Effect of Field Stimulation on Cellular Repolarization in Rabbit Myocardium
Implications for Reentry Induction

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We have investigated the effects of electric field stimulation on membrane repolarization in rabbit papillary muscles and assessed the consequences of these effects for the dispersion of intracellular potentials and the production of a propagation wave front or unidirectional block in relatively refractory tissue. The stimuli studied had electric field strength of 0.25–14 V/cm, duration of 2 msec, and field orientation along or across the myocardial fibers. The field strengths to excite the muscles in diastole were 0.68 or 1.23 V/cm for stimuli oriented along or across the fibers, respectively (p<0.01, along versus across). A 2.5-V/cm stimulus given near the end of the action potential (AP) produced either no response or, after increasing the stimulus delay only 2–3 msec, a full response with almost no AP durations that were intermediate. For stimulation along and across the fibers, respectively, given at 70% of the AP duration, a 4-V/cm stimulus produced AP prolongation (measured at 90% repolarization) of 20% and 4% (p<0.05), an 8-V/cm stimulus produced AP prolongation of 36% and 20% (p<0.05), and a 14-V/cm stimulus produced AP prolongation of 36% and 30% (p=NS). For either orientation, AP prolongation by stimuli of 8 V/cm or 14 V/cm increased gradually as the stimulus delay was increased. The different effects in relatively refractory tissue of stimuli of 2.5 V/cm compared with 8 V/cm can explain the propagation wave front and block that occur with electrically induced functional reentry in the heart. After stimulation with fields below a critical strength (~5 V/cm), a large intracellular potential difference may occur among cells that are sufficiently recovered to become excited by the stimulus and cells that are not sufficiently recovered to become excited, consistent with the reported propagation wave front where the two groups of cells are closely opposed. After stimulation with fields above the critical strength, differences in intracellular potentials among cells during repolarization may be decreased, and the intracellular potentials may be in a range in which sodium current is inactivated, consistent with the reported absence of a propagation wave front. Thus, the different effects of low and high electric field strengths can account for the “critical point” mechanism for unidirectional block and reentry. (Circulation Research 1992;70:707–715)

Key Words • myocardial stimulation • action potential • myocardial repolarization • refractory period • graded response • reentry • rotors • spiral waves • vortices • excitable media

Electrical initiation of reentry occurs in normal myocardium around a point where a critical electric shock field strength (5 V/cm for the particular waveform studied) intersects tissue that is critically refractory (i.e., just coming out of its refractory period).1,2 Under these conditions, extracellular mapping studies have indicated that an activation front first occurs after the shock where the critically refractory tissue intersects a shock field weaker than the critical electric field strength but that an activation front does not occur where the shock field is stronger than the critical strength. Activation then propagates around the “critical point” into the region of the stronger field, initiating reentry. The mechanisms for the production of an activation front in the region where the shock field strength is <5 V/cm and the unidirectional block in the region where the strength is >5 V/cm are unknown. It is hypothesized that, in the region with the lower field strength, an activation wave front propagates from the tissue that is sufficiently recovered to become directly excited by the shock into the tissue that is refractory to the shock.1 Where a field strength >5 V/cm occurs in the relatively refractory tissue, it is proposed that a graded response is produced that does not support a propagated activation front.3 The electric field strengths that are needed to produce such responses intracellularly have not been previously determined or correlated with the electric field strengths needed to produce reentry.

The effects of electric field stimulation given in the refractory period on the repolarization of the intracel-
lular action potential (AP) may ultimately be explained by basic membrane mechanisms such as voltage- and time-dependent ionic currents. For example, changes in the transmembrane potentials are probably induced during the stimulus pulse; these changes, in turn, alter the ionic currents after the pulse. However, the directions and magnitudes of the changes in transmembrane potentials induced during a field stimulus pulse and the location of these changes in the myocardium have not as yet been reported. Furthermore, the effects of induced transmembrane potential changes on the inward and outward membrane ionic currents that influence the timing of repolarization of the AP are not fully known. Most of what is known of the voltage dependence of ionic currents applies to uniform transmembrane potential changes, not the simultaneous hyperpolarization and depolarization expected in different parts of the membrane during field stimulation of the myocardium. Hence, the effects of electric field stimulation at strengths that initiate reentrant rotors in the heart on the intracellular AP cannot be reliably inferred from existing knowledge.

