Experimental paper

An investigation of inter-shock timing and electrode placement for double-sequential defibrillation

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Abstract

Background: Double-Sequential Defibrillation (DSD) is the near-simultaneous use of two defibrillators to treat refractory VF. We hypothesized that (1) risk of DSD-associated defibrillator damage depends on shock vector and (2) the efficacy of DSD depends on inter-shock time.

Methods: Part 1: risk of defibrillator damage was assessed in three anaesthetized pigs by applying two sets of defibrillation electrodes in six different configurations (near-orthogonal or near-parallel vectors). Ten 360J shocks were delivered from one set of pads and peak voltage was measured across the second set. Part 2: the dependence of DSD efficacy on inter-shock time was assessed in ten anaesthetized pigs. Electrodes were applied in lateral-lateral (LL) and anterior-posterior positions. Control (LL Stacked Shocks; one vector, two shocks \( \sim 10 \text{s} \) apart) and DSD therapies (Overlapping, 10 ms, 50 ms, 100 ms, 200 ms, 500 ms, 1000 ms apart) were tested in a block randomized design treating electrically-induced VF (n \( \sim 89 \) VF episodes/therapy). Shock energies were selected to achieve 25\% shock success for a single LL shock.

Results: Part 1: peak voltage delivered was 1833 \( \pm \) 48 V (mean \( \pm \) 95\% CI). Peak voltage exposure was, on average, 10-fold higher for parallel than orthogonal vectors (p \( < \) 0.0001). Part 2: DSD efficacy compared to Stacked LL shocks was higher for Overlapping, 10 ms, and 100 ms (p \( < \) 0.05); lower at 50 ms (p \( < \) 0.05); and not different at 200 ms or longer inter-shock times.

Conclusion: Risk of DSD-associated defibrillator damage can be mitigated by using near-orthogonal shock vectors. DSD efficacy is highly dependent on the inter-shock time and can be better, worse, or no different than stacked shocks from a single vector.

Institutional Protocol Number: University of Alabama at Birmingham Institutional Animal Care and Use Committee (IACUC) Protocol Number 06860.

Keywords: Double-sequential defibrillation, Defibrillator damage, Refractory ventricular fibrillation

Introduction

For patients with VF cardiac arrest, defibrillating the heart is a crucial link in the chain of survival. Defibrillation is probabilistic and characterized by a dose response curve; increasing shock size increases the probability that a shock will terminate VF (within limits) and delivering repeated shocks over time eventually terminates VF in most patients.\textsuperscript{3} Confronted with shock-resistant VF in individual patients, healthcare providers have sometimes resorted to using two defibrillators “at once”, a procedure called double-sequential defibrillation (DSD) that is considered off-label use.

Several publications report the practice of DSD in individual or series of cases.\textsuperscript{4-20} In these cases, when the rhythm was VF after several countershocks, a second set of pads were applied and two defibrillators triggered manually to deliver two shocks at about the same time. The therapy delivered by DSD varies widely in practice; with many approaches to pad
placement and no reports of ways to precisely control the relative timing of the two shocks.21-24 Good science is needed to guide the practice of DSD, both to inform the selection of pad placement and to identify optimal timing of the shocks. If defibrillator damage occurs,25 it is likely caused by exposure of circuits of one defibrillator to high voltages generated by the other defibrillator during therapy delivery, which can potentially be mitigated by appropriate placement of the four pads. Defibrillation efficacy likely varies with relative shock timing, as suggested by earlier studies of internal and transthoracic defibrillation.26-28

We hypothesized that the magnitude of the exposure of one defibrillator to the voltage generated by the other would vary widely with positioning of the two pairs of electrodes. Second, we hypothesized that, for some DSD shock timings, shocks from two defibrillators would have higher defibrillation efficacy than two shocks delivered, over time, from a single defibrillator.

Methods

This investigation conformed to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1996) and was approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee.

The study included two protocols. Protocol 1 investigated how the relative placement of two pairs of defibrillation electrodes affected the magnitude of exposure of one defibrillator to the voltage delivered by a second defibrillator. Protocol 2 investigated the dependence of DSD efficacy on the relative timing of the two shocks.

