Effect of Pulse Separation Between Two Sequential Biphasic Shocks Given Over Different Lead Configurations on Ventricular Defibrillation Efficacy

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Background. Two sequential biphasic shocks delivered over separate lead configurations markedly improve defibrillation efficacy compared with a single shock alone. We investigated the effect of varying the intershock interval between sequential biphasic shocks on defibrillation.

Methods and Results. Defibrillation thresholds (DFTs) were obtained in six dogs for shock separations ranging from 0.2 to 125 msec. The first shock was given from a catheter electrode in the right ventricular apex to a patch on the left lateral thorax; the second was from a small patch on the left ventricular apex to a catheter electrode in the right ventricular outflow tract. When the interval between shocks was ≤10 msec or ≥75 and ≤125 msec, the mean DFTs were less than that previously found for the first shock by itself (4.2 versus 7.4 J, p = 0.002). At a separation of 50 msec, however, there was a marked rise in the DFT to 27 J. The mean DFT for the second shock at a delay of 50 msec was not different from the mean DFT previously found for the second shock by itself (7.2 versus 7.0 J). These results were confirmed in another six dogs using defibrillation probability-of-success curves. In 12 other dogs, probability-of-success curves were generated for delays between shocks as a percentage of the activation interval during ventricular fibrillation. Minimum defibrillation energy requirements were at two separations, 0.2 msec and 90% of the activation interval.

Conclusions. The optimal intershock interval between two sequential biphasic shocks is either ≤10 msec or ≥75 and ≤125 msec. The marked rise in the DFT at a shock separation of 50 msec, requiring more energy than that for the first shock alone, suggests that the second shock at this time delay is likely to reinduce fibrillation after it is halted by the first shock until the second shock is strong enough to defibrillate independently of the first shock. (Circulation 1992;85:2267–2274)

Key Words • fibrillation, ventricular • defibrillation • shocks, sequential • death, sudden

The concept of cardiac defibrillation by multiple shocks was first suggested by Wiggers1 more than 50 years ago. Orias,2 in 1953, proposed a theoretical mechanism for sequential shocks: a second shock can capture additional cells that are refractory at the time of the first shock, activating a sufficient amount of tissue to extinguish fibrillation. Multiple-pulse defibrillation has been studied by several groups using various shock waveforms with fixed intervals between shocks over a single lead system. Early investigators3,4 focused on intervals of 75 and 100 msec and found a reduction in the total energy required to defibrillate compared with a single shock. Later investigators,5–8 in contrast to the earlier results, found that double pulses actually required more total energy than a single pulse but that the peak voltage and current were reduced.

Over the last few years, investigators have studied single and sequential pulses given across a variety of electrode configurations9–18 and found that sequential pulses delivered over two different lead orientations provided a significant improvement in defibrillation over a single pulse alone. The optimal separation between pulses in these studies was 0.2 msec. A recent study found that a double-pulse shock with a separation timed to 85% of the activation interval during ventricular fibrillation (VF) was as effective as a single-pulse shock of the same total energy but required less peak current than the single-pulse shock.19 It has also been shown that giving two sequential biphasic shocks over two separate lead configurations, with the second pair of electrodes located in areas where the potential gradient field created by the first pair of electrodes is weak, markedly improves defibrillation efficacy compared with a single biphasic shock given to either of the pairs of electrodes alone.20 The purpose of our study was to determine the effect of pulse separation between the...
two sequential biphasic shocks given through these two pairs of electrodes.

Methods

This study comprised three similar yet separate protocols. In part 1, defibrillation thresholds (DFTs) were obtained for predetermined time delays between sequential shocks ranging from 0.2 to 125 msec. In part 2, defibrillation probability-of-success curves were generated for predetermined time delays of 0.2, 60, 80, 100, and 120 msec. Ventricular effective refractory periods (ERPs) during sinus rhythm and activation intervals during VF also were obtained in part 2. In part 3, defibrillation probability-of-success curves were obtained for delays that were not fixed a priori but were based on the activation interval during each episode of VF, ranging from 70% to 140% of the activation interval. The common portions of each protocol are described first.

Animal Preparation

Twenty-four mongrel dogs (mean weight, 22.4±2.3 kg) were studied. Anesthesia was induced with pentobarbital (30–35 mg/kg i.v.) and maintained with a dose of 0.05 mg/kg/min as needed. Skeletal muscle paralysis was induced with succinylcholine (1 mg/kg i.v.) and maintained with a dosage of 0.25–0.50 mg/kg no more than once per hour as needed. Animals were intubated with a cuffed endotracheal tube and attached to a mechanical ventilator (Harvard Apparatus, South Natick, Mass.). Two peripheral veins and the femoral artery were cannulated. The arterial blood pressure and the ECG surface lead II were monitored. Ringer’s lactate solution was infused continuously. Blood gas values and electrolyte levels were checked regularly and maintained within normal limits.