The purpose of this study was to determine whether shocks having timings and electric field strengths that encompass the critical point produce effects on the intracellular AP that explain the critical point mechanism for the induction of reentry. Since myocardial electrical properties are anisotropic and hence the effects of electric fields may depend on the fiber orientation, the effects were determined for electric fields oriented along and across the myocardial fibers.

**Materials and Methods**

Seven rabbits weighing 5–6 pounds were anesthetized with intravenous pentobarbital. The heart was rapidly removed and placed in Tyrode's solution at room temperature, and a right ventricular papillary muscle 3.3±0.3 mm long and 0.8±0.3 mm wide was carefully removed and placed in an experimental bath. The muscle was positioned near the center of the 4×4-cm bath and oriented parallel with the sides of the bath. The muscle was superfused at a rate of 3–3.5 ml/min, and ~3 mm of superfusing solution was present above and below the muscle. The solution contained (mM) glucose 11, CaCl₂ 1.8, NaCl 125, KCl 5.4, MgCl₂ 1.05, NaHCO₃ 24, and NaH₂PO₄ 0.42, with a pH of 7.4, and was bubbled with a mixture of 95% O₂–5% CO₂. The temperature, monitored with a miniature probe (Physitemp, Clifton, N.J.) in the solution below the muscle, was held at 36.5–37°C. Four flat 1×3.8-cm chlorided silver electrodes were attached to the sides of the bath to perform field stimulation (stimulus S2). The 2-msec constant-voltage S2 pulse was applied to either of the pairs of electrodes at opposite sides of the bath to produce an S2 electric field oriented along or across the longitudinal axis of the muscle. The S2 voltage was adjusted to control the electric field strength in the bath. The electric field strength (i.e., potential gradient) for each S2 orientation was determined from a square array of tungsten-wire 50-micrometer diameter electrodes positioned around the muscle. The differential recording amplifier for the S2 potential gradient measurements had an input resistance of 10¹² Ω. The interelectrode distances of ~5 mm in each direction were measured with a microscope and graduated reticle. The distance measurements were performed at the end of the experiment after the solution level was lowered to eliminate errors due to light diffraction where the recording electrodes entered the solution.

An intracellular AP was recorded with a glass microelectrode near the center of the muscle and a fine-wire extracellular reference electrode near the microelectrode tip. The intracellular and extracellular potentials were passed through a wideband differential electrometer (model 773, World Precision Instruments, New Haven, Conn.).

The leads of the isolated S2 source were connected to the amplifier ground through two 30-kΩ resistors. This minimized the potential change in the center of the bath and, hence, the common-mode potential at the amplifier inputs when S2 was applied.

The muscle was paced (stimulus S1) near the tendinous end at a rate of 0.5 Hz with an isolated bipolar 2-msec constant-current pulse of 1.5 times the diastolic threshold strength. After a 1-hour stabilization period, the diastolic excitation thresholds were determined for S2 electric fields oriented along or across the muscle fibers. In each trial, a single S2 was applied at the end of the diastolic interval in the absence of S1. The intracellular AP was monitored to determine whether the S2 produced excitation. For each preparation, the threshold determinations were repeatable to within ~3%.

The S2 strength was then increased to produce electric fields of approximately 2.5, 4, 8, and 14 V/cm. These S2 strengths were chosen to include the range and approximate distribution of electric field strengths that were previously shown to produce rotor-type reentry in the intact heart. At each S2 strength, S2 was given at S1-S2 intervals that scanned the relative refractory period. For a given S2 strength and S1-S2 interval, trials were performed with S2 electric fields oriented along or across the fibers. The order of the S2 orientations was alternated. Recordings for the two orientations were obtained from the same cellular impalement. For each trial, an intracellular recording was obtained for an S1 paced beat (control beat) and for the following S1 paced beat during which the S2 shock was given (test beat). AP prolongation was determined by subtracting the AP duration at 90% repolarization of the control beat from the total duration of the response to S1 and S2 of the test beat.

