Effects of Monophasic and Biphasic Shocks on Action Potentials During Ventricular Fibrillation in Dogs

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This study determined the response of action potentials during ventricular fibrillation (VF) to timed monophasic and biphasic shocks. A floating glass microelectrode was used to record intracellularly from the anterior right ventricle in 10 open-chest dogs. After 10 seconds of electrically induced VF, 5-millisecond monophasic and 2.5/2.5-millisecond biphasic shocks or 16-millisecond monophasic and 8/8-millisecond biphasic shocks were given via mesh electrodes on either side of the microelectrode. Monophasic and biphasic truncated exponential shocks of 5 V/cm were given with coupling intervals timed from the beginning of a VF action potential to the shock range from 50 to 70 milliseconds in 5-millisecond increments. Each coupling interval for each waveform was tested during a different VF episode. The interval between successive activations during VF was 86 ± 15 milliseconds (mean ± SD). The refractory period during VF was 61 ± 5 milliseconds for 5-millisecond monophasic shocks and 66 ± 6 milliseconds for 2.5/2.5-millisecond biphasic shocks (P < 0.05). At each coupling interval, action potential duration at 50% repolarization (APD50) was significantly prolonged by the shocks compared with the mean preshock APD50 (P < 0.05). APD50 duration increased significantly with increases in the coupling interval (P < 0.05) for both monophasic and biphasic waveforms. For all coupling intervals together, APD50 prolongation as a percent of the mean preshock APD50 was 170 ± 55%, 192 ± 45%, 151 ± 44%, and 175 ± 45% for 5- and 16-millisecond monophasic and 2.5/2.5- and 8/8-millisecond biphasic waveforms, respectively. This APD50 prolongation was greater for monophasic than biphasic shocks and was greater for longer than shorter waveforms (P < 0.05). Thus, during VF, (1) the refractory period for 5-V/cm truncated exponential waveforms lasting 5 milliseconds is approximately 75% of the VF activation interval; (2) the refractory period is shorter for monophasic than for comparable biphasic waveforms; (3) both monophasic and biphasic 5-V/cm shock fields cause prolongation of action potential duration; (4) prolongation of action potential duration increases as the coupling interval increases; and (5) prolongation of action potential duration is greater for monophasic shocks and for longer shock waveforms. (Circulation Research 1993;73:325-334)

KEY WORDS • action potential • refractory period • ventricular fibrillation • electrical defibrillation

Recent studies suggest that one reason a defibrillation shock might fail is that the shock reinitiates ventricular fibrillation (VF) by stimulating relatively refractory myocardium.1,2 It has been proposed that electrical stimulation during the vulnerable period may be an important factor for the initiation of VF by prolonging the duration of the action potential of relatively refractory tissue.3-5 Depending on its strength and the time it is delivered during the action potential, a shock can have at least three effects on the tissue: (1) no response, (2) prolongation of action potential duration and refractoriness, or (3) stimulation of a new action potential.6-9 These three responses can be induced in different regions of the myocardium by a shock given during regular paced rhythm and can then lead to the initiation of reentry and VF. Recently, it has been proposed that defibrillation involves not only stimulation but also prolongation of refractoriness by the shock.6,9-12 Although the changes in intracellular action potentials caused by electrical stimuli with different waveforms have been studied in paced rhythm by several investigators,5,7,9,13 only a single study by Dillon14 has investigated the changes in action potentials caused by electrical shocks during VF in isolated rabbit hearts. The Dillon study documented the existence of action potential prolongation by the shock but did not measure the strength of the extracellular electric field generated by the shock. We are not aware of any previous study in which the response of VF action potentials to the shock was recorded in the heart in situ and in which the extracellular field strength was also measured.

The purpose of this study was to determine how cardiac cells respond to monophasic and biphasic shocks during VF by recording from a floating microelectrode in the intact hearts of open-chested dogs. The
study attempted to answer four questions. (1) What is the refractory period to the shocks during VF? (2) Do the shocks extend action potentials during VF? (3) How do these effects differ for long and short waveforms? (4) How do these effects differ for monophasic and biphasic waveforms?

Materials and Methods

Surgical Preparation

Ten mongrel dogs weighing 20±1.6 kg were anesthetized with morphine (1.5 mg/kg) and α-chloralose (75 mg/kg IV) and were ventilated with 30% to 60% oxygen through a respirator (Harvard Apparatus, South Natick, Mass). Ringer’s lactate was infused continuously. α-Chloralose and morphine were given when needed to maintain an appropriate depth of anesthesia throughout the study. A 10-mg bolus of succinylcholine was given intermittently to control muscle contraction induced by the electric shocks. Normal body temperature was monitored with a rectal thermistor and maintained with a heat lamp and a heating blanket. An arterial line was inserted through a femoral artery to monitor the systemic blood pressure. Normal metabolic status was maintained by taking blood samples every 40 minutes to determine the pH, PO2, PCO2, and CO2 content and Na+, K+, and Ca2+ concentrations and by administering electrolytes and changing the oxygen concentration of inspired air.

