Effects of Atrial Defibrillation Shocks on the Ventricles in Isolated Sheep Hearts

Richard A. Gray, PhD; José Jalife, MD

Background—The effects of cardioversion of atrial fibrillation on the activation sequence of the ventricles have not been previously studied. In this study we examined the events in the ventricle that follow the application of atrial defibrillatory shocks.

Methods and Results—We used video imaging technology to study the sequence of activation on the surface of the ventricles in the Langendorff-perfused sheep heart. We recorded transmembrane potentials simultaneously from over 20,000 sites on the epicardium before and after biphasic shocks applied by a programmable atrial defibrillator. The first epicardial activation after the shock depended on both the voltage and timing of the shock. During ventricular diastole, shocks as low as 10 V produced ventricular excitation, although the time between the shock and the first epicardial activation (latency) was ~30 ms. As the shock voltage was increased to 120 V, latency decreased to zero and the entire epicardium was depolarized within 30 ms. For 120-V shocks delivered late in systole, the depolarization sequence produced by the shock was similar to the previous repolarization sequence. Shocks of 120 V applied 150 to 300 ms after the previous ventricular excitation induced ventricular fibrillation. Ventricular fibrillation was induced by multiple focal beats after the shock, which produced waves that propagated but broke down into reentry within regions of high repolarization gradients.

Conclusions—These results demonstrate that atrial defibrillation shocks excite the ventricles even at low shock voltages. In addition, ventricular fibrillation can be induced by shocks given in the vulnerable period by producing focal patterns that break down into reentrant waves. (Circulation. 1998;97:1613-1622.)

Key Words: cardioversion • defibrillation • fibrillation • ventricles

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and, although it is not immediately life-threatening, increases the risk of stroke.1 Recently, the possibility of implanting an atrial defibrillator in patients has been investigated,2-5 and the effects of cardioversion of atrial fibrillation have been studied.6-12 It appears that the most efficient means to terminate AF electrically is to apply a biphasic shock with the duration of each phase equal to 3 ms with the electrode catheters placed in the right atrium (RA) and the coronary sinus (CS).11 Although atrial cardioversion can induce ventricular fibrillation (VF) if the shock is applied during the T wave, or if the preceding RR interval is short, it appears to be safe if properly timed.13 Some data exist regarding the sequence of events in the atria after cardioversion of AF; however, the detailed events in the ventricle resulting from atrial defibrillation shocks are not known. However, the effects of electrical shocks on the ventricles have been extensively studied especially in regards to the initiation of VF and ventricular fibrillation.13,14 The most extensive study of the sequence of activation during VF induction resulting from a strong electric field was performed by Shibata et al.15 They studied the effect of shocks in dogs with electrodes located on the apex of the left ventricle (LV) and the right atrium (RA) during atrial and ventricular pacing. They found that for atrial pacing, when shocks were applied within a certain interval after the sensed R wave of the ECG or "vulnerable period," VF ensued. Shibata et al15 found that the activation sequence in response to shocks with atrial pacing was complex and sometimes resulted from a discrete focus and other times resulted from broad wave fronts propagating away from the border of a region directly excited by the shock. The patterns resulting from shocks during ventricular pacing were more simple but were both focal and reentrant. Although repolarization was not measured in these studies, the authors presumed that the activation sequence after the shock was related to the previous recovery sequence. Much earlier, Moe et al16 found that the first few beats after a localized shock that induced VF were focal, not reentrant, and suggested that these beats were essential to the initiation of VF, which eventually was sustained by reentrant waves. More recently, studies have shown that the dispersion of repolarization is related to the induction of VF. Kirchoff et al17 showed that the dispersion of repolarization measured from seven map recordings was a better predictor of the vulnerable period than T-wave parameters from the ECG. In addition, Kuo et al18 increased repolarization dispersion by using temperature gradients and

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From the Department of Pharmacology, SUNY Health Science Center at Syracuse, NY.
Correspondence to José Jalife, MD, Department of Pharmacology, SUNY Health Science Center at Syracuse, 766 Irving Ave, Syracuse, NY 13210.
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demonstrated that there was a critical amount of dispersion required to induce VF for localized shocks.

