Mechanism of Ventricular Defibrillation for Near-Defibrillation Threshold Shocks
A Whole-Heart Optical Mapping Study in Swine

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Background—To study the mechanism by which shocks succeed (SDF) or fail (FDF) to defibrillate, global cardiac activation and recovery and their relationship to defibrillation outcome were investigated for shock strengths with approximately equal SDF and FDF outcomes (DFT_50).

Methods and Results—In 6 isolated pig hearts, dual-camera video imaging was used to record optically from ~8000 sites on the anterior and posterior ventricular surfaces before and after 10 DFT_50 biphasic shocks. The interval between the shock and the last ventricular fibrillation activation preceding the shock (coupling interval, CI) and the time from shock onset to 90% repolarization of the immediate postshock action potential (RT_90) were determined at all sites. Of 60 shocks, 31 were SDF. The CI (59±6 vs 52±6 ms) and RT_90 (108±6 vs 88±8 ms) were significantly longer for SDF than FDF episodes. Spatial dispersions of CI (36±5 vs 34±3 ms) and RT_90 (40±6 vs 40±8 ms) were not significantly different for SDF versus FDF episodes. The first global activation cycle appeared focally on the left ventricular apical epicardium 78±32 ms after the shock.

Conclusions—For near-threshold shocks, defibrillation outcome correlates with the electrical state of the heart at the time of the shock and on RT. Global dispersion of RT was similar in both SDF and FDF episodes, suggesting that it is not crucial in determining defibrillation outcome after DFT_50 shocks. (Circulation. 2001;104:1313-1319.)

Key Words: mapping ■ defibrillation

Despite extensive investigation, defibrillation mechanisms continue to be debated.1–3 Whole-heart electrical mapping of defibrillation in dogs and pigs has shown that after shocks near the defibrillation threshold (DFT) in strength, the immediate postshock activation pattern is mainly focal and is similar for both successful (SDF) and failed (FDF) defibrillation episodes.4,5 Epicardial reentry is infrequently observed.6 The similarity of the first postshock activations suggests that the immediate myocardial responses to the shock alone may not determine defibrillation success but rather that the first several postshock cycles may influence shock outcome.5 Electrical mapping, however, cannot detect activation for up to tens of milliseconds after the shock and provides no direct measure of repolarization after the shock.5,7,8

Optical mapping does not have these limitations.9,10 Optical mapping studies in isolated rabbit hearts have reported that reentry caused by unidirectional propagation of activation immediately after the shock is responsible for FDF.3,10 SDF has been proposed to occur when a shock sufficiently prolongs and synchronizes repolarization, decreasing the dispersion of repolarization and thus preventing conduction block, which can lead to reentry and ventricular fibrillation (VF).9,11 These results, however, were obtained from a relatively small epicardial region with shocks well below the DFT.

The present study was designed to resolve these disparate electrical and optical mapping results by using optical mapping to study an experimental preparation similar to that used in electrical mapping studies. Specifically, we investigated how the cardiac state at the time of the shock and global postshock activation and recovery relate to shock outcome in isolated perfused pig hearts with shocks near the DFT in strength.

Methods

Experimental Preparation
Six pigs (20 to 25 kg) of either sex were anesthetized and maintained under physiological conditions as described previously.3 Heparin (500 U/kg IV) was injected, and 1 to 2 L of cold normal saline was infused via the jugular vein. Then, 1 L cold (~4°C) saline was poured into the pericardial cradle. After the aorta had been clamped, the heart was quickly removed, immersed in cold saline, mounted on a Langendorff-type apparatus, and perfused at a constant flow of 220 mL/min with 37°C modified Tyrode’s solution (in mmol/L: NaCl 123, KCl 4.5, CaCl₂ 1.8, MgCl₂ 0.98, NaHCO₃ 20, Na₂HPO₄ 1.01, and dextrose 11, plus bovine albumin 0.04 g/L, gassed with 95% O₂, 5% CO₂). The heart was defibrillated if it was in VF. An ECG was...
recorded by electrodes on the right (RV) and left (LV) ventricular epicardium, grounded to the aortic root.