The chest was opened, and the heart was suspended in a pericardial cradle. The epicardial surface was kept moist by a thin film of Tyrode’s solution. Two round defibrillation electrodes (25 mm in diameter) were sutured to the right atrium and to the left ventricular apex for defibrillation (Fig 1A). A pair of stainless-steel wires was sutured on the anterior wall of the left ventricle for inducing VF. A silicone rubber ring containing eight epicardial extracellular recording electrodes and one Ag-AgCl reference electrode for the intracelluar recording electrode was sutured on the anterior wall of the right ventricle (Fig 1B). To eliminate amplifier saturation, an Ag-AgCl reference electrode was positioned so that the recording-reference electrode axis was approximately parallel to the two mesh shock electrodes. Six suture lines were inserted through the ring and attached to the chest retractor to reduce the local movement of the heart and maintain a stable intracellular recording. Two mesh shock electrodes (25×4 mm) were sutured just outside the ring to create a test shock field in the ring area (Fig 1A).

**FIG 1.** Schematic representation of the recording electrodes and examples of the recorded action potentials. In panel A, an anterior view of the heart is shown including the right atrium (RA), right ventricle (RV), and left ventricle (LV). Patch defibrillation electrodes (DF) are sutured on the apicalateral LV and RA. A ring is sutured to the anterior RV. A 5-V/cm potential gradient was created in the tissue beneath the ring by a shock delivered through two mesh electrodes on either side of the ring labeled “test shock.” As shown in panel B, the ring contains extracellular electrodes to record the extracellular potential gradient created by the shock and contains the reference electrode for the intracellular electrode. A floating glass microelectrode is inserted into the center of the ring to record the intracellular potential. Panel C shows an example of action potentials recorded before, during, and after ventricular fibrillation (VF). A test shock of 5 V/cm was given after 10 seconds of VF followed by a defibrillation shock. Panel D shows the determination of action potential amplitude (APA) and of APD50 for four preshock action potentials and for the action potential during which the shock was given after a predetermined coupling interval (CI). APD50 is defined as the interval from the maximum time derivative of the upstroke of the action potential to the time for the action potential to decline to 50% of its APA.
**Experimental Protocol**

A 5-millisecond monophasic and a 2.5/2.5-millisecond biphasic shock (each phase lasting 2.5 milliseconds) were tested in five of the animals, and a 16-millisecond monophasic and an 8/8-millisecond biphasic shock were tested in the other five animals (Fig 2). The leading edge of the second phase of the biphasic shocks was equal in size but opposite in polarity to the trailing edge of the first phase (Fig 2). These truncated exponential shocks were delivered by a defibrillator (model HVS-02, Ventritex, Sunnyvale, Calif) through the mesh electrodes. Shock potentials were recorded from the eight epicardial electrodes on the ring in unipolar mode with respect to the left leg. Based on known calibration signals, the shock potential recorded by each electrode was calculated by a computer program. The potential gradient across the ring was calculated from the shock potentials and the distances between electrodes as previously described. Briefly, potential within the ring was approximated by a linear function of the position on the surface. The shock potentials measured at eight points on the ring were used to determine the coefficients of this function by means of a least-squares fit. The values of gradients were obtained by taking the magnitude of the spatial gradient of the linear potential function. This procedure yields the surface gradients only, but previous studies have indicated that the contribution of the transmural component to the total gradient is likely to be small on the exposed epicardium. The output of the defibrillator was adjusted to achieve a 5-V/cm potential gradient field at a time point approximately halfway through the shock waveform. The estimates of the leading edge voltage gradients were 5.9 V/cm and 8.2 V/cm for the 5-millisecond and 16-millisecond shock waveforms, respectively.

After stable recordings of intracellular action potentials were obtained, VF was induced by a 60-Hz alternating current through the wires on the anterior wall of the left ventricle. After 10 seconds of VF, a test shock of 5 V/cm was given at a predetermined coupling interval. The coupling interval was timed from the upstroke of the action potential during VF and was controlled by a software timer that was triggered by a real-time action potential dV/dt detector. The coupling interval ranged from 50 to 70 milliseconds and was scanned in 5-millisecond increments. Thus, five different coupling intervals were tested. Each coupling interval for each waveform was tested during a different VF episode. The action potentials were continuously recorded before, during, and after the test shock (Fig 1C). Then a defibrillation shock from a second Ventritex defibrillator was given through the defibrillation electrodes to halt the VF. Except for a few cases, such as the one shown in Fig 1C, the microelectrode was withdrawn from the heart just before the strong defibrillation shock was given to avoid damage to the microelectrode preamplifier. Before the next episode, the microelectrode tip was reinserted into a cell near the center of the ring. There was a 5-minute interval between VF episodes. Both the monophasic and biphasic waveforms were tested twice at each coupling interval.

