Mechanisms of Ventricular Fibrillation Induction by 60-Hz Alternating Current in Isolated Swine Right Ventricle

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Background—The mechanisms by which 60-Hz alternating current (AC) can induce ventricular fibrillation (VF) are unknown.

Methods and Results—We studied 7 isolated perfused swine right ventricles in vitro. The action potential duration restitution curve was determined. Optical mapping techniques were used to determine the patterns of activation on the epicardium during 5-second 60-Hz AC stimulation (10 to 999 μA). AC captured the right ventricles at 100±65 μA, which is significantly lower than the direct current pacing threshold (0.77±0.45 mA, P<0.05). AC induced ventricular tachycardia or VF at 477±266 μA, when the stimulated responses to AC had (1) short activation CLs (128±14 ms), (2) short diastolic intervals (16±9 ms), and (3) short diastolic intervals associated with a steep action potential duration restitution curve. Optical mapping studies showed that during rapid ventricular stimulation by AC, a wave front might encounter the refractory tail of an earlier wave front, resulting in the formation of a wave break and VF. Computer simulations reproduced these results.

Conclusions—AC at strengths less than the regular pacing threshold can capture the ventricle at fast rates. Accidental AC leak to the ventricles could precipitate VF and sudden death if AC results in a fast ventricular rate coupled with a steep restitution curve and a nonuniform recovery of excitability of the myocardium. (Circulation. 2000;102:1569-1574.)

Key Words: electrical stimulation ■ electrophysiology ■ mapping ■ action potentials

Leakage of 60-Hz alternating current (AC) through the heart by electromedical devices may result in the accidental induction of ventricular tachycardia (VT) or fibrillation (VF). Swerdlow et al recently reported that in humans, AC as low as 40 μA can result in VT or VF. The mechanisms by which AC of such low current strength can induce VF are unknown. Previous studies by other investigators2-4 showed that a single premature stimulus and repetitive stimuli at short coupling intervals can induce reentry by means of nonuniform recovery of the excitability of epicardial cells. Although these studies provided mechanistic insights into the generation of the first reentrant wave front during rapid pacing, the mechanisms by which the initial reentry degenerates into VF remain unclear. In the present study, we used high-density optical mapping techniques5 to study both the activation and the repolarization patterns during AC stimulation in isolated swine right ventricles (RVs).6 Transmembrane potential (TMP) was recorded from single cells by use of standard glass microelectrodes to determine the action potential duration (APD) restitution curve. We also performed computer simulations to investigate the underlying mechanisms in more detail. The purpose was to test the following hypotheses: (1) The development of sustained VF depends on a steep slope of the APD restitution curve. (2) Nonuniform recovery of excitability is important in the generation of initial conduction block during AC stimulation.

Methods

Tissue Preparation

The research protocol was approved by the Institutional Animal Care and Use Committee and followed the guidelines of the American Heart Association. Seven farm pigs (25 to 32 kg) of either sex were used in the study. Details of this model have been reported elsewhere. Briefly, each pig was anesthetized, and the heart was quickly removed. The right coronary artery was cannulated and perfused with Tyrode's solution (37±0.5°C, pH 7.4±0.5) at a flow rate of 30 mL/min. The composition of the Tyrode's solution was as follows (mmol/L): NaCl 125.0, KCl 4.5, MgCl2 0.5, CaCl2 0.54, NaH2PO4 1.2, NaHCO3 24.0, and glucose 5.5, along with albumin 50 mg/L. The RV was placed in a tissue bath with the epicardium facing up for optical mapping. A "pseudo-ECG" was recorded and monitored by a pair of bipolar electrodes with one pole on each end of the tissue to determine whether the ECG characteristics were compatible with VT or VF.
Recording Methods

The optical mapping system used in the present study was similar to that reported previously by Lin et al. The RVs were stained for 20 minutes with 1 to 2 μmol/L di-4-ANEPPS (Molecular Probes, Inc.) added to the Tyrode’s solution. The dye was then excited by using quasi-monochromatic light (500±30 nm) from a stabilized 250-W tungsten-halogen lamp (Oriel Corp). The induced fluorescence was collected through a 600-nm long-pass glass filter (R60, Nikon) and a 25-mm/stop 0.85 video lens (Fujinon CF25L, Fuji Photo Optical Co) with a 12-bit digital charge-coupled device camera (CCD camera, Dalsa, Inc). The frame-to-frame sampling interval was 3.75 ms. The camera acquires from 96×96 sites simultaneously over a 35×35-mm2 area, resulting in a spatial resolution of 0.13 mm2 per pixel. To minimize tissue contraction during pacing, 5 mmol/L diacetyl monoxime (DAM) was added to the solution. TMs were recorded from a surface cell by use of standard glass capillary electrodes.

Study Protocol

All hearts developed VF during excision, and the VF continued in the excised RV. The RV was first cardioverted and paced via a pair of closely spaced bipolar electrodes on the epicardium. All pacing pulse widths were 5 ms. Direct current (DC) pacing threshold was the lowest current strength that resulted in consistent ventricular capture. The dynamic APD restitution curve was determined by pacing the RV with the same pair of bipolar electrodes at 400-ms pacing interval with use of twice diastolic threshold current for 8 beats and then followed immediately by 8 beats of pacing at 350-, 300-, 280-, 260-, 240-, 230-, 220-, 210-, 200-, 190-, 180-, 170-, and 150-ms cycle lengths (CLs). To avoid confusion, we use the term pacing interval to denote the interval between pacing stimuli. The term CL refers only to the interval between consecutive cardiac activations, whether induced or spontaneous.

Induction of VT or VF was attempted by the following methods: (1) Rapid fixed-rate pacing is the method in which each pacing train included 19 beats, and there was an interval of at least 20 seconds between pacing trains. The pacing interval started at 300 ms and was progressively shortened to 200 ms in 20-ms decrements and thereafter in 10-ms decrements until VF was induced or 2:1 capture resulted. (2) AC stimulation is the method in which current output began at the root mean square of delivered AC at 10 μA and was increased in 10-μA increments up to a value of 200 μA and then in 50-μA increments to the maximum output of 999 μA. VF was defined by rapid irregular and sustained activations after cessation of pacing. VT was defined by regular activations that lasted >3 consecutive beats after the cessation of pacing.

By use of a CCD camera, the patterns of activation were recorded. During each pacing stimulus, TMP was also recorded at the same time. To correlate the times of TMP recordings with the patterns of activation, we used a programmable stimulator to send electrical signals simultaneously to the AXON acquisition system, to the AC stimulator, and to trigger a red LED light to shine at the edge of the tissue. Activation was determined by isointensity lines; the repolarization wave backs were indicated by pixels crossed the threshold intensity during depolarization or invasion of the tissue by use of standard glass capillary electrodes.

Computer Simulation Studies

Our mathematical model begins with the 2D cable equation10,11:
\[
\frac{\partial V}{\partial t} = -I_{\text{mem}} + \frac{1}{\rho_S} \frac{\partial^2 V}{\partial x^2} + \frac{1}{\rho_p} \frac{\partial^2 V}{\partial y^2}
\]
where \(C_m\) is the transmembrane capacitance, \(V\) is TMP, \(S\) is the surface-to-volume ratio, and \(\rho_S\) and \(\rho_p\) are the transverse and longitudinal resistivity, respectively. We set \(C_m = 1 \mu F/cm^2\), \(S = 2000 \text{ cm}^{-1}\), and \(\rho_S = \rho_p = 0.5 \text{ kOhm cm}\) (ignoring anisotropy). We use \(I_{\text{calc}} = I_{\text{L}1} + I_{\text{K}} + I_{\text{Na}}\), where \(I_{\text{L}1}\) is the fast Na current, \(I_{\text{K}}\) is the slow inward current, \(I_{\text{K}}\) is the time-dependent K current, \(I_{\text{Na}}\) is the plateau K current, and \(I_{\text{K}}\) is the background current, from the Luo-Rudy I (LR1) ventricular action potential model.2 We simulated a 9 cm×9 cm tissue, by use of a 600×600 grid, with “no-flux” boundary conditions:
\[
\frac{\partial V}{\partial x} \bigg|_{x=0} = \frac{\partial V}{\partial y} \bigg|_{y=0} = \frac{\partial V}{\partial y} \bigg|_{y=L_y} = 0
\]
where \(L_x = L_y = 9\) cm is the length of the side of the square. We altered the maximum conductance and kinetics of the LR1 model to change APD and APD restitution. Details of the changes are described in the corresponding figure legend. APD restitution was obtained by simulating a 1D cable equation11 with the pacing site at one end of the cable and a no-flux boundary condition at the other end. By progressively decreasing the pacing interval, we obtained the restitution curves.

Inhomogeneity in the tissue was modeled according to the mapping results of Laurita et al. We changed the maximum K channel conductance throughout the tissue as follows:
\[
\overline{G_{K_i}(x,y)} = G_{K_i}(2-0.8(x+y))/(L_x + L_y)
\]
where \(G_{K_i} = 0.282 \text{ mS/cm2}\) is the value in the LR1 model for \(K_i = 5.4 \text{ mmol/L}\). AC stimulation was delivered over a 0.6-mm diameter area in the center of the tissue by use of a current defined by \(I_{\text{AC}} = \sqrt{2I_0} \cdot \sin(2\pi f t)\), where \(I_0\) is the amplitude of the AC stimulus and \(f = 60\) Hz.

We used an advanced numerical method11 to integrate Equation 1. The adaptive time step varied from 0.01 to 0.2 ms. The space step was 0.015 cm. All simulations were carried out on a 433-MHz DEC Alpha workstation.

Data Analysis

The single-cell TMP was analyzed to determine the diastolic interval (DI, the time between 90% of repolarization of the preceding action potential to the phase 0 of the current action potential) and the APD from phase 0% to 90% repolarization (APD0-90). APD0-90 was plotted against the preceding DI, and the restitution curve was generated by exponential fit with the use of ORIGIN (Microcal Software, Inc.).

The data acquired by the optical mapping system was converted to pseudo color animation for online analysis. In each recorded frame, pixels were assigned red to yellow to represent depolarization if the intensity was lower than the average intensity of the whole sequence. Conversely, high-intensity pixels were assigned blue to light blue to represent repolarization. To visualize the direction of wave propagation and depolarization, we used the following methods: The optical signal acquired by each pixel was first averaged with 8 of its neighboring pixels. The operator then manually selected a threshold above which a pixel was deemed to have registered depolarization. Usually a threshold value of ~50% of the optical intensity was used. In a given frame, the isointensity lines were drawn wherever adjacent pixels crossed the threshold intensity during depolarization or repolarization. The depolarization wave fronts were indicated by red isointensity lines; the repolarization wave backs were indicated by blue isointensity lines. Using this method, we were able to visualize the wave-front and wave-back interaction. The junction between the red and blue lines is a wave break.

Data are expressed as mean±SD. Student t tests were used to compare the means of 2 groups of data. The Fisher exact test was used to compare the inducibility of VF by fixed-rate pacing and by AC. When there were >2 groups of data, ANOVA with Newman-Keuls post hoc analyses was performed. The Fisher exact test was used to compare the probability of inducing VF or VT by AC and by rapid ventricular pacing.

Results

The experiments lasted an average of 171±35 minutes. The RV weights at the end of the experiments averaged 54.5±9.2 g. The DC pacing thresholds at the beginning and at the end of the experiment were 0.77±0.45 mA and 1.06±0.71 mA, respectively (P=NS). In all 4 RVs incubated with triphenyltetrazolium chloride, which stains viable tissue brick red, allows us to delineate the borders of viable tissue.
Induction of VT or VF

AC stimulation had a lower current threshold for ventricular capture (100±65 μA) than did the DC pacing threshold at the beginning of the experiment (P<0.05). Increasing the AC current amplitude resulted in progressively faster ventricular activation CLs and eventually in the induction of VF (Figure 1). Alternans of CL and APD also progressively increased at greater current strength. Six RVs had both VF and VT induced, and 1 had only VT induced. Among the VF/VT episodes, 20 had both TMP and optical mapping recordings. Only these 20 episodes were included in the analyses for APD, CL, and DI. The current strength associated with either VT or VF induction was 477±266 μA. (If we consider only the induction of VF, then the current strength must reach 529±280 μA.) The average AC-stimulated CL and DI immediately before the onset of VT or VF were 128±14 and 16±9 ms, respectively. In comparison, fixed-rate rapid pacing induced VT or VF in only 1 of the 7 RVs (P<0.005), with the shortest activation CLs (180±47 ms) before 2:1 conduction block occurred. In 4 RVs, DIs could be accurately analyzed during rapid fixed-rate pacing. The shortest DIs achieved by rapid pacing were 29±13 ms (P=0.002 compared with AC). During dynamic APD restitution curve determination, the shortest activation CL achieved during pacing was 188±41 ms, and the shortest DI achieved was 43±18 ms (P<0.001 compared with AC). No VT or VF was induced.

Slope of APD Restitution Curve and Induction of VT or VF

The slope of the APD restitution curve is an important factor that determines the induction of VT or VF. Figure 2 shows a typical example from one RV. The slope to the left of the dashed line was >1; the slope to the right was <1. Note that in this RV, the shortest DIs associated with rapid pacing (green triangles) were >51 ms and that none of these were associated with the induction of either VT or VF. The red squares show the AC induction of either VT or VF. Note that all VT or VF episodes occurred to the left of the dashed line and that all episodes were induced only by AC stimulation.

The data presented in Figure 2 are typical for all 7 RVs studied. In these 7 RVs, the induction of VT or VF was always associated with DIs that fell in the steep (slope >1) portion of the APD restitution curve. The maximum slope of the APD restitution curve averaged 1.67±0.6 in all RVs studied. All RVs had a maximum APD restitution slope of >1 at the shortest DI. The range of DIs over which the slope was >1 averaged 20±11 ms.

Optical Mapping of Induction of VT or VF by AC Stimulation

The induction of VF or VT by AC was always associated with very rapid ventricular stimulation and a very short DI, as presented above. At very short DIs, wave fronts may run into the wave back of a previous excitation, where the tissue is not fully recovered, leading to conduction block. This head-to-tail interaction results in wave break (Figure 3). Figure 3A shows that AC stimulation resulted in rapid successive ventricular captures. The first wave front is shown in frame 113, and the second is shown in frame 162. Corresponding panels in Figure 3B show that the first activation wave front began to recover in frame 153. However, before its recovery was complete, the second wave front was initiated (red lines, frame 162). Because of the short DI, the wave front of the second activation merged into the wave back of the preceding activation (head-to-tail interaction).

Frame 162 shows that the left lower portion of the mapped region was slow in recovery (area surrounding by blue line). When the next wave front arrived, this area of delayed repolarization resulted in conduction block and the splitting
of the incoming wave front (yellow arrow in frame 170 of Figure 3B).

Figure 3C shows the optical signals recorded from sites 1 to 5, indicated in panels A and B. A first long downward arrow indicates rapid propagation of the first wave front. The second downward arrow indicates that the second wave front arrived before the full recovery of the first wave front; ie, propagation overtook recovery. Therefore, the wave front arrived when cells 1 to 5 had repolarized by 59%, 55%, 49%, 48%, and 43%, respectively. Conduction block occurred around cell 4. The third (long downward) arrow shows that the sequence repeats itself with the next AC-induced impulse, resulting in further conduction block and the onset of VF. The horizontal double line segments underlie the complex low amplitude electrograms associated with the core of reentry. The complex activations were first registered in cells 4 and 5, where the initial wave break occurred. The complex activation then moved to cells 3, 2, and 1 as VF was induced.

Optical mapping data were available in 17 episodes of VF induction. Among them, 16 episodes showed wave breaks within the mapped region, as shown in Figure 3. The first wave break occurred 3±1 beats (344±102 ms) after AC first captured the ventricle. The mechanisms of the wave break are compatible with the head-to-tail interaction, as shown in Figure 3.

Computer Simulation
To better understand the mechanisms by which AC stimulation induces VF, we carried out computer modeling simulations. Because the APD restitution slope has been strongly implicated in the genesis of wave break–causing VF, we compared 2 cases: one for steep APD restitution (Figure 4A) and the other for shallow APD restitution (Figure 4B). In each case, AC strength was increased gradually. For small AC strength, no action potentials were activated (I_0=5 μA in Figure 4Ac and 4Bc). When the AC strength was increased to a critical value, activations occurred periodically with long CLs. After discontinuing AC, no spontaneous action potentials occurred, and the tissue was quiescent (I_0=6.8 μA in Figure 4Ac and 4Bc). With further increases in the AC amplitude, the rhythm of the tissue depended on APD restitution. With a steep APD restitution, activation patterns became more and more complex, first with nonsustained VT and later with sustained VF (Figure 4Ac and 4Ad). For example, for I_0=9 μA, irregular activation persisted for several beats after AC and then stopped. For I_0=15 μA, the irregular activation persisted; this occurrence was initially due to figure-8 reentry, which then degenerated to multiple wavelets consistent with VF (Figure 4Ad). These results are similar to the experimental findings in Figure 1. In contrast, if the APD restitution curve was shallow, activation remained regular as AC strength was increased. All electrical activity stopped immediately on discontinuation of AC stimulation, even when I_0 was increased to 20 μA (Figure 4Bc). The activation patterns for each beat always showed a target wave (Figure 4Bd), with no wave break occurring despite similar fixed electrophysiological heterogeneity in these 2 cases (Figure 4Ab and 4Bb).

We also carried out simulations for conditions other than the 2 shown in Figure 4. Our major results can be summarized as follows: (1) If there is no preexisting heterogeneity, no wave break can be induced, even though the APD restitution curve is as steep as in Figure 4Aa. (2) If the tissue is extremely inhomogeneous, a wave break can be induced if the stimulus site is located in the short APD area, even when APD restitution is as shallow as in Figure 4Ba. (3) A wave break can be induced in slightly heterogeneous tissue when APD restitution is steep but not when APD restitution is shallow. Therefore, heterogeneity is necessary for a wave
Swerdlow et al previously demonstrated that AC can capture the human ventricles at an extremely low current strength and induce VT or VF with a current output of 1 mA. In the present study, we reproduced this finding in swine RVs. We found that the mechanism by which AC stimulation induces VF is related to 2 factors: (1) a steep slope of APD restitution curve and (2) the nonuniform recovery of excitability.

Role of APD Restitution Steepness

Recently we studied the mechanisms of induction of VF by rapid pacing. Computer simulations showed that the maintenance of VF was dependent on the inhomogeneity induced by steepness of APD and conduction velocity restitution. In the present study, our computer simulations extend these earlier findings by showing that the steepness of APD restitution is also important in facilitating the initial wave break and reentry that lead to VF. For the same degree of fixed electrophysiological heterogeneity (Figure 4Aa and 4Bb), no wave break occurred with shallow APD restitution (Figure 4Bd). Steep APD restitution is needed to induce VF (Figure 4Ad). This finding suggests that steep APD restitution and fixed tissue heterogeneity are synergistic in causing the initial wave break and reentry that ultimately lead to VF. Steep APD restitution plays an important role in the initiation of VF by AC stimulation, as well as in VF maintenance.

Compatible with computer simulation studies, the present study found that in swine RVs, AC results in fast ventricular rate response and short DIs. The short DIs are associated with the steep portion of the APD restitution curve (Figures 2 and 4). Only at critically short DIs was VF induced (Figure 2). These results are generally compatible with the restitution hypothesis of VF, recently reviewed by our group.

Nonuniform Recovery of Excitability

Han and Moe proposed that the nonuniform recovery of excitability underlies the induction of VF by an electrical stimulus. This hypothesis has been supported by many subsequent studies. Gough et al, for example, found that there is a relationship between dispersion of refractoriness and the induction of reentry. Laurita et al and Pastore et al demonstrated a direct relationship between nonuniform recovery of excitability and induction of reentry by premature stimuli or by rapid pacing. In the present study, we extend these observations by demonstrating the importance of nonuniform recovery of excitability in the induction of wave break and VF in a 3D cardiac preparation. According to the multiple wavelet hypothesis, formation of new wavelets occurs through the process of wave break (or wave splitting), in which a wavelet breaks into new (daughter) wavelets. Wave break occurs at sites of electrophysiological inhomogeneity.

Figure 4. Computer simulation of induction of VF by AC stimulation in electrophysiologically heterogeneous 2D tissue. Aa, Steep APD restitution curve, with slope >1 over wide range of DIs (dashed line indicates slope=1). Parameters changes in LR1 model were \( G_{Na} = 16 \text{ mS/cm}^2 \) and \( G_{si} = 0.055 \text{ mS/cm}^2 \). We also modified some time constants from LR1 model: we slowed \( j \) gate of \( h \) by \( \tau_j \rightarrow 5 \tau_j \) and sped up \( d \) and \( f \) gates of \( I_{Na} \) by \( \tau_d \rightarrow 0.6 \tau_d \) and \( \tau_f \rightarrow 0.6 \tau_f \). Ab, Fixed heterogeneity of APD distribution, as indicated by color scale, in tissue during pacing at 400 ms (see Equation 3). Ac, Action potential responses at increasing different AC strength (as marked at end of each trace). Arrow indicates time at which AC stimulation was discontinued. Ad, Snapshots of membrane voltage at different times during and after cessation of highest strength AC stimulation level (lower trace in panel Ac), showing that VF was initiated. In color scheme, voltage decreases from 20 mV to -90 mV (from red to blue). AC strength is \( I_0 = 15 \mu A \). B through Bd, Analogous results for case of shallow APD restitution. To decrease slope of APD restitution to <1 in LR1 model, parameters changes were as follows: \( G_{Na} = 16 \text{ mS/cm}^2 \), \( \tau_j \rightarrow 5 \tau_j \), \( \tau_d \rightarrow 0.2 \tau_d \), \( \tau_f \rightarrow 0.2 \tau_f \), and \( G_{si} = 0.09 \text{ mS/cm}^2 \). AC strength in panel Bd is \( I_0 = 20 \mu A \).
geneity, where regions of refractoriness provide opportunities for reentry to form. The present study and that by Laurita et al. confirm that epicardial cells are intrinsically heterogeneous in their repolarization properties. This intrinsic heterogeneity provides a substrate for reentry formation during rapid pacing. When a portion of the incoming wave front encounters refractory tissue while other portions continue to propagate, wave break occurs.

**Limitations of the Study**

There are several important limitations of the present study. One is that the optical mapping was limited to the surface. It is likely that some wave breaks were not mapped by this technique. Another limitation was that the results of the present study may not be applicable to diseased myocardium. A third limitation is that we did not extensively study all possible intrinsic spatial differences that might have influenced the induction of VF by a 60-Hz current.

A fourth limitation is related to the need to use DAM in the present study. DAM is known to flatten the APD restitution curve and may thereby inhibit the induction of VF. This effect might have decreased the probability of VF induction by rapid pacing. However, we had no difficulties in inducing VF with AC stimulation that shortened the DI sufficiently to engage in the steep portion of the APD restitution curve. The use of DAM might have magnified the difference between fixed-rate rapid pacing and AC stimulation and strengthened the conclusion that AC is more effective than fixed-rate pacing in the induction of VF.

**Acknowledgments**

This study was supported by a Sarnoff Fellowship (Dr Voroshilovsky), by an American Heart Association (AHA) Western States Affiliate Beginning Grant-in-Aid (Dr Qu), by a fellowship grant from Yonsei University (Dr Lee), by a Cedars-Sinai ECHO Foundation Award (Dr Karagueuzian), by National Institutes of Health grants P50-HL-52319, HL-58533, and HL-44880, by University of California Tobacco-Related Diseases Research Program (GRT-0020), by AHA Grants-in-Aid 9750623N and 9950644N, by the Ralph M. Parsons Foundation, Los Angeles, Calif., by the Kawata and Laubisch Endowments, UCLA, and by the Pauline and Harold Price Endowment, Cedars-Sinai Medical Center. The authors thank Avile McCullen, Pei-Li Yan, Melling Yuan, Ling-Tao Fan, Nina Wang, and Elaine Lebowitz for their assistance.

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_Circulation_. 2000;102:1569-1574
doi: 10.1161/01.CIR.102.13.1569

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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