A defibrillation catheter with 34-mm platinum-coated titanium coil electrodes (Guidant Corp) was inserted into the RV apex (Figure 1A). An electrode at the catheter tip delivered 60-Hz alternating current to induce VF. A titanium mesh electrode (2.5-cm diameter) was sutured to the right atrium (Figure 1A). Biphasic truncated exponential shocks (6/4 ms) were delivered to the RV coil (cathodal, first phase) and the right atrium mesh electrode (anodal, first phase) from a defibrillator (Ventritex HVS-02). Delivered voltage and current were recorded on a waveform analyzer (DATA 6100, Analogic Inc), from which total delivered energy was calculated.

Video Imaging
After an acclimation period of ≥15 minutes, a 20-mL bolus of the voltage-sensitive dye, di-4-ANEPPS (Molecular Probes) at 10.4 μmol/L, was injected into the aorta (with 2 to 3 later injections of 5 mL). The excitation-contraction uncoupler 2,3-butanedione monoxime (DAM, 20 mmol/L) was added to the perfusate to stop motion artifacts. Two high-speed charge-coupled device (CCD) digital video cameras (MiCam01 ICX082, Sci-Media Ltd) acquired images of 64×96 pixels at 250 frames per second with 14-bit resolution from the anterior and posterior surfaces of the heart (Figure 1B), as described elsewhere. Each pixel recorded from a 0.66×0.14-mm² area of heart surface. After filtering with a 5-point median temporal filter, the fluorescence signals were normalized such that the minimum and maximum values, and thus the action potential amplitudes (APAs), for all sites were identical. No spatial filtering was performed. The signal-to-noise ratio was 19±3.

Mapping of Defibrillation
Figure 1C illustrates a VF ECG recording after DAM was added. The tracing demonstrates an irregular VF morphology, suggesting that VF was not converted to a periodic rhythm by the DAM concentration used. VF was induced and the heart was continuously perfused for 10 seconds, after which defibrillation shocks were applied. The defibrillation shock strength that gave an approximately equal number of SDF and FDF episodes (DFT<sub>50</sub>) was determined as described previously. Ten DFT<sub>50</sub> shocks were delivered to each heart. Optical mapping began 0.5 second before each shock and ended 2.5 seconds after the shock. If the shock failed, a rescue shock (20 to 30 J) was delivered within 5 seconds. At least 2 minutes was allowed to elapse between VF episodes. An average of 28±5 shocks was delivered to each heart.

Data Analysis
Depolarization and repolarization times (RTs) were calculated at each recording site as the time at which the fluorescence signal crossed a threshold value, with temporal linear interpolation between frames. The threshold for depolarization was 50% of the first
postshock APA (Figure 2A), whereas various thresholds were used to compute RT, as noted. VF cycle length (VFCL) and VF action potential duration (APD) were calculated from each episode as the global spatial average of the last 5 activations preceding the shock.2 The 50% depolarization and repolarization thresholds were used to compute VF APD. The coupling interval (CI), ie, the time interval between 50% depolarization of the last VF action potential preceding the shock and the shock onset, was determined (Figure 2A). After the shock, complete repolarization was always achieved, and RTs were computed for threshold values of 50% (RT50), 75% (RT75), and 90% (RT90) repolarization for all sites.11 The total depolarization time (TDT),11 ie, the sum of CI and RT, was also determined.

For each defibrillation episode, we calculated the following for each parameter: (1) the global spatial mean and (2) the global spatial SD (ie, dispersion). The data in Figure 2B represent the parameter’s mean, and the error bars are its SD across all episodes. The global spatial SD of each parameter was computed from the values of all the pixels recorded from the heart surface (∼8000 sites). Thus, the data in Figure 2C represent the parameter’s dispersion, and the error bars are its SD across all episodes.

The first 5 postshock cycles were analyzed.3 Sinus beats were excluded in the analysis for SDF episodes. Because cycles 2 to 5 often did not reach 75% or 90% repolarization, a 50% threshold was used to compute RTs for these cycles. The intercycle interval (ICI), the interval between 2 successive cycles, was determined for depolarization and repolarization (ICI-R). Cycle 1 ICI was the postshock interval. The wavefront conduction time (WCT), the time it took activation to completely traverse the ventricles, and the time for repolarization of each cycle to completely traverse the ventricles (the wavetail conduction time, WCT-R) were determined. The ratio of WCT cycle[n] to ICI cycle[n+1] was called the overlapping index.13 An index >1 indicates an overlap of successive cycles. An index for the repolarization pattern, ie, the ratio of WCT-R cycle[n] to ICI-R cycle[n+1], was also determined.

