Tunnel Propagation of Postshock Activations as a Hypothesis for Fibrillation Induction and Isoelectric Window

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Abstract—Comprehensive understanding of the ventricular response to shocks is the approach most likely to succeed in reducing defibrillation threshold. We propose a new theory of shock-induced arrhythmogenesis that unifies all known aspects of the response of the heart to monophasic (MS) and biphasic (BS) shocks. The central hypothesis is that submerged “tunnel” propagation of postshock activations through shock-induced intramural excitable areas underlies fibrillation induction and the existence of isoelectric window. We conducted simulations of fibrillation induction using a realistic bidomain model of rabbit ventricles. Following pacing, MS and BS of various strengths/timings were delivered. The results demonstrated that, during the isoelectric window, an activation originated deep within the ventricular wall, arising from virtual electrodes; it then propagated fully intramurally through an excitable tunnel induced by the shock, until it emerged onto the epicardium, becoming the earliest-propagated postshock activation. Differences in shock outcomes for MS and BS were found to stem from the narrower BS intramural postshock excitable area, often resulting in conduction block, and the difference in the mechanisms of origin of the postshock activations, namely intramural virtual electrode–induced phase singularity for MS and virtual electrode–induced propagated graded response for BS. This study provides a novel analysis of the 3D mechanisms underlying the origin of postshock activations in the process of fibrillation induction by MS and BS and the existence of isoelectric window. The tunnel propagation hypothesis could open a new avenue for interventions exploration to achieve significantly lower defibrillation threshold. (Circ Res. 2008;102:737-745.)

Key Words: ventricular fibrillation ■ electric shock ■ postshock activation ■ bidomain model ■ spiral wave

Defibrillation by high-energy electric shocks is the only reliable procedure for termination of ventricular fibrillation; however, it could result in myocardial dysfunction and damage.1 Furthermore, recent metaanalysis of industrial reports2 concluded that thousands of patients have been affected by high-voltage component implantable cardiac defibrillator malfunctions, causing psychological trauma. Comprehensive knowledge and appreciation of the mechanisms by which a shock interacts with the heart is the approach most likely to succeed in reducing shock energy. The presence of an isoelectric window (IW) following unsuccessful defibrillation attempts3-5 led to the understanding that an electric shock terminates ongoing fibrillation but then reinitiates it; hence the mechanisms of fibrillation induction and its reinitiation (unsuccessful defibrillation) are the same. Indeed, striking similarities between these mechanisms have been found, particularly with regard to propagation of the first global postshock activation (PA) and IW duration.4-6 The similarity is supported by the significant correlation between upper limit of vulnerability (ULV) and DFT.7,8 Therefore, elucidating the origin of PAs resulting in fibrillation induction is expected to provide invaluable insight into the mechanisms of defibrillation failure and could contribute significantly to the effort to find novel ways to appreciably lower DFT.

Although numerous hypotheses9-12 exist for the mechanisms of PA origin, none provides comprehensive mechanistic explanation of the following findings:

1. Earliest PA following near-ULV (or near-DFT) shocks occurred after the epicardium recovered completely from shock-induced direct excitation.3,5
2. IW increased as shock strength increased.4,6,13
3. For both monophasic (MS) and biphasic (BS) shock waveforms, earliest PAs arose, following weak shocks, in areas of high extracellular potential gradient, but moved to areas of low extracellular potential gradient as shock strength increased.4,6,13
4. DFT superiority and lower ULV for BS14 and the relation to PA origin and propagation patterns.

In our recent study15 on arrhythmogenesis with external MS, we demonstrated that shock outcome and the type of post-

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shock arrhythmia induced by the shock depend on the location of the intramural postshock excitatable area formed by shock-induced deexcitation of previously refractory myocardium. In the present study, we extend these findings and propose a new theory of postshock propagation and shock-induced arrhythmogenesis that unifies all known aspects and findings regarding the postshock electric behavior of the heart following MS and BS and addresses the issues outlined above. Specifically, we hypothesize that submerged “tunnel” propagation of PA through shock-induced intramural excitatable areas underlies fibrillation induction with MS and BS and the existence of IW. The goal of this study is to test this hypothesis and provide a comprehensive set of mechanisms for fibrillation induction with electric shocks for all ranges of shock strengths and the MS and BS waveforms used in clinical practice.

