillary muscle and the start of the test stimulation. During this interval mechanical activity decreased to some extent (6) and use of intracellular microelectrodes was facilitated.

The transmembrane potentials of single fibers were recorded by means of glass capillary microelectrodes (7) filled with 3 M KCl (8), conventional cathode followers and D.C. amplifiers, and a switched-beam oscilloscope (9). In most experiments a differential record of the transmembrane potential was obtained by employing two microelectrodes, one inside and the other immediately outside the area of membrane under study. Careful adjustment of the position of the extracellular electrode tip ensured that the records showed the actual displacement of transmembrane potential even during the passage of the stimulus current. Measurements made with single ended input are noted in the Results. Records of transmembrane potential were calibrated by applying known voltages between the tissue bath and ground.

Two techniques were employed for membrane polarization. In one the papillary muscle was drawn part way into a plastic tunnel which connected two chambers and allowed only a very small space around the muscle for flow of Tyrode solution (Fig. 1 *A*). Six small polarizing electrodes were located in the plastic tunnel; one or more of these were connected to one pole of the current source and half of the tissue bath to the other pole. The recording electrodes were located in the opposite half of the tissue bath. The other technique for polarization employed silver electrodes insulated by thick glass up to the tip. These electrodes were applied directly to the surface of the papillary muscle (Fig. 1 *B*). Stimulation of single fibers by means of intracellular microelectrodes was not employed because of the difficulty encountered in passing large, long duration current pulses. A resistance of 10 megohms was placed in series with the polarizing electrodes to ensure constant current output from the stimulator.

RESULTS

The experimental results reported may for convenience be divided into three groups: (*a*) a comparison of the effects on membrane potential of depolarizing and repolarizing current pulses which were below the threshold for all-or-nothing repolarization and which were applied at various intervals during the action potential; (*b*) the effects on membrane potential of pulses of current which were applied early during the plateau and which lasted throughout most of or all of the action potential; and (*c*) the effect of short pulses of repolarizing current which were strong enough to evoke propagated repolarization.

(*a*) *Subthreshold Repolarizing Pulses.*—Fig. 2 shows the effect on the mem-

brane potential of a single papillary muscle fiber of depolarizing and repolarizing current pulses of 30 msec. duration. The depolarizing pulses were long enough to permit the membrane potential to reach a reasonably steady level and the repolarizing pulses were well below the threshold for all-or-nothing

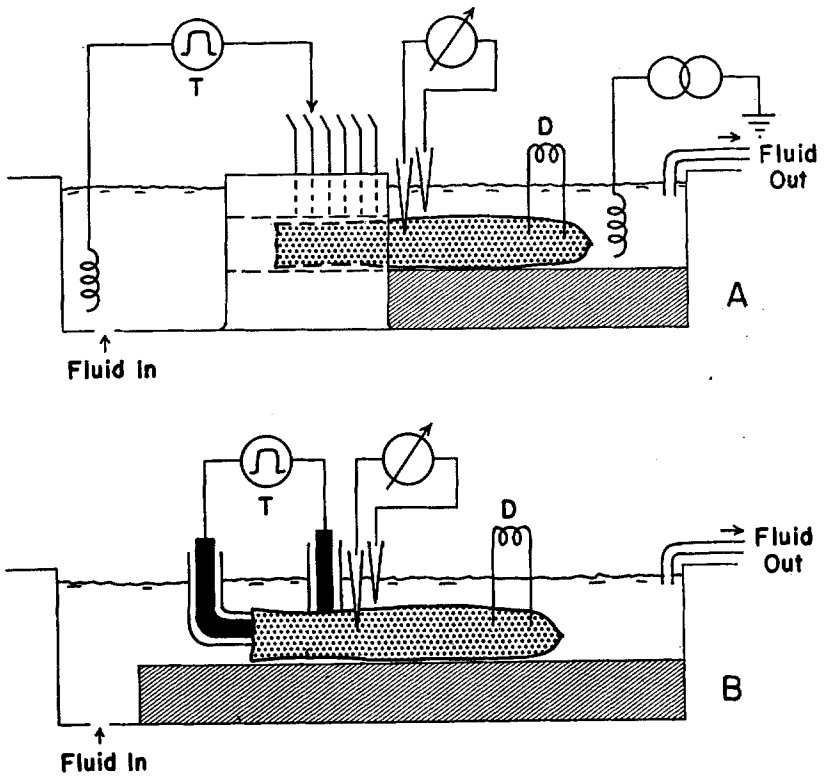

FIG. 1. (A) Papillary muscle partially drawn into a narrow tunnel which connects two baths. Polarization applied between an electrode in the left hand bath and one or more of the electrodes in the tunnel. Recording made with microelectrodes at the point of emergence of the muscle from the tunnel. Drive electrodes marked *D*. Test electrodes marked *T*.

(B) Papillary muscle in single bath. Polarization applied through a pair of external electrodes indicated by heavy lines. Recording with microelectrodes near one of the polarizing electrodes. Drive electrodes marked *D*. Test electrodes marked *T*.

repolarization. It can be seen that the repolarization produced was regenerative in the sense that comparable current strengths displaced the membrane potential much more in the direction of repolarization than they did in the direction of depolarization.