SDF and FDF data were compared by 1-way ANOVA. When statistical significance was found, individual comparisons were performed with Fisher’s post hoc test. Values are shown as mean±SD. Differences are considered significant for a value of P<0.05.

Results

Thirty-one of the 60 shocks were SDF episodes. The DFT50 was 817±194 V. Mean heart weight was 164±16 g. Mean VFCL was 92±12 ms in SDF and 93±11 ms in FDF (P=NS). VF APD was 50±10 ms in SDF and 49±9 ms in FDF (P=NS).

Cardiac State at Shock Onset and Resulting Myocardial Response

CI (Figure 2B) was significantly longer for SDF (59±7 ms, 64% VFCL) than FDF (52±6 ms, 56% VFCL) episodes. Global spatial dispersion12 of CI (Figure 2C), however, was not different (36±5 versus 34±3 ms). Shocks prolonged the APD, because TDT50 was significantly longer for SDF (97±13 ms) and FDF (88±8 ms) for VF APD. TDT90 for SDF (165±22 ms) and FDF (139±11 ms) was also much longer than VFCL. RT50, RT75, and RT90 were all significantly longer for SDF than FDF episodes (Figure 2B). As a result, TDT50, TDT75, and TDT90 were also significantly longer for SDF than FDF episodes.

Because previous studies suggest that the small region in which the shock field is weakest and from which activation cycles arise after the shock most influences defibrillation outcome,5,13 CI and RT75 at 700 pixels (4.6 cm²) were determined in this region (LV apex) plus 2 others as control regions (RV apex overlying the shocking electrode and LV base). CIs from the LV apex (62±9 versus 52±9 ms), RV apex (60±12 versus 53±9 ms), and LV base (59±10 versus 52±10 ms) were all significantly longer for SDF than FDF episodes. RT75, however, was significantly different between SDF (60±16 ms) and FDF (50±7 ms) episodes only at the LV apex. RT75 at the RV apex (63±15 versus 58±6 ms) and LV base (59±7 versus 57±7 ms) was not different. There was no difference for the global dispersion of CI and RT75 between SDF and FDF in any of these regions.

Synchronous Repolarization and Shock Outcome

Although RT and TDT were longer for SDF than FDF episodes (Figure 2B), the global spatial dispersions of RT and TDT were not different (Figure 2C). Maps of CI and RT are shown in Figure 3, illustrating the distribution and the absolute values of these 2 parameters across the whole ventricular epicardium from the SDF and FDF episodes. Typical plots and optical recordings from FDF and SDF episodes in Figure 4 illustrate the relationship of CI, RT75, and TDT75. RT75 from either defibrillation outcome did not vary with CI, suggesting that shocks synchronized RT in both FDF and SDF episodes. The broad vertical width of RT75 in both FDF and SDF episodes, however, demonstrates that RT75 was not constant for a given CI (Figure 4). TDT75 was directly related to CI for both FDF and SDF episodes (r=0.96 for FDF and 0.93 for SDF episodes), suggesting a positive, monotonic dependence of TDT on CI, because RT was not a strong function of CI.

First Postshock Cycle

After the shock, complete repolarization always occurred (Figure 4, B and D). First postshock ectopic activation occurred 78±32 ms after shock onset and propagated across the entire ventricular epicardium. This first postshock activation always arose focally at the apex and propagated away in all directions in an organized pattern and was similar for both FDF and SDF episodes (Figure 5). Cycle 1 ICIs (73±12
versus 84±46 ms) and WCTs (132±20 versus 127±19 ms) were not different for FDF and SDF episodes.

Repolarization began at the apex and ended at the base for both FDF and SDF episodes, like the activation pattern (Figure 6). Although cycle 1 ICI-R was not different for FDF (130±19 ms) and SDF (159±65 ms) episodes, cycle 1 WCT-R was significantly longer for FDF (178±22 ms) than SDF (163±17 ms) episodes.