A left lateral thoracotomy was performed in the fifth intercostal space. The heart was exposed and suspended in a pericardial cradle. A small (4.3-cm²) stainless steel defibrillating patch electrode with no insulation on the back was sutured to the left ventricular apex. Three plunge recording electrodes were inserted into the left ventricle and one into the right ventricle. The chest was closed in layers and evacuated under negative pressure. Two defibrillating catheters (Endotak C, CPI, St. Paul, Minn.) were used, each with distal spring electrodes that have a surface area of 2.95 cm². The first catheter was inserted into the right ventricle through the right jugular vein; the second was inserted into the right ventricular outflow tract via the left jugular vein. The catheters were positioned by use of fluoroscopy: the right ventricular catheter against the right ventricular wall at the apex and the outflow tract catheter in the outflow tract of the right ventricle within 1 cm of the pulmonic valve. For catheter-patch defibrillation, an external electrode patch (R2 Pad, child, DaRox Corp., Niles, Ill.) with a surface area of 41.0 cm² was placed on the left lateral side of the dog over the palpable cardiac apical impulse. The first shock was given from the distal electrode of the right ventricular catheter (cathode for the first phase of the biphasic shock) to the cutaneous patch (anode for the first phase); the second shock was given from the epicardial patch electrode on the left ventricular apex (cathode for the first phase of the second shock) to the distal electrode on the catheter in the right ventricular outflow tract (anode for the first phase). The cathode and anode were reversed for the second phase of each shock. For backup defibrillation, two large electrode patches (Fast-Patch, Physio-Control, Redmond, Wash.) were attached to the lower sternum and to the right lateral chest wall. The patches were attached to an external defibrillator (LifePak 8, Physio-Control). Fibrillation was induced through one of the defibrillating catheters with a 60-Hz generator.

Two 150-μF defibrillators (Ventritex HVS 02, Sunnyvale, Calif.) were used for all of the test shocks. The phases for each of the biphasic pulses were 3.5 and 2.0 msec in duration (Figure 1). To mimic the output of a single capacitor defibrillator, the leading edge voltage of the second phase of the first shock (V2L) and the first and second phases of the second shock (V2L and V4L) were set equal to the nearest 10 V to the trailing edge voltage (V2T) of the previous phase, which was calculated from the formula

$$V_T = V_I e^{-t/RC}$$

where $V_T$ is the leading edge voltage of the previous phase, $t$ is the duration of the phase, $R$ is the resistance estimated by the resistance from the previous shock, and $C$ is the capacitance (150 μF). There was a fixed interphase separation of 0.1 msec between the trailing edge of the first phase and the leading edge of the second phase for each biphasic shock. All defibrillation attempts were performed with the respirator off and the animal at end expiration. After the initiation of fibrillation, 15 seconds elapsed before the defibrillation test shock was applied. The initial leading edge voltage was
250 V for each shock separation for the first dog; for subsequent dogs, the starting voltage was the mean DFT that was calculated from the previous studies. If a defibrillation shock failed, a rescue shock of higher voltage was given through the first pair of electrodes. If the rescue shock failed, a backup rescue shock was given with the external defibrillator. One dog early in the study could not be defibrillated at one of the delays tested (50 msec) even at a leading edge voltage of 900 V. After this dog, the highest voltage tested was set to a limit of 650 volts. During each attempted defibrillation, the applied voltage and the current through each set of electrodes were sampled by a waveform analyzer (DATA 6100, Data Precision, Danvers, Mass.), and the impedance between the electrodes and the total delivered energy of each phase of the two pulses were computed. The time period between test shocks was 5 minutes. The sequence of order for testing each time delay was randomized to account for variation during the course of the experiment. When the study was completed, the chest was opened and the positions of the catheters were confirmed. The heart was then removed, weighed, and preserved in formalin.

Part 1

In part 1, DFTs were obtained for each of the predetermined intershock intervals of 0.2, 0.5, 1.0, 2.5, 5.0, 7.5, 10, 25, 50, 75, 100, and 125 msec by a modified Purdue technique.21 Depending on the success or failure of the shock, the leading edge voltage was decreased or increased, respectively, by 40 V. When the transition from failure to success or success to failure was found, a final shock was tested midway between the successful and unsuccessful shocks. The lowest successful voltage defined the DFT for each separation. The DFT was thereby established within 20 V. Six dogs were used in part 1.

Part 2

In part 1, it was noted that there was a decrease in the DFT when the interval between shocks was either short (<10 msec) or long (>75 msec and ≤125 msec) and that there was a marked rise in the DFT at 50 msec. In part 2, defibrillation probability-of-success curves were obtained focusing on the region between 50 and 125 msec to determine whether the lowest DFT in this region was lower than that of essentially no delay between shocks at all, i.e., a delay of 0.2 msec. Ventricular ERPs during sinus rhythm and activation intervals during VF were also obtained.