Animal preparation

Swine (n = 13, 9 neutered males, 2 females, 2 males; Yorkshire mix; ~10-16 weeks old) were pre-mediated with intramuscular injections of telazol (~4.4 mg/kg) and xylazine (~4.4 mg/kg), intubated, and anesthetized with isofluorane (1-5% inhalation). Pressure-controlled ventilation was adjusted to hold the end-tidal CO2 between 30-45 mmHg (~10-15 ml/kg/min). ECG and femoral artery pressure were monitored and fluid administered intravenously at 5-10 ml/kg/h throughout the procedure. The thorax was shaved and defibrillation electrodes placed (QUIK-COMBO, Physio-Control, Redmond, WA). A bipolar pacing catheter (PACEL Right Heart Curved Catheter, Daig, Minnetonka, MN) was placed in the tip of the right ventricle for VF induction.

Protocol 1: high voltage exposure

In three pigs (31, 30.5, 25 kg) in normal sinus rhythm, six different electrode configurations (A-F) were tested (Fig. 1). Configurations A, C, and E formed near-parallel defibrillation vectors; configurations B, D, and F formed near-perpendicular/orthogonal vectors. With each configuration of pads, we delivered five 360 J shocks across one pair of pads while measuring the voltage across the second pair of pads, then switched the delivery and measurement pads and delivered 5 more shocks. Peak voltage values were compared using an ANOVA with post-hoc Tukey-Kramer correction (Matlab, Mathworks, Natick, MA).

Protocol 2: efficacy of DSD

Experimental setup

Defibrillation efficacy was measured using a combination of commercial and custom equipment (Fig. 2). Defib1 delivered biphasic truncated exponential (BTE) shocks on a lateral-lateral (LL) vector and Defib2 delivered BTE shocks on a lateral-posterior (LP) vector. The shock area was 45 x 45 cm. The setup was repeated for each of the four pads, with Defib1 delivering the shocks. Each shock was repeated 30 times. The data was analyzed using previously published methods. The shock area was 45 x 45 cm. The setup was repeated for each of the four pads, with Defib1 delivering the shocks. Each shock was repeated 30 times. The data was analyzed using previously published methods. The shock area was 45 x 45 cm. The setup was repeated for each of the four pads, with Defib1 delivering the shocks. Each shock was repeated 30 times. The data was analyzed using previously published methods. The shock area was 45 x 45 cm. The setup was repeated for each of the four pads, with Defib1 delivering the shocks. Each shock was repeated 30 times. The data was analyzed using previously published methods.

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Fig. 2 - Experimental setup. Defibrillators 1 and 2 (Defib1 and Defib2, respectively) were placed in the mode for synchronized cardioversion. Lead II of the ECG from each device was connected to a shock delay controller (see text for description). A switch allowed rapid transition between experimental therapies and rescue shocks from the defibrillator (Rescue Defib). Defibrillation electrodes from Defib1 were placed on the animal in the LL positions and electrodes from Defib2 were placed in the AP positions. A 50 Ω resistor was placed in series with the pig and each study defibrillator. The current and voltage generated by Defib1 and 2 were monitored and recorded for each shock.

shocks on an anterior-posterior (AP) vector (LIFEPAK 20 and 15, respectively, Physio-Control, Redmond, WA), forming approximately orthogonal shock vectors. A custom Shock Delay Controller based on an Arduino Uno microcontroller generated pulses resembling QRS complexes, on two outputs, with pre-programmed time delays. These outputs were connected to the Lead II ECG inputs of Defib1 and Defib2. Both defibrillators were set up to perform synchronized cardioversion and each delivered a shock upon detecting a pulse from the Shock Delay Controller.

A 50-Ω resistor placed in series between the animal and each test defibrillator approximated the average transthoracic impedance of human patients. Consequently, the defibrillators delivered clinically representative shock waveforms; the current and voltage waveforms of all shocks were recorded. A third defibrillator was available to connect rapidly, without a series resistor, for delivery of rescue shocks (200–360 J) when study therapies failed to defibrillate.