**Subsequent Postshock Cycles**

The first 5 postshock cycles for both SDF and FDF episodes all arose focally at the apex and propagated toward the base. No epicardial reentry was observed during any cycle in any shock episode. Unlike cycle 1, ICIs of cycles 2, 3, 4, and 5 were significantly longer for SDF than FDF episodes (Figure 7A). Like cycle 1 ICI, cycle 1 WCT was not different for FDF and SDF episodes (Figure 7B). Starting at cycle 2, however, WCTs were progressively longer in FDF than in SDF episodes. The overlapping index was greater in FDF than in SDF episodes for all cycles (Figure 7C).

Like the activation ICI, the repolarization ICI (ICI-R) was not different between SDF and FDF episodes for cycle 1 (Figure 8A). ICI-Rs for cycles 2, 3, 4, and 5 were significantly longer for SDF than FDF episodes. WCT-R for cycle 1 was significantly longer in FDF than in SDF episodes (Figure 8B), unlike the WCT of cycle 1. Starting at cycle 2, WCT-Rs were progressively longer for FDF than SDF episodes, similar to the WCT for activation. Also similar to activation, the overlapping index for repolarization was significantly greater for FDF than SDF for all cycles (Figure 8C).

**Discussion**

The disparities of the results obtained from electrical and optical mapping studies could be partly due to differences in their experimental setup and design.14 To resolve these
disparities, this study used optical mapping to study defibrillation under conditions similar to those in electrical mapping studies. In addition to testing the hypothesis that optical and electrical mapping studies should give similar findings under the same conditions, this optical mapping study extends the findings from electrical mapping studies because it has (1) no blackout period during the shock, (2) finer spatial resolution, and (3) the ability to record repolarization.

The major findings in this study are as follows: (1) The CI in SDF is greater than in FDF. (2) Shocks prolong RT in both SDF and FDF. RT in SDF, however, is longer than in FDF episodes. (3) The global spatial dispersion of RT is not different for SDF and FDF episodes. (4) Activation during cycle 1 is similar for SDF and FDF episodes; after a 78±32-ms postshock interval, activation appears focally at the LV apex and conducts centrifugally to the base. Epicardial reentry did not occur. (5) Repolarization during postshock cycle 1 is different, with SDF shorter than FDF episodes. (6) For both activation and repolarization of postshock cycles 2 to 5, ICI was progressively longer and WCT was shorter for SDF than for FDF episodes.

State of the Heart at Shock Onset and Defibrillation Outcome

Although activation during VF is complex, it exhibits a level of spatial and temporal organization.15 Our results demonstrate that the cardiac state at the time of the shock is different for SDF and FDF shocks (Figure 2B). The mean CI in SDF is longer than in FDF episodes, suggesting that the phase of the VF action potential in all or part of the ventricles at the time of the shock is important in determining shock outcome.16 RT75 at the LV apex, ie, the weak potential gradient area, was also significantly longer for SDF than FDF episodes. This result suggests that not only the global state of the heart at the time of the shock, but also the local myocardial responses at the LV apex where the postshock cycles arose, are crucial in determining the shock outcome.

Postshock Repolarization and Defibrillation Outcome

Like the CI, RT was longer after SDF than FDF shocks (Figure 2). Previous studies proposed that SDF shocks not only prolong but also synchronize RT, decreasing the dispersion of repolarization.11,17,18 Dillon11 proposed the constant-RT hypothesis, based on his observation in rabbit hearts that SDF but not FDF shocks caused a constant RT, regardless of when during the VF action potential the shock was delivered. In the present study, however, synchronization of RT was observed in both SDF and FDF episodes, because RT did not change with CI (Figure 4). The global spatial dispersion of RT was not different either between SDF and
FDF episodes (Figure 2C). According to the constant-RT hypothesis, SDF should have a very small dispersion of RT (2 to 5 ms in the rabbit heart), and FDF should have a wider dispersion. The similar RT plots with a wide band in both SDF (33 ms, Figure 4C) and FDF (25 ms, Figure 4A) suggest that constant RT is not necessary for SDF. These findings suggest that for shocks near the DFT, RT prolongation is more important than postshock constant RT in determining shock outcome.

