Influence of Postshock Epicardial Activation Patterns on Initiation of Ventricular Fibrillation by Upper Limit of Vulnerability Shocks

Nipon Chattipakorn, MD, PhD; Jack M. Rogers, PhD; Raymond E. Ideker, MD, PhD

Background—Shocks of identical strength and timing sometimes induce ventricular fibrillation (VFI) and other times do not (NoVFI). To investigate this probabilistic behavior, a shock strength near the upper limit of vulnerability, ULV, was delivered to yield equal numbers of VFI and NoVFI episodes.

Methods and Results—In 6 pigs, a 504-electrode sock was pulled over the ventricles. ULV was determined by scanning the T wave. S1 pacing was from the right ventricular apex. Ten S2 shocks of approximate ULV strength were delivered at the same S1-S2 coupling interval. Intercycle interval (ICI) and wave front conduction time (WCT) were determined for the first 5 postshock cycles. ICI and the WCT of cycle 1 were not different for VFI versus NoVFI episodes (P=0.3). Beginning at cycle 2, ICI was shorter and WCT was longer for VFI than NoVFI episodes (P<0.05).

Conclusions—The first cycle after shocks of the same strength (ULV) delivered at the same time has the same activation pattern regardless of shock outcome. During successive cycles, however, a progressive decrease in ICI and increase in WCT occur during VFI but not NoVFI episodes. These findings suggest shock outcome is (1) deterministic but exquisitely sensitive to differences in electrophysiological state at the time of the shock that are too small to detect or (2) probabilistic and not determined until after the first postshock cycle. (Circulation. 2000;101:1329-1336.)

Key Words: electrophysiology n fibrillation n shock

A strong stimulus during the vulnerable period can induce repetitive responses that either halt without inducing ventricular fibrillation (VF) or degenerate into VF. Most proposed mechanisms of VF induction based on this finding, such as the nonuniform dispersion of refractoriness hypothesis, imply that activation immediately after the shock in a successful VF induction (VFI) differs from that in a failed VF induction (NoVFI).

Previous studies that used a range of shock strengths and timings showed that the interval between the shock and the first global postshock activation is shorter for VFI than for NoVFI shocks. However, comparison of VFI and NoVFI episodes after shocks of the same strength has not been reported. In this study, we determined activation patterns after shocks of identical strength and timing. A shock strength near the upper limit of vulnerability that induced VF in 50% of the trials (ULV) was used. We tested the hypothesis that the activation pattern immediately after VFI shocks differed from that after NoVFI shocks.

Results

Thirty of the 60 shocks in the 6 pigs were VFI episodes. One VFI episode was excluded because the last S1 stimulus did not capture. A shock at ULV produced a shock voltage of 498±112 V. The mean coupling interval (CI) at which VF was induced with ULV shocks was used as the S1-ULV CI (sCI); the sCI was 214±14 ms. To determine ULV, 15±11 shocks were required. The diastolic pacing threshold (DPT) was 0.2±0.1 mA. Heart weight was 154±45 g. For each animal, delivered shock voltage for the 10 ULV shocks was nearly constant (%SD of 0.1 to 0.3). Repeatability of the shock potential distribution at the 504 electrodes was measured in 1 pig. The mean correlation coefficient of the potentials was 0.995±0.004 for all 10 shocks.

The preshock interval and wave front conduction time (WCT) of the last paced cycle before the shock was not different between VFI and NoVFI episodes (Table 1). The similarity of the last paced cycle before the shock (Table 2) was not different, which suggests that the activation sequence of the last paced cycle was constant for all 10 shock episodes.

Cycle 1 Site of Earliest Activation

Cycle 1 sites of earliest activation (SEAs) were always at the anterolateral left ventricle (LV). While the cycle 1 SEA varied slightly between animals, it was highly repeatable for each animal (Table 3), showing that the first postshock cycle varied in the same epicardial region regardless of shock outcome.
Maximum first derivative (dV/dt) of activation at the cycle 1 SEA was not different for VFI and NoVFI episodes (Table 3). Mean dV/dt at the SEA of cycles 2 to 5 was less negative than that of cycle 1 for VFI episodes \((P, 0.01)\). However, no dV/dt differences were found among the first 5 postshock cycles in NoVFI episodes. For VFI episodes, SEA repeatability for cycles 2 to 5 (Table 3) was slightly lower than for cycle 1 because the SEA of cycles 2 to 5 moved a short distance (2 \pm 3 electrodes) away from the cycle 1 region of earliest activation (REA). However, the SEA of cycles 2 to 5 in NoVFI episodes moved a much greater distance away from the cycle 1 REA, 9 \pm 4 electrodes \((P, 0.002) vs VFI episodes\).