Fig. 3 shows the change in transmembrane potential resulting from current pulses of equal strength and opposite polarity applied at various intervals during the action potential. In Fig. 3 A, B, and C, the repolarizing current was well below the threshold for all-or-nothing repolarization and the displacement of membrane potential toward the resting potential was greater than the displacement in the opposite direction. At the end of the polarizing pulses the ac-

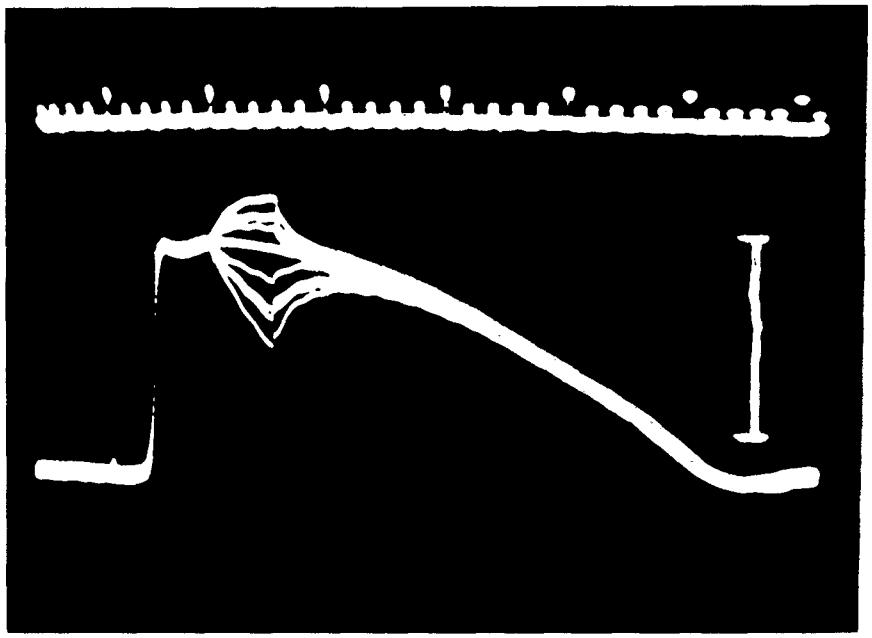

FIG. 2. The effect of depolarizing and repolarizing pulses of 30 msec. duration on the action potential of a single fiber of papillary muscle. Time calibration, 10 msec. and 50 msec. Voltage calibration, 100 mv.

tion potential resumed the same voltage-time course as the control. In Fig. 3 D, however, both the repolarization and depolarization persisted after the end of the pulse and caused shortening and lengthening of the action potential respectively. In Fig. 3 E the lengthening was more marked than the shortening, while in Fig. 3 F the change in membrane potential during the repolarizing pulse was almost purely passive whereas the depolarizing current was followed by a small local response.

The effects of longer and stronger pulses are shown in Fig. 4. In this series the sustained shortening or prolongation could be seen even after the earliest pulses. The effect of the depolarizing pulse showed a steady progression: the later the pulse the longer and more marked was the prolongation of the action

potential. After the end of the repolarizing pulse, however, a new phenomenon appeared: the shortening of the action potential was more marked in Fig. 4 B than in 4 A, but it was less prominent again in Fig. 4 C. This was true in spite

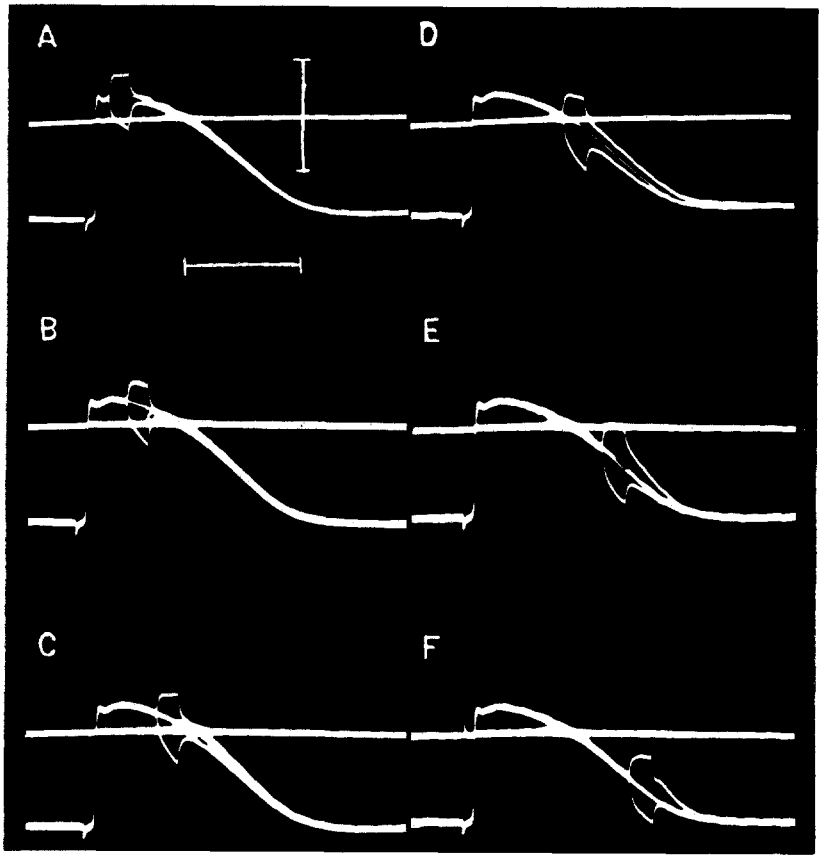

FIG. 3. The effect on membrane potential of repolarizing and depolarizing pulses of 20 msec. duration and constant strength applied at different intervals during the action potential. Time calibration, 100 msec. Voltage calibration, 100 mv.