**Postshock Activation Cycles and Defibrillation Outcome**

Although CI and RT were longer for SDF than for FDF episodes, the first global postshock activation pattern was not different between the 2 outcomes (Figure 7). Consistent with

**Figure 6.** Repolarization patterns of postshock cycle 1 after same FDF (A) and SDF (B) episodes as shown in Figure 5. Recording sites at which repolarization reached 50% APA at any time during each 20-ms interval are black. A, Repolarization began 166 ms after shock and traveled from apex toward base like activation pattern in Figure 5A. It took 204 ms to complete repolarization. Repolarization of postshock cycle 2 (arrow) appeared at apex before cycle 1 had completed repolarization of base. B, Repolarization began 159 ms after shock and had a pattern similar to that in A but was completed more quickly (176 ms). Earliest repolarization of cycle 2 also began at apex (arrow) before repolarization of cycle 1 was complete.

**Figure 7.** ICI (A), WCT (B), and overlapping cycle index (C) of first 5 postshock activation cycles. An overlapping index >1 (dashed line) indicates that activations from both cycles are present on epicardium simultaneously. *P<0.05 vs FDF for that cycle.

**Figure 8.** ICI-R (A), WCT-R (B), and overlapping cycle index (C) of postshock repolarization pattern of first 5 cycles. An overlapping index >1 (dashed line) indicates that repolarizations from both cycles are present on epicardium simultaneously. *P<0.05 vs FDF for that cycle.
in vivo porcine electrical mapping studies using the same shocking electrode configuration, activation of the first postshock cycle arose focally at the LV apex after a postshock interval (65±10 ms in an electrical mapping study, P=NS) and propagated toward the base in both SDF and FDF episodes (Figure 5). Epicardial reentry was never observed during the first postshock cycle, unlike in optical mapping studies using rabbit hearts. These differences could be due to differences in species, electrodes, and shock strengths. Although all shocks in our study were near the DFT, in the rabbit studies most shocks were much weaker.

We found that repolarization of the first cycle, which could not be observed in electrical mapping studies, was different between the 2 outcomes. Although repolarization began at the apex and ended at the base in all episodes and the cycle 1 ICI-R was not different for the 2 outcomes, the WCT-R was longer for FDF than SDF episodes (Figure 8). Because the origin of successive postshock cycles was from the same region as the first cycle, the slow repolarization of cycle 1 combined with the short ICI of FDF episodes could have caused the slow propagation and repolarization of successive cycles (Figures 7 and 8, A and B), leading to block, reentry, and VF after cycle 5.

Limitations
Because only the epicardial surface was recorded, intramural or endocardial reentry could have been missed. The focal origin of postshock activation could represent epicardial breakthrough of reentrant activation. Because of the frame rate of our camera and the defibrillation waveform duration, we were not able to determine the pattern of the change in transmembrane potential caused by the shocks. Although there are no data regarding these patterns in large hearts, results from rabbit hearts and computer simulations suggest that the medium surrounding the heart plays an important role and that biphasic waveforms may act to homogenize shock-induced polarization. We also did not attempt to quantify the small, locally propagating activation that has been reported to occur quickly after the shock.

We used DAM to stop cardiac motion, which has been shown to affect electrical activity. Because our aim was to compare activation and repolarization after 2 defibrillation outcomes, the effect of DAM on the interpretation of the results was minimized, because we compared SDF and FDF under the same conditions. The pattern of postshock activation from this study is consistent with electrical mapping studies using pig hearts without DAM. Also, comparison of our results with normal and diseased human hearts must be made with caution because of the differences in species, application of DAM, and absence of intrinsic neurological innervation.

Conclusions
This optical mapping study in isolated pig hearts confirmed most of the results of electrical mapping studies in vivo pig hearts for DFT50 shocks. In addition, optical mapping revealed that defibrillation outcome depends on CI and RT but not the dispersion of the repolarization created by the shock. Although CI and RT were longer in SDF than FDF episodes, activation of the first postshock cycle was similar. The repolarization pattern of the first postshock cycle may influence shock outcome.

Acknowledgments
This study was supported in part by National Institutes of Health research grants HL-63267 and HL-42760 and an award from the American Heart Association, Southeast Affiliate (0060295B).

References
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Circulation. 2001;104:1313-1319
doi: 10.1161/hc3601.094295

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
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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