### Table 1. Preshock Interval and WCT of Last Paced Cycle

<table>
<thead>
<tr>
<th></th>
<th>VFI</th>
<th>NoVFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preshock interval, ms</td>
<td>203 \pm 14</td>
<td>203 \pm 13</td>
</tr>
<tr>
<td>WCT, ms</td>
<td>60 \pm 6</td>
<td>59 \pm 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Correlation of Potential</th>
<th>Temporal Lag, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFI-VFI</td>
<td>0.9998 \pm 0.0002</td>
<td>1 \pm 1.5</td>
</tr>
<tr>
<td>VFI-NoVFI</td>
<td>0.9998 \pm 0.0006</td>
<td>1 \pm 1.5</td>
</tr>
<tr>
<td>NoVFI-NoVFI</td>
<td>0.9997 \pm 0.0009</td>
<td>1 \pm 1</td>
</tr>
</tbody>
</table>

### Table 2. Mean Correlation and Temporal Lag of Last Paced Cycle

### Table 3. Repeatability of SEA and dV/dt

<table>
<thead>
<tr>
<th>Postshock Cycle</th>
<th>SEA Repeatability, %</th>
<th>dV/dt, V/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFI</td>
<td>NoVFI</td>
<td>VFI</td>
</tr>
<tr>
<td>1</td>
<td>93 \pm 10</td>
<td>97 \pm 8</td>
</tr>
<tr>
<td>2</td>
<td>60 \pm 33</td>
<td>50 \pm 50</td>
</tr>
<tr>
<td>3</td>
<td>44 \pm 29</td>
<td>0 \pm 0</td>
</tr>
<tr>
<td>4</td>
<td>33 \pm 29</td>
<td>0 \pm 0</td>
</tr>
<tr>
<td>5</td>
<td>16 \pm 24</td>
<td>0</td>
</tr>
</tbody>
</table>

*\(P < 0.01\) vs cycles 2 through 4 in VFI episodes.

### Figure 1.
Examples from same animal of postshock cycle 1 for VFI (A) and NoVFI episodes (B) and of paced cycle (C). Electrode sites at which dV/dt was \(\geq -0.5\) V/s at any time during a 10-ms interval are black. Numbers above frames indicate start of each interval in milliseconds relative to start of shock. Sock orientation is shown in Figure 7D. Arrows indicate SEA for each cycle. A, Cycle 1 arose at anteroapical LV, propagated toward anterobasal LV, and blocked over RV apex. B, Cycle 1 arose in same region as in A and propagated similarly. C, Activation initiated by pacing from anterobasal epicardial LV propagated without slowing across apex.
Cycle 2 from this NoVFI episode (Figure 2, B1) followed a pathway similar to the VFI cycle 2 but began later and conducted faster. Overlapping cycles were absent. Cycles 3 (B2) and 4 (B3) arose after long delays from different SEAs and had fast WCTs (73 and 38 ms, respectively). Cycle 4 was sinus and not analyzed.

**Postshock Intercycle Intervals**

The mean intercycle interval (ICI) (Figure 4A) of cycle 1 did not differ between VFI (51±23 ms) and NoVFI episodes (n=24, 68±78 ms). The SD of NoVFI episodes was high because of 1 episode with an extremely long postshock interval (461.5 ms). This episode had its SEA near the posterobasal LV, whereas the SEAs from other episodes in this animal were at the anteroapical LV. If this NoVFI episode is excluded, the mean postshock interval for NoVFI episodes becomes 54±23 ms (P=0.6 vs VFI). ICIs for VFI episodes were significantly shorter than for NoVFI episodes for cycle 2 (138±38 vs 387±312 ms) and cycle 3 (132±31 vs 389±193 ms) (n=12 and 10, respectively). For cycle 4, the mean ICI for VFI (126±40 ms) was shorter than for NoVFI (484±182 ms) episodes; however, the difference was not significant, probably because there were only 5 NoVFI episodes with a fourth ectopic cycle. ICIs of cycle 5 were not compared because only 1 NoVFI episode had a cycle 5 (537 ms). ICIs of cycle 5 for VFI episodes were 128±41 ms.

