Pacing After Shocks Stronger Than the Upper Limit of Vulnerability
Impact on Fibrillation Induction

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Background—After upper-limit-of-vulnerability (ULV) shocks of the same strength and coupling interval (CI) during the T wave, (1) the epicardial activation pattern (EAP) for the first postshock cycle is indistinguishable between shocks that do (VF) and do not (NoVF) induce ventricular fibrillation (VF) and (2) $\geq 3$ cycles in rapid succession always occur during VF but not during NoVF episodes. To study the role of these rapid cycles, rapid pacing was performed after a shock stronger than the ULV that by itself did not induce rapid cycles and VF.

Methods and Results—A 504-electrode sock was sutured to the heart in 6 pigs to map EAPs. The S2 shock strength and S1-S2 CI at the ULV were determined by T-wave scanning with an up/down protocol. Ten shocks 50 to 100 V above the ULV (aULV) were delivered at the same S1-S2 CI to confirm that VF was not induced. Then, the postshock interval after aULV shocks was scanned with an S3 pacing stimulus from the LV apex until the shortest S2-S3 CI that captured was reached. This was repeated for S4, S5, etc., until VF was induced. To induce VF, 3 pacing stimuli (S3-S5) with progressively shorter CIs were required; S3 or S3, S4 never induced VF. After cycle S5, which induced VF, 2 EAP types occurred: focal (74%) and reentrant (26%).

Conclusions—At least 3 cycles with short CIs are necessary for VF induction after aULV shocks. Cycles S3-S4 may create the substrate for cycle S5 to initiate VF. (Circulation. 2000;101:1337-1343.)

Key Words: mapping • fibrillation • shock

Ventricular fibrillation (VF) induction is probabilistic and dependent on shock strength and timing.1,2 For shock strengths near the upper limit of vulnerability (ULV), the global dispersion of refractoriness immediately after the shock and the characteristics of the first postshock cycle may not be sole determinants of VF induction.3 Instead, the number and rapidity of activation cycles soon after the shock appear to determine whether secondary reentry occurs, leading to VF.3 These findings suggest that 3 ectopic, repetitive, overlapping cycles after near-ULV strength shocks are required to initiate VF.3

We tested the following hypotheses dealing with near-ULV shocks during the vulnerable period: (1) The key determinant of VF induction is the number and rapidity of postshock cycles, not the characteristics of the first postshock cycle. (2) At least 3 postshock cycles with overlapping activation fronts are necessary to initiate VF.3

Results
The shock above the ULV (aULV) was 550±58 V. The mean coupling interval (CI) for S1-aULV shocks was 224±13 ms. Diastolic pacing thresholds (DPT) at the endocardial right ventricular (RV) apex and the anteroapical left ventricle (LV) were 0.2±0.0 and 0.2±0.1 mA, respectively. Heart weight was 163±8 g. Of the 60 VF episodes induced by postshock pacing, 58 were analyzed. The other 2 episodes were not included because the last S1 stimulus did not capture.

Postshock Activations
The aULV shock alone never induced VF. Intercycle intervals (ICIs) of the first 4 ectopic cycles (Figure 1A) were very long (517±126, 319±28, 518±162, and 474 ms, respectively). There was only 1 fourth and no fifth ectopic cycle in any NoVF episode. Wavefront conduction times (WCTs) (Figure 1B) were relatively short and constant (56±16, 61±2, 66±5, and 63 ms for cycles 1 through 4, respectively). The overlapping index was always <1 (Figure 1C), indicating no overlap in any NoVF episode.

During post-aULV pacing, VF was never induced by single (S3) or double (S3-S4) stimuli, even at the shortest coupling interval (CI) that captured (107±32 and 130±11 ms for S2-S3 and S3-S4, respectively). When the third pacing stimulus (S5) was added, it always induced VF for the
shortest CI that captured (118±12 ms) and for up to 20 ms longer than the shortest CI that captured. For this 20-ms CI range, new activations after the S5 cycle always appeared spontaneously even though no further stimulus was delivered.

For an S4-S5 CI that was >20 ms longer than the shortest CI that captured, VF was never induced and no or only 1 ectopic cycle appeared before sinus rhythm resumed.