To test the proposed hypothesis, the global 3D activity in the ventricles must be analyzed. Although optical mapping provides high-resolution information regarding epicardial activity, the methodology is insufficient in resolving depth information. For instance, PA could remain undetected optically if they propagate intramurally. Thus, it is paramount to use alternative approaches in gaining insight into postshock behavior within the tissue depth. Our group has recently developed a realistic computer model of stimulation/defibrillation in the rabbit heart21; simulations with this model have proven invaluable in understanding various aspects of the response of the heart to shocks.15 We use this realistic model to achieve the goals of the present study.

**Materials and Methods**

Transmembrane potentials calculated in the anatomically based rabbit ventricular model described previously15,16 were based on the bidomain representation. The model incorporated realistic geometry and fiber orientation (Figure 1A and 1B); blood in cavities and perfusing bath were also represented (Figure 1C). The ventricles were paced at the apex, and shocks were delivered through plate electrodes occupying the vertical borders of the perfusing chamber (distance, 3.92 cm).

To represent membrane kinetics, we used a modified version of the Luo-Rudy model17 augmented for defibrillation studies and equipped with representation of membrane electroporation. Parameter values as and numeric approaches can be found elsewhere.16 Validity of the bidomain approach has been demonstrated by a body of research.15,18,19 The rabbit ventricular model of stimulation/defibrillation has been very well validated by experimental measurements.15

Eight pacing stimuli of 2-ms duration and strength twice-diastolic threshold were applied at a cycle length of 300 ms to achieve steady state. Shocks were delivered at various coupling intervals between onset of the last pacing stimulus (assumed as time 0) and shock onset. MS duration was 10 ms, and BS was 6/4 ms, the latter considered the optimal waveform for defibrillation.14 Tilt for both waveforms was 62.0%. Applied field at shock onset (leading edge) represented shock strength. Polarity of MS and the first pulse of BS was anodal, ie, electrode near the left ventricle was the anode (Figure 1).

Shock-induced arrhythmias were considered “sustained” or “non-sustained” if the shock induced ≥4 or <4 postshock beats, respectively.20 In accordance with experimental studies,3–6,13 we defined the “initiating PA” as the first PA to originate within the ventricles after shock end, and the “earliest-propagated PA” as the PA that appeared on the epicardium at the earliest timing following shock end. Clearly, the initiating PA may not become the earliest-propagated PA because it may die out before reaching the epicardium. The IW, observed on the epicardium, was defined as the time interval between shock end and appearance of earliest globally propagated PA.3–6

A filament is 3D organizing center around which a scroll wave rotates. We applied a method used previously21 to detect the filaments.

**Results**

**MS Outcomes**

The MS vulnerability grid, ie, the 2D grid representing MS outcomes for a range of shock-delivery coupling intervals (80 to 260 ms in 20-ms increments) and a range of shock strengths (4 to 24 V/cm in 4 V/cm increments), is shown in Figure 2A (top), together with the epicardial preshock transmembrane potential distributions (bottom). The area of vulnerability (AOV) encompassing episodes of arrhythmia induction, both sustained (filled circles) and nonsustained (open circles), has somewhat of a triangular shape occupying coupling intervals from 100 to 240 ms and shock strengths at and below 20 V/cm. AOV is surrounded by episodes of arrhythmia noninduction (bars). ULV, the highest shock strength that does not induce sustained arrhythmia, was ∼18 V/cm.