of the fact that the membrane potential had been displaced somewhat more during the pulse in Fig. 4 C than in Fig. 4 B. The explanation for this change is that excitation evoked by the break of the pulse had begun to appear after the end of the pulse in Fig. 4 C and this break excitation wiped out the shortening of the action potential. The response evoked by the break of the pulse grew progressively larger as the pulse was applied later and eventually, in Fig. 4 E, assumed the appearance of a normal action potential elicited prior to the end

of repolarization (10). Although the effect of depolarizing pulses is not strictly passive when long pulses are used it is still of interest to attempt to obtain the active change in membrane potential during a repolarizing pulse. This result

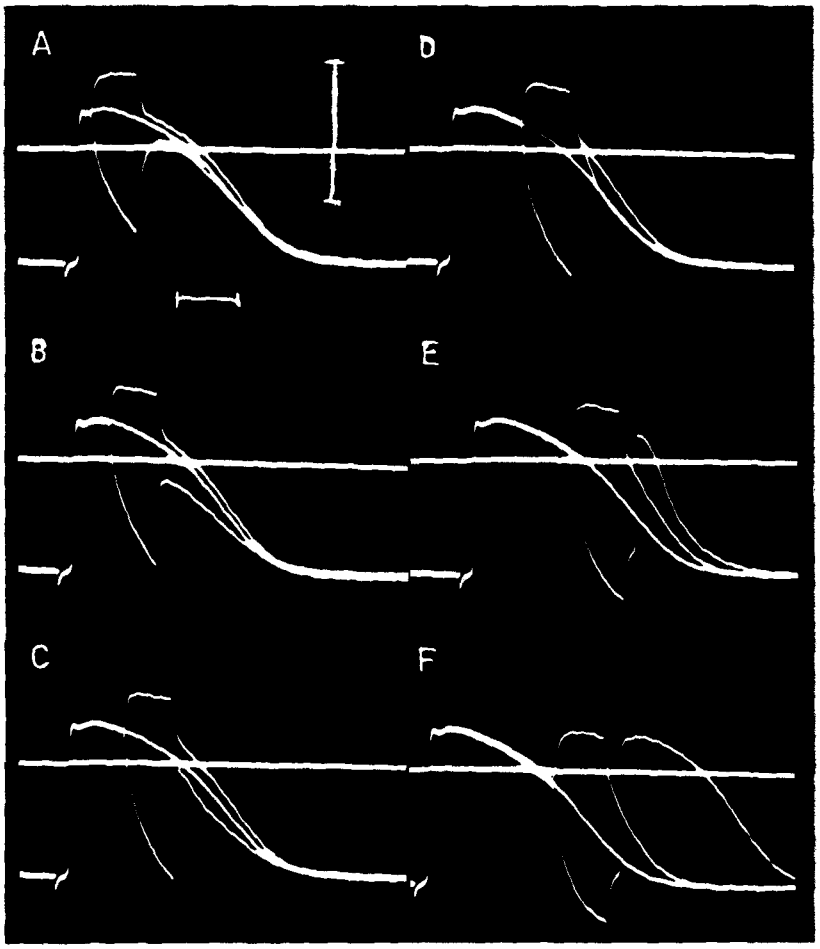

FIG. 4. The effect on membrane potential of depolarizing and repolarizing pulses of 70 msec. duration and constant strength applied at different intervals during the action potential. The pulses are both longer and stronger than those shown in Fig. 3. Time calibration, 80 msec. Voltage calibration, 100 mv.

may be regarded as at least an approximation to the active component of repolarization contributed by changes in the membrane during passage of a repolarizing pulse. Fig. 5 shows the results of such a calculation made by subtracting the voltage change effected by a cathodal pulse from that effected by

the anodal pulse of the same current strength. The applied pulses and the course of the action potential after the end of each pulse are shown by dotted lines. The normal action potential is shown by a solid line as is the active change contributed by the membrane. It is possible to continue the active change by a line (dashes) which may be regarded as the path the repolarized action potential would have followed in the absence of break reexcitation. It seems that the active component of the induced repolarization follows a course similar to that of a normal action potential of short duration, such as that seen at high rates.

(*b*) *The Effect of Longer Current Pulses.*—The demonstration that sustained

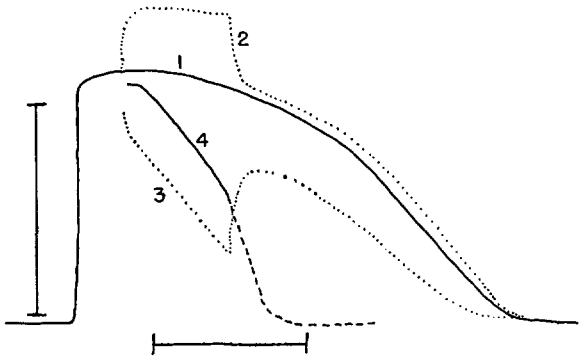

FIG. 5. The effect of a repolarizing pulse (3, dotted) and a depolarizing pulse (2, dotted) on the membrane potential of a single fiber of papillary muscle. The normal action potential is shown in a solid line (1) and the active change in membrane potential during the repolarizing pulse, obtained by subtracting from the change during the pulse the change seen with the depolarizing pulse, is shown by a solid line (4). The course of persistent recovery which would presumably have been seen in the absence of break excitation is shown by dashes. Time calibration, 100 msec. Voltage calibration, 100 mv.

