Synchronization of ventricular fibrillation with real-time feedback pacing: implication to low-energy defibrillation

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The most effective way to terminate fatal ventricular fibrillation (VF) is through the delivery of high-energy electrical shocks. Because the amount of membrane depolarization required to reach threshold is typically ~30 mV, the question of why successful defibrillation requires hundreds of volts has become a standing puzzle lasting several decades. Such a conceptual conflict has prompted many theoretical and experimental studies (3, 10, 24, 26, 29, 32, 39) to understand the action of strong shocks and has also led to many attempts to design low-energy defibrillation and pacing strategies (2, 14, 23, 25).

Two approaches have been employed to lower the defibrillation requirements. The first approach involves optimization of the shock waveforms and shock timing. Historically, since the major breakthrough in the 80s with the use of biphasic shock waveforms, subsequent efforts in optimizing shock waveform have resulted in only limited success in reducing defibrillation requirements (19, 21, 22). Similarly, the reduction of defibrillation threshold from optimizing shock timing has been found to be ~20% (13, 15). The second approach, encouraged by the existence of excitable gaps during VF (14, 33), uses low-energy pacing pulses in hope of “capturing” myocardium during VF and subsequently terminating VF (23). VF termination that uses low-energy pulses to passively or interactively pace the fibrillatory myocardium is very desirable. Such an approach, if successful, is expected to result in dramatically reduced energy requirements for VF termination. The passive paradigm, such as overdrive pacing (ODP), delivers a constant frequency pulse train seeking to capture the irregular rhythm and to gain control. ODP has been shown to be effective in capturing a small region of the heart (14, 25), but its defibrillation effect is unclear. Antitachycardia pacing, the clinical application of ODP, is effective in terminating slow ventricular tachycardia (VT), but it is not effective in terminating faster VT or VF. On the other hand, interactive paradigms such as chaos control (7, 11, 35) seek to deliver energy based on real-time, electrical feedback from the myocardium. The stimuli are delivered irregularly based on the nonlinear dynamics of the heart. Application of nonlinear control has allowed termination of pacing-induced alternans (8) and conversion of VF to a different “state” of arrhythmia (11), but spontaneous termination of VF has not been demonstrated with any of the interactive pacing algorithms. Moreover, the technique to detect and to pace the excitable gaps in real time has not been fully developed, preventing investigators from thoroughly evaluating the pacing approach.

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Wavefront synchronization and synchronization of repolarization are important for VF termination (9, 17, 34). It has been suggested, at least in single reentry, that pacing during the excitable gaps may help decrease the dispersion of VF activations or extinguish the vortex by moving it to an inexcitable boundary, leading to termination (4, 18, 23). In the present study, we designed a novel pacing strategy [synchronized pacing (SyncP)], aiming not to capture VF but to synchronize wavefront propagation through pacing in the excitable gaps. We developed a system that detects excitable gaps using optical recording signals and performed multielectrode pacing in the excitable gaps with a real-time feedback algorithm. The new pacing strategy is expected to synchronize activation of fibrillatory wavefronts and to facilitate spontaneous termination. The purposes of this study were to test the efficacy of SyncP in facilitating spontaneous VF termination and to compare it with conventional ODP and high-frequency pacing (HFP).

MATERIALS AND METHODS

This study protocol was approved by the Institutional Animal Care and Use Committee and followed the guidelines of the American Heart Association.

Optical mapping of the isolated rabbit heart. Seventeen New Zealand White rabbits, weighing 4.1 ± 0.3 kg (4.5 ± 0.7 mo old), were injected with 1,000 units of heparin and anesthetized with ketamine (20 mg/kg) and xylazine (5 mg/kg) through an intravenous injection. After a midline sternotomy with 95% O2-5% CO2. Coronary perfusion pressure was regulated between 80 and 95 mmHg, and the hearts were exposed to air. A quadripolar catheter was placed into the pulmonary artery trunk for continuous bipolar recording and the induction of VF.

The tissues were stained with 0.5 μM di-4-ANEPPS (Molecular Probes). Laser light of 532-nm wavelength (Verdi, Coherent) illuminated the tissues, and epifluorescence was collected through a long-pass filter with a cutoff wavelength of 600 nm (R60, Nikon) with a high-speed charge-coupled device camera (430 frames/s, model CA D1–0128T, Dalsa). Image acquisition was controlled by custom-designed software based on LabView and the IMAQ Vision toolset (National Instrument). We mapped the left ventricular anterior wall (20 × 20 mm²), acquiring 128 × 128 sites simultaneously. A 3 × 3 spatial averaging was performed on the optical recordings in real time to increase the signal-to-noise ratio. The electromechanical uncoupler cytochalasin D (Sigma) was added to the perfusate at a concentration of 5 μM to inhibit tissue contraction.

Multielectrode pacing protocols. Four pacing electrodes (10 mm apart, Teflon-coated stainless steel with 0.3 mm diameter) were placed in the field of view. A reference site was randomly selected from the periphery of the mapping field to detect the timing of activation. The optical action potentials were monitored from the sites immediately adjacent to (<2 mm) each pacing electrode and the reference site (circles in Fig. 1, A and B). Figure 1B shows the SyncP algorithm. The main task of the algorithm was to detect threshold crossing from optical recordings at the reference site as well as the four pacing sites. Threshold levels were independently set in real time for the reference site and the pacing sites to 40% of the maximum optical potential amplitude. Two types of pacing algorithms were tested. In the independent mode (Fig. 1C), each pacing electrode was independently controlled. The pacing current was delivered when optical potential of the reference site and near a pacing site (marked by x). LAD, left anterior descending coronary artery. B: synchronized pacing (SyncP) algorithm. The first two traces are optical electrograms registered on the reference site and near a pacing electrode. The third line shows the time of electrical stimulus (S) given through the pacing electrode above. C: independent SyncP; D: simultaneous SyncP; E: overdrive pacing (ODP); F: high-frequency pacing (HFP).

Fig. 1. Pacing protocols. A: four unipolar pacing electrodes (e1, e2, e3, and e4) were positioned on the left ventricular anterior wall of the isolated rabbit heart. Ventricular fibrillation (VF) cycle length (VFCL) and spatial dispersion of VFCL (SDCL) were measured from 3 sites in the paced area (marked by +) and 2 sites in a nonpaced area (marked by x). LAD, left anterior descending coronary artery. B: synchronized pacing (SyncP) algorithm. The first two traces are optical electrograms registered on the reference site and near a pacing electrode. The third line shows the time of electrical stimulus (S) given through the pacing electrode above. C: independent SyncP; D: simultaneous SyncP; E: overdrive pacing (ODP); F: high-frequency pacing (HFP).
pacing sites was in the excitable gap in most cases. However, if the waves were already synchronized between the reference site and all the pacing sites, then none of the four electrodes were in excitable gaps when the reference site was activated.

ODP and HFP were performed with the same electrodes. For ODP, we measured the baseline VF cycle length (VFCL) and then paced the hearts at a pacing cycle length of 90% VFCL (Fig. 1E). For HFP, pacing was performed an average of 14.6 ± 9.0 times for each heart (Fig. 1F). We used three different HFP frequencies in each rabbit heart (43 Hz, n = 23; 87 Hz, n = 42; 217 Hz, n = 64). VF was induced by high current (5 mA) endocardial burst pacing in the right ventricle with a pacing cycle length of 50–80 ms. All pacing protocols were performed in VF sustained for ≥30 s. We recorded 1.84 s (800 frames) of each pacing protocol by optical mapping and kept continuous bipolar recordings. These protocols were tested with random sequences, and we waited ≥1 min after each pacing protocol to minimize the effects of the previous pacing protocol on the following protocol. If VF terminated within 3 s after the cessation of pacing, then it was regarded as pace terminated. The number of pacing episodes were as follows: SyncP, 106 episodes (61 independent SyncP and 45 simultaneous SyncP); ODP, 48 episodes; and HFP, 129 episodes. Stimulation currents of 2, 5, and 10 mA were tested for the SyncP and ODP protocols. For HFP, 1, 2, and 5 mA and subthreshold currents (80% of threshold) were used.

Spontaneous termination of VF has been a major concern for defibrillation studies in small hearts (20). Therefore, we did additional experiments to evaluate the time-dependent spontaneous termination rate in three hearts and compared the termination rate of simultaneous SyncP (5 mA) and sham pacing (0 mA) in another three hearts.

**Data analysis.** The pacing termination rate and energy consumption were evaluated for each protocol. To calculate the required electrical energy, we used the formula \( \varepsilon = I^2R \), where \( \varepsilon \) is the energy, \( I \) is the pacing current, and \( R \) is the resistance.

**Table 1. Changes of VFCL and SDCL by each pacing protocol**

<table>
<thead>
<tr>
<th>Pacing Protocol</th>
<th>VFCL (ms)</th>
<th>SDCL (ms)</th>
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<tbody>
<tr>
<td></td>
<td>Paced area</td>
<td>Nonpaced area</td>
</tr>
<tr>
<td><strong>SyncP (n = 70)</strong></td>
<td></td>
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</tr>
<tr>
<td>Preparing</td>
<td>62.4 ± 17.6</td>
<td>62.9 ± 15.2</td>
</tr>
<tr>
<td>Pacing</td>
<td>61.9 ± 17.7</td>
<td>62.6 ± 15.0</td>
</tr>
<tr>
<td>Postpacing</td>
<td>62.7 ± 17.4</td>
<td>62.8 ± 14.9</td>
</tr>
<tr>
<td><strong>ODP (n = 42)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparing</td>
<td>62.2 ± 17.7</td>
<td>64.0 ± 14.5</td>
</tr>
<tr>
<td>Pacing</td>
<td>61.5 ± 17.9</td>
<td>63.8 ± 14.4</td>
</tr>
<tr>
<td>Postpacing</td>
<td>61.4 ± 16.3</td>
<td>64.0 ± 14.0</td>
</tr>
<tr>
<td><strong>HFP (n = 42)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparing</td>
<td>62.1 ± 24.5</td>
<td>62.0 ± 23.6</td>
</tr>
<tr>
<td>Pacing</td>
<td>61.8 ± 25.9</td>
<td>61.3 ± 23.0</td>
</tr>
<tr>
<td>Postpacing</td>
<td>61.7 ± 25.6</td>
<td>61.5 ± 24.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rabbits. VFCL, ventricular fibrillation cycle length; SDCL, spatial dispersion of VFCL; SyncP, synchronized pacing; ODP, overdrive pacing; HFP, high-frequency pacing. *\( P < 0.01 \); †\( P < 0.05 \).
resistance. The measured resistance from the 100-μm active electrode to the large mesh reference electrode was \(~1\) kΩ (ranging from 0.8 to 1.2 kΩ). In 70 episodes of SyncP (36 independent SyncP and 34 simultaneous SyncP), 42 episodes of ODP, and 42 episodes of HFP, optical action potentials of 2,400 frames (5.52 s) of prepacing, pacing, and postpacing periods (800 frames for each) were recorded. VFCL and the spatial dispersion of VFCL (SDCL) at five different sites (3 sites in the paced area and 2 sites in the nonpaced area) were analyzed (Fig. 1A). We compared the VFCL and SDCL during the prepacing period with those during the pacing and postpacing periods. VFCL was computed at each site, and SDCL was then computed from the SD of these means. Other VF episodes were not used for this analysis due to insufficient recording of pre- and postpacing periods. To calculate the phases of the optical signal, the optical action potential of each pixel during a cycle was mapped to an angular value between \(-\pi\) and \(\pi\) using a time-delay embedding method. Phase maps were constructed from the entire image sequence, and phase singularities were identified using image convolution (6).

Fisher’s exact test and multivariate linear regression analysis were used to compare the pacing termination rate and energy consumption, respectively. ANOVA with Newman-Keuls tests were used to compare VF characteristics of prepacing, pacing, and postpacing periods, currents, and number of electrodes.

RESULTS

SyncP induces wavefront synchronization. Figure 2 shows the voltage maps during two VF cycles using the

![Fig. 3. Phase maps and phase singularity maps of prepacing (A), pacing (B), and postpacing (C) periods of SyncP. The numbers in the right bottom corner are the frame numbers. Left and middle: these phase maps were chosen arbitrarily every 10 frames at each period, and areas of the same color are in the same phase. Arrows mark the phase singularity points. Right: cumulative phase singularity point maps over 100 frames. Phase singularity points are marked with light blue dots. Unfilled white circles represent the location of pacing electrodes. The number of phase singularities in the pacing area is significantly reduced during and after pacing.](image-url)
independent SyncP protocol. An activation is detected at the reference site in frame 577. In the mean time, pacing sites e2 and e3 are in excitable gaps, and pacing current is delivered (indicated by a plus sign over the circles in Fig. 2). The pacing causes synchronization of depolarization (frame 587) and repolarization (frame 607). In the next cycle, the activation starts from the middle of the pacing area (frame 623) that covers the reference site. At this time, sites e3 and e4 are in the excitable gaps and fire, resulting in synchronization of depolarization (frame 633) and repolarization (frame 683). Because there is a loop delay of one frame between the activation at the reference site and the firing of the pacing electrodes, the reference site is always adjacent to, but not exactly at, the border of the depolarization (red) and repolarization (blue) areas during pacing.

To quantify the degree of synchronization, we calculated the SDCL and phases of VF at prepacing, pacing, and postpacing periods. SyncP decreased SDCL significantly during pacing and postpacing periods compared with prepacing periods in the paced area but not outside the pacing area (Table 1). In ODP and HFP, no differences were found in SDCL among the three periods (Table 1). ODP was partially effective in decreasing the postpacing SDCL in only a limited range of VFCLs (from 8.6 ± 4.0 to 5.7 ± 2.1 ms at VFCL between 65 and 80 ms; from 7.6 ± 2.4 to 8.7 ± 3.5 ms at VFCL <65 or >80 ms, \( P < 0.01 \)). Independent SyncP and simultaneous SyncP showed similar SDCL during pacing [5.1 ± 2.7 vs. 4.6 ± 3.9 ms, respectively, \( P = \) not significant (NS)] and postpacing periods (5.5 ± 3.1 vs. 5.4 ± 3.0 ms, respectively, \( P = \) NS). The SDCL in the paced area was lower than in the nonpaced area regardless of the pacing protocol, primarily because the sites used to measure spatial dispersion in the nonpaced area were widely separated, whereas those in the paced area were close together (Fig. 1A). During the prepacing period, as shown in Fig. 3, various phases coexist, and 6–12 phase singularity points are always present (9.08 ± 3.13 points/frame). However, during the pacing period, color phase maps become homogenous, and the number of phase singularity points decrease (5.38 ± 2.59 points/frame, \( P < 0.001 \)). Cumulative 100-frame (230 ms) phase singularity point maps also show a decrease in the number of phase singularity points during pacing and imme-

Fig. 4. Examples of ventricular tachycardia/VF termination by Sync P. The solid horizontal bars represent pacing periods. A and B: bipolar electrograms. C and D: optical action potentials. A: independent SyncP terminated VF. B: continuous tracing showing VF termination 2.6 s after simultaneous SyncP. C: independent SyncP changed VF to VT followed by termination in 1.6 s (not shown). D: simultaneous SyncP terminated VF.
SyncP showed a higher pacing termination rate with lower electrical energy than ODP and HFP. We observed termination of VF within 3 s after heart pacing in 6 of 11 rabbits. The status of the heart was continuously monitored for at least 1 min after the cessation of pacing. No episode of spontaneous defibrillation occurred between 3 s and 1 min. Figure 4 shows examples of VF termination by SyncP. The VF pacing termination rates were 16.0% by SyncP (17/106 episodes), 2.1% by ODP (1/48 episodes, \( P < 0.01 \)), and 1.6% by HFP (12/29 episodes, \( P < 0.0001 \); Fig. 5). The pacing termination rate of independent SyncP (14.8%, 9/61 episodes) was similar to that of simultaneous SyncP (17.8%, 8/45 episodes, \( P = \text{NS} \)). The mean delivered electrical energy was significantly lower in SyncP compared with ODP (\( R^2 = 0.416, P < 0.0001, 95\% \) confidence interval; Fig. 5). The energy consumptions according to the pacing currents were also lower in SyncP than in ODP (2, 5, and 10 mA) and in HFP (2 and 5 mA), respectively (Table 2). Within the two SyncP protocols, independent SyncP required significantly lower electrical energy than simultaneous SyncP (Fig. 5 and Table 2).

Spontaneous termination was rare without pacing. To measure the spontaneous termination rate in rabbit hearts, we allowed VF to persist for >5 min. We experienced a 16.0% spontaneous termination rate in 81 episodes of VF in 3 rabbit hearts, and most (92.3%, 12/13 episodes) occurred within 15 s of induction. No spontaneous termination occurred after 28 s of sustained VF in this control study. To further test the significance of pacing-induced VF termination against spontaneous termination, we conducted a separate study to compare the effects of simultaneous SyncP (5 mA) and the same protocol with 0 mA for sham pacing in three additional hearts. Under these conditions, the termination rates of SyncP and sham pacing were 23.3% (7/30 episodes) and 3.3% (1/30 episodes), respectively (\( P < 0.05 \)). From these control experiments, it appeared that spontaneous termination after 30 s of sustained VF was quite rare, and SyncP was a significant intervention in facilitating spontaneous termination.

### DISCUSSION

A novel finding of this study is that SyncP decreased the complexity of fibrillation in the pacing area through synchronization of activation. To our knowledge, this is the first experimental attempt to synchronize VF wavefronts using interactive pacing in the excitable gaps. SyncP could terminate VF in ~15% of the total episodes. We also demonstrated that applying SyncP during VF results in a higher termination rate than that of ODP or HFP.

An important feature of SyncP was the use of depolarization of a local reference site to guide the pacing pulse delivery. Pacing current was delivered only when the reference site was depolarized. This reference site served as an endogenous timing reference whose frequency varied with the overall progression of VF but could be distinctive from neighboring sites. Our results support the concept that adaptive pacing is superior to the fixed-frequency pacing in synchronizing and terminating irregular wavefronts. The use of a local reference is fundamentally different from other types of synchronized defibrillation, which time the shock to the peak or trough of globally recorded electrical signals (13, 15). Future studies will determine whether using a global frequency reference in SyncP is effective in achieving the synchronization effects.

Feedback control of VF has been studied in mathematical modeling (4, 18). While these modeling data demonstrated satisfactory termination of single, symmetrical vortex, a detailed analysis on the termination of multiple vortexes resembling more realistic VF has not been shown. In addition, the eventual termination of reentry requires pushing or shifting the vortex to the inexcitable border of the tissue. In the present study, there was no evidence of vortex extinction at the ventricular borders when the synchronized pacing was

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**Table 2. Electrical energy consumption of each pacing protocol**

<table>
<thead>
<tr>
<th>Pacing Protocol</th>
<th>10 mA</th>
<th>5 mA</th>
<th>2 mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent SyncP (n = 61)</td>
<td>8.67 ± 6.27</td>
<td>2.85 ± 2.33</td>
<td>0.65 ± 0.40</td>
</tr>
<tr>
<td>Simultaneous SyncP (n = 45)</td>
<td>25.42 ± 9.65</td>
<td>6.64 ± 2.94</td>
<td>1.46 ± 0.61</td>
</tr>
<tr>
<td>ODP (n = 48)</td>
<td>31.80 ± 12.24</td>
<td>7.63 ± 3.67</td>
<td>1.59 ± 0.83</td>
</tr>
<tr>
<td>HFP (n = 58)</td>
<td>93.60 ± 84.82</td>
<td>16.90 ± 13.06</td>
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</table>

Values (in mJ) are means ± SE; n, no. of rabbits. *\( P < 0.0001 \); †\( P < 0.001 \); ‡\( P < 0.05 \).
applied. Our pacing algorithm was designed to directly stimulate the excitable gaps, whereas Biktashev and Holden (4) used a time delay from the activation of the monitoring site to stimulate the tissue, and the important concept of “cessation phase” suggested by Krinsky et al. (18) is not applicable in fibrillation with multiple vortexes. Nevertheless, our results are consistent with the suggestion from these models that the defibrillation requirement could be lowered by at least an order of magnitude using feedback control.

**Multisite ODP and HFP.** ODP has been a classical method for terminating reentrant tachycardia. There have been a few trials using ODP to control rapid VT that is faster than the usual VT detection zone of implantable cardioverter-defibrillator (1, 5). However, the success of pace termination is limited by myocardial refractoriness, excitable gaps, conduction time to the circuit, and circuit abolition or reinitiation (36). It was reported that the incidence of postpacing acceleration of monomorphic VT increases and the chance of termination decreases with decreasing prepacing tachycardia cycle length, which carries a risk of VF perpetuation. ODP may pace at partially repolarized temporal excitable gaps and accelerate VF (12). The electrical energy consumption of ODP is also higher than that of SyncP because ODP is random, regardless of tissue excitability. Therefore, the efficacy of ODP is variable depending on the characteristics of the arrhythmia.

HFP with subthreshold current has been reported to be effective not only in inhibition of premature ventricular extrastimuli (31) but also in termination of sustained VT in animals (28) and in humans (30). Subthreshold HFP may interrupt reentry by prolonging repolarization (37), inducing supernormal conduction (27), or inducing local release of catecholamine (30). However, all these studies were performed with endocardial pacing electrodes. In the present study, we could not observe any effective control of VF with an epicardial HFP protocol.

**Possible mechanisms of VF termination with SyncP.** One possible explanation of the defibrillation mechanism of SyncP is the electrical reduction of available tissue mass to sustain VF. Kim et al. (16) demonstrated that as tissue mass was decreased, the number of wavefronts decreased, and the lifespan of reentrant wavefronts increased, resulting in a parallel decrease of the dynamic complexity of VF. Although SyncP did not mechanically reduce tissue mass, pacing could have induced a “virtual reduction” of tissue mass that enlarged the synchronized area and decreased the dynamic complexity of VF, leading to the termination of fibrillation. From our data, we estimated that the approximate tissue mass surrounded by the pacing electrodes was 9–11% of the ventricular mass. Further studies could explore such a mechanism by changing the size of the synchronized area using optimized electrode placement. A second possible mechanism is that SyncP eliminated the excitable gap in a small heart and led to conduction block and halting the reentrant circuit. This is likely the case when pacing in the excitable gaps without a reference site. Our initial trial with such an approach failed to capture or terminate VF. Another potential mechanism is that the pacing was performed in a dominant domain, where it halted the mother rotor (38). In the present study, because we performed optical mapping only on a limited area on the heart, such a mechanism cannot be directly established.

The most promising hypothesis is that local synchronization of activation facilitates spontaneous termination. VF can be classified as sustained or transient depending on whether it can spontaneously revert into sinus rhythm. Transient VFs exhibit a higher degree of synchronization than the sustained ones (34). It is likely that SynP induced an enhanced wavefront organization during VF, converted sustained VF into transient VF, and eventually led to spontaneous termination.

**Limitations.** One limitation of the present study is that we mapped a limited epicardial area, and SyncP could be applied only to this limited area. The second limitation is that we used cytochalasin D to eliminate the motion artifacts, and this drug might facilitate VF termination. However, this uncoupler was also used in the control study of spontaneous VF termination, the sham pacing protocol, and in ODP and HFP. The use of cytochalasin D did not appear to invalidate the comparison between SyncP and other pacing protocols. Finally, clinical application of the SyncP protocol is not feasible at present due to technical constraints such as the toxicity of the dye and motion artifacts.

In conclusion, this is the first attempt to synchronize and terminate VF using multielectrode, feedback pacing in the excitable gaps. We demonstrated that optical recording-guided, real-time SyncP had a higher successful pacing termination rate while requiring lower electrical energy than ODP or HFP.

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**DISCLOSURES**

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