**Signal Recordings**

Simultaneous intracellular and extracellular recordings were made with a computer-assisted cardiac mapping system. Cardiac activations before and after the shock were recorded in bipolar mode with AC-coupled amplifiers with a 5-Hz high-pass filter. Approximately 5 milliseconds before the test shock, the microprocessor switched attenuators in front of each amplifier so that the shock potentials could be recorded in unipolar mode with low gain and DC coupling. Immediately after the test shock, the attenuators were switched out, and the gains and coupling of the amplifiers were returned to the initial preshock state to record activations. For intracellular recordings, a conventional microelectrode (tip resistance, 10 to 30 MΩ, filled with 3 M KCl) was mounted on a 30-μm Ag-AgCl spiral wire to allow the microelectrode to follow cardiac motion. Action potentials were recorded at the center of the ring as the difference in voltage between the intracellular microelectrode and an extracellular Ag-AgCl reference electrode fixed on the ring (Fig 1B). The action potentials were passed through a high-impedance capacitance-compensation preamplifier (model 750, WP Instruments, Inc, New Haven, Conn). The signal after preamplification was recorded by the mapping system simultaneously with the eight extracellular signals. No attenuator circuit was used for the intracellular recordings. Both intracellular and extracellular signals were recorded digitally with 12-bit accuracy at a rate of 8000 samples per second per channel and were stored on VCR tape for off-line analysis.

**Terminology**

The action potential amplitude (APA) was defined as the difference between the maximum depolarization potential reached by that action potential and the minimum repolarization potential reached at the end of the previous action potential (Fig 1D). As can be seen in Fig 1C, the minimum repolarization potential was usually less negative than the resting diastolic potential. Repolarization of an activation potential was usually interrupted by the upstroke of the succeeding action potential because of the rapid activation rate during VF. The VF APD\(_{50}\) was defined as the interval from the maximum time derivative of the upstroke of the action potential (V\(_{max}\)) to the time for the action potential to

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**Figure 2. Diagram of the shock waveforms. Panel A represents the monophasic waveforms with 5-millisecond (dashed lines) and 16-millisecond durations. Panel B represents the biphasic waveforms with 2.5/2.5-millisecond (dashed lines) and 8/8-millisecond durations.**

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decline to 50\% of its APA during VF (Fig 1D). The mean preshock APD$_{50}$ was obtained by averaging the VF APD$_{50}$ of the last four action potentials just before the test shock. The shock APD$_{50}$ was defined as the interval from the $V_{\text{max}}$ of the last action potential preceding the shock to the time for the action potential to decrease to 50\% of its APD following the test shock (Fig 1D). A longer duration, such as APD$_{50}$, was not used because a propagated response sometimes reactivated the tissue before the action potential after the test shock had reached this longer duration. The shock APD$_{50}$ was normalized by dividing it by the mean preshock APD$_{50}$ to compensate partially for variation among different animals and different VF episodes. Thus, a shock APD$_{50}$ of greater than 100\% indicated that the action potential during which the shock was given was prolonged compared with the mean action potential duration just before the shock.

Shock-induced action potential was used to refer to a new action potential induced by the shock. When the test shock induced a response that occurred immediately after the shock without a latency between the end of the shock and the beginning of the response and that caused a shock APD$_{50}$ of 150\% or more (ie, a response at least 50\% longer than the mean preshock VF APD$_{50}$), it was assumed that the shock had induced a new action potential rather than prolonging the previous action potential.7 The refractory period during VF, which was determined for the 5-millisecond monophasic and 2.5/2.5-millisecond biphasic shocks, was taken to be the shortest coupling interval for which a shock-induced action potential was recorded.

The effect of field stimulation by defibrillation electrodes is different from that of local stimulation by a pacing electrode since local stimulation initiates a propagated activation front.3,7 Thus, initiation of a new action potential by the pacing electrode can be ascertained if activation is observed to propagate away from the stimulus site. Field stimulation, however, can cause new action potentials to occur simultaneously throughout a large volume of tissue. It is also possible for the shock field to induce refractory period prolongation in the tissue bordering the area in which new action potentials were stimulated. For these reasons, a propagated activation front may not conduct away from every cell in which a new action potential is stimulated by the shock. Thus, the conventional measurement of the refractory period by determining the shortest coupling interval at which a stimulus initiated a propagated response is not suitable for the field stimulation that occurs during defibrillation shocks.