The potentials were digitized at a sampling rate of 1,000 Hz with an NB-MIO16H data acquisition circuit board (National Instruments, Austin, Tex.) and stored on a Macintosh IIX computer (Apple Computer, Cupertino, Calif.). The AP duration at 90% repolarization was measured from the computer recordings using the Labview system (National Instruments). APs were also monitored during the experiments with a digitizing oscilloscope.

Results

**Action Potential Prolongation and Excitation: The Impact of the Shock Field Orientation**

The intracellular recordings in Figure 1 show the effect of an S2 electric field having a potential gradient...
of 8.1 V/cm oriented along or across the myocardial fibers. The S1-S2 interval was 200 msec in the superimposed recordings. The repolarization after S2 of either orientation occurred later than the repolarization of the control AP, shown as the interrupted tracing. The AP prolongation was greater for S2 oriented along the fibers compared with across the fibers. A greater effect of S2 oriented along the fibers compared with across the fibers also occurred for S2 given in diastole and having strengths near the diastolic excitation threshold. When S2 was oriented along the fibers, the diastolic excitation threshold was 0.68±0.16 V/cm. When S2 was oriented across the fibers, the threshold was 1.23±0.27 V/cm, which was significantly greater than the threshold for S2 along the fibers (p<0.01).

Figure 2 shows graphs of the AP prolongation versus the S1-S2 interval for S2 electric fields of 2.3, 4, 8.1, and 12.9 V/cm. Each data point represents a different S2 trial. The S1-S2 interval and the AP prolongation are given as a fraction of the control AP duration at 90% repolarization, which was 147 msec. Thus, an AP prolongation of 1 would represent a response that had a duration as great as the duration of the control AP.

**Figure 1.** Superimposed recordings showing action potential prolongation produced by a field stimulus having an electric field strength of 8.1 V/cm (S2) oriented along or across the myocardial fibers. The recordings were obtained from one cellular impedance. The stimulus interval S1-S2 was 200 msec. The repolarization of the control action potential, which did not receive an S2, is shown as the interrupted tracing. S2 produced a small rapid depolarization and a prolongation of the repolarization time of the action potential compared with the control. The prolongation produced by S2 oriented along the fibers was greater than the prolongation produced by S2 oriented across the fibers.

**Figure 2.** Graphs showing action potential (AP) prolongation versus the stimulus interval S1-S2 for electric field stimuli (S2) of 2.3, 4, 8.1, and 12.9 V/cm. Each data point represents a different trial. The results were obtained from one cellular impedance. The S1-S2 interval and the AP prolongation are given as fractions of the control AP duration at 90% repolarization. The control AP duration, which had a mean value of 147 msec, was constant to within 4 msec. Panel A: The 2.3 V/cm S2 given as late as the time of 90% repolarization of the AP produced only a small AP prolongation. When S2 of this strength was given only 2–3 msec later, a new AP was produced. Panel B: When the 4 V/cm S2 was given as early as the midpoint of the AP, S2 had no effect. When given late in relation to the AP repolarization, S2 produced a new AP. The 4 V/cm S2 produced AP prolongation when given at intermediate S1-S2 intervals. The AP prolongation was greater for S2 oriented along compared with across the myocardial fibers. Panel C: When the S2 electric field strength was 8.1 V/cm, like the results for the 4 V/cm S2, there was an intermediate range of S1-S2 intervals in which a greater AP prolongation occurred for S2 oriented along the fibers compared with across the fibers. Panel D: When the S2 strength was 12.9 V/cm, AP prolongation occurred for S2 given as early as the midpoint of the AP. For this S2 strength, the AP prolongation was not markedly different for S2 along versus across the fibers.
Data points at an S1-S2 interval of 1 would represent an S2 given at the time of 90% repolarization of the AP. Figure 2A shows that the 2.3-V/cm S2 given even as late as the time of 90% repolarization of the AP produced only a small AP prolongation. When the 2.3-V/cm S2 was given only 2–3 msec later, a new AP was produced. The sudden production of a new AP indicates the all-or-none response for an S2 of this strength.