The purpose of our study was to investigate the effects of shocks applied to the heart to terminate AF on the ventricles. We investigated the sequence of activation on the surface of the ventricles after atrial defibrillation shocks applied throughout the ventricular cycle. Because we recorded transmembrane activity we could record repolarization events before the shock and relate them to the events after the shock.

Methods

Experimental Protocol

Langendorff-Perfused Sheep Heart Preparation
Young sheep of either sex (weight, 16 to 25 kg) were anesthetized with sodium pentobarbital (35 mg/kg) and the heart was rapidly removed and connected to a Langendorff system as described elsewhere. Briefly, the coronary arteries were continuously perfused at a flow rate of 130 to 160 mL/min with warm (36° to 38°C) Tyrode solution buffered to a pH of 7.4. The solution consisted of the following (mmol/L): NaCl, 148; KCl, 5.4; CaCl₂, 1.8; MgCl₂, 1.0; NaHCO₃, 24; NaH₂PO₄, 12; glucose, 5.5. A bipolar electrogram (EG) was recorded by taking the difference of two extracellular electrodes placed on the RV and LV near the AV groove, which allowed us to monitor both atrial and ventricular activity. We added diacetyl monoxide (DAM) to the Tyrode solution (10 mmol/L) to stop the heart’s contraction. A bolus injection of 15 mL of the dye di-4-ANEPPS (10 μg/mL) dissolved in DMSO was injected into the coronary arteries. Two defibrillation catheters with 6-cm coil electrodes (InControl Inc) were inserted through the vena cava to the RA and the CS. A custom-made programmable defibrillator (InControl Inc) was used to deliver a biphasic shock (duration of each phase was 3 ms). Atrial fibrillation was induced by burst pacing with a bipolar coaxial electrode placed on the epicardial surface of the right atrium. Acetylcholine was added to the Tyrode solution at a concentration of 10⁻⁶ mol/L to facilitate the induction of sustained AF.

High-Resolution Optical Mapping
A diagram of the experimental setup is presented in Fig 1A. The light from two tungsten-halogen lamps was collimated and bandpass filtered (520±30 nm) together with a heat filter. A 50-mm objective lens was used to collect the emitted light. The emitted light was transmitted through a long-pass emission filter (590 nm) and projected onto a CCD video camera (Cohu 6500). The video images were acquired with an A/D frame grabber (Epix) at a rate of 120 frames/s (sampling at 8.33 ms; hereafter referred to as 8-ms sampling intervals). The frame grabber board was mounted on a Gateway Pentium computer, which was used to process the imaged data. Recordings were made from various surfaces by rotating the heart (Fig 1, B through D). Therefore, recordings from multiple surfaces were not obtained simultaneously.

Image and Signal Processing

Signal Processing
To reveal the signal, the background fluorescence was subtracted from each frame. Low-pass spatial filtering (weighted average of 7×15 neighboring pixels resulting in a spatial resolution under 1.5 mm) was applied to improve the signals. The signal (F) from each site was stretched such that the minimum value from the episode was 0 and the maximum value was 255 to correct for spatial nonuniformities in fluorescence intensity. By assuming that resting membrane potential was ~−80 mV and the action potential amplitude was 100 mV, we could approximate transmembrane potential values (V' in mV) according to the following relationship: V'=(100/255)*F−80.

Repolarization and Depolarization Maps
Depolarization maps were generated from each time series, F, in two ways. First, the maximum change in F between two frames was used to label a wave front. Second, a point in the time plot was labeled as a wave front if F became >160 in that frame (this cutoff roughly corresponds to a membrane potential of ~−15 mV). The depolarization maps for these two methods were the same for paced beats and the first beat after a shock; however, after shocks that induced VF, the membrane potential remained elevated and the slope...
of the upstrokes decreased in some areas leading to differences between the two methods. Therefore this cutoff method (F>160) was used to calculate depolarization maps. The repolarization time (RT) for each site was calculated as the time when F decreased to <64 (V<−55 mV, which corresponds to APD₉₀) after a three-point moving average temporal filter was applied to F to minimize the effects of noise on the repolarization tail. Because the iris of the video camera was open during the entire sampling interval, motion-induced smearing occurred and therefore a region of pixels perpendicular to the motion of the depolarization and repolarization processes activated in a single frame. Thus the depolarization and repolarization maps are composed of bands, not lines. Note that these bands derived from video images required no interpolation of data.