**Data Analysis**

APD$_{50}$ was determined with the aid of a computer program as previously described.7 The APA was determined by taking the difference between the minimum and maximum values of the calibrated action potential in a time interval, selected interactively by the investigator, that began just before and ended just after the upstroke of the action potential. APD$_{50}$ was sought between two other user-defined points in the repolarization segment of the action potential (ie, the point immediately after the shock artifact and the point at the end of repolarization) so that the shock artifact was avoided for calculation of action potential amplitude and APD$_{50}$. APD$_{50}$ was the time between $V_{\text{max}}$ of the action potential just before the shock and the point at which the value of the action potential had fallen to the minimum value as defined above plus 50\% of the APA. The APD$_{50}$ was not available in those cases in which the shock artifact occurred at the time of APD$_{50}$. Such cases were not included in the statistical analysis. The interval between successive activations was the time between $V_{\text{max}}$ for the beat under consideration and $V_{\text{max}}$ for the preceding beat. The above values were determined for the five action potentials before the shock, as shown in Fig 1C. Every recording at the same coupling interval from all dogs was pooled for each waveform. The data were analyzed using analysis of variance (Student-Newman-Keuls test) and the nonpaired $t$ test. A value of $P<.05$ was interpreted as significant. Values are given as the mean±1 SD.

**Results**

During sinus rhythm, APA was 105±8 mV and APD$_{50}$ was 155±20 milliseconds. Just before the shock after 10 seconds of VF, APA was 61±15 mV, APD$_{50}$ was 64±14 milliseconds, and the interval between successive activations was 86±15 milliseconds. If the APD$_{50}$ of the first of the four action potentials just before the shock was taken as 100\%, then the mean APD$_{50}$ for the second, third, and fourth was 99±31\%, 104±28\%, and 101±32\% of this value, respectively ($P=\text{NS}$). Thus, the mean APD$_{50}$ during VF was relatively consistent from cycle to cycle for the relatively short time of four cycles.

**Refractory Period During VF**

The shortest coupling interval that captured the tissue (ie, the refractory period) was 61±5 milliseconds for the 5-millisecond monophasic (n=8) and 66±6 milliseconds for the 2.5/2.5-millisecond biphasic shock (n=8). These values were significantly different ($P<.05$). Therefore, cells were excitable approximately 71\% of the time for the 5-V/cm monophasic waveform (61 msec/86 msec) and 77\% of the time for the 5-V/cm biphasic waveform (66 msec/86 msec).

In Fig 3, the normalized APD$_{50}$ for the shortest coupling interval that induced a new action potential (labeled 0 msec) is compared with the normalized APD$_{50}$ for a coupling interval 5 milliseconds shorter (labeled −5 msec) for the 5-millisecond monophasic and the 2.5/2.5-millisecond biphasic waveforms. There was a significant increase in APD$_{50}$ between these two coupling intervals (Fig 3B). There was no significant increase before or after times of −5 milliseconds and 0 milliseconds as shown in Fig 3B, which further implies that a new action potential was caused by the field stimulation during VF at 0 millisecond. Such a jump in APD$_{50}$ suggests that there was a quantitative change in transmembrane currents to cause a new action potential by the field stimulation of the defibrillation shock at 0 millisecond. Therefore, for those cases in which the shock APD$_{50}$ was at least 50\% longer than the mean preshock APD$_{50}$, it was assumed that extension of the portion of the complex after the shock did not represent action potential prolongation but a new action potential and signified capture of the tissue by the shock at that coupling interval. For the particular experiment shown in Fig 4, this jump in APD$_{50}$ occurred between the 60- and 65-millisecond coupling interval for the 5-milli-sec-
ond monophasic shock and between the 65- and 70-millisecond coupling interval for the 2.5/2.5-millisecond biphasic shock. Thus, we assumed that the 5-millisecond monophasic shock induced a new action potential at a coupling interval of 65 milliseconds whereas the 2.5/2.5-millisecond biphasic shock induced a new action potential at a coupling interval of 70 milliseconds in this animal. For the 16-millisecond monophasic and 8/8-millisecond biphasic shocks, this large jump was not usually observed within the range of coupling intervals of 50 to 70 milliseconds. The mean value of normalized APD50 was more than 150% even for a coupling interval of 50 milliseconds as shown in Fig 5. Therefore, the refractory period appeared to be less than 50 milliseconds for the 16-millisecond monophasic and 8/8-millisecond biphasic shocks.

**Fig 3.** Panel A shows normalized APD50 for the coupling interval at which the shock was said to induce a new action potential (0 millisecond) and for the coupling interval 5 milliseconds shorter than this time (−5 milliseconds) for the 5-millisecond monophasic and the 2.5/2.5-millisecond biphasic trials. (APD50 is defined as the interval from the maximum time derivative of the upstroke of the action potential to the time for the action potential to decline to 50% of its APA.) A large jump in normalized APD50 occurs for all individual trials when the coupling interval is increased from −5 to 0 milliseconds. Only 16 sets of ventricular fibrillation episodes were included, because in the other four ventricular fibrillation episodes, an APD50 of more than 150% occurred for the shortest coupling interval tested (50 milliseconds) or because the shock was given at the time of APD50. Panel B shows the mean and standard deviation of normalized APD50 for the trials shown in Panel A for coupling intervals of −10 milliseconds (n=13), −5 milliseconds (n=16), 0 millisecond (n=16), and +5 milliseconds (n=13). The mean normalized APD50 for the coupling interval labeled −5 milliseconds is significantly smaller than for that labeled 0 millisecond (P<.01) for both monophasic and biphasic waveforms; the differences between −10 and −5 milliseconds and between 0 and +5 milliseconds are not significant.