Figure 2B shows the effect of the 4-V/cm S2 electric field applied along or across the fibers. S2 produced AP prolongation when given at S1-S2 intervals of −0.8–1. When given near the midpoint of the AP (S1-S2=0.5), the 4-V/cm S2 did not prolong the AP for either S2 orientation. When S2 was given late in relation to the AP repolarization, a new AP was produced for either S2 orientation. At intermediate S1-S2 intervals of −0.8, S2 along the fibers had a greater effect than S2 across the fibers.

Figure 2C shows that when the S2 electric field strength was 8.1 V/cm, AP prolongation occurred for S2 given during the second half of the AP. Again there was an intermediate range of S1-S2 intervals in which a greater AP prolongation occurred for S2 oriented along the fibers compared with across the fibers.

Figure 2D shows that when the S2 electric field strength was increased to 12.9 V/cm, AP prolongation became noticeable for S2 given as early as an S1-S2 interval of 0.5. Unlike the results for the weaker S2, the AP prolongation produced by the 12.9-V/cm S2 was not markedly different for S2 oriented along the fibers compared with across the fibers.

The control AP duration at 90% repolarization in the seven experiments was 151±32 msec. For S2 electric fields having a strength of 2.5±0.1 V/cm, which produced all-or-none responses, the smallest S1-S2 interval that resulted in a new AP was 152±33 msec for S2 oriented along the fibers and 156±33 msec for S2 oriented across the fibers (p=NS). For stimulation with an S1-S2 interval of 20–80% of the control AP duration at 90% repolarization (an S1-S2 range in which the cells were highly refractory and hence the responses were not new APs), S2 of 4.1±0.2 V/cm produced AP prolongation of 20±12% (p<0.05) for S2 oriented along the fibers and 4±4% (p=NS) for S2 oriented across the fibers; for the same range of S1-S2 intervals, S2 of 8.3±0.3 V/cm produced AP prolongation of 36±8% (p<0.05) for S2 oriented along the fibers and 20±4% (p<0.05) for S2 oriented across the fibers, and S2 of 14±1 V/cm produced AP prolongation of 36±13% (p<0.05) for S2 oriented along the fibers and 30±9% (p<0.05) for S2 oriented across the fibers (p values were calculated by comparison with zero AP prolongation, mean±SD for seven preparations). For the 4.1- and 8.3-V/cm S2, the AP prolongations corresponding to the two S2 orientations were significantly different (p<0.05, along versus across). For the 14-V/cm S2, the AP prolongations corresponding to the two orientations were not significantly different.

Assessment of the Impact of Shocks on the Dispersion of Repolarization

Figure 3 illustrates the ability of a shock at an electric field strength of 8.4 V/cm (a value probably greater than the critical strength127) to decrease the dispersion of repolarization. The recordings are superimposed and aligned with the shock time. The decrease in the dispersion of repolarization can be assessed by considering the time from the shock to repolarization after the shock. If the shock had not affected repolarization, the variation in the repolarization times of the recordings in Figure 3 would equal the 140-msec variation in the S1-S2 interval indicated by the dispersion of the AP phase-zero depolarizations in the left part of Figure 3. The variation in the repolarization times in Figure 3 was only 100 msec (i.e., it was decreased by 40 msec). This decrease corresponds to a decrease in the dispersion of repolarization for cells that receive the shock at the various times during the APs shown. There was a window of times during the AP in which the variation of repolarization time after the shock was negligible (S1-S2=130–170 msec). This window occurred at −68% of the control AP duration at 90% repolarization, which was 221 msec in this experiment. When the shock was applied at times earlier than the window (S1-S2=90–110 msec), the repolarization time after the shock became greater. The repolarization time also became greater when the shock was applied at times later than the window (S1-S2>180 msec). When the shock was applied sufficiently late in the AP, a new AP was produced (e.g., S1-S2=230 msec).

The effect of a shock at a low electric field strength on the cell's repolarization time is shown in Figure 4. The
two shock-aligned recordings show the markedly different responses that occurred after the 1.6-V/cm shock with only a small change in the shock timing. This indicates the all-or-none response that occurs with low field strengths.