**Postshock WCTs**

The WCT (Figure 4B) of cycle 1 did not differ between VFI (116±19 ms) and NoVFI episodes (113±16 ms). The mean WCTs of cycles 2 (172±51 vs 99±44 ms), 3 (203±51 vs 83±18 ms), and 4 (197±55 vs 59±25 ms) were significantly longer for VFI than for NoVFI episodes (P<0.01). WCT of the single cycle 5 for NoVFI episodes was 58 ms. WCT of cycle 5 for VFI episodes was 210±53 ms.

In all VFI episodes, overlap occurred during cycles 2 to 3, 3 to 4, and 4 to 5 (overlapping index >1) but not cycles 1 to 2 (overlapping index <1) (Figure 4C). In contrast, there was no overlap among the first 5 ectopic cycles in any NoVFI episode.

**Correlation of 504 Electrograms of Cycle 1**

The similarity function, $s_p$, and temporal lag, $\tau_{mw}$, were compared for all possible combinations of first cycles in each animal and divided into 3 groups: VFI versus VFI, VFI versus NoVFI, and NoVFI versus NoVFI episodes (Table 4). There were no differences in any group for either variable. The very
Figure 3. Selected electrograms from episodes shown in Figure 1. A, Polar map with numbers 1 through 5 representing sites where 5 electrograms shown in B through D were recorded. Arrows represent direction of propagation of activation. B, Electrograms from NoVFI episode. Multiple vertical lines are shock artifact. Activation was earliest in electrogram 1 and latest in electrogram 5. Second deflection in electrogram 1 was an activation in cycle 2. C, Electrograms from VFI episode. Second deflection in electrogram 1 was activation during cycle 2. D, Electrograms from B (dotted) and C (solid) superimposed.
high similarity and short temporal lag among different episodes indicate that first postshock cycles were nearly identical whether or not VF was initiated.

**Cycle 2 in NoVFI Episodes**

In NoVFI episodes, cycle 2 could be divided into 2 distinct subgroups. Subgroup 1 \( (n=7) \) had a short ICI, long WCT, and same REA as cycle 1. Subgroup 2 \( (n=6) \) had a long ICI, short WCT, and different REA than cycle 1.

ICIs in subgroup 1 were all \(<200\) ms \((142\pm27\) ms\) but were all \(>400\) ms \((672\pm228\) ms\) in subgroup 2 \((P<0.002)\). Although the cycle 2 ICI of subgroup 1 was not different from that in the VFI episodes, in subgroup 2 it was significantly longer than in the VFI episodes \((P<0.002)\). Subgroup 1 all had WCTs \(>100\) ms \((135\pm21\) ms\), whereas subgroup 2 all had WCTs \(<80\) ms \((56\pm12\) ms, \(P<0.01)\). WCTs of both subgroups were significantly shorter than WCTs of cycle 2 in VFI episodes \((P<0.004)\).

Cycle 2 SEA repeatability in subgroup 1 \((63\pm48\%\) was different \((P<0.04)\) from subgroup 2 \((0\pm0\%\) in NoVFI episodes. Cycle 2 SEA repeatability in VFI episodes \((60\pm33\%\) was different from that of subgroup 2 \((P<0.007)\) but not subgroup 1. Thus, cycle 2 SEAs in the No-VFI subgroup with longer ICIs (subgroup 2) moved to a different site, whereas in the NoVFI group with shorter ICIs (subgroup 1), as well as in VFI episodes, they mostly remained in the REA of cycle 1. The mean dV/dt for cycle 2 in VFI episodes also differed from that of subgroup 2 \((-3.2\pm1.7\) V/s\) but not of subgroup 1 \((-2.2\pm0.6\) V/s\) in the NoVFI episodes.

Thus, episodes could be distinctly divided into 3 groups: (1) VFI, (2) NoVFI subgroup 1, and (3) NoVFI subgroup 2. The propagation patterns (Figure 5) as well as electrograms (Figure 6) of cycle 1 from these 3 groups were nearly identical. Cycle 2 for groups 1 and 2 were also similar but not quite identical (Figure 5). Group 3 had a different REA and shorter WCT than did groups 1 and 2.
Discussion

**Similarity of First Postshock Cycle Regardless of Shock Outcome**

Our major finding is that the first cycle after a ULV \( V \) shock that induces \( V \) cannot be distinguished from that after a shock of identical strength and timing that does not induce \( V \). This finding was apparent in the activation sequence animations and in the similarity of the following first-cycle variables: (1) SEA repeatability, (2) postshock interval, (3) WCT, (4) \( dV/dt \) at the SEA, (5) similarity function, and (6) temporal lag.