**Prolongation of APD50 by the Shock**

Fig 4 shows examples of recorded action potentials before and after the test shocks. As the coupling interval increased, 5-millisecond shocks (total duration) prolonged the action potential duration until a sufficiently long coupling interval was reached and the tissue was captured, whereas 16-millisecond shocks often captured the myocardium even at a coupling interval of only 50 milliseconds.

Fig 5A demonstrates that the mean normalized APD50 for the next to last VF action potential just before the shock (the duration of the action potential numbered 4 in Fig 1D divided by the mean duration of action potentials 1 to 3 times 100) was approximately 100%, which verifies that the method used to evaluate action potential prolongation indicated no significant

**Fig 4.** Examples of action potentials recorded before and after test shocks during ventricular fibrillation. On the y axis are the four different waveforms and on the x axis are the coupling intervals of 50 to 70 milliseconds. The top two sets of tracings were recorded in one animal and the bottom two sets in another. The voltage and time scales are shown in the lower right corner. The action potential duration is increased (1) with an increase in coupling intervals for all shock waveforms, (2) for monophasic compared with biphasic waveforms of the same total duration, and (3) for longer compared with shorter waveforms of the same number of phases.
change in APD$_{50}$ in the absence of a shock. The mean action potential duration was prolonged by both monophasic and biphasic shocks at each coupling interval ($P<0.05$, Figs 5B and 5C) with standard deviations similar to that when no shock was given (Fig 5A). Fig 5 shows all responses, including those in which the APD$_{50}$ was more than 150%, that were labeled as new shock-induced action potentials for the purpose of determining the refractory period in the previous section. The prolongation of action potential duration was significantly greater as the coupling interval increased ($P<0.05$). For the same total shock duration, the prolongation of action potential duration was greater for the monophasic than for the biphasic waveform. The shock APD$_{50}$ for the 5-millisecond monophasic waveform was 8% to 26% longer than for the 2.5/2.5-millisecond biphasic waveform and was 14% to 22% longer for the 16-millisecond monophasic waveform than for the 8/8-millisecond biphasic waveform. For all coupling intervals taken together, the shock APD$_{50}$ for the 5-millisecond monophasic shock was 170±55% of the mean pre-shock APD$_{50}$, which differed significantly ($P<0.05$) from that for the 2.5/2.5-millisecond biphasic shock, which was 151±44%. Similarly, the shock APD$_{50}$ was 192±45% for the 16-millisecond monophasic and 175±45% for the 8/8-millisecond biphasic waveform ($P<0.05$).

The longer waveforms had a greater ability to prolong the action potential duration than did the shorter waveforms ($P<0.05$), especially at shorter coupling intervals when the cells were in an earlier portion of the action potential (Fig 5C). The correlation between normalized post-shock APD$_{50}$ and shock coupling interval was 1) shock APD$_{50}$=0.05×CI+1.4×100 (r=0.73) for 5-millisecond shock duration and 2) shock APD$_{50}$=0.03×CI−0.1×100 (r=0.44) for 16-millisecond shock duration, where CI represents the coupling interval. The coefficients in these two equations (0.05 and 0.03) were much less than 1, indicating that no constant post-shock repolarization time as defined by Dillon$^{11}$ was observed. In each individual animal, there were no sudden large increases in the amount of action potential prolongation with increases in the coupling interval for the longer waveforms, and the mean action potential durations were all greater than 150%. No large sudden increase with coupling interval was seen in the mean duration of the action potentials for the shorter waveforms either even though jumps were seen in the individual series of shocks when the action potential duration increased from less than 150% to more than 150% (Fig 3). The gradual increase in the prolongation of the mean normalized APD$_{50}$ at increasing coupling intervals, instead of the jump seen for each individual series of shocks, occurred because of differences in the refractory period between animals or between the two different replicates in the same animal. The same shock waveform at the same coupling interval could sometimes cause prolongation of the action potential and other times could initiate a new action potential during different VF episodes or in different dogs.