Figure 5 illustrates the effects of shocks having electric field strengths from 1.4 to 14.6 V/cm. The variation in the time from the shock to 90% repolarization (S2-R90), on the vertical axis of Figure 5, corresponds to the dispersion of repolarization after the shock. If a shock of a given strength had not affected repolarization, the plot would be a line with a slope of −1. For the 8.4- or 14.6-V/cm shocks given over a 100-msec-wide range of S1-S2 intervals, the variation in S2-R90 was only 35 msec, or one third of what it would have been if the shock had no effect. The S1-S2 window for the production of a constant S2-R90 was 60–90 msec, or −54% of the control AP duration at 90% repolarization, which was 140 msec in this experiment. The absence of an effect of the 1.4- or 2.5-V/cm shocks for most times during the AP is indicated where the slope of the S2-R90 curve is −1. The sudden increase in the S2-R90 interval, due to the production of a new AP, is seen for the weak shocks given late in the action potential.

**Implications for the Induction of Reentry**

The intracellular potentials after S2 can explain the propagation wave front in a region of the heart where the S2 electric field strength is less than a critical electric field strength and the block where the S2 strength is greater than the critical strength.18 Figure 6 shows intracellular potentials 10 msec after S2 measured in repeated trials from a single cellular impalement. The values are shown on a map of intersecting lines of S2 electric field strengths and states of cellular refractoriness patterned after Figures 2–4 of Frazier et al.1 In the region where the S2 electric field strength was low, the cells that were directly activated by S2 are close (upper right of Figure 6) to cells that were not directly activated; thus, a large intracellular potential gradient of ~0.5 V/cm occurs that would initiate propagation from right to left in the upper part of the figure. The intracellular potential gradient along a line of S2 electric field strengths of 15 V/cm is small (largest value is only 0.017 V/cm for S1-S2 intervals of 210–220 msec) and therefore much less likely to initiate a propagation wave front. The intracellular potentials in the region where the S2 electric field strength was ~8–15 V/cm were from −23 to +28 mV. In this range of intracellular potentials, sodium channels are largely inactivated,10 further preventing a propagation wave front.

**Discussion**

**Action Potential Prolongation Produced by Field Stimulation: The Impact of the Field Orientation**

The orientation of the stimulus electric field with respect to the myocardial fibers is one of the factors that determine the AP prolongation by field stimulation. The
Figure 6. Intracellular potentials after electric field stimulation (S2). The measurements were obtained from intracellular recordings with one cellular impalement for which various S2 electric field strengths oriented along the fibers and S1-S2 stimulus intervals were tested. The intracellular potentials, given in millivolts within the graph, occurred 10 msec after S2 was applied. The intracellular potentials are graphed with the S2 electric field strength on the vertical axis and the state of refractoriness, or S1-S2 interval, on the horizontal axis to correspond with the spatially dispersed stimulus strengths and states of refractoriness that induce reentry in the heart.[1] The 1-cm calibration bar is approximate and is based on an assumed conduction velocity of 65 cm/sec for the repolarization wave of the preceding S1 beat.[1] The isopotential contours, determined by bivariate polynomial interpolation[6] and smoothing by hand, represent intracellular potentials from −45 to 25 mV in 10-mV increments. Contours for intracellular potentials more negative than −45 mV are not shown because of uncertainty in the interpolation. In the region where the S2 electric field strength is approximately 1.5 V/cm, an abrupt boundary (upper right) occurs between the tissue that is directly excited by S2 and the tissue that is not directly excited. A large intracellular potential gradient at the boundary, −0.5 V/cm, can account for the initiation of propagation from right to left that has been reported in the region having a low electric field strength.[1,8] The large intracellular potential gradient at the boundary is comparable to that which occurs at a propagation wave front in myocardial tissue with normal intercellular connections. In the region having a high S2 electric field strength, there is no abrupt boundary between high and low intracellular potentials. Instead, on the line of an S2 strength of 15 V/cm, the largest intracellular potential gradient, ignoring discontinuities of intracellular resistance, is only 0.017 V/cm. Also, the intracellular potentials on the 15-V/cm line are in the range in which sodium current is inactivated.[10] The absence of a large intracellular potential gradient and the presence of intracellular potentials that inactivate sodium current, a current important for propagation, explain the absence of propagation after a shock where the electric field strength during the shock is high.[1,8]