Most studies reporting differences of activation sequences and dispersion of refractoriness between \( V \) and \( N \) episodes used multiple shock strengths and coupling intervals. \(^{6,7}\) Those studies found that \( N \) correlated with a lower dispersion of refractoriness immediately after the shock, whereas \( V \) correlated with a greater dispersion of refractoriness. However, in those studies the shock strengths of \( N \) episodes were higher than those of \( V \) episodes. Thus, absence of \( V \) induction may not have been secondary to a lower dispersion of refractoriness; rather, both lack of \( V \) induction and a lower dispersion of refractoriness could have been

---

**Figure 5.** Examples from same animal of first 2 cycles in \( V \) (A), \( N \) with short ICI (B), and \( N \) with long ICI (C) episodes. A1, B1, and C1: Cycle 1. SEAs (arrows) were all in same region and started 45, 48, and 49 ms after shock, respectively. Activation patterns are all similar. WCTs in A1, B1, and C1 were 122, 120, and 116 ms, respectively. A2, B2, and C2: Cycle 2. ICI in C2 was longer (454 ms) than in A2 (132 ms) and B2 (146 ms), whereas WCT in C2 (77 ms) was shorter than in A2 (154.5 ms) and B2 (118 ms). SEAs in A2 and B2 but not C2 were in same region as cycle 1. Overlapping cycle was present only for \( V \) episode (A2, cycle 3 begins at 297 ms).
secondary to higher shock strength. To evaluate this possibility, we kept shock strength and timing constant. Our results suggest that when shock strength and timing are constant, differences in the dispersion of refractoriness are not large enough to cause measurable differences in postshock activation sequences and potentials. However, differences may exist immediately after the shock that are too small to be detected. These very small differences, according to the Chaos theory, could cause prominent differences after several cycles.

Association of Overlapping Cycles With VFI
Although differences between VFI and NoVFI episodes were first seen at cycle 2, a prominent distinction was not universally seen until cycle 3. This is because cycle 2 in 1 NoVFI subgroup behaved similarly to cycle 2 in the VFI episodes. However, no overlapping cycles were present in either No-VFI subgroup, whereas they were always present in the VFI group. Overlapping cycles may not be the direct cause of VF induction but may be a marker for short ICIs and long WCTs that are responsible for unstable reentry and VF induction. However, these results imply that at least 3 ectopic cycles with overlap by the third cycle may be required to initiate VF. If so, a method to halt the initiation of ectopic cycles in the REA could prevent VF even if it is applied as late as the third postshock cycle. Recent defibrillation and VF induction studies support this hypothesis.

Implications for Mechanism of VF Induction
It has been proposed that VF occurs by 2 mechanisms, an initiating mechanism that may involve ectopic unifocal impulses and a maintaining mechanism that involves reentry. Our results are consistent with reentry as a consequence of the initial accelerating, overlapping cycles observed in the VFI episodes. The rapid activation rate that led to the overlap of wave fronts also probably caused action potential duration to shorten and dV/dt to slow in the second to fifth cycles, possibly leading to unidirectional block, wave front fractionation, and reentry. In addition, the degeneration from the first postshock activation to VF could also be due to the nonuniform recovery of excitability of cardiac muscle after the premature stimulation of the first few postshock cycles.

Study Limitations
Although we did not observe epicardial reentry, intramural reentry cannot be ruled out because we did not record transmurally. The similarity of the first postshock cycle was based on epicardial recordings; therefore differences may have existed intramurally. The first postshock cycles could have differed in ways too small to be detected in our maps. Epicardial reentry may have been missed because it was too small to be detected by electrodes 4 mm apart or because part of the pathway consisted of activations that were so slow and small that the recordings did not meet our activation criterion.

Conclusions
The first postshock cycle has the same epicardial activation sequence regardless of shock outcome (VFI vs NoVFI), which suggests that large global differences in conduction or tissue refractoriness caused by the shock are not always the primary factors determining VF induction. Unidirectionally propagating epicardial activation followed by several ectopic, radially spreading impulses precedes VF. A progressive decrease in ICI and increase in WCT, resulting in overlapping cycles, heralds VF initiation.

Acknowledgments
This study was supported in part by National Institutes of Health research grants HL-28429 and HL-42760.

References
Influence of Postshock Epicardial Activation Patterns on Initiation of Ventricular Fibrillation by Upper Limit of Vulnerability Shocks
Nipon Chattipakorn, Jack M. Rogers and Raymond E. Ideker

Circulation. 2000;101:1329-1336
doi: 10.1161/01.CIR.101.11.1329

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 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:
http://circ.ahajournals.org/content/101/11/1329

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/