repolarization is induced by the current pulses and propagated throughout the muscle is extremely difficult because of the break excitation just described. For this reason very long pulses were employed with the hope of diminishing break excitation by postponing the break of the pulse. Fig. 6 A and B shows the effect of progressively lengthening depolarizing and repolarizing pulses when the current strength and make time were held constant. Again it can be seen that displacement of membrane potential in the direction of repolarization was much more marked than in the direction of depolarization. However, excitation evoked by the break of the pulse abolished sustained repolarization after the end of the longer repolarizing pulses. Fig. 6 C simply shows a single pulse of each polarity. Fig. 6 D shows the effect of varying the strength of a repolarizing pulse of constant duration. The action potentials occurring on the break were larger when the strength of the repolarizing pulse was larger.

The effect of repolarizing pulses which lasted considerably longer than the action potential is shown in Fig. 7. At the end of each of the pulses break excitation occurred but it is not seen on the record. This figure has two points of special interest. First, although equal increments of current were employed the change in membrane voltage by no means increased in equal steps. Much less change resulted from the first two intensities than from the third and fourth. This is taken as further evidence for regenerative repolarization. Second, the

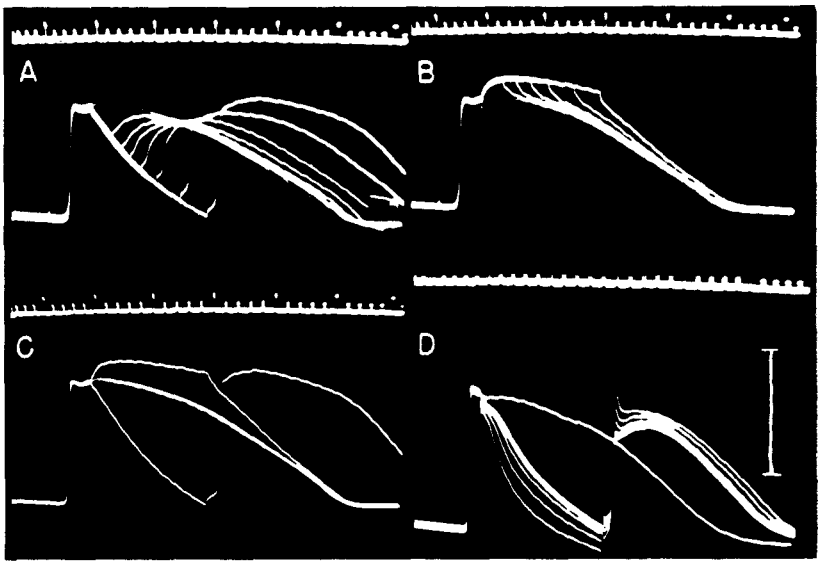

FIG. 6. The effect on membrane potential of a long (100 msec.) repolarizing pulse (A) and depolarizing pulse (B) as a pulse of fixed make time is progressively lengthened. The effect of a single pulse of each polarity is shown in C. The effect of varying the strength of a repolarizing pulse of fixed duration and fixed make time is shown in D. Time calibration, 10 msec. and 50 msec. Voltage calibration, 100 mv.

change in membrane voltage which was observed during the action potential is very much greater than the change which is seen with the same current as it continues into diastole. In particular the shortening effected by strength 3 (indicated by arrow) is very large compared to the small hyperpolarization caused by the same pulse during diastole. This is taken as evidence that the change during the action potential is an active one and not merely a displacement of membrane potential analogous to hyperpolarization. The change shown in the figure is far greater than can be accounted for by the change in membrane resistance which is believed to occur during the transition from plateau to diastolic membrane potential (11).

(*c*) *The Effect of Short, Strong Pulses.*—The observations presented up to this point offer support to the view that repolarizing current applied during the action potential effects a change in membrane potential which is regenerative in nature. They do not, however, have much bearing on the question of propagation. The existence of regenerative behavior is a prerequisite for propagation