Experimental protocol
The same experimental timeline was followed in 10 pigs (29.4 ± 2.5 kg) (Fig. 3A). After delivery of three 100-J conditioning shocks (*Fig. 3A) for stabilization of the skin-electrode interface impedance, the defibrillation threshold (DFT) was measured for Defib1 shocks along the LL vector. We used Dixon’s up-and-down small sample method8 as applied by McDaniel et al.9 The energy setting to use in subsequent steps of the experiment was chosen to be one Dixon step-size lower than the DFT, chosen to achieve ~25% first shock success for a single LL Vector shock. Defib1 and Defib2 were both set to that same energy. We performed nine blocks of randomized tests per animal. In each block we tested every therapy once.

Nine defibrillation therapies were tested: two control therapies and seven DSD therapies (Fig. 3B). Control therapies were delivered by a single defibrillator along a single vector, LL or AP, and consisted of up to two “stacked” shocks delivered approximately 10 s apart. DSD therapies were delivered by two defibrillators, with delivery of a shock along the LL vector and another shock along the AP vector. Seven DSD timing relationships were tested: sequential shocks, separated by intervals of 1000, 500, 200, 100, 50, and 10 ms (trailing edge of first shock to leading edge of second shock), and overlapping shocks (≤7 ms between leading edges of the shocks).

Each test of a therapy consisted of one episode of VF (Fig. 3C). VF was induced by briefly connecting a 9-volt battery to the RV bipolar electrode; then, after 10 s the randomized therapy was administered. If the therapy failed (twice for stacked shocks), up to three rescue shocks were performed. Following defibrillation, the animal recovered for at least four minutes before the next episode was initiated. A successful shock was defined as absence of a shockable rhythm five seconds after shock. Post-shock bradycardic rhythms were briefly paced by manually thumping the chest. If more than seven of the nine therapies in a randomization block failed (or succeeded), the energy settings on both Defib1 and Defib2 were increased (or decreased) by one Dixon step size for the next block (Fig. 3A).

Comparison of shock success
The primary outcome was 1st shock success for DSD therapies versus two-shock cumulative success for Stacked LL Shocks, therefore comparing therapy delivered by two defibrillators with therapy from one defibrillator with equal total energy. We also compared Stacked AP Shocks with Stacked LL Shocks to determine if a change in shock vector could explain the outcomes observed from the DSD therapies. First shock success was defined as the number of 1st shocks (or pair of shocks for DSD) that successfully terminated VF, divided by the number of VF episodes in which a therapy was tested. Two-shock cumulative success was defined as the number of 1st or 2nd shocks that were successful divided by the number of VF episodes. We performed statistical comparison using a logistic regression general linear model. (SAS Co, Cary, NC).

Results

Study 1: high voltage exposure

Each animal received 60 shocks, 10 for each electrode configuration, giving a total of 180 shocks for the study and 30 shocks per pads configuration. The peak voltage applied along the active vector in Study 1 was 1833 ± 48 V (mean ± 95% confidence interval). The corresponding peak voltage measured across the passive pair of pads, the voltage to which the second defibrillator would be exposed, varied 50-fold with the placement of the two sets of defibrillation pads, ranging from 390 ± 48 V for configuration A to 8 ± 3 V for configuration F (Fig. 1). Compared to Pads Configuration A, all other configurations led to significantly lower peak voltage exposure (p < 0.0001). Compared to near-parallel Pads Configurations A, C, and all near-orthogonal Pads Configurations (B, D, and F) resulted in significantly lower peak voltage exposure (p < 0.0001). Near-orthogonal Pads Configurations exhibited an average 10-fold decrease in peak voltage exposure compared to near-parallel configurations.
Fig. 3 – Experimental Protocol. (A) The experimental time line starting with animal preparation, followed by conditioning shocks (*), the Dixon Protocol, and the block randomized comparison of therapy efficacy. A* indicates when shock energy was adjusted if needed. (B) Plots of the experimental therapies compared in this study. Therapies consisted of LL Stacked Shocks or AP Stacked Shocks or one of seven different DSD therapies with different timing between the two DSD shocks (first shock from LL, second shock from AP). The protocol tested each therapy up to 9 times in each animal with a target of 90 episodes of VF (i.e., 1st shocks) per therapy at study completion. (C) Protocol for a single episode of VF for testing a randomized experimental therapy. In each animal, up to 81 such episodes were performed for comparison of therapy efficacy. LL and AP Stacked Shocks were delivered with approximately 10 s in between the first and second shocks. Two-shock cumulative success for LL and AP Stacked Shocks were compared to 1st shock success of DSD therapies.

