Effects of shock strengths on ventricular defibrillation failure

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Abstract

Background: The mechanism of defibrillation is controversial. Reentry appearing immediately after the shock has been shown to be responsible for defibrillation failure in some studies while other studies have demonstrated that a rapid train of focal activations with the first focus appearing >50 ms after the shock is responsible for failed defibrillation. We tested the hypothesis that both patterns can occur, but at different shock strengths. Methods and results: Biphasic 6/4 ms shocks of 100–900 V in 100-V increments were given after 10 s of ventricular fibrillation from electrodes in right ventricular apex and right atrium in five isolated pig hearts. Transmembrane activity was optically mapped from the anterior and posterior epicardium using two CCD cameras. The defibrillation threshold (DFT) was 786±199 V. The interval from the shock to the earliest post-shock activation was zero for shocks <400 V but increased with increasing shock voltage to 62±6 ms at 800 V. The number of post-shock phase singularities, which is related to reentry incidence, decreased continuously from pre-shock values for 100-V shocks to zero as the shock strength increased to 600 V. Focal activations were observed after shocks >600 V with no epicardial reentry present. Conclusion: Reentry is responsible for defibrillation failure for low-strength shocks. As the shock strength approaches the DFT, a focal epicardial activation pattern becomes responsible for failed defibrillation. Thus, the mechanism of defibrillation failure depends on shock strength, with focal activation as the mechanism for the clinically important near-DFT strength shocks.

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1. Introduction

Although defibrillation has been practiced for decades, its mechanism is still debated [1–3]. Optical mapping studies using small animals (i.e. rabbits and guinea pigs) found that reentrant activation immediately after the shock is the pattern responsible for failed defibrillation [2–5]. However, in epicardial electrical mapping studies and a recent optical mapping study in large animals (i.e., pigs and dogs) using shocks near the defibrillation threshold (DFT) in strength, no immediate post-shock reentry was observed [6–9]. Instead, following a ~40–50 ms quiescent period after the shock (the post-shock interval) a rapid train of focal activations occurred. A recent three-dimensional mapping study of defibrillation using near-DFT shocks in pigs demonstrated a similar finding [10]. However, earlier electrical mapping studies in dogs reported that the post-shock interval decreased as the shock decreased to a strength well below the DFT [11] and that reentry was sometimes observed following shocks creating only a weak electrical field in the tissue [12].

It is important to resolve this discrepancy because of its implications for improving defibrillation. It has been suggested that various shock strengths may play different roles, causing the disparity of findings [13,14]. In the present study, optical mapping was performed to record transmembrane activity of the whole ventricular epicardium following a wide range of shock strengths in isolated pig hearts, which more closely resemble human hearts in size than do rabbit or guinea pig hearts. We tested the following hypotheses: (1) reentry is responsible for defibrillation failure with shocks well below the DFT, and (2) focal activation is responsible for defibrillation failure with near-DFT shocks.
2. Materials and methods

This study was approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee. The protocol followed the guidelines of the National Institute of Health standards defined by the United States Department of Agriculture Animal Welfare Act and outlined in the Guide for the Care and Use of Laboratory Animals, National Institute of Health Publication #85-23, revised 1996.

2.1. Experimental preparation

Five pigs (20–25 kg) of either sex were anesthetized and maintained under physiologic conditions as described elsewhere [6]. The heart was isolated and perfused at a constant flow of 220 ml/min with 37 ± 1 °C Tyrode’s solution (in mM: NaCl 123, KCl 4.5, CaCl₂ 1.8, MgCl₂ 0.98, NaHCO₃ [20], Na₂HPO₄ 1.01, and dextrose [11] plus bovine albumin 0.04 g/l), and gassed with 95% O₂, 5% CO₂ similar to a method described previously [9]. An ECG was recorded by epicardial electrodes on the right (RV) and left ventricles (LV) with the ground on the aortic root.

A catheter with a 34-mm platinum coated titanium coil defibrillation electrode (Guidant) was inserted into the RV apex. A titanium mesh electrode (2.5-cm diameter) was sutured to the right atrium. Biphasic, truncated exponential shocks (6/4 ms) were delivered to the RV coil (cathodal, first phase) and the right atrial mesh electrode (anodal, first phase) from a defibrillator (Ventritex HVS-02).