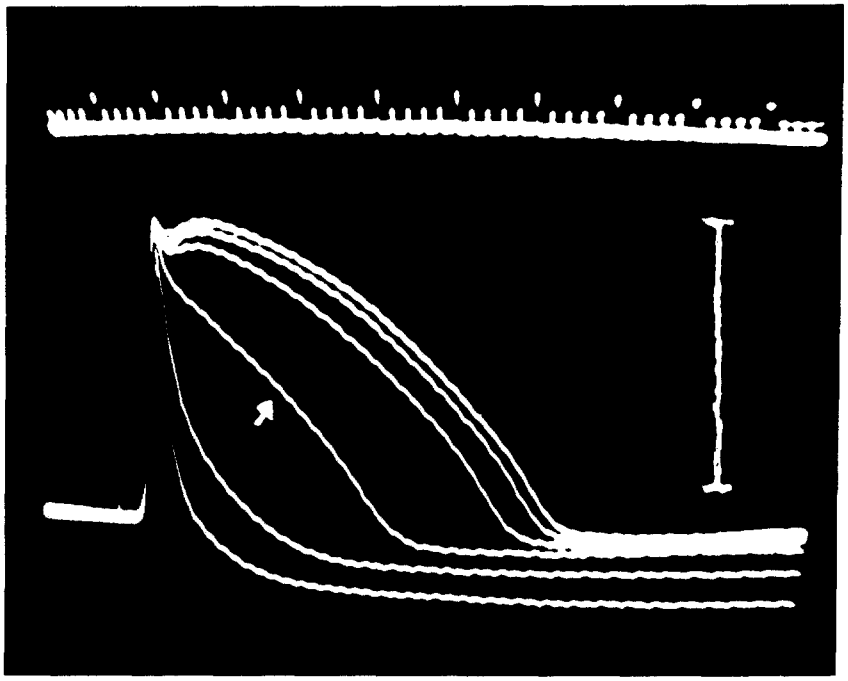

FIG. 7. The effect on the membrane potential of repolarizing pulses of duration longer than the action potential and of different strengths. The trace indicated by an arrow is discussed more fully in the text. Time calibration, 10 msec. and 50 msec. Voltage calibration, 100 mv.

but does not establish its existence. Fig. 8 shows the effect on membrane potential of a strong, moderately long repolarizing pulse applied early during the plateau of the action potential. The papillary muscle used in this experiment was 6.5 mm. in length. The record in Fig. 8 A was obtained with the microelectrode 0.5 mm. from the site of the repolarizing electrode. In this record marked shortening of the action potential was observed; however, following the end of the pulse there was some evidence of local depolarization evoked by the break of the pulse. Figure 8 B shows a record obtained with the microelectrode 3 mm. from the site of the polarizing electrode. It can be seen that the electrotonic spread of the current pulse was very slight but nevertheless the

shortening of the action potential was clear. Fig. 8 C shows a record taken 5.5 mm. from the polarizing electrode. In this record no electrotonic spread of the current pulse is seen but shortening of the action potential is clearly visible in the form of early repolarization. Fig. 8 D shows a record obtained at the same site as that in Fig. 8 A. In this record the strength of the current pulse was great enough to produce more displacement of membrane potential than was

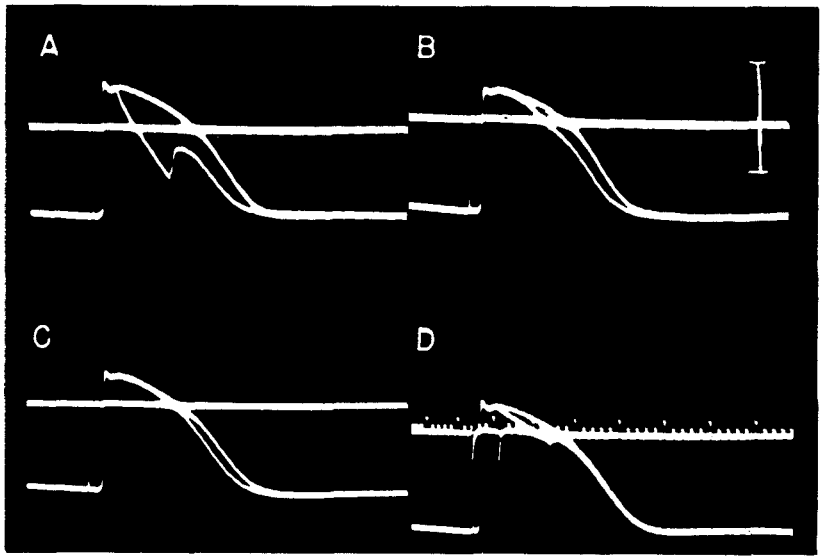

FIG. 8. Effect on membrane potential of a repolarizing pulse sufficiently strong to evoke propagated repolarization. Records taken 0.5 mm. from the repolarizing electrode (A), 3.0 mm. from the repolarizing electrode (B), and 5.5 mm. from the repolarizing electrode (C). The record shown in D is taken 0.5 mm. from the repolarizing electrode but the strength of the pulse is much less than in A, B, and C. Time calibration, 10 msec. and 50 msec. Voltage calibration, 100 mv. The vertical lines descending from the time calibration are drive and stimulus markers.

caused by electrotonic spread in Fig. 8 B or 8 C; it is clear, however, that no shortening of the action potential resulted. It therefore can be concluded that the shortening of the action potential at the more distant sites (Fig. 8 B and C) is the result of the early repolarization in the surround of the polarizing electrode and not the result of electrotonic spread of the polarizing current. In short, these figures suggest the possibility that the repolarization induced by the current pulse is propagated throughout the muscle.

Presumably propagation of earlier and more marked shortening could be demonstrated by the use of stronger repolarizing currents, such as were employed in the experiment shown in Fig. 7. However, such current strengths

initiate break excitation which either propagates for some distance or produces apparent lengthening of the action potential by electrotonic spread to distal sites. This effect is shown clearly in Fig. 9. In this figure the records on the upper trace are taken 0.5 mm. from the polarizing electrode and those on the

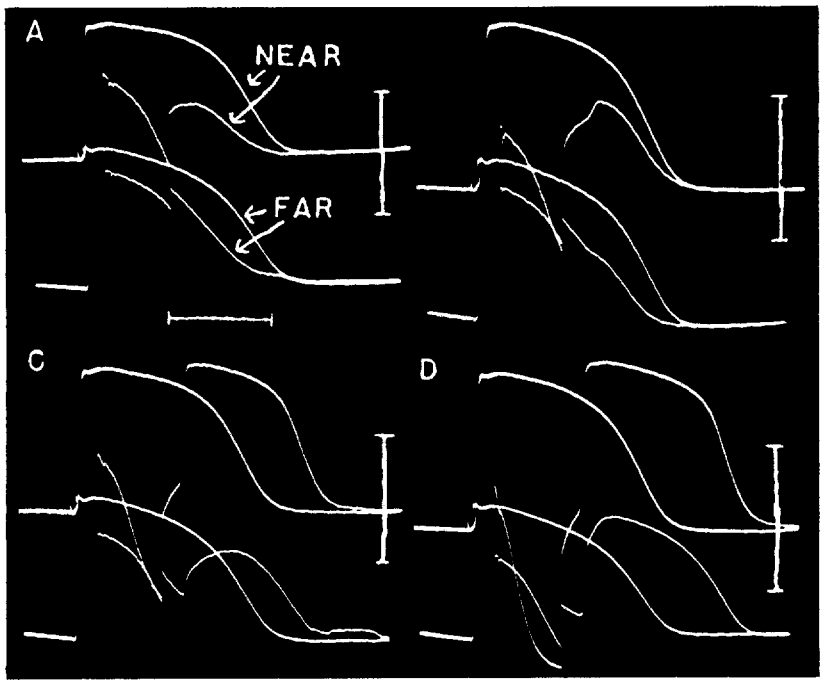

FIG. 9. The upper trace in each record is recorded 0.5 mm. from the repolarizing electrode and the lower trace is recorded 4.0 mm. from the repolarizing electrode. The records are not differential. Shortening at both sites is seen with the weakest strength of repolarizing current (A). Progressive increase of strength produces more and more marked break excitation (B, C, D) which eventually propagates to the distant site (D). Time calibration in A, 100 msec. Voltage calibrations, 100 mv. Label is missing from B, the upper right hand figure.

lower trace are from a site 4 mm. distant. In this experiment the recordings were not differential and thus the displacement of the membrane potential during the flow of polarizing current is distorted by stimulus artifact. In Fig. 9 A the current pulse induced premature repolarization at the near electrode which appears to have been propagated to the distal recording site. As the strength of the polarizing current was increased break local response appeared near the polarizing electrode and was recorded with appropriate decrement at the distal site. In Fig. 9 C a full sized action potential was recorded near the polarizing

electrode after the break. This action potential appeared as a lengthening of the action potential at the distal site and represents either electrotonic spread or local response. In Fig. 9 D a still stronger repolarizing pulse gave rise after the break to a full sized action potential in the vicinity of the polarizing electrode; at the distal site a smaller but probably propagated action potential was also seen. In normal muscle therefore, it is difficult and at times impossible

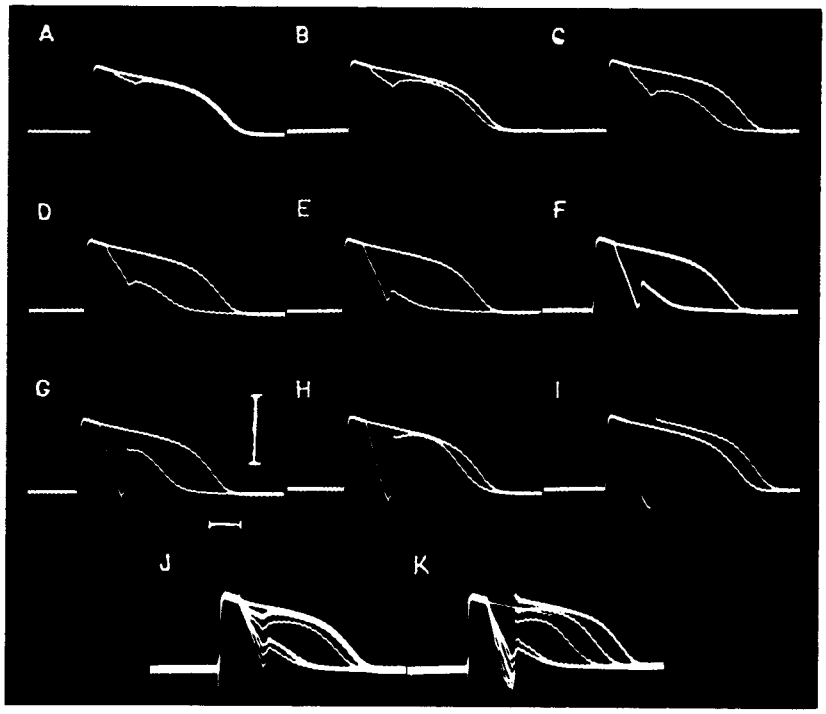

FIG. 10. The effect of repolarizing pulses on the action potential of a single fiber of papillary muscle in a medium containing 25 per cent of the normal Ca^{++} concentration. Gradual increase in strength produces increasing repolarization (A–E) followed by increasing break excitation (F–I). Superimposed traces in the repolarizing ranges are shown in J. Superimposed pulses in the reexcitation region are shown in K. Calibrations in G. Time, 100 msec. Voltage, 100 mv.

to produce by means of pulses of current a shortening of the action potential as marked and sustained as that which can be produced by means of sustained polarization (see Fig. 7).