**Definitions**

For clarity, we have defined the following terms: (1) latency=(time of FEA)−(time of shock), and (2) delay=(time of shock)−(time of sensed R wave before the shock). In addition, we classified the heart rhythm after the shock as VF only if >10 rapid beats occurred.

**Statistics**

The data are presented as mean value±SD. Comparisons were performed with the use of individual Student's t tests.

**Results**

**Overview**

Hearts from eight sheep were used. After the experiments, the heart chambers were emptied of solution and the entire hearts were weighed (187±22 g). After DAM was added to the solution, conduction from the atria to the ventricle ceased in seven hearts. Therefore, we inserted an electrode inside the RA and paced the septum near the His bundle at various BCLs. In the heart in which AV conduction was normal, we either paced the septum (although we could not capture at large BCLs) or gave shocks during sinus rhythm. The depolarization sequence resulting from septal pacing is shown in Fig 2. Isochrone maps of depolarization from (A) posterior, (B) RV, and (C) anterior surfaces demonstrate rapid activation of the ventricles. The time of the FEA occurred 25 ms after septal stimulation at both the base of the posterior surface of the heart along the LAD (A) and along the borders of the RV including the RV apex (B). These recordings were not obtained simultaneously, so differences of <8 ms between panels may not be significant. The entire surface was depolarized within 75 ms of stimulation, and the apparent CV measured from the epicardium was extremely rapid (100 to 400 cm/s). The pattern of depolarization as well as the rapid depolarization of the ventricles suggest that the epicardial surface was activated from deeper layers.

**Effect of Shocks During Diastole**

The effect of shocks during diastole were studied by giving shocks with delay=600 ms. First we studied the effect of shock voltage on the activation of the ventricles as shown in Fig 3. Isochrone maps illustrate the depolarization sequence on the posterior surface for various strength shocks during ventricular diastole: A, 10 V; B, 20 V; C, 50 V; and D, 120 V. For the 10-V shock, the first epicardial activation occurred 33 ms after the shock as a breakthrough pattern. For shock voltages of 20 to 120 V, the activation patterns were similar with activation from base to apex, although the first epicardial activation occurred 25 ms after the shock for 20 V, 17 ms after the shock for 50 V, and during the shock for 120 V. For moderate shock voltages (20 to 120 V) the time for total epicardial activation was rapid (33 ms), indicating transmural propagation. E, Relation between latency and shock voltage. Latency decreased with increasing shock voltage for shocks given during diastole and was well fit by linear regression (P=.0002).

![Figure 2. Activation pattern during His bundle stimulation. Depolarization maps of activation after septal stimulation at cycle length of 1 second. Views from posterior (A), RV (B), and anterior surfaces (C). The first epicardial activation occurs 25 ms after septal stimulation at both the base of the posterior surface of the heart along the LAD (A) and along the borders of the RV including the RV apex (B). D, Electrogram demonstrating narrow QRS complexes indicative of rapid ventricular excitation. The T wave represents repolarization and the small undulations reflect AF.](image)

![Figure 3. Effect of shock voltage. Depolarization maps illustrating the activation pattern on the posterior surface for various strength shocks during ventricular diastole: A, 10 V; B, 20 V; C, 50 V; and D, 120 V. For the 10-V shock, the first epicardial activation occurred 33 ms after the shock as a breakthrough pattern. For shock voltages of 20 to 120 V, the activation patterns were similar with activation from base to apex, although the first epicardial activation occurred 25 ms after the shock for 20 V, 17 ms after the shock for 50 V, and during the shock for 120 V. For moderate shock voltages (20 to 120 V) the time for total epicardial activation was rapid (33 ms), indicating transmural propagation.](image)
Repolarization Patterns

The repolarization sequence on the surface of the ventricles was determined mainly by APD and not the depolarization sequence as shown by others for the guinea pig$^{19}$ and the dog.$^{20}$ The average APD from the anterior surface of the heart was 303±27 ms and the dispersion of repolarization defined as the spatial variance of APD$^{20}$ was 36 ms$^2$ (BCL=1000 ms). Examples of depolarization and repolarization sequences resulting from pacing from various sites are shown in Fig 5. Septal pacing at BCL=1000 ms (A), pacing from RV at BCL=1000 ms (B), and pacing from LV apex at BCL=1000 ms (C) resulted in varied depolarization patterns. For septal pacing (A) the FEA occurred at the base of the RV, whereas for epicardial pacing (B and C), the depolarization wave propagated uniformly away from the stimulus site. Repolarization was heterogeneous and was similar for all three stimulation protocols (bottom). The RV repolarized first with the base recovering earliest. The latest region to repolarize was low in the LV near the PDA. The difference in time between the earliest and latest sites to repolarize was 150 ms.

The depolarization sequence after a shock during late systole followed the previous repolarization pattern, as shown in Fig 6. Repolarization on the LV free wall resulting from pacing at the LV apex was homogeneous with a 100-ms difference between the first and last sites to repolarize (A). Recordings from three sites with short, medium, and long repolarization times are shown in B. The sequence of depolarization after a shock with delay=300 ms followed the previous repolarization sequence (C). The recordings from three pixels demonstrate that activation times after a shock were inversely related to the transmembrane potential preceding the shock and hence directly related to the repolarization time of the previous beat (D). Ventricular excitation resulting from the shock was obscured in the shock artifact in the EG, but the repolarization sequence in C can be observed shortly after the shock followed by the next paced beat (E).

Effect of the Timing of the Shock

When shocks were given shortly after the sensed R wave (delay=20 to 100 ms). VF was not induced, probably because the heart was in its absolute refractory state. VF was induced at delays=150 to 300 ms, during the vulnerable period of the ventricles. Shocks given at delays > 300 ms never induced VF. The data were binned in 50-ms increments centered at 0, 50, 100, and so on, and the percent induction of VF versus delay is plotted in Fig 7. At delays ranging from 230 to 300 ms the shocks sometimes elicited one to eight extra beats. When > 8 beats were induced, VF was sustained and defibrillation was required to stop the arrhythmia.

The time of the FEA was a function of the delay at a shock voltage of 120 V (the data were binned in 50-ms increments and plotted in Fig 8). Latency is the difference between datum and the dashed identity line (time of FEA=delay). At long delays (>300 ms), the time of the FEA occurred during the shock, therefore latency was equal to zero and the time of the FEA was equal to the delay. At shorter delays (150 to 300 ms) in which the shock elicited a response (either one or multiple beats including VF), FEA occurred after the shock with nonzero latency. The latency decreased from 131 ms at delay=150 ms to 10.4 ms at delay=300 ms. Recordings from a site in the LV are shown for a shock given early during recovery (delay=150 ms) with a long
Fig. 6. Depolarization pattern after a shock was determined by previous repolarization pattern. A, Repolarization pattern on LV free wall resulting from pacing at the LV apex. Repolarization was heterogeneous, with a 100-ms difference between the first sites and last sites to repolarize. B, Recordings from three sites numbered according to the repolarization times (1 through 3, as indicated in A and C). C, Isochrone map of the depolarization process after a shock with delay=300 ms. D, Effect of shock on three sites shown in B. The sequence of depolarization is such that the first sites that repolarized were the first to become depolarized after the shock. E, The electrogram illustrates that the shock was given just past the peak of the T wave while recovery was still occurring, although the shock did not induce VF.

Latency (latency=133 ms) and for a shock given late during recovery (delay=300 ms), in which the FEA occurs during the shock (latency=0 ms).