2.2. Mapping of defibrillation

Diacetyl monoxime (DAM, 20 mM/l) was added to the perfusate to stop cardiac motion. The heart was stained with di-4-ANEPPS (10.4 μM/l, Molecular Probes), infused via the aortic root cannula. Ventricular fibrillation (VF) was induced by delivering 60-Hz alternating current for 3–5 s to the RV apex via an electrode at the catheter tip. After 10 s of VF, shocks of 100–900 V in 100 V increments were delivered in nonrandomized order. Transmembrane activity from the anterior and posterior epicardial surfaces was recorded from 0.5 s before until 2.5 s after each shock by 2 CCD cameras as described previously [9,15]. Each pixel was recorded from an epicardial area of 0.66 × 0.14 mm². The fluorescence signals were filtered using a 5-point temporal filter. All recordings were normalized such that the minimum and maximum values, and thus the action potential amplitude (APA), for all sites was identical [9]. No spatial filtering was performed. The signal-to-noise ratio was 19 ± 3.
2.3. Data analysis

Following each shock, the post-shock interval, defined as the interval from shock onset to time of the earliest post-shock activation, was determined. An activation was identified when the optical recording increased from below 50% of the APA in one frame to above 50% of the APA in the next frame [9]. The number of pixels which registered activations occurring during the single optical frame were calculated (1) immediately before each shock was delivered (#PRE) and (2) at the post-shock interval (#POST). The transmembrane patterns were converted to “phase maps” as described previously [16] and phase singularities were identified using an automated algorithm [17]. Although all phase singularities may not represent complete reentrant pathways, a phase singularity is always present for complete reentry. Thus, the number of phase singularities at any instant is greater than or equal to the number of reentrant waves. The number of phase singularities was determined: (1) for the last VF cycle immediately before each shock, and (2) for the first cycle immediately after the end of each shock.

Fig. 4. Examples from the same heart of phase maps of the last cycle before the shock (left panel) and the first cycle after shocks (right panel) of 100 V (A), 200 V (B), 600 V (C), and 800 V (D) that failed to defibrillate. Colors represent phase and + and − indicate phase singularities of opposite chirality. Phase singularities and reentry were observed during VF just before the shock in all cases. (A–B) Post-shock phase singularities were observed after failed 100 and 200 V shocks. Visual analysis of animations of the optical recordings indicated that many of the phase singularities represented reentrant activations occurring immediately after the shock so that the post-shock interval was 0. (C–D) No phase singularities were observed after the 600 and 800 V shocks, consistent with the zero #PS-POST in Fig. 3. For the 600 V shock, activation propagated away in all directions from two early sites, one at the apex and the other at the lateral base of the left ventricle, both of which appeared after a post-shock interval of 42 ms. For the 800 V shock, a single wavefront of activation appeared at the apex and propagated away in all directions in a focal pattern after a post-shock interval of 72 ms.
Data were compared using one-way analysis of variance. When statistical significance was found, individual comparisons were performed with Fisher’s post-hoc test. Values are shown as mean ± standard deviation. Differences are considered significant for \( P \leq 0.05 \).

3. Results

The DFT was 786 ± 199 V. Shocks of 100–400 V in strength always failed to defibrillate (Fig. 1). As shock strength increased, the incidence of successful defibrillation also increased, reaching 100% for 900 V shocks (Fig. 1).

The post-shock interval was 0 for shocks weaker than 400 V and increased to 62 ± 6 ms at 800 V (Fig. 2). There were no ectopic beats after 900 V shocks, which all succeeded; therefore the post-shock interval was not determined. There was no significant difference in \#PRE (561 ± 50 pixels) among shock episodes. However, \#POST decreased with increasing shock strength up to 500 V and was significantly smaller than \#PRE for shocks ≥ 200 V (Fig. 2).

The number of phase singularities during VF immediately before the shock did not vary with shock strength (Fig. 3). However, the number of phase singularities immediately after the shock decreased continuously from pre-shock values to 0 as the shock strength increased from 100 to 600 V. The number of phase singularities immediately after the shock was statistically smaller than the number of phase singularities immediately before the shock for all shocks stronger than 200 V.

Examples of the phase maps before and after different strength shocks are shown in Fig. 4. During VF, reentrant activations were always observed before the shock for all shock strengths, as determined by visual examination of computer animations of the optical recordings as well as by a decrease in the number of phase singularities. Following weak shocks (Fig. 4A–B), phase singularities and reentry also were observed immediately after the shock (post-shock interval = 0). Following near-DFT shocks (Fig. 4C–D), a non-zero post-shock interval was observed and reentry was absent, consistent with a zero number of phase singularities immediately after the shock for shocks ≥ 600 V (Fig. 3). Focal activations were always observed after 600 to 800 V shocks in all hearts, and the number of foci during the first post-shock activation cycle decreased to one for 700 and 800 V shocks.