An episode of arrhythmia noninduction is presented in Figure 2B (Movie I in the online data supplement, available at http://circres.ahajournals.org). A 24 V/cm MS created regions of positive and negative membrane polarization (230 ms), called virtual electrodes (VEs), formed because of the interaction between applied field and tissue structure.22 Following shock end, the strongly negatively polarized left ventricular (LV) epicardium was excited very quickly by break excitations; thus the entire epicardium became refractory (270 ms). At that time, although there was no activation on the epicardium (back surface not shown), an intramural wavefront (“initiating” PA, white surface marked by an asterisk in 270-ms transparent views) propagated under the repolarizing epicardial layers. This activation died out ∼45 ms after shock end without making a breakthrough onto the epicardium (275 ms), ie, not becoming the earliest-propagated PA.
Within AOV, there were 2 types of earliest-propagated PAs, either following IW or not. Figure 2C (supplemental Movie II) presents an episode of earliest-propagated PA following IW (16 V/cm MS). Formation of VEs, quick excitation of LV epicardium, and synchronous epicardial repolarization (230 to 270 ms) were similar to Figure 2B. However, a wavefront, which originated again deep within the wall (white surface marked by an asterisk in transparent 270-ms panels) remained submerged until it made a breakthrough onto the epicardium as the earliest-propagated PA (310 ms), resulting in intramural reentry (350 ms), as it occurs in ventricular tachycardia/fibrillation.23 IW was 80 ms.

Figure 2D presents earliest-propagated PA without IW (supplemental Movie III). Activation emerged from the boundary between oppositely polarized areas around the apex right after the end of the 4 V/cm MS (210 ms). This mechanism is referred to as “VE-induced phase singularity.”11 The activation propagated toward the base (220 ms) and formed a transmural scroll wave (250 ms), degenerating later into fibrillation (290 to 330 ms).

BS Outcomes

The BS vulnerability grid is shown in Figure 3A. AOV was again distributed triangularly, but was narrower than for MS, ranging in coupling intervals from 150 to 240 ms and in shock strengths 12 V/cm and below. BS ULV was lower than MS, being 14 V/cm.

Figure 3B (supplemental Movie IV) illustrates an example of arrhythmia noninduction after 16 V/cm BS. VEs induced by the 6-ms-long first pulse (226 ms) reversed sign following the 4-ms-long second pulse (230 ms). Transmembrane potential gradient between virtual anodes and cathodes at shock end was markedly lower than at the end of the first pulse (compare green-colored areas at 226 and 230 ms). Thereafter, the second pulse-induced RV strong virtual anode was immediately activated by break excitations (240 ms), and the entire epicardium almost synchronously repolarized (260 ms). Similar to MS, an activation arose, which remained submerged (asterisk in transparent 260-ms view), propagating under the repolarizing epicardial layers; the wavefront vanished at 55 ms without appearing on the epicardium (285 ms).

Within AOV, there were again 2 types of earliest-propagated PA. Figure 3C (supplemental Movie V) presents an example of earliest-propagated PA following IW induced by 12 V/cm BS. The initial response (226 to 260 ms, epicardial views) was similar to that in Figure 3B. However, the wavefront originating 20 ms after shock end, at 260 ms (asterisk in 260-ms transparent view), which remained submerged for another 35 ms, made a breakthrough onto the epicardium as the earliest-propagated PA (285 ms), resulting in intramural reentry (310 ms). IW was 55 ms.

Earliest-propagated PA appearing without IW is shown in Figure 3D (4 V/cm BS, supplemental Movie VI). VEs (226 to 230 ms) were similar to those in Figure 3B and 3C, except that transmembrane potential gradient between VEs was lower than in these 2 cases. Thereafter, low-amplitude activations slowly propagated (zigzag arrows, 240 ms), emerging later as full-blown wavefronts (255 ms, surface view). This mechanism is referred to as “VE-induced propagated graded response.”12 The activations resulted in a transmural scroll wave.
wave (255 ms, transparent views), degenerating into fibrillation (270 to 310 ms).

**Effect of Shock Strength on IW**

Figure 4A and 4B portrays the dependence of IW on shock strength based on data from episodes within MS and BS AOVs. In both cases, IW following near-ULV shocks was ∼60 ms. However, the slope of the least-mean-square approximation line for BSs was steeper than for MSs (4.6 versus 2.1 ms/cm/V).