AP prolongation for an S2 of 4–8 V/cm was greater when the electric field was oriented along the myocardial fibers than across the fibers. When the S2 strength was increased to 14 V/cm, however, the AP prolongation became similar for the two S2 orientations. These results can be explained on the basis of two stages of the myocardial response to field stimulation: stage 1, a transmembrane component of the applied stimulus current that alters the transmembrane potential during the stimulus pulse but does not require changes in membrane ionic conductances; and stage 2, a regenerative transmembrane ionic current due to the transmembrane potential dependence of the membrane ionic conductances. In stage 1 the change in the transmembrane potential is determined by linear passive properties of myocardium; hence, the change in the transmembrane potential is proportional to the stimulus strength, whereas in stage 2 it is limited by the availability of transmembrane ionic driving forces (e.g., the difference between the transmembrane potential and the equilibrium potential for each ion) and membrane ion channels.

Diastolic excitation by electric field stimulation depends on the ability of stage 1 to bring the transmembrane potential to a threshold potential for a regenerative response in stage 2 that produces an AP phase-zero depolarization. The lower electric field strength needed for diastolic excitation by S2 oriented along fibers compared with across fibers suggests a greater ability of S2 along fibers to produce a transmembrane potential response in stage 1.

A greater stage 1 response for S2 electric fields oriented along fibers compared with across fibers could explain the greater AP prolongation by 4- or 8-V/cm S2 along fibers compared with across fibers, assuming that the stage 2 response to S2 of these strengths given to relatively refractory myocardium is greater for a greater
stage 1 response. This assumption is supported by the greater AP prolongation for a given S2 orientation when the S2 electric field strength was increased from 4 to 8 V/cm. However, the 14-V/cm S2 did not produce a significantly greater AP prolongation for S2 along fibers compared with across fibers even though, like the weaker S2, the stage 1 response to the 14-V/cm S2 would be greater for S2 along fibers compared with across fibers. The similarity of the AP prolongation for 14-V/cm S2 along fibers compared with across fibers could be due to limited amounts of transmembrane ionic driving forces or membrane ion channels in stage 2. If true, a greater stage 1 response (e.g., for 14-V/cm S2 along fibers compared with across fibers) would not further increase the stage 2 ionic current. Limited amounts of stage 2 ionic driving forces or channels can also explain the similarity of AP prolongation by the 8-V/cm S2 along fibers compared with the 14-V/cm S2 along fibers. Under this interpretation of the results, limitation of the stage 2 response occurs with an electric field strength of 8 V/cm oriented along the fibers, whereas it occurs with a higher field strength for fields oriented across the fibers.

A greater stage 1 response for S2 along the fibers compared with S2 across the fibers would be consistent with the greater length of the cells in the direction along the myocardial fibers. Also, the myocardial resistance is lower in the direction along the myocardial fibers. An electric field of a given strength would produce a greater myocardial current density when the field is oriented along the fibers compared with across the fibers. Increased current density might increase the ability to stimulate the cells.

The Importance of Action Potential Prolongation for Electrical Defibrillation or Cardioversion

The distribution of repolarization in the heart is an important factor in most hypotheses of arrhythmias and fibrillation. The changes in cellular repolarization that are produced by an electric shock may be important for defibrillation. For example, the repolarization delay produced by a sufficiently strong electrical stimulus during the relative refractory period can prevent postshock activation and hence may prevent the cells from becoming excited by a reentrant wave front. The assessment of the effect of a shock on the dispersion of repolarization indicates that the electric fields having strengths of 8–14 V/cm decrease the variation of repolarization times by 30% (Figure 3) or more (Figure 5). This suggests that the amount of tissue that is in a given state of refactoriness at an instant after the stimulus increases at least 40%. The continuation of a reentrant arrhythmia requires that tissue somewhere in the reentrant pathway is sufficiently recovered to become excited. Excitable gaps during reentrant ventricular tachycardia in endocardially frozen rabbit hearts are only 23% of the pathway and, in leading circle reentry, can be much less. Given that the amount of tissue is fixed, a 40% increase in the amount of tissue that is refractory can be sufficient to abolish the excitable gap and hence interrupt reentrant arrhythmias.