It is possible, however, to obtain this marked shortening if the extracellular Ca^{++} concentration is reduced. For unknown reasons such reduction separates the thresholds for sustained repolarization and break excitation (see Discussion). Fig. 10 shows the results obtained when repolarizing pulses of increasing

strength were applied to a papillary muscle in Tyrode solution containing 25 per cent normal Ca^{++}. Fig. 10 A to 10 E shows a steady increase in the degree to which repolarization was evoked and sustained. There is, between Fig. 10 B and 10 C, the discontinuity in the change of membrane voltage for an equal change in current strength which has been demonstrated above. In Fig. 10 F a further increase in current strength began to evoke break excitation; moreover, this break excitation could be continuously graded by increasing the current strength until an action potential of normal amplitude resulted. Fig.

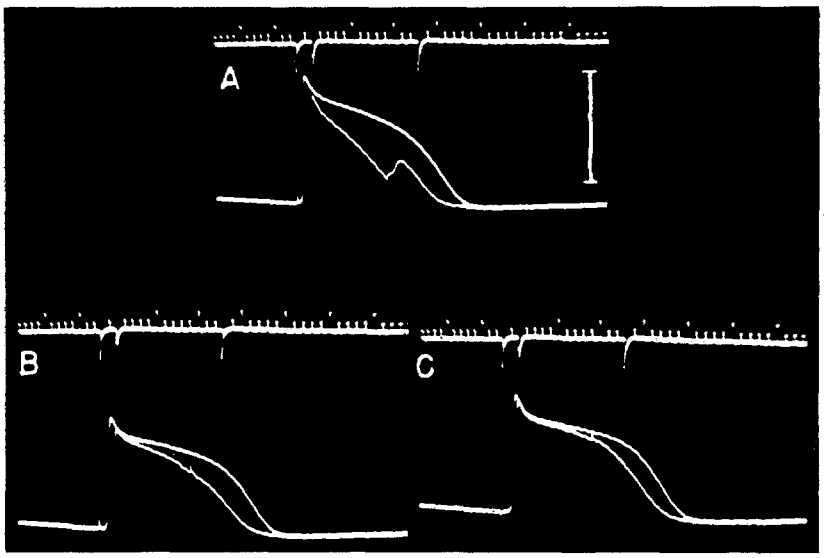

FIG. 11. Propagation of repolarization in a fiber in a medium containing 25 per cent of the normal Ca^{++} concentration. Records at 0.5 mm. from the repolarizing electrode (A), 2 mm. from the repolarizing electrode (B), and 4.0 mm. from the repolarizing electrode (C). Time calibration, 10 msec. and 50 msec. Voltage calibration, 100 mv.

10 J and K shows the progressive change in repolarization and reexcitation on superimposed sweeps.

In the partially decalcified muscle the absence of break excitation at current strengths which produce early and complete repolarization makes it easier to demonstrate marked shortening of the action potential recorded at a distance from the polarizing electrode. Fig. 11 shows records obtained from an experiment similar to that of Fig. 8. In Fig. 11 A the record obtained 0.5 mm. from the polarizing electrode reveals minimal break excitation and marked shortening of the action potential. Records obtained 2 mm. (Fig. 11 B) and 4 mm. (Fig. 11 C) from the polarizing site show shortening of the action potential

which is much more marked than that obtained in normal Tyrode solution (compare with Fig. 8). This observation indicates that the marked shortening of the action potential and apparent propagation of extremely early repolarization are difficult to demonstrate under normal conditions solely because of the occurrence of break excitation.

DISCUSSION

The principal difficulty which arises in the interpretation of the above results comes about because of the slowness with which the repolarization propagates. If the propagation velocity is taken as 0.2 meter/sec. (see below) and the duration of the phase of rapid repolarization is considered to be 50 msec. the "wave of repolarization" is 10 mm. long. The most convincing evidence for true propagation would the obtaining of a record at a distance of more than 10 mm. from the repolarizing electrode. One would expect, if the repolarization is propagated, that an action potential recorded at that distance would show no departure whatever from its normal path during the entire duration of the stimulus but would nevertheless show shortening as it came under the influence of the propagated repolarization. The record seen in Fig. 11 C nearly but not quite meets this criterion. Our records therefore do not offer the most unequivocal possible evidence for propagation of repolarization.

One point requires discussion. The fact that shortening is less and less marked the farther one records from the anode admits three possible explanations. It may mean that repolarization propagates more slowly than depolarization. Only if the two conduction velocities were identical would one expect to find a wave form of constant shape (and in particular of constant duration) as one moved farther from the repolarizing electrode. Also, since repolarization does occur spontaneously, spontaneous repolarization will occur at sites distant from the repolarizing electrode before propagation of repolarization could reach such sites. A second possibility is that the wave of repolarization propagates as rapidly as depolarization but with decrementing effect. It seems to us that the slowness of the voltage change in the recovery phase as compared with that in the wave of depolarization would support the idea that repolarization does propagate more slowly than depolarization. A third possibility, that repolarization propagates at a diminishing velocity with constant effect cannot be ruled out on the basis of our evidence. It may be pointed out that the steepness of the repolarization does not diminish as distance from the repolarizing electrode is increased.

The interpretation preferred by us at present is the first one described above: namely that repolarization proceeds with a constant but slow velocity. If it should prove that repolarization is a propagated process in normal heart (see discussion below) then the fact that repolarization propagates more slowly than depolarization would have a curious consequence: the total duration of the

action potential should increase as the potential travels along a fiber. Since the action potential is about 20 cm. long it is difficult to find a preparation on which this point may be examined.

The existence of all-or-nothing repolarization has now been demonstrated in four preparations: Purkinje fiber (1), squid giant axon treated with TEA (12), the isolated node of Ranvier (13), and mammalian heart muscle. Propagated repolarization has been shown to exist only in Purkinje fibers and isolated preparations of cardiac muscle. One question which naturally arises is whether or not propagation of repolarization plays any part in the normal repolarization of the intact heart. There is no evidence which bears on this question. It is unlikely that repolarization ever spreads in a propagated manner from a single focus over the entire heart. On the other hand the evidence presented above makes the conclusion almost inevitable that cells which repolarize early must accelerate repolarization of cells nearby. The idea has therefore been advanced that it is probably correct to think of repolarization in the whole heart as a propagated process with multiple foci of origin (4).

The main reason that a single focus does not become the pacemaker for repolarization in the whole heart is that the propagated repolarization has a very low conduction velocity. Since each cell is in a sense a pacemaker for repolarization many cells begin to repolarize before a slowly spreading wave of propagated repolarization can reach them. No value was given for conduction velocity under Results because of the uncertainty of measurement. If the point at which the plateau ends and rapid repolarization begins is taken as the time of arrival of the propagated repolarization a conduction velocity of 0.2 meter/sec. can be calculated from the records in Fig. 6. This value may not be correct but it is certain that the velocity is low compared with that of propagated depolarization (see also Weidmann (11)).

No theory of the ionic basis for propagated repolarization can be offered because there is no theory which adequately explains the ordinary repolarization of cardiac muscle (14). If the repolarization is caused by a flow of K^+ then presumably K^+ permeability is voltage sensitive (15). One point may be made with respect to impedance. There is reason to believe that the phase of rapid repolarization is associated with a drop in membrane resistance from the high value during the plateau to the diastolic value (11). This observation accords well with the idea of repolarization as regenerative and propagated. The observation that regenerative changes in membrane potential developed during the passage of repolarizing current does cast some doubt on the validity of using anodal current pulses for measuring membrane impedance during the action potential. Presumably if pulses are used which are sufficiently short and sufficiently weak reliable information may be obtained.

No studies of the contractile process were made in the work reported above. Presumably the propagated relaxation reported by Biedermann is the result of

the propagated repolarization which has been demonstrated. The only positive statement which can be made about the relationship between repolarization and relaxation in cardiac muscle is that repolarization always precedes relaxation. Tension may persist, however, for some time after repolarization.

The observations on graded break excitation are nearly as interesting as those on all-or-nothing repolarization and are the subject of further investigation. It might be mentioned that in isolated Purkinje fibers the sequence of events following the break of repolarizing current pulses is different from that noted in cardiac muscle (16, 17). In the Purkinje fibers break excitation is produced by current strengths weaker than those required for maintained repolarization whereas stronger current strengths do not induce break excitation. In other words, Purkinje fibers show the so called "no-response phenomenon" (17): weak anodal stimuli excite at a time when strong ones do not. Because of this fact, sustained repolarization may be evoked in Purkinje fibers merely by using sufficiently strong stimuli. It is also of interest that the graded break local response seen in Fig. 10 F or G may be converted into a full sized action potential by a weak, short cathodal stimulus applied early during the rise of the local response. Later, during or after the peak of the local response, cathodal stimuli of the same strength are without effect. The break local response therefore shows refractoriness entirely analogous to that of the propagated action potential.

The question of propagation of the break responses elicited by strong repolarizing currents is complex. In some cases such break responses are completely non-propagated, even though of full size, and thus are analogous to a membrane action potential. In other cases, depending on the strength of the repolarizing pulse and the time of the break, the break action potential may arise out of a local response of long duration as in Fig. 9 C and D. Under such conditions considerable repolarization may take place at more distal sites before the rapidly rising phase of the break response appears and it is likely that in certain cases propagation does take place (see Fig. 9 D).

It would seem from the results reported that the threshold for repolarization in cardiac muscle is less clearly demarcated than that of Purkinje fibers (1). One possible explanation has been offered above. Another is that under the conditions of these experiments the transmembrane potential in the vicinity of the polarizing electrode was not completely uniform; for this reason after the break of the pulse any area of membrane undergoing regenerative all-or-nothing repolarization was under the depolarizing influence not only of break response in some areas but of a membrane potential returning to the normal plateau level in other areas. This may be related to the finding that in normal muscle propagated repolarization could be uniformly elicited only at a time quite close to the normal transition of plateau to rapid repolarization. The effects of decreased extracellular Ca^{++} cannot be explained. It is possible,

however, to offer a tentative mechanism within the framework of the ionic hypothesis. Weidmann (18) has shown that lowered Ca^{++} concentrations result in less activation of Na^{+} carrier at a given level of membrane potential. Also, in studies of nerve (19) it has been shown that low Ca^{++} slows the time course of inactivation-reactivation of Na^{+} carrier. Both these effects, if operative, would diminish the likelihood of break reexcitation at a given level of membrane potential.

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