**Discussion**

Although VF is responsible for approximately one in five deaths in the United States,$^{18,19}$ much remains to be learned about the nature of the action potentials during VF.$^{20,21}$ and very little is known about how action potentials are affected by shocks during VF.$^{21}$ For example, the refractory period, an electrophysiological quantity of fundamental importance, has not previously been determined by direct measurement from fibrillating cells. Although studies have shown the effects of a shock on the action potential during paced rhythm,$^{6,7,9,12,13,22}$ it has not been known if the findings pertained to defibrillation shocks delivered during VF, because the activation rate, metabolic state, and autonomic tone during VF may be quite different from the conditions that exist during regular paced rhythm. Adding to this concern are the findings of dramatic differences between action potentials during paced rhythm and during VF. Compared with action potentials during paced rhythm, action potentials during early VF exhibit decreased amplitude, shortened duration, and no diastolic intervals between action potentials.$^{20,23,24}$

Action potentials during VF and the effect of defibrillation-strength shocks on them have been recorded in isolated rabbit hearts treated with a potentiometric dye.$^{11}$ Optical recordings from the dye furnish an estimate of the mean action potential of the many cells within and around the spot of light that is shone on the heart. Action potentials during VF also have been recorded in animal hearts by floating microelectrodes.$^{20,23,24}$ The present study extends the use of the floating microelectrode to the recording of the effects of
defibrillation-strength shocks on VF action potentials in a single myocyte of the ventricle. With the use of a ring of extracellular electrodes closely spaced around the floating microelectrode, this new technique was also able to measure the extracellular potential gradient in the region from which the transmembrane potential was recorded by the floating microelectrode. The extracellular potential gradient has been reported to be an important variable in determining whether stimulation\(^{14}\) and defibrillation\(^{25-29}\) occur.

The present study used this new technique to demonstrate that, although the action potentials during VF differ markedly from those during regular rhythm, the cardiac cells during VF still exhibit several basic electrophysiological characteristics observed in regular rhythm: (1) Cells in VF are excitable and can be stimulated to undergo a new action potential. (2) The cells in VF have a refractory period during which they cannot undergo a new action potential when stimulated with a potential gradient of 5 V/cm with truncated exponential waveforms lasting 5 milliseconds. (3) The cells in VF can have their action potential prolonged by a shock without the induction of a new action potential.\(^{5,11}\)

The refractory period of a 5-V/cm potential gradient for a 5-millisecond monophasic shock, which is probably the approximate potential gradient needed to defibrillate with a 50% probability of success using this waveform,\(^{27,28,30}\) was 61±5 milliseconds. Since the activation rate during VF in this study was 86±15 milliseconds, cells during early VF were inexcitable approximately 71% of their VF cycle length (61 msec/86 msec) for this particular shock duration and potential gradient. The remaining 29% of the cells could be directly excited by the shock to undergo a new action potential. If VF is maintained by many simultaneously present wandering wavelets,\(^{31-33}\) then approximately 1/86th of the cells should activate every millisecond, and the fraction of cells at each point of the VF action potential cycle should be evenly distributed and approximately the same from instant to instant during VF. If so, our results imply that approximately 71% of the ventricular myocardium is refractory to this particular shock at any instant during VF. Just as the refractory period during regular rhythm is a function of stimulus strength and duration, as indicated by the strength-duration curve,\(^{34}\) the mass of ventricular myocardium that is refractory to a shock during VF may vary with different shock strengths and waveforms as shown in this study and in Dillon’s report.\(^\text{11}\) Thus, the fraction of cells directly excited by a defibrillation shock probably depends on the field strength and waveform of the shock.

It has been hypothesized that cells activate almost as soon as they pass through their absolute refractory period during VF so that the excitable gap is either small\(^\text{35}\) or nonexistent.\(^\text{36}\) For this reason, the activation rate has been used as an estimate of the refractory period during VF,\(^\text{37}\) yet our study suggests that an excitable gap of approximately 29% of the VF activation cycle length may exist for the shock strength and waveform we tested. The explanation for this apparent discrepancy is probably that the potential gradient of 5 V/cm generated by the 5-millisecond truncated exponential monophasic shock used in this study, which is about five times diastolic threshold for normal cardiac cells,\(^\text{14}\) is a larger stimulus than that created by the propagating activation fronts during VF.

Under certain conditions, cells in regular rhythm that are in their refractory or relative refractory periods have been shown to respond to stimuli not with a new full action potential but with prolongation of the existing action potential.\(^\text{2}\) This response occurs when refractory cells are exposed to a large stimulus or relatively refractory cells are exposed to a stimulus slightly smaller than required for a new action potential. The prolongation of action potential duration within a myocardial region causes a concomitant prolongation of refractoriness.\(^{6,9}\) Recent evidence obtained during regular rhythm suggests that prolongation of action potential duration and refractoriness by the shock is important for defibrillation in at least two different ways.\(^{5,8,9,38}\) First, prolongation of refractoriness may prevent the appearance of an activation front following the shock. Normally, when tissue that undergoes activation adjoins tissue that does not, an activation front arises at the border of the activated region and propagates through the tissue that was not originally activated. By prolonging refractoriness in the cells immediately adjacent to the region in which new action potentials are induced, the shock may prevent the formation of new activation fronts since the tissue into which the activation fronts would propagate are too refractory to support them.\(^\text{39}\) Second, refractory period prolongation may make it more likely that any activation fronts that do appear after the shock will die out by encountering refractory tissue rather than continuing on to sustain VF.\(^\text{5,11,12}\)

This study demonstrated that prolongation of action potential duration was induced during VF by a 5-V/cm potential gradient field, a shock strength near that required for defibrillation with a 5-millisecond monophasic waveform. It also showed that the amount of action potential prolongation during VF increased as the shock was delivered later in the action potential (Fig 5), which was similar to the findings in regular rhythm. Thus, this study suggests that the responses of myocardial cells to shock fields observed during regular rhythm, such as direct excitation and prolongation of action potential duration,\(^ {6,9}\) can be extrapolated to VF although the specific potential gradient levels and coupling intervals for a certain result in VF differ from those in regular rhythm.