Induction of Ventricular Fibrillation
The sequence of depolarization after a shock that induced VF was complex. In general, the first beat after the shock followed the previous repolarization sequence, as shown in Fig. 6. Fig. 9 illustrates the repolarization sequence of the beat before the shock (1) as well as the depolarization sequence of the first (2) and second (3) beats after the shock (see the EG at the bottom for intervals used to construct repolarization and depolarization maps) from the posterior (A), RV (B), and anterior (C) surfaces of the heart for a shock (delay=240 ms) that induced VF. There was very little dispersion of repolarization on the posterior and anterior surfaces; however, RT
These pixel recordings were taken involved VF induction. When a shock with delay = 300 ms resulted in an FEA during the shock (latency = 133 ms), C, Recording from a site in the LV when the shock was given at delay = 150 ms, in which the time of the FEA occurred long after the shock (latency = 0 ms). Both of the episodes from which these recordings were taken involved VF induction. Therefore these points lie along the identity line indicated by the dashed line and their latency values were near zero. B, Recording from two consecutive episodes in which pacing the septum at BCL = 936 ms resulted in excitation of the ventricles 335 ms after the shock (X). The second beat after the shock first appeared on the epicardium of the anterior surface 225 ms after the shock (asterisk in Fig 9C3). There were regions of block on the anterior surface, but epicardial reentry was not observed in the two beats after the shock (2 and 3), as indicated by the quiescent interval between the last activation in the beat after the shock and first activation in the second beat after the shock (83 ms). These recordings were not obtained simultaneously, so care should be taken in compar-
Figure 9. Induction of VF. Repolarization (top) and depolarization (middle and bottom) sequences resulting from a 120-V shock with delay=240 ms on the A, posterior; B, RV; and C, anterior surfaces of the heart. There is very little dispersion of repolarization on posterior and anterior surfaces. Repolarization occurred first on the RV free wall. The first epicardial activation occurred on the anterior surface near the base 8.33 ms after the shock (asterisk in Fig 9C2). The second beat after the shock first appeared on the epicardium of the anterior surface 225 ms after the shock (asterisk in Fig 9C3). There were regions of block on the anterior surface, but epicardial reentry was not observed in the two beats after the shock (middle and bottom), as indicated by time interval between last activation in the beat after the shock and first activation in the second beat after the shock (83 ms). These recordings were not obtained simultaneously. The electrogram at the bottom indicates sinus rhythm before the shock and a narrow QRS complex after the shock before degeneration into VF.

Pacing the septum within the vulnerable period never induced VF but resulted in either a propagated response or no response. This finding suggests that (1) the ventricular beat after the shock is unlikely to induce VF by interacting with the repolarization process of a shock induced activation, and (2) the shocks given during the vulnerable period affected a large region of the ventricles that was fundamentally different than point stimulation.
Figure 10. Reentry induction. Repolarization (A) and depolarization maps (B through F) from the anterior surface for time intervals indicated at the bottom during an episode in which a shock with delay=250 ms induced VF. A, Repolarization map of the beat preceding the shock demonstrated heterogeneous recovery with early repolarization near the LAD and late repolarization in the RV and base of the LV. B, Depolarization sequence after pacing the septum at BCL=1000 ms. The first epicardial activation occurred at the base of the RV and rapidly completed depolarization of the anterior surface within 50 ms. C, Depolarization sequence of the first beat after the shock follows the repolarization sequence. FEA occurred at the apex of the LV 83 ms after the shock. D, Depolarization sequence of second beat after the shock was similar to the first beat with areas of slow conduction that appeared to be related to heterogeneous repolarization times. E, Depolarization sequence of third beat after the shock was similar to the first two beats, but a reentrant wave rotating clockwise (+) formed, resulting from conduction slowing in the previous two beats. F, A short time later, another reentrant wave formed at a region of high repolarization time gradient in the paced beat.
We found that the time of the FEA was related to delay such that at short delays there was a lag between the shock and the activation did not proceed on the epicardium as a planar proximity of the RA and CS coils to the ventricles. However, the patterns indicated transmural propagation (Fig 4).

Effects of Shocks on the Ventricle During Diastole
Shocks with voltages as low as 10 V excited the ventricles apparently through local activation near the base of the ventricles. This is not surprising, considering the close proximity of the RA and CS coils to the ventricles. However, the activation did not proceed on the epicardium as a planar wave, as might be expected, but as a breakthrough pattern after a delay indicating that the depolarization wave propagated from the endocardium (Fig 3A). For stronger shocks, however, a region of the epicardium was directly excited and the time for complete ventricular excitation was very rapid and the patterns indicated transmural propagation (Fig 4).