Study 2: efficacy of DSD

We collected data from 795 episodes of VF. Each animal received 112 ± 10 shocks (mean ± standard deviation) for therapy comparison, 3 conditioning shocks from each set of electrodes, and 12 ± 1 shocks for the Dixon protocol. One experimental block and 6 episodes of VF were excluded from analysis due to failure of equipment to deliver the intended therapy. The number of VF episodes for each therapy is shown in Fig. 4.

The efficacy of DSD varied substantially with the timing of the two shocks (Fig. 4). DSD therapies with Overlapping, 10 ms, and 100 ms inter-shock timings provided significantly greater shock success than Stacked LL Shocks (p < 0.05) while DSD with 50 ms inter-shock timing provided significantly lower shock success than Stacked LL Shocks (p < 0.05). Efficacies of DSD therapies with inter-shock timings of 200, 500, and 1000 ms were not significantly different than Stacked LL Shocks. There was a difference in efficacy between single shocks on LL and AP vectors (30% vs 48%, p < 0.05) but no significant difference in efficacy of two stacked shocks on LL and AP vectors (58% vs 66%, p > 0.05). The frequency of post-shock bradycardic rhythms was recorded in three animals; it was no higher for DSD therapies than LL or AP therapies.

Discussion

The practice of DSD has become more common in the last few years despite a paucity of objective evidence to inform that practice. In our experimental study, we gathered objective evidence useful in selecting pad placement that could reduce risk of defibrillator damage, and we explored the relationship between the timing of the two shocks and defibrillation efficacy. Our main findings are that (1) varying the relative position of the two electrode pairs...
caused a 50-fold variation in the proportion of the voltage applied across one pair of electrodes that appeared across the second pair of electrodes, and (2) defibrillation efficacy varies substantially with inter-shock timing.

**Electrode location**

Theoretically, a defibrillation shock from a pair of electrodes (active electrode pair) generates a distribution of electrical potential across the body surface (body surface potentials). Relative to the areas distant from the electrodes, the body surface potentials are highly negative near the cathode and highly positive near the anode. When a second defibrillator is connected to two more electrodes placed on the body, the voltage applied to that defibrillator is the difference between the body surface potentials at the locations where the additional electrodes are placed. When the passive pair of electrodes is placed perpendicularly to the active pair, the passive electrodes are placed in regions with approximately the same potential, creating a small voltage difference between the pair. On the other hand, when the passive electrode pair is placed parallel to the active pair, one electrode is placed in a high potential region with the other in a lower potential region thus leading to a large voltage difference between the electrodes.

Our observation that selecting DSD with near-orthogonal defibrillation vectors significantly decreases the exposure of one defibrillator to high voltage generated by the other defibrillator is consistent with theory. However, the magnitude (>50) of difference observed is notable. Picking pad positions on near-orthogonal vectors can substantially decrease high voltage exposure and should decrease the risk of one defibrillator damaging the other. This is important because today’s defibrillators were not designed to withstand DSD and can, rarely, sustain damage from the procedure.25

**DSD timing**

We found that DSD shocks along two orthogonal vectors worked better than two stacked shocks along a single vector, provided the two DSD shocks were 10 ms or less apart or were 100 ms apart. Furthermore, in conditions where single LL shocks had 30% success, combining that shock with a second, overlapping shock from a second device on an orthogonal vector failed to defibrillate in only 1/84 tests (1.2%). On the other hand, DSD with shocks 50 ms apart worked significantly worse than two stacked shocks from a single defibrillator. DSD with shocks 200 ms or more apart provided no benefit compared to two stacked shocks along a single vector. In other words, compared to therapy from one defibrillator, DSD appears to only be beneficial if the timing of the shocks is tightly controlled, with overlapped shocks possibly being the most effective.