A limitation of this study is that it was not possible, by using the straightforward method that can be used with point stimulation, to differentiate directly between a new action potential and one that resulted from prolongation of the previous action potential. Augmentation of an action potential by a point stimulus is called a new action potential if it leads to a propagated activation front and is called action potential prolongation if it does not, but this method cannot be used to judge the response at a particular site in myocardium that is undergoing field stimulation. Even if the site experienced a new action potential, an activation front might not propagate away from the site since the stimulus field might have induced a new action potential or action potential prolongation in all of the surrounding tissue. In almost all cases for 5-millisecond waveforms, action potentials were extended either considerably less than or considerably more than 50% with few intermediate values (Fig 3). Therefore, we used 50% extension as the
division between action potential prolongation and a new action potential. If this assumption is incorrect because action potential prolongation may extend the action potential more than 50%, then the refractory periods during fibrillation that are given in this article are too short.

For a 5-millisecond monophasic waveform, Dillon\textsuperscript{11} reported that a “constant repolarization time” was produced during VF; i.e., when the coupling interval of the shock was increased by a certain time interval, the APD\textsubscript{50} was increased by the same time interval. The extracellular potential gradient created by the shock was not measured in the Dillon study but was probably higher than 5 V/cm (S. M. Dillon, personal communication). We did not observe a constant repolarization time for the 5-millisecond monophasic and biphasic waveforms at a potential gradient of 5 V/cm. For example, as shown in Fig 5, for the 2.5/2.5-millisecond biphasic waveform, the normalized APD\textsubscript{50} at a coupling interval of 70 milliseconds (201%) was 88% greater than that for the coupling interval of 50 milliseconds (113%). Since the mean APD\textsubscript{50} was 64 milliseconds, APD\textsubscript{50} increased 56 milliseconds (64 millisecond times 88%) with a 20-millisecond increase in coupling interval for this waveform instead of the 20-millisecond increase that would have been predicted from the results of Dillon. This finding suggests that the amount of action potential prolongation during VF is a function of the shock waveform and potential gradient in addition to the coupling interval as has been reported for shocks during regular rhythm.\textsuperscript{7,12,39}

The 16-millisecond monophasic waveform prolonged action potential duration more than the 5-millisecond monophasic waveform particularly at shorter coupling intervals (Fig 5). The greater response to the longer waveform is consistent with a classical strength-duration relation, although this relation may be more complex for a truncated exponential waveform than for a square wave.\textsuperscript{40} Since the 5-V/cm potential gradient was measured at the midpoint of the waveform (2.5 milliseconds for the 5-millisecond shock and 8 milliseconds for the 16-millisecond shock) and the waveform had a time constant of approximately 15 milliseconds, the leading edge voltage of the 16-millisecond waveform was approximately 40% greater than for the 5-millisecond waveform. Also, since the coupling interval was specified for the onset of the waveform, at any given coupling interval the 16-millisecond waveform extended 11 milliseconds later into the previous action potential than did the 5-millisecond waveform. Mean action potential duration was greater than 150% for the 16-millisecond shocks even at 50 milliseconds, the shortest coupling interval investigated. Therefore, it is possible that all of the responses to the 16-millisecond monophasic waveforms were new action potentials, although it is not known if a sudden change to an action potential duration of much less than 150% would have occurred if the coupling interval had been decreased to less than 50 milliseconds. Alternatively, the long duration shocks may have been powerful enough to induce a type of prolongation of the duration of depolarization similar to that observed by Dillon.\textsuperscript{8,11} This type of response differs from a new action potential in two ways: (1) It can be induced at any time throughout the action potential including the refractory period. (2) There is not a sudden increase in duration of repolarization when the shock is given slightly later during the VF action potential as occurs when the stimulus is given at the shortest coupling interval that initiates a new action potential. Instead, prolongation of depolarization gradually increases as the coupling interval is gradually increased through the VF action potential.\textsuperscript{11}