For all VF episodes, ICIs for the first 5 postshock activations were 138±31, 137±13, 111±19, 141±25, and 132±25 ms (Figure 1A). The first 3 cycles were paced (S3-S5), and the last 2 were spontaneous. ICIs of the S3-S5 cycles for VF episodes were shorter than for the first 3 spontaneous cycles for NoVF episodes (P<0.01). Because only 1 fourth and no fifth ectopic cycles appeared during NoVF episodes, these cycles were not compared. WCTs for the first 5 cycles for VF episodes were 89±10, 147±13, 191±31, 175±35, and 161±40 ms, respectively (Figure 1B). The WCT of the S3-S5 cycles for VF episodes was longer than for NoVF episodes (P<0.01). Although there was no overlap between cycles 1 and 2 for VF episodes (Figure 1C), overlap cycles occurred starting at the transition from cycle 2 to 3 (index >1). Because 3 postshock pacing stimuli always induced VF, no S6 or S7 stimuli were given.

In VF induced by sub-ULV shocks (Figure 2), the first 5 spontaneous postshock cycles showed activation patterns similar to those of the post-aULV pacing-induced cycles. ICIs of cycles 2 (150±15 ms), 3 (124±28 ms), 4 (130±13 ms), and 5 (122±10 ms) were not different from those of the post-aULV pacing VF inductions. However, the ICI of cycle 1 (66±15 ms) was shorter for sub-ULV than for post-aULV pacing VF inductions (P<0.001, Figure 1A). WCTs of the first 5 cycles (104±16, 138±22, 180±18, 182±22, and 171±9 ms, respectively) after sub-ULV VF inductions were not different from those in the post-aULV pacing VF inductions. Overlapping cycles were always found during the transition from cycles 2 to 5 (Figure 1C). However, there was no overlap during the transition from cycle 1 to 2 in any episode. Maps of 1 VF episode induced by a sub-ULV shock in 1 animal are shown in Figure 2, demonstrating that the site of 1 VF episode induced by a sub-ULV shock (S2). Each frame shows, in black, electrode sites at which dV/dt was ≤−0.5 V/s at any time during a 20-ms interval. Numbers above frames indicate start of each interval in ms relative to shock onset. Sock orientation is shown in top left frame. Electrogram taken from 1 electrode is shown above frames. Activation of first 5 postshock cycles first appeared at anteroapical LV (frames 60, 220, 380, 500, and 640) and propagated away in a focal pattern. Successive cycles appeared faster and propagated more slowly than their predecessors. RVOT indicates right ventricular outflow tract.
of earliest activation (SEA) of cycles 1 to 5 was in the anterior LV apex, where the S3-S7 pacing electrode was placed.

**Activation With Post-aULV Pacing**

Activation appearing spontaneously after the S5 paced cycle in all VF episodes exhibited 2 patterns: focal and reentrant. Of the 58 VF episodes, a focal pattern was found in 43 (74%) and a reentrant pattern in 15 (26%).

Reentry was always in the posteroapical RV toward the RV apex (Figure 3). The 3 paced activations propagated across the ventricles in a focal pattern with progressive slowing from cycles 1 (S3) to 3 (S5) in the apical and posterior RV.

**Figure 3.** Example of reentry and electrograms from another VF episode in the same animal as for Figure 2. A, S3, S4, and S5 pacing stimuli in electrogram correspond to frames 130, 270, and 390, respectively. S3 and S4 cycles propagated in a focal pattern with propagation slowing progressively at posteroapical RV. S5 cycle blocked at RV apex (frames 530 to 590). Anterior and posterior fronts of this cycle then propagated around RV apex, initiating figure-8 reentry. B, Electrograms a through e are part of reentrant loop and correspond to locations shown on map. Numbers are times in ms from shock onset. Arrows show directions of wavefront propagation. Dashed arrows show 2 cycles of reentry as seen in A. Asterisks show activation propagating from ectopic foci. An ectopic focal activation arose on epicardium near site c (corresponding to frame 830, white circle in A), interrupting reentrant loop (asterisk at 833 ms), halting reentry.
overlying the S2 electrode. Activation propagated anteriorly and posteriorly around the region of slow conduction, toward the RV base, collided at the posterobasal RV, and terminated for cycles 1 (frames 210 to 250) and 2 (frames 410 to 470). Cycle 3 (S5) appeared on the epicardium at the LV apex (frame 410) as cycle 2 (S4) activated the RV apex, causing overlapping cycles. Cycle 3 activation blocked (frames 530 to 570) on reaching the posterior RV apex, allowing the anterior and posterior fronts to create figure-8 reentry by reactivation of the posteroapical RV (frames 590 to 650, arrows), initiating the first nonpaced cycle (cycle 4). This pattern repeated in cycle 5 (frames 750 to 810), which was interrupted when a new ectopic focus appeared at the anterobasal RV (frame 830, white circle). This focal activation front collided with the reentrant front of cycle 5, interrupting reentry. Next, multiple foci appeared on the epicardium, degenerating into VF (Figure 3B).