In contrast with the possibility that the AP prolongation may interrupt or terminate a reentrant arrhythmia, the prolongation may contribute to the initiation of reentry. Such electrically induced reentry may cause defibrillation to fail by restarting fibrillation.

The Importance of Action Potential Prolongation for Rotor Initiation Around a Critical Point

In the critical point mechanism, reentry occurs where contours of spatially dispersed states of refractoriness, isofactoriness lines, intersect contours of spatially dispersed stimulus electric field strengths, isostimulus lines. The contour lines need not be straight lines. The isofactoriness lines correspond to states of the recovery process that have been described in excitable media theory. The isostimulus lines, along which the stimulus strength is constant, correspond to states of the excitatory process. The excitatory state increases rapidly when the medium is stimulated, which corresponds to the phase-zero depolarization of the cell membrane in the myocardium. The recovery state corresponds to the recovery of excitability during the repolarization of the cell membrane. The recovery state is reset by an increase in the excitatory state and changes slowly thereafter. It is postulated that critical states of each of the excitatory and recovery processes occur when a stimulus of an appropriate strength is given at an appropriate time during the recovery. When a line corresponding to one of the critical excitatory states intersects a line corresponding to one of the critical recovery states, a critical point is produced in an excitable medium. An excitation wave front occurs on one side of the critical point and then pivots around the critical point, provided that a sufficient amount of the medium exists on all sides of the critical point and that the medium on the respective sides contains excitatory and recovery states that include values greater than and less than the critical states. The theoretical framework involving the critical point has been used to explain vortices in several chemical and biological excitable media and in computer simulations (for references see Reference 21).

The different effects of the weak versus strong S2 electric field stimuli can explain the initiation of rotors of reentry in the heart by an appropriately timed stimulus. On a line of low S2 electric field strength (e.g., 1 or 2 V/cm), there is a state of refractoriness near the end of an AP where some cells have very little response (i.e., are not excited), whereas other cells that are only a few milliseconds more recovered have a very large depolarization (i.e., are directly excited) (Figure 6). Intracellular current from the cells that have the large depolarization to the cells that are not excited should initiate a propagation wave front at the border of the excited and nonexcited cells. The wave front then propagates along the line of low S2 electric field strength into the region that was not excited by the S2. On a line of high S2 electric field strength (e.g., 8 or 14 V/cm), there is no abrupt boundary between excited and nonexcited regions. The cells that are too refractory to become directly excited by the shock undergo prolongation of the AP. The prolongation is greatest for the cells that are most recovered and gradually becomes less for cells that are less recovered (Figure 2D). Without a region of excited cells adjacent to a region of nonexcited cells, intracellular current is small; hence, a propagation wave front does not occur immediately after the S2.
where the S2 electric field strength is high. Such a propagation wave front is further prevented by the prolonged period of voltage-dependent inactivation of sodium current that is due to the prolongation of the AP. At a later time, the region in which the AP was prolonged by the strong S2 electric field recovers enough to become excited again by a propagation wave front. The wave front that was initiated where the S2 electric field was weak then propagates into the recovered region, which produces pivoting of the propagation wave front around the critical point (i.e., counterclockwise rotation in Figure 6). When the region that was directly excited by the S2 recovers, the wave front continues to pivot into that region and eventually reaches its origin. Thus, by propagating around a critical point, the wave front completes the first cycle of reentry. Extracellular mapping studies in the intact heart have indicated that the center of the reentrant circuit occurs at a critical electric field strength of $-5 \text{ V/cm}$ for a 3-msec truncated exponential waveform, which is greater than the values that consistently produced all-or-none responses ($-2 \text{ V/cm}$) and less than the values that consistently produced AP prolongation ($-8 \text{ V/cm}$) in the present results.