4. Discussion

The major findings in this study are as follows: (1) the post-shock interval was zero at low strength shocks (<400 V) but increased monotonically as shock strength increased, (2) \#POST became significantly smaller than \#PRE as shock strength increased to ≥ 200 V, (3) the number of phase singularities immediately after the shock decreased as shock strength increased and was zero for shocks ≥ 600 V, (4) defibrillation did not reach 100% success until shock strength was 900 V, even though all phase singularities immediately after the shock were completely terminated and no reentry was observed for shocks ≥ 600 V, (5) focal activation occurred following shocks ≥ 500 V.

4.1. Reentry as a mechanism of failed defibrillation at weak strength shocks

Reentry immediately following the shock has been demonstrated as the mechanism responsible for failed defibrillation in optical mapping studies using small heart models [3–5]. Most of these studies used weak shock strengths [18,19]. One exception is a study by Efimov et al. [3–5] which reported that after shocks that defibrillated isolated rabbit hearts, post-shock reentry was observed twice. The activation pattern after the other shocks was not reported. Optical or electrical studies in large hearts with failed near-DFT shocks have uniformly reported a post-shock interval followed by several rapid focal activation cycles that eventually degenerate back into reentry and VF [6–10]. The present study suggests that both results are valid and that the mechanism of defibrillation failure depends on the shock strength. There was no post-shock interval at weak shock strengths and reentry was always observed immediately after these shocks, consistent with previous reports [3,11,18]. For shocks < 600 V, reentry was documented after the shock by both animated maps and the number of phase singularities immediately after the shock, supporting the hypothesis that reentry is responsible for defibrillation failure [3–5].

4.2. Focal mechanism of failed defibrillation for near-dft shocks

Although the number of phase singularities immediately after the shock was 0 and reentry was not observed for shocks ≥ 600 V, defibrillation success did not reach 100% until shock strength was 900 V (Fig. 1). These results suggest that immediate post-shock reentry is not responsible for failed defibrillation for shock strength near the DFT.

As shock strength approached the DFT, a post-shock interval developed and increased as shock strength increased (Fig. 2). Instead of reentry, earliest post-shock activation always propagated centrifugally away from the early site in a focal pattern, after a brief post-shock interval. These findings are consistent with previous optical and electrical mapping studies of near-DFT shocks that reported that the first several post-shock cycles always arise and propagate away from the early site in all directions in a focal pattern [6–9]. Therefore, with the same species and a similar near DFT shock strength, focal activity rather than immediate post-shock reentry was
observed regardless of the mapping technique used to record cardiac electrical activity. It is possible that focal activation observed in this and other studies represents epicardial breakthrough resulting from reentry occurring intramurally or subendocardially. However, a recent three-dimensional mapping study of defibrillation using near-DFT shocks demonstrated that the earliest post-shock activation always arises focally and immediate post-shock reentry was not observed in that study [10]. Thus, it is unlikely that the activation pattern observed in the present study arises from intramural reentry.

5. Limitations

Although DAM may change VF activation patterns [20], it does not convert VF to ventricular tachycardia in isolated swine hearts [9]. In addition to suppressing motion, DAM was used so we could compare our results with previous defibrillation studies that used a similar agent to stop cardiac motion [3,8,9,18]. It must be noted that this study was performed in an ex vivo model. Therefore, extrapolation of the results to an in vivo heart must be done with caution [22].

6. Conclusion

We found drastically different mechanisms for defibrillation failure at low and high strength shocks in swine. At low strength shocks, propagation with reentry was responsible for failed defibrillation. As shock strengths increased to just below the DFT, the number of phase singularities immediately after the shock decreased to 0 and immediate post-shock reentry was absent, yet defibrillation still failed. Defibrillation failure for near-DFT shocks was the result of a rapid train of focal activations that were not present before the shock.

7. Clinical implication

A recent study has shown that the DFT was markedly decreased after the administration of a drug that prevents the occurrence of delayed after depolarizations, raising the possibility that these focal activations may arise from triggered activity [21]. If future studies demonstrate these cycles arise from triggered activity, eliminating the triggered activity pharmacologically or by electrical stimulation may improve defibrillation efficacy.

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