Figure 4. Example of focal activation from another VF episode in same animal. S3, S4, and S5 stimuli occurred in frames 150, 270, and 390, respectively. S3, S4, and S5 cycles all propagated in a focal pattern without blocking at RV apex. Fourth cycle appeared spontaneously on epicardium (frame 530) near S3-S5 pacing site without an exogenous stimulus and propagated in a focal pattern across ventricles (frames 550 to 690).

Figure 5. Example of NoVF episode with 2 postshock pacing stimuli in same animal. S3 and S4 pacing stimuli occur in frames 130 and 270, respectively. S3 and S4 cycles propagated in a focal pattern similar to those in Figure 3. No activation spontaneously arose on epicardium after S4 cycle. After a long pause, sinus rhythm resumed (not shown).
An example of an epicardial focal pattern is shown in Figure 4. Focal activations of cycles 1 (S3, frames 170 to 250) and 2 (S4, frames 290 to 450) were similar to those in Figure 3 but propagated faster because the S3 stimulus was delivered 20 ms later. Cycle 3 activation (S5) propagated toward the RV apex without blocking (frames 410 to 590). Before cycle 3 activated the entire epicardium, cycle 4 activation appeared spontaneously on the apical epicardium close to the pacing site (frame 530) and propagated in a focal pattern (frames 560 to 690). Cycle 5 arose from multiple ectopic foci (frame 670) before cycle 4 terminated. Overlap was found in all cycle transitions except from cycles 1 to 2. No reentrant activation was seen during the first 5 cycles.

![Figure 6](example.png)

**Figure 6.** Example of NoVF episode with 3 postshock pacing stimuli in same animal. S3 and S4 stimuli occurred in frames 130 and 270, respectively. S5 stimulus was delivered 30 ms later than in Figure 3 (frame 410). S5 cycle appeared focally on epicardium shortly before S4 activation had completely traversed ventricles. There was no spontaneous activation on epicardium after S5 cycle. A long pause was present before a sinus beat occurred (not shown).

![Figure 7](example.png)

**Figure 7.** Example of VF episode induced by 5 pacing stimuli (P1-P5) without an S2 shock. P1 and P2 cycles both propagated across entire epicardium before next cycle appeared. Overlapping cycles began during transition from P3 to P4 cycles (frame 560). After last paced cycle (P5), 2 ectopic foci (frame 760, arrows) appeared spontaneously and were followed by multiple ectopic foci that led to VF (not shown).
The importance of the S5 stimulus and its CI is emphasized in Figures 5 and 6. When the S5 stimulus was not given (Figure 5) or was given at an S4-S5 CI 30 ms longer than the shortest CI that captured (Figure 6), no new spontaneous activation appeared after the last paced cycle, and a long pause occurred before sinus rhythm resumed. In a few cases, a single ectopic cycle occurred before sinus rhythm resumed.

**Pacing Without aULV Shocks**

VF was never induced when P1, P1-P2, P1-P2-P3, or P1-P2-P3-P4 stimuli were delivered at any CI after 10 S1 stimuli. When 5 stimuli (P1-P5) were delivered, VF was not induced at a strength of 5 to 10 times DPT. After the P5 cycle, there was either a pause or, occasionally, only 1 or 2 ectopic cycles before sinus rhythm resumed. However, in the 2 animals in which P1-P5 strength was increased to 20 times DPT, 4 episodes of VF (2 in each animal) were induced when all 5 stimuli were at the shortest CIs that captured (208±14, 138±7, 121±15, 116±17, and 126±31 ms, respectively). In all 4 VF episodes, 1 or 2 ectopic foci always appeared spontaneously on the epicardium close to the pacing site after the last paced (P5) cycle before degeneration into VF (Figure 7). This pattern was similar to that in the VF induction episodes by 3 pacing stimuli after an S2 shock. However, without the S2 shock, spontaneous activations never appeared on the epicardium after the third or fourth pacing stimulus. Furthermore, without an S2 shock, VF induction was not reproducible, because the ectopic focus occurred only rarely after the P5 paced cycle.