**Limitations of the Study**

The interpretation of the findings in terms of the spatial dispersion of repolarization and intracellular potential is based on the previously observed consistency of propagation velocity of the repolarization wave during which the shock is applied and an assumption that the intercellular connections in the myocardium do not prevent intracellular potential gradients such as those shown in Figure 6. This assumption is supported by experimental evidence. Large intracellular potential differences over small distances occur during propagation in normally coupled rabbit papillary muscles (authors' unpublished observations) and during repolarization after electrical stimulation in myocardial fibers. Therefore, it can be assumed that the intracellular potential differences described in Figure 6 are not prevented by intercellular connections. Since the connections may decrease the intracellular potential gradients, the differences shown indicate the upper limit of the differences that occur in the heart.

The experiments were performed at a longer S1 cycle length than occurs in vivo. Experimental evidence suggests that results qualitatively similar to the present results could be obtained with a shorter S1 cycle length. Repolarization prolongation by shocks occurs during basic pacing at a cycle length of 350 msec in dog hearts. Also, refractory period extension by shocks, which is related to AP prolongation, occurs at cycle lengths shorter than those used here.

**Conclusion**

The effects of electric field stimulation on the myocardial intracellular AP reported here can explain a mechanism for the induction of reentry by a premature electrical stimulus. For tissue in which the refractory state is distributed, stimulus electric field strengths above or below a critical value of $-5 \text{ V/cm}$ produce either graded prolongation of the repolarization of the intracellular AP or an all-or-none response, respectively. Although the existence of the basic all-or-none or graded responses in relatively refractory myocardium was known from previous studies, the stimulus electric field strengths required to produce these responses were not previously known. Since such intracellular responses have been hypothesized to be important for the initiation of reentrant rotors by electric field stimulation, this study determined whether the responses are produced by the electric field strengths that are known to initiate reentrant rotors. The results indicate for the first time the close agreement between the electric field strengths that produce graded prolongation of repolarization and the strengths that produce block in critically refractory tissue in the heart. The graded prolongation, which is shown here to decrease intracellular potential differences and depolarize the cells to intracellular potentials at which sodium current is inactivated, accounts for the block in a region of the heart that receives electric fields stronger than the critical strength. The all-or-none response, shown here to occur for electric fields weaker than the critical strength, introduces a region of excited cells in close proximity to a region of cells that are not excited and are nearly repolarized and hence increases the intracellular potential difference at the boundary between the regions. This accounts for the initiation of the propagation wave front seen where the electric field is weaker than the critical strength. Thus, the magnitude of the critical electric field strength above or below which these markedly different types of effects (graded versus all-or-none) occur agrees qualitatively with the $-5 \text{ V/cm}$ value of the electric field reported for the center of the stimulus-induced reentrant rotor.

The measurements of the effects of electric fields weaker than $14 \text{ V/cm}$ on relatively refractory tissue indicate for the first time that electric fields oriented along the myocardial fibers are more able to prolong the repolarization than are fields oriented across the fibers. Thus, fiber orientation, important for myocardial characteristics such as resistance and conduction velocity and the occurrence of conduction block, is also important for excitation and prolongation of repolarization produced by electrical stimulation. The greater effectiveness observed for electric fields oriented along the fibers compared with across the fibers implies that block and reentry may occur with a weaker electric field when the field is oriented along the fibers.

For an electric field strength of $14 \text{ V/cm}$, orienting the field along rather than across the myocardial fibers does not significantly increase the prolongation of repolarization. Furthermore, when the electric field is oriented along the fibers, increasing the field strength from 8.3 to $14 \text{ V/cm}$ does not increase the prolongation of repolarization. This suggests that an upper limit of the amount of prolongation by these stimuli exists and that, for electric fields oriented along the fibers, the limit is reached with an electric field of $-8 \text{ V/cm}$.

**Note added in proof.** A description of cellular effects of electric shocks in rabbit heart was published after this article was submitted.

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Circ Res. 1992;70:707-715
doi: 10.1161/01.RES.70.4.707

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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World Wide Web at:
http://circres.ahajournals.org/content/70/4/707

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