**PA Origin**

The mechanisms underlying the lower ULV of BS versus MS, resulting from initiating PAs that originated from intramural VEs and propagated through intramural postshock excitable areas are analyzed in Figure 5. Figure 5A presents transmembrane potential distributions in an apex-to-base cross-section during (226 ms), at the end of (230 ms), and 10 ms after (240 ms) 16 V/cm MS and BS at a coupling interval of 220 ms. The MS episode was just below ULV and resulted in arrhythmia, whereas the BS episode was above the corresponding ULV and arrhythmia was not induced. At MS end, a large intramural excitable area was formed in the LV wall (230 ms). At BS end, the second pulse reversed the polarity of some of the VEs created by the first pulse and, in particular, the strong negative polarization on the LV epicardium (see filled triangles). The asymmetrical change in transmembrane potential by the second BS pulse resulted in a much smaller LV intramural postshock excitable area (240 ms), ultimately resulting in a different shock outcome.

The mechanism of origin of the initial PA following MS and BS of strengths just below the respective ULVs differed significantly. For 16 V/cm MS, because subepicardial layers were strongly hyperpolarized after the shock, they became quickly excited by fast propagation (indicated by open triangles at 245 to 250 ms, Figure 5B). Note that this quick excitation, which did not propagate globally in the ventricles, does not fall into the PA category. Meanwhile, the initiating PA (asterisk in 240-ms inset), which originated at the high transmembrane potential gradient boundary between oppositely polarized VEs around the apex, propagated at a slower velocity toward the base through the LV intramural excitable area (white arrows, 240- to 260-ms insets) until it broke onto the LV epicardium as the earliest-propagated PA. This breakthrough was possible because at that time epicardial transmembrane potentials had decreased and transmembrane potentials were in the isoelectric window (255 ms, transparent views), degenerating into fibrillation (270 to 310 ms).

Figure 4A, Vulnerability grids for BSs, encompassing episodes of no response and sustained and nonsustained arrhythmias. Episodes in blue denote arrhythmia induction following IW. Preshock states are shown at bottom. B through D, Shock-induced responses: arrhythmia noninduction (B) and induction of sustained arrhythmia with (C) and without (D) IW. Zigzag arrows denote propagated graded responses. Other symbols and abbreviations as in Figure 2. Supplemental Movies IV through VI are movie supplements to B through D, respectively.
potential gradients were low; thus the wave was able to find excitable tissue to propagate through.

The origin of the initiating PA following 12 V/cm BS given at 220-ms coupling interval is analyzed in Figure 5C. The initiating PA, in the form of a damped wave, originated at the boundary between a recovered area unaffected by the second pulse (outlined by open triangles at 235 ms) and the second pulse-induced depolarized area (ie, between sites 1 and 2 at 226 ms) as a VE-induced propagated graded response (zigzag arrow, 240 ms). This occurred deep within the wall, and the initiating PA proceeded transmurally toward the LV epicardium (250 to 290 ms), where tissue had already recovered and transmembrane potential gradient was low, becoming the earliest-propagated PA. The action potentials at sites 1 to 3 (Figure 5D) have distinctive features indicating the onset of propagated graded response10: slowly rising depolarization at site 2 (green arrow) and electrotonic depolarization at site 1 caused by the adjacent graded response (red arrow).

Finally, initiating PAs induced by MSs and BSs of above-ULV strength (Figures 2B and 3B) originated via each of the respective mechanisms described above. However, in both cases, the activation terminated soon thereafter because it reached refractory tissue before the LV epicardium repolarized enough to allow a breakthrough (data not shown).

**SW Filament Associated With the Initial PA**

As shown in Figure 6A and 6B, initiating PAs induced by 16 V/cm MS and 12 V/cm BS (just below the respective ULVs) were characterized by a closed-loop organizing center of reentrant activity, known as “O-filament.” The O-filament ensuing from MS was typically long and followed the contour of the ventricular wall (Figure 6A), whereas that originating from BS was much smaller (Figure 6B). In both cases, activity was “mushroom-like,” consistent with a scroll wave rotating around a filament ring,23 and therefore the earliest-propagated PA exhibited a focal pattern (Figure 6C). We analyzed other cases and found that when a segment of the O-filament happened to reach the epicardium within the first scroll wave rotation, a U-filament then developed and the
earliest-propagated PA exhibited unidirectional pattern rather than focal (data not shown).

The dynamic length of the filament (calculated as number of finite elements comprising the filament at a given instant of time) during and after MS and BS of strength just below ULV is presented in red and green, respectively, in Figure 6D. For 16 V/cm MS given at 220-ms coupling interval (red line), the filament was long during the shock; however, it continuously shortened following shock end, reaching a plateau before the earliest-propagated PA appeared (red asterisk). For 12 V/cm BS of the same coupling interval (green), the filament was shorter at shock end than for 16 V/cm MS (compare red and green dots), continuing to shorten rapidly until the earliest-propagated PA appeared (green asterisk). In both cases, filament length increased again after IW.

Fillet length during and after BS of above-ULV strength (16V/cm, same strength and coupling interval as in MS case) is presented in blue in Figure 6D. The filament was markedly shorter at shock end (blue dot) and its length decreased the fastest, reaching 0. The time of filament annihilation occurred before the end of IW for 12 V/cm BS.

Discussion
This study focuses on the poorly understood 3D aspects of postshock propagation in the heart, providing novel analysis of the mechanisms underlying PA origin and its subsurface propagation in the process of fibrillation induction by MSs and BSs. The study used the capabilities of state-of-the-art 3D realistic heart modeling, which, already experimentally validated,15 provides a unique opportunity to explore behavior in the depth of the ventricular walls not achievable by any imaging technique thus far. The main findings are:

1. Intramural (initiating) PAs exist during IW following near-ULV MSs and BSs.
2. Regardless of shock waveforms, IW is a function of shock strength.
3. All initiating PAs following near-ULV MSs and BSs arise deep within the myocardium and propagate through the intramural excitable area until emerging on the epicardium as the earliest-propagated PAs.
4. Intramural VE-induced phase singularity and intramural VE-induced propagated graded response are responsible for arrhythmogenesis induced by near-ULV MSs and BSs, respectively.
5. BSs result in narrower intramural excitable area and shorter filament length than MSs of the same strength.

Mechanisms of Origin of Initiating PA by Near-ULV Shocks
The simulation results revealed that the initiating PA following near-ULV shocks emerged from intramural VEs. This finding is consistent with experimental and numeric studies11,24 which have documented that the shock strength necessary for extinguishing ongoing fibrillation is much lower than ULV or DFT. For near-ULV MS, the initiating PA arose from oppositely polarized intramural VEs around the apex, where the transmembrane potential gradient was the largest, via the VE-induced phase singularity mechanism.11 In contrast, following near-ULV BS, the initiating PA originated via the VE-induced propagated graded response mechanism.12 The onset of the graded response was near the base, at the site of largest transmembrane potential gradient, ie, at the intramural boundary between recovered area unaffected by the BS second pulse and the area depolarized by it.

The initiating PA following shocks of near-ULV strength, an activation associated with an O-filament, propagated through the tunnel of intramural LV postshock excitable area. It made a breakthrough on the LV epicardium as the earliest-propagated PA, exhibiting either focal or unidirectional pattern, consistent with experimental observations.25

Interestingly, the mechanisms of initiating PA induction by near-ULV shocks mimicked those of induction by shocks of strength far below the ULV (Figures 2D and 3D, respectively) in the role played by VEs, namely VE-induced phase singularity for MS and VE-induced propagated graded response for BS. Therefore, we here conclude that the mechanism of origin of the initiating PA is determined predominantly by shock waveform rather than strength.

Location of Origin of Earliest-Propagated PA as a Function of Shock Strength
The epicardial site of origin of the earliest PA site moved from the area of large transmembrane potential gradient to the area of low transmembrane potential gradient as shock strength increased (for MSs, compare C and D in Figure 2; for BSs, C and D in Figure 3). Experimental studies using MSs4,6 and BS13 have reported that for weak shocks, the earliest PA always originated in areas of large extracellular potential gradient, but the site of origin moved away to areas of low extracellular potential gradient as shock strength increased. Although the transmembrane potential gradient was not recorded in these experiments,4,6,13 areas of large extracellular potential gradients correspond to areas of large transmembrane potential gradients (strong VEs) in cases when shock electrodes are far from each other,19 as in our case and in the aforementioned experimental studies.4,6,13 Thus, our simulation results regarding the location of origin of earliest PA are consistent with experimental evidence.

Mechanism of IW by Near-ULV Shocks
The simulations demonstrated that the earliest-propagated PA following near-ULV MSs and BSs appeared after the LV epicardium repolarized completely; this is consistent with experimental observations.3,5,20,26 IW duration following MS and BS increased as shock strength increased, being ≈60 ms for near-ULV shocks (Figure 4A and 4B), consistent with experimental results.4,6,13 This behavior is explained by tunnel propagation of initiating PA through the LV wall. Tunnel propagation is sustained by the intramural excitable areas and by the refractoriness of LV epicardial layers, which keeps the activation submerged, creating IW. The reason why such conditions exist for near-ULV shocks rest with the fact that the shock polarizes surfaces and intramural tissue via different mechanisms.22 Surface polarization (arising from present redistribution) is typically very strong, whereas intramural VEs (arising from fiber curvature and rotation) are of lesser magnitude and often of opposite sign to that of the surface.
At MS end, the regions of strongest negative polarization are located on the ventricular surfaces. Of these the most important is the LV epicardium, because it is above the location where intramural excitable areas are formed.\(^{15}\) Activations rapidly propagate through the negatively polarized LV epicardium immediately after the shock is withdrawn; these are typically initiated by numerous break excitations (Figure 3B and 3C, 240 ms). The conduction velocity through areas of strong negative polarization is faster than through mildly hyperpolarized or near-resting-potential areas\(^{24}\); thus the LV epicardium becomes quickly excited (Figure 5B, open triangles), confining the PA to propagate through the slower-conducting LV intramural excitable area (tunnel propagation) until the LV epicardium recovers from the initial excitation.

During BS, the LV epicardium experiences strong negative polarization at the end of the first phase and becomes strongly positively polarized at the end of the second phase (see Figure 5A, filled triangles). The strong depolarization of the LV epicardium serves to prevent the intramural excitation from exiting and keeps it “in the tunnel.” Thus the differences in “tunneling” between MS and BS is that for MS, quick depolarization of the negatively polarized LV epicardium occurs by fast propagation through it, whereas for BS, it is achieved by shock polarity reversal.

Tunnel propagation also explains how the earliest-propagated PA could arise without any apparent present sources on the epicardium. Other hypotheses for PA origin, such as stimulus-induced critical point,\(^{9}\) VE-induced phase singularity,\(^{11}\) propagated graded response,\(^{10,12}\) cannot explain alone these findings. Tunnel propagation is consistent with transmural plunge electrode recordings, demonstrating that site of PA origin was within the myocardium rather than on the surface.\(^{3,26}\)

Furthermore, we demonstrate here that for near-ULV BSs, activations originated in the midmyocardium with a certain delay (≈20 ms, Figure 5C and 5D); this delay was attributable to the fact that intramural VEs following BS are weaker than following MS and thus provide less of an excitatory stimulus at the boundary between oppositely polarized VEs, the site of PA origin. Intramural delays in plunge electrode recordings for near-DFT BSs have been also detected experimentally,\(^{26}\) although these were typically longer than the values reported here because the plunge electrodes were unlikely to have been located at the exact site of origin of the intramural activation. Finally, it is important to appreciate the fact that differences in delays measured here might differ from those measured experimentally attributable to the fact that experiments were conducted on larger hearts, canine or swine, which also have different electrophysiological properties.

**Sensitivity of Tunnel Propagation to Shock Strength and Timing**

Tunnel propagation requires that LV epicardium remains refractory for a period of time, whereas propagation takes place through the LV intramural excitable areas. This condition is achieved only above minimum shock strength (shock strengths corresponding to episodes colored in pink in Figure 2 and all episodes above them in MS vulnerability grid, and episodes colored in blue in Figure 3 and all episodes above them in BS vulnerability grid). For MS, the shock has to be strong enough to ensure strongly negatively polarized LV epicardium at shock end, through which fast propagation occurs, leading to depolarization of LV epicardium soon thereafter. For BS, the shock has to be sufficiently strong so that the second phase can reverse the negative polarization induced by the first, leading to depolarization of the LV epicardium at shock end.