**Discussion**

**Number and Rapidity of Postshock Activations Determine VF Induction**

Our major finding is that ≥3 rapid activations are required to initiate VF after shocks 50 to 100 V stronger than the ULV. The first and second postshock cycles are not the sole determinants for VF induction, as shown by the similarity of these cycles for VF and NoVF episodes. The third cycle, however, led to VF initiation when it appeared so rapidly that it overlapped in time with the second cycle. When the third pacing stimulus was absent or was delivered ≥30 ms after the shortest CI that captured, VF was never induced. Thus, the short ICI and long WCT of the first 2 postshock cycles appear to create the substrate for VF initiation by the third cycle.

Without the S2 shock, VF was not induced by 3 premature pacing stimuli at any CI. Furthermore, in the absence of the shock, VF was only occasionally induced by 5 premature stimuli that required a greater strength than that used to induce VF by pacing after S2 shocks. This finding is consistent with a report by Hamer et al.\(^4\) that showed that VF induction depended on the strength and timing as well as the number of premature stimuli.

Our study also demonstrates that VF can always be induced by 3 postshock stimuli with short CIs. Thus, in addition to the premature stimuli, the shock also plays a significant role in VF induction, perhaps because the strong shock field prolonged refractoriness in the posteroapical RV near the S2 electrode, which in turn caused postshock activation to slow and block in that region, creating the substrate for reentry.\(^5\) Without the shock, 3 cycles, no matter how rapid, are not sufficient to cause block.

**Mechanism for VF Induction**

Both focal\(^6\)–\(^8\) and reentrant\(^9,10\) patterns have been reported to initiate VF, as observed in this study after 3 paced cycles. Because the spontaneous focal activations appeared close to the pacing site, they could have arisen from ectopic foci or Purkinje fibers excited by strong electrical stimulation.\(^11\) Alternatively, intramural reentry is possible, because 3D mapping was not performed.

Although epicardial reentry was seen in some cases in this study, it was not observed during the first 5 postshock cycles in our previous study, in which VF was induced by a ULV\(_{50}\) shock.\(^3\) This may be a result of the differences in the S2 shock strength used in the 2 studies. A shock 50 to 100 V above the ULV, but not a ULV\(_{50}\) shock, could be strong enough to cause slow propagation and block, allowing reentry to occur. Also, the local S3-S5 stimuli after aULV shocks may have had different effects than the spontaneously arising activation fronts after ULV\(_{50}\) shocks.

Whatever the cause of these spontaneous activations, this study emphasizes the importance of not just the first but of several cycles after shocks of near-ULV strength on VF induction. Future studies need to focus on the small arrhythmogenic area at the SEA in the low-voltage-gradient area near the LV apex,\(^12\) because this study suggests that the primary determinant of the outcome of shocks near the ULV could be limited to this small region, at least in normal hearts.

**Study Limitations**

The requirement of 3 pacing stimuli for VF induction after the aULV shocks may not apply to all conditions. The number of stimuli required for VF induction could differ depending on shock strength, drugs, heart size, cardiac disease, and species.

Because only epicardial mapping was performed, intramural reentry cannot be ruled out. The mapping array had 4-mm interelectrode spacing, which may be too coarse to detect microreentry. Because optical mapping was not performed, the changes in action potentials and repolarization patterns were not investigated.

**Summary**

After shocks of near-ULV strength, the number and rapidity of postshock cycles induced by the shock are primary determinants of VF induction. The progressive decrease in ICI and increase in WCT of the first several cycles, as well as the effect of the shock, are essential for VF induction. These findings support the hypothesis that the immediate postshock activation pattern is not the sole determinant for the shock outcome for shocks near ULV strength in normal hearts and that a minimum number of cycles (3 in this study) are necessary to initiate VF after ULV shocks.\(^3\)

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References
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