Effect of Timing of the Shock
We found that the time of the FEA was related to delay such that at short delays there was a lag between the shock and the FEA, whereas at long delays there was no lag, supporting previous results. What happens during the long latencies for shocks with short delays is not clear. Our data suggest that this long latency is not due to excitation and slow conduction velocity on the epicardium. Our data demonstrate that the shock-induced depolarization sequence was similar to the previous repolarization sequence (see Figs 6 and 10) when the shocks were given near the peak of the T wave, which supports the notion that tissue polarization occurs during the shock but cannot propagate because of surrounding refractory tissue, which when it becomes excitable allows propagation.

Induction of VF
It is well known that stimulating the ventricles during the vulnerable phase induces VF. We found that this vulnerable phase in our sheep hearts was 150 to 300 ms after the sensed R wave, which is slightly longer than the range found in dogs (110 to 200 ms) and rabbits (182 to 211 ms). It is not clear how VF is initiated by shocks in the vulnerable period; however, the elegant studies of Shibata et al suggest the critical point hypothesis. By pacing the ventricles and recording the sequence of activation after a shock during the vulnerable phase, they found that a pair of counterrotating waves could be formed at certain reproducible regions in the heart. However, the events after shocks given during atrial pacing, which presumably had more heterogenous activation and recovery sequences, were very complex and were not presented. Our data suggest that for the electrode configuration we used in the isolated sheep heart, the first few beats after a shock were focal, although they led to the initiation of reentrant waves as suggested by Moe et al. Our data demonstrate that the reentrant waves form as the result of waves propagating into regions of refractoriness. By analyzing the transmembrane potential at various sites (eg, see Fig 6D and Fig 10), we can speculate about the mechanism underlying the breakdown to ventricular fibrillation. The FEA appears in the region that is the most repolarized, and a wave propagates away from this region but encroaches on increasingly depolarized tissue. In a region of intermediate repolarization, the wave slows down and dV/dt decreases. This delay at intermediate repolarization regions allows the sites with long repolarization times to recover and when the wave front finally reaches these regions it propagates similar to near the FEA site. It is possible that these sites with intermediate repolarization times are at a potential near or above the sodium current threshold when the wave front reaches this region. The slow upstroke delays the subsequent repolarization in this region. Therefore the wave front from the second beat also reaches the region of intermediate repolarization before the sodium current recovers. This positive feedback may lead to conduction block in this region creating the conditions for reentry (see Fig 10, site 2). Although our data refute the idea that epicardial reentry was induced by the shock, we cannot rule out that the shock depolarized the endocardium resulting in transmural reentry. The mechanisms for the focal beats is unclear, although there is evidence that high-energy shocks can induce repetitive firing and frequently focal patterns occur after ventricular defibrillation shocks.

Limitations
Our studies were restricted to one electrode configuration and a single waveform, therefore the dependence of the results on these parameters remains unclear. The spatial distribution of APD and hence the repolarization sequence varied considerably in the hearts. This variability might have been real; APD distribution has not been well characterized on the entire heart surface in any species. On the other hand, APD

Discussion
Nonuniform repolarization occurs in the heart as reflected in the T-wave duration. However, the process of repolarization is not well characterized, in part because only recently have the techniques become available to record transmembrane potential from a large number of sites. In our studies the repolarization sequence was determined mainly by the APD and not the depolarization sequence (Fig 5), confirming earlier studies. The variance of APD in our studies was 36 ms, which is smaller than that reported for guinea pig studies. The maximum difference of repolarization times in our studies was ~150 ms, considerably longer than other studies, which might be explained by species differences or by the large recording surface and the large number of recording sites of our system.
gradients might have been due to localized ischemia. TTC staining identifies necrotic regions only and does not reflect transient ischemia. Extended ischemia (>5 minutes) seems unlikely because the first sites to repolarize were the first to depolarize after a shock, suggesting a direct relation between APD and refractoriness. We used the drug DAM to eliminate motion, which has effects on the heart including reducing APD. We only recorded from the epicardial surface, although excitation of the deeper layers may have been important. Recordings from various surfaces of the heart were not made concurrently, although identical protocols were accomplished; however, because of the 8-ms sampling interval, episodes may have been offset in time. The presence of fat on the heart interfered with the fluorescent recordings and decreased the quality of signal slightly along the LAD and dramatically at the AV groove.

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