The defibrillation probability-of-success curves were generated using an up/down technique.22 In the first study of part 2, the leading edge voltage for the initial shock was the mean DFT from part 1. For subsequent studies, the initial shock was the mean ED50 voltage (i.e., the voltage associated with 50% predicted successes as determined from the defibrillation probability-of-success curve) that was obtained during the previous studies in part 1. For the remaining shocks, the voltage and success of the immediately preceding shock for that delay determined the voltage selected. If the previous shock failed, then the voltage was increased by one step (20 V); for a successful shock, the voltage was decreased by one step. This procedure of testing defibrillation with increasing/decreasing voltages was continued until a total of 15 shocks was delivered. One defibrillation probability-of-success curve was established for each of the predetermined time delays of 0.2, 60, 80, 100, and 120 msec for each dog. Six dogs were used in part 2.

To determine the ventricular ERP, the diastolic threshold was determined using a train of 10 S1 stimuli delivered through the rate-sensing electrode at the distal tip of the defibrillating catheter in the right ventricular apex. The S1 and S2 strengths were both set at twice diastolic threshold with an S1–S2 interval of 300–350 msec. The S2–S1 interval was decremented in 5-msec steps until the S1 did not capture; the S1 interval was then increased by 15 msec and decremented by 2 msec. The ventricular ERP was the longest interval not producing a propagated response using the 2-msec steps. The ventricular ERP was measured before every fifth defibrillation test shock. The activation interval during VF, i.e., the mean interval between sequential activations, was obtained using strip chart recordings (Astro-Med, West Warwick, R.I.) from one of the plunge electrodes amplified through a bioelectric amplifier (Hewlett Packard 8811A, Palo Alto, Calif.). The activation interval was measured before every fifth defibrillation test shock by dividing the time over which the activations were recorded (10 seconds) by the total number of activations that were identified during this period.

Part 3

The data collected in part 2 suggested that the time delay between sequential shocks at which the lowest ED50 occurred was related to the activation interval during VF. These data are similar to the results reported by Sweeney et al20 for paired monophasic shocks through a single set of electrodes. In part 3, therefore, defibrillation probability-of-success curves were established for separations between sequential shocks based on percentages of the activation interval during VF and were compared with the curve for a 0.2-msec separation as a control. The intershock separations tested were 70%, 80%, 90%, 100%, 110%, 120%, 130%, and 140% of the activation interval during VF.

Activation intervals were estimated during each episode of VF from the surface ECG limb lead II. The signal was amplified with an external cardiac monitor (LifePak 7D, Physio-Control) and recorded with a Macintosh II computer (Apple Computer, Cupertino, Calif.) and LAB-VIEW 2 software (National Instruments, Austin, Tex.). Each recording consisted of four seconds of VF sampled at a rate of 1 kHz with a resolution of 12 bits. A fast Fourier transform was performed and the peak frequency determined by selecting the frequency with the highest Fourier coefficient. The activation interval was then assumed to be the reciprocal of this frequency. To increase the computation speed, no window was applied. After the activation interval was estimated, the computer determined the desired interval between the two shocks and triggered the defibrillators with the appropriate delay. The delay was confirmed by the waveform analyzer. Because approximately 10 seconds elapsed between the time when VF was sampled and the time the shock was delivered, the activation interval during the 4
seconds of VF immediately before the shock was estimated in the same manner for comparison. The total time to sample the 4 seconds of VF, obtain the fast Fourier transform, estimate the activation interval, sample another 4 seconds of VF, and deliver the shocks was approximately 15 seconds. The activation intervals during VF from the plunge electrodes were also determined as described above in part 2.

The defibrillation probability-of-success curves were generated using the same up/down technique as described in part 2. Twelve dogs were used in part 3: in four dogs, the delays were 0.2 msec and 70%, 80%, 90%, and 100% of the activation interval; in another four dogs, the delays were 0.2 msec and 90%, 100%, 110%, and 120% of the activation interval; and in the last four dogs, the delays were 0.2 msec and 110%, 120%, 130%, and 140% of the activation interval.

Statistical Analysis

In part 1, all comparisons between mean DFT values of leading edge voltage, peak current, and total energy were made using Hotelling's $T^2$ statistic. In part 2 and part 3, defibrillation probability-of-success curves were generated using probit regression analysis (SAS, Cary, N.C.). The leading edge voltages, peak currents, and total energies associated with 50% predicted successes ($ED_{50}$) were calculated. Comparisons of $ED_{50}$ among the different delays were made by ANOVA and paired $t$ tests. