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Method of Post-Shock Synchronized Pacing in the Excitable Gaps

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Abstract—**Ventricular fibrillation (VF) can be synchronized with a novel synchronized pacing technique (SyncP) using low-energy pacing pulses, which causes pace termination of VF. Synchronized pacing (SyncP) is defined as optical recording guided real-time detection and stimulation of spatiotemporal excitable gaps. In this paper, we investigate the effect of post-shock SyncP strategy on improvement of defibrillation efficacy. After a near-threshold defibrillation shock, when the reference site detected the earliest activation of the reinitiated VF, a 5-mA electric stimulus was delivered from the post-shock pacing electrode to depolarize the excitable gap. This area of wavefront synchronization may lead to a change in the timing of VF propagation, which is important for VF termination. Here, we implemented the concept of post-shock synchronized pacing by a real-time feedback mechanism and demonstrated a successful VF termination by the post-shock SyncP strategy. Further optimization of this technique may prove effective in improving the defibrillation efficacy for low-energy ventricular defibrillation.**

I. Introduction

Ventricular fibrillation (VF) is a very fast, irregular heart rhythm in the lower heart chambers (ventricles). As a result, the ventricles begin to quiver instead of contraction, and they can no longer pump blood form the heart to the rest of the body. It is the most common cause of cardiac sudden death, which accounts for 300,000 to 400,000 deaths annually in the US [1,2].

To effectively terminate VF, delivery of high-energy shocks is often used, which causes significant pain in patients and requires high stored energy. Substantial efforts have been devoted to improve the defibrillation efficacy [3-5]. Recently, use of low-energy electrical pulses to pace the myocardium during the arrhythmia has attracted great interest [6,7]. When VF wavefronts propagate across the tissue, there are regions of tissue that can still be excited by external stimulation. These regions are called "excitable gaps"[8,9]. The excitable gaps can be captured with a pacing frequency slightly higher than the fibrillation frequency, which is known as "overdrive pacing." However, the limited success of this approach to VF termination may be attributed to the instability of the VF frequency. Alternatively, optical recording guided real-time detection and stimulation of spatiotemporal excitable gaps – synchronized pacing (SyncP) – can cause pace termination of VF with millijoule energy [7]. The SyncP approach has been shown experimentally to be eight times more likely to terminate VF than simple overdrive pacing [7]. The concept of pacing during VF is based on the use of low-energy pulses to capture the fibrillatory tissue, preferably during the excitable gaps [9-11]. Enlargement of the captured region may eventually lead to VF termination.

Pre-shock SyncP technique has previously been demonstrated to effectively improve efficacy of defibrillation by synchronizing VF activations and increasing probability of shock delivery to the unexcitable low-voltage gradient. Accordingly, the spatiotemporaly controlled defibrillation (STCD) strategy using defibrillation shocks followed by SyncP may also be effective in defibrillation efficacy improvement. The post-shock VF reinitiation usually shows several cycles of regular beats followed by more fragmental wave propagation. It is hypothesized that if the early regular propagation can be interrupted, then the VF reinitiation will be terminated. Since the post-shock SyncP has not been demonstrated, the objective of this study is to implement the concept of this technique and apply a post-shock synchronized pacing for potential VF termination.

II. Methodology

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

A. Optical Mapping of the Isolated Rabbit Heart

Ten New Zealand White rabbits (weight of 4 to 5 kg) were intravenously injected with 1000 units of heparin and anesthetized with ketamine (20 mg/kg) and xylazine (5 mg/kg). After a midline sternotomy, the whole heart was isolated and perfused with 37˚C Tyrode solution (composition in mM: 125 NaCl, 4.5 KCl, 0.25 $MgCl_2$, 24 $NaHCO_3$, 1.8 NaH_2PO_4, 1.8 $CaCl_2$, and 5.5 glucose) through ascending aorta. The coronary perfusion pressure was regulated between 80 and 95 nnHg. The tissues were stained with 0.5 μM di-4-ANEPPS (Molecular Probes; Eugene, OR). After illumination by excitation laser light at 532 nm, and the epifluorescence from the heart tissues was collected through a long-pass filter (cutoff wavelength: 600 nm) with a high-speed charge-coupled device camera (485 frames/s, model CA D1-0128T; Dalsa; Waterloo, Ontario, Canada).

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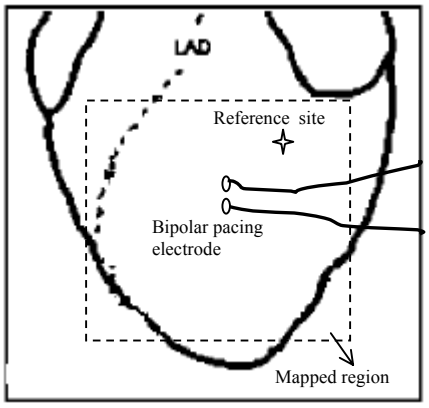

Figure 1. Schematic diagram of heart structure and location of reference site and biopolar post-shock pacing electrode in the mapped region.

Image acquisition was controlled by a custom-designed program based on Labview™ and the IMAQ Vision toolset (National Instruments; Austin, TX). Signals from 128×128 sites were acquired simultaneously in the mapped region of the left ventricular (LV) anterior wall (20×20 mm^2; Fig. 1). Electromechanical uncoupler cytochalasin D (Sigma Aldrich; St. Louis, MO) was added to the perfusate at a concentration of 5 μM to inhibit tissue contraction.

B. Post-shock Synchronized Pacing Protocol

VF was induced by burst pacing (cycle length: 50-80 ms, 5-ms pulse duration, 5-mA current for 10-20 s) in the left ventricle apex. Before performing post-shock pacing, we waited at least 30 seconds to avoid spontaneous VF termination. Defibrillation electrode (anode) was placed in the right ventricle while the reference pad (cathode) against the heart posterior wall. The post-shock pacing electrode (Teflon-coated stainless steel, 0.3-mm diameter) was in contact with the epicardium of the LV anterior wall in the mapped region.

In the SyncP technique, a "reference site" is required in addition to the physical post-shock pacing site (Fig. 1). The reference site was used to determine the timing of activation immediately after defibrillation shock delivery. The activation is defined as the crossover of the threshold level which is independently set in real time for the reference and post-shock pacing sites to 40% of the maximum optical potential amplitude. The action potentials were monitored optically at sites directly adjacent to (<2 mm) the reference site. To perform STCD, the algorithm incorporated in the custom-designed Labview™ program is: immediately after the defibrillation shock delivery (50-300 V), when (1) the reference recording site is depolarized by a VF wavefront above the threshold level and (2) the post-shock pacing site is below threshold, a 5-mA electrical stimulus (3-ms duration, rectangular pulse) was delivered from the post-shock pacing electrode by a real-time feedback mechanism. The reference site was placed in the mapped region arbitrarily based on the prediction of early site location.

III. Results and Discussion

A. Feasibility of Post-shock SyncP

The pupose of defibrillation of VF is to apply a controlled electrical shock to the heart, which leads to depolarization of the entire electrical conduction system of the heart. When the defibrillation shock is strong enough, there is an isoelectric window which is the time instance between the shock and the initiation of the first postshock action potential when the entire mapped field is homogeneously repolarized [12,13]. To improve the defibrillation efficacy by spatiotemporaly controlled defibrillation followed by SyncP, the post-shock pacing electrode needs to discharge electrical stimulus to heart tissues when the reference site is depolarized by a VF wavefront (first activation following isoelectric window) to a potential above the threshold level after defibrillation shock. Fig. 2 shows the isochrone map of first beat propagation in the mapped region after near-threshold (250 V) shock delivery, demonstrating a successful post-shock synchronized pacing. The reference site, placed in the right upper corner, detected the reinitiated VF activation and depolarized by its propagation. Consequently, in the meantime, a firing of 5-mA electric stimulus was performed at the post-shock pacing site, creating a functional block area. This area of synchronized activation may lead to a change in the timing of VF propagation, which is important for VF termination [4,14,15]. This result shows that the feasible post-shock SyncP technique can be an effective strategy for manipulation of timing during VF propagation. Previous applications of other SyncP protocol have led to successful VF termination [7,16].

The success rate for the delivery of SyncP stimulus after defibrillation shock is about 50%. The main cause for the unsuccessful cases is misplaced reference sites. Based on the algorithm, the location of the reference site is critical for accurate and timely post-shock pacing stimulus. While the reference site is fixed at a certain time, the location of early site often varies and is difficult to predict. When the reference site is not around the early site where the propagation of first beat starts after shock delivery, the post-shock pacing electrode will either not discharge or function

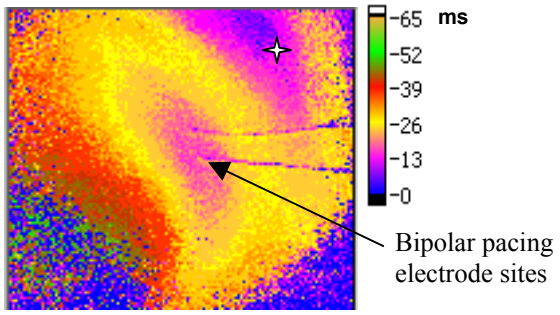

Figure 2. Isochrone map of first beat propagation after defibrillation shock at 250 V. Plus sign indicates the location of the reference site (right upper corner).

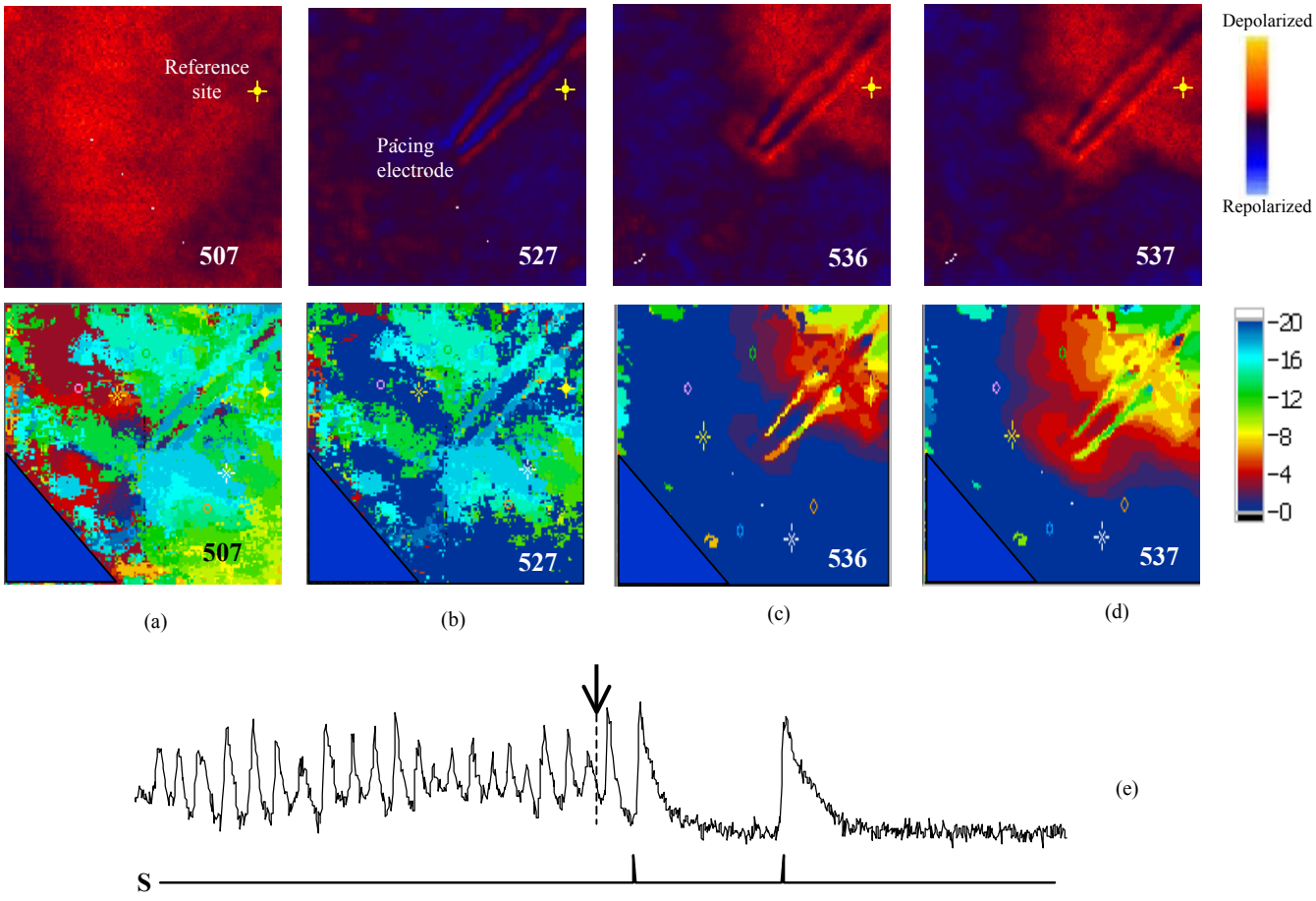

Figure 3. Voltage and isochrone maps indicating firing of 5-mA electric stimulus discharged by the post-shock synchronized pacing electrode. The frame numbers are indicated in the corners of each figure. In voltage maps, the red color represents deolarization, and the blue color, repolarization. (a) Depolarization by shock; (b) Isoelectric window; (c) Firing of post-shock Sync P; (d) Wavefront synchronization during VF; (e) Optical recording data of pre-shock VF, shock timing (arrow), and post-shock pacing (S: post-shock pacing stimulus).

with a wrong timing. Multiple reference sits around the mapped region may improve the accuracy of early site detection and efficiency of post-shock synchronized pacing.

B. VF Termination by Post-shock SyncP

Fig. 3 shows a successful VF termination by STCD strategy using defibrillation shock at 300V followed by synchronized pacing. The optical mapping data consists of pre-shock VF, defibrillation shock, and post-shock SyncP. After the shock delivery (Fig. 3a), an "isoelectric window" (IW) was present (Fig. 3b). When the first beat activation was detected by the reference site, the post-shock pacing electrode was activated to deliver a 5-mA electric stimulus to the myocardium around the pacing sites (Fig. 3c). With the external stimulus on the excitable gaps, the wavefront synchronization during VF propagation was achieved (Fig. 3d). Wavefront synchronization and synchronization of repolarization are important for VF termination. Experimental and theoretical studies [7,17] showed that pacing during the excitable gaps aided in decreasing the dispersion of VF activations, eventually leading to VF termination. As shown in the optical recording data (Fig. 3e), the VF was successfully terminated by the post-shock SyncP strategy.

Previously, at least two mechanisms have been proposed to explain the defibrillation effect of synchronized pacing. One possible explanation of the defibrillation mechanism of SyncP was that the 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 [7]. Another possibility is that pacing in the dominant tissue area that is likely to exhibit a "mother rotor" behavior will suppress VF conduction. In addition to these possible mechanisms, in the post-shock pacing mode, the objective is to perturb the activation timing of reentry that may terminate the post-shock reentry. More systematically designed studies are under way to better understand the mechanism. This will be beneficial for further optimizing the post-shock SyncP strategy to effectively improve the defibrillation efficacy with a combination of low-energy shock and pacing stimulus.

IV. Conclusion

A feasibility study of post-shock synchronized pacing was performed to investigate the effect of a novel post-shock pacing technique on improving the defibrillation efficacy. Termination of VF was demonstrated with interference of the time of wave propagation during the initial stage of VF reinitiation, a strategy employing optical recording guided real-time detection and stimulation of spatiotemporal excitable gaps. Perfection of this strategy may prove to be promising in VF management with low-energy shocks and pacing pulses.

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