It is intriguing that a 16-millisecond truncated exponential monophasic waveform does not require less voltage or energy for defibrillation than does a 4- or 8-millisecond monophasic waveform (and so presumably a 5-millisecond waveform also) with the same time constant.\textsuperscript{41} If both stimulation of myocardium and prolongation of action potential duration are important for defibrillation, it might be assumed that if one waveform is better able than another to stimulate myocardium, to prolong action potential duration, or to do both, then the first waveform should be more efficacious for defibrillation than the second. Surprisingly, this does not appear to be the case as illustrated by the 5- and 16-millisecond monophasic waveforms. An even more striking counter-example is the biphasic waveform. The biphasic waveforms examined in this study probably defibrillate with lower voltage and energy than do the monophasic waveforms of the same duration.\textsuperscript{41,42} However, the results of this study indicate that the biphasic waveforms stimulate less well and cause less prolongation of action potential duration than do the monophasic waveforms of the same duration (Fig 5). This result agrees with several previous studies that compared the effects of biphasic and monophasic in paced rhythm,\textsuperscript{7,13,43} again suggesting that the results of studies obtained during regular rhythms have application to VF.

Our results do not completely agree with the results obtained by Jones et al.\textsuperscript{44,45} and Swartz et al.\textsuperscript{9} Using a computer model with the Beeler-Reuter action potential,\textsuperscript{46} they found that a short biphasic waveform (3/2 milliseconds) did not stimulate or prolong action potential duration as effectively as a monophasic waveform of the same total duration (5 milliseconds), which agrees with our results. However, in experiments with chick embryo cells, they found that long biphasic waveforms (total duration, 5 to 40 milliseconds) stimulated better and caused more action potential prolongation than did monophasic waveforms of the same or half of the same total duration.\textsuperscript{9,44,45} Jones et al explained these results based on the hyperbolic shape of the strength-duration curve.\textsuperscript{44} Increases in duration for waveforms shorter than the chronaxie caused a large increase in stimulation efficacy, but increases in durations for longer waveforms caused less change because the effects of these longer waveforms were already nearly equal to the maximum effect that occurs at the rheobase. They pointed out that each phase of the long biphasic waveform was longer than the chronaxie and hence had near maximum effect, whereas the phases of the shorter biphasic waveform were shorter than the chronaxie and thus had less of an effect than a monophasic waveform of the same total duration whose single phase was as long as both phases together of the biphasic waveform.\textsuperscript{45} Although we found that the longer biphasic waveform stimulated better and caused more action potential prolongation than the shorter biphasic waveform, neither was as efficacious for stimulating or prolonging action potential duration as was the monophasic wave-
of the same duration. One difference between the studies that may be responsible for this discrepancy is that the simulation and chick embryo studies were performed with square waves, whereas our study was performed with truncated exponential waveforms since this is the type of waveform used in implantable defibrillators. As discussed by Koning, truncated exponential waveforms do not stimulate as well as square waves with the same leading edge voltage and do not necessarily follow a classic hyperbolic strength-duration curve.

Even though a particular biphasic waveform may be better able to defibrillate than a monophasic waveform of the same total duration, the results of this study indicate that the biphasic waveform may be less able to stimulate myocardium or to prolong action potential duration than the monophasic waveform. Thus, stimulation of tissue and prolongation of recovery by the shock may not be the only factors for defibrillation. Other possible factors are the detrimental electrophysiological effects caused by the shock, such as transient conduction block in the regions of high potential gradient (greater than 60 to 70 V/cm) near the defibrillation electrodes. These regions of block may lead to reentry that reinitiates VF soon after the shock. Compared with a 10-millisecond monophasic waveform, a 5/5-millisecond biphasic waveform has been shown to cause a smaller region of conduction block, and the conduction block that does occur has been shown to be shorter lived in regions of high potential gradients. Thus, the 2.5/5-millisecond biphasic waveform may also cause less conduction block than the 5-millisecond monophasic waveform in regions of high potential gradient, which raises the possibility that this is an important factor for defibrillation. However, the 5-millisecond monophasic waveform, because it delivers less charge and energy than the 16-millisecond monophasic waveform, would be expected to cause less conduction block even though it probably defibrillates at least as well or better than the 16-millisecond monophasic waveform. This suggests that a detrimental effect in the high gradient region is not the most important factor affecting defibrillation efficacy.

As suggested previously, the volume of tissue in which direct excitation or prolongation of refractoriness occurs may be less important for defibrillation than are the number and location of activation fronts and the electrophysiological state of the myocardium following the shock. For example, an activation front may be less likely to block, reenter, and reinitiate fibrillation if it arises in more recovered tissue and is adjacent to myocardium that experiences less action potential prolongation and hence less extension of refractoriness. These considerations suggest that a complete understanding of the mechanisms of defibrillation has not yet been achieved. Whatever the mechanisms of defibrillation, these results (1) suggest that the behavior of myocardium to shocks during regular rhythm is qualitatively similar to that during VF and (2) support the conclusions obtained from experiments in paced rhythm that the efficacy of stimulation and prolongation of refractoriness cannot be used as the sole direct predictors of the efficacy of defibrillation for a waveform.

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