Our results in swine are consistent with previous work in other species. Johnson et al. showed in dogs that delivering two shocks through two internal shock vectors, either 10 ms or less apart or between 75 and 125 ms apart, provided higher defibrillation efficacy than a single shock; lower efficacy for shocks 50 ms apart was attributed to the second shock re-inducing fibrillation.27 Sweeney et al. showed in dogs that two monophasic pulses along a single internal vector separated by 75-90 ms defibriliated with half the energy of two shocks separated by 50 ms.31 Using monophasic shocks, McDaniel later confirmed the existence of the same detrimental shock separation at 50 ms in transthoracic defibrillation in calves.27 Our present study with transthoracic biphasic shocks in pigs confirms prior findings of dual shock timings with higher and lower efficacy and adds to this body of evidence by showing a potential benefit of dual shocks that are overlapping. We also found a loss of dual shock synergy (i.e., shocks are statistically independent) when shocks are separated by 500 ms or more, and a trend towards negative synergy for shocks 200 ms apart. Although historical studies proposed choosing the interval separating the two shocks based on VF cycle length, the results in dogs, calves, and now pigs all find consistently poor efficacy for shocks separated by 50 ms.

In clinical practice today, DSD is performed by manually depressing the shock buttons on two defibrillators. Inconsistency in timing of manually triggered DSD shocks results from various mechanisms including human ability, switch debouncing, and device-to-device differences in timing from button press to the beginning of the high-voltage pulse. As a result, DSD today has highly variable shock timing which cannot consistently achieve improved efficacy and may sometimes result in therapy less effective than a single shock (the human equivalent of 50 ms shock separation).

**Dual cardioversion of AF**

Dual-shock cardioversion of refractory AF has been utilized for several years but the literature is limited to experience using monophasic defibrillators.28–30 These studies reported improved AF termination with dual-cardioversion compared to single shocks, perhaps because the two shocks are usually synchronized to the same R-wave, enabling nearly simultaneous delivery. No reports of device damage were made in these studies but the therapy circuits of monophasic devices are markedly different from those of biphasic defibrillators and tend to be more robust.

**Refractory VF and DSD**

Refractory VF is rare and recurrent VF is common. In out-of-hospital VF cardiac arrests, Koster et al. report 92% first shock success and 48% refibrillation within the subsequent CPR period, only 0.4% stayed in VF through three shocks. In out-of-hospital cardiac arrest, distinguishing refractory VF from recurrent VF is challenging; with current technology, there is a 1-2 second gap in display of ECG...
after shock delivery preventing rhythm interpretation during the time when VF is most likely to recur. 27,28 Distinguishing between refractory and recurrent VF is important because only the patients with refractory VF need a more effective defibrillation therapy. For patients with recurrent VF, shocks have successfully terminated VF and will likely do so again, so DSD is unlikely to help. The low prevalence of true refractory VF along with inconsistent shock timing may explain why the largest retrospective analyses of DSD efficacy for persistent VF to-date have reported no benefit. 2.7,11,12,14,39 To develop a potentially beneficial DSD therapy for refractory VF, further research and technology development are needed.

Limitations

This study was in pigs with normal hearts and episodes of electrically induced VF; several steps removed from cardiac arrest in humans. Prior research indicates that longer periods of VF (20 s–7 min) may have similar or lower defibrillation thresholds. 40–42 Although geometry of the thorax differs markedly from humans, the principles relating relative placement of the two pairs of pads and exposure of one defibrillator to the voltage of the other defibrillator are likely the same. Also, although the absolute efficacies of the therapies studied would presumably be different in humans, the relative efficacies of the therapies tested are likely to be good indicators of relative efficacies for the therapies applied to humans in VF. This study used termination of fibrillation as its primary end-point and cannot address return-of-spontaneous circulation or survival outcomes of DSD. This study did not investigate the effect of VF cycle length; it may or may not be necessary to account for species differences in VF cycle length to translate to humans our findings about DSD shock timing and efficacy. We only studied DSD with orthogonal vectors; DSD with the two shocks along a single vector, or along parallel vectors, may act differently, and may be inadvisable because of risk of defibrillator damage.

Conclusions

For dual defibrillation, placing the two pairs of defibrillation pads so as to provide two near-orthogonal vectors would reduce the exposure of each defibrillator to high voltage from the other. Two shocks from two defibrillators, delivered along two orthogonal vectors, would provide better defibrillation efficacy than two stacked shocks from one defibrillator, but only for certain timing relationships that would require precise control of defibrillator shocks.

Conflicts of interest

TGT and FWC are full time employees of Physio-Control/Stryker. GPW and SBM have a research grant from Physio-Control/Stryker. TGT, FWC, and GPW have submitted one or more patent applications for devices that perform DSD.

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