Above ULV, all episodes are characterized with tunnel propagation, independent of shock timing. Coupling interval determines only the minimum shock strength needed for such propagation because the shorter the coupling interval, the more tissue is depolarized preshock, aiding weaker MS and BS shocks in achieving fast LV epicardial depolarization. Thus, minimum shock strength needed for tunnel propagation decreases as coupling interval decreases (down-sloping of pink/blue regions in Figures 2A and 3A).

**Lower ULV for BS**

Anderson et al\(^{24}\) conducted 2D defibrillation simulations and concluded that BS superiority stemmed from reduction of postshock excitable areas and suppression of break excitations. In this study, we observed similar behavior: narrower postshock excitatory area attributable to asymmetrical change in transmembrane potential during BS and initiation of PA not via break excitation. However, in the ventricles these took place deep inside the wall rather than on the surface. The intramural VE-induced propagated graded response became the mechanism responsible for arrhythmogenesis following optimal BS because the second pulse eliminated the substrate for VE-induced phase singularity\(^{11}\) induced by the first. In addition, we documented shorter filament lengths at shock end and faster filament shortening after BS (Figure 6D). These findings provide further mechanistic insight into the superiority of BS over MS.

**Fundamental Nature of Uncovered Mechanisms and Clinical Implications**

Initiating PA origin, tunnel propagation, and epicardial breakthrough mechanisms uncovered here are fundamental because their existence is underpinned only by ventricular structure and VE formation mechanisms. Figure 7 provides evidence of the robustness of these mechanisms. Panels A and B present MS episodes of earliest-propagated PA for two different pacing sites, on LV and RV epicardium. Despite the vastly different preshock state, shock outcome was the same: LV intramural excitable area, tunnel propagation of initiating PA and epicardial breakthrough followed by fibrillation induction, with IW of 52 ms (A) and 55 ms (B).

Similarly, although this study focused on fibrillation induction, it is logical to expect that the findings will remain valid for defibrillation failure following near-DFT shocks. This is attributable to the fundamental nature of the mechanisms involved and because the state of refractoriness in the ventricles determines only the minimum shock strength needed for tunnel propagation to occur. To confirm this, we present an episode of defibrillation failure (Figure 7C).
Despite the numerous preshock scroll waves (see filaments), MS failed by identical mechanisms, with IW of \( \approx 55 \) ms.

We purposefully used a uniform applied field (external electrodes) to reveal mechanisms of 3D postshock propagation; in this manner events were not masked by field nonuniformity. The mechanisms uncovered are directly applicable to external defibrillation, but they remain true for implantable cardiac defibrillator configurations, as demonstrated by a preliminary study.\(^{27}\) Therefore, we assert that targeting to decrease or fully eliminate the intramural postshock excitable areas holds the key to lowering DFT. In our preliminary study,\(^ {27}\) the intramural excitable area was decreased by relocating the return electrode (active can) toward the region of the sternum, resulting in \( \approx 30\% \) decrease in ULV. Clearly, the mechanisms uncovered here offer a new target in the quest to achieve low-voltage defibrillation.

**Study Limitations**

The limitations of the ventricular model have been described elsewhere.\(^{15,16}\) These include limitations of membrane model and lack of small-scale tissue heterogeneities. Although small-scale heterogeneities most likely result in formation of microscopic VEs during the shock and in diastole,\(^ {28}\) there is currently no experimental evidence that they play a major role in postshock propagation in the 3D organ, the focus of the present study. Furthermore, patterns of postshock propagation on the epicardium of the rabbit model match well these determined experimentally,\(^ {15}\) with no evidence of micro-VE contribution. Finally, the ventricular model did not include Purkinje network; depolarization-induced automaticity from Purkinje fibers could be a different mechanism for PA origin\(^ {29}\) in addition to those presented here.

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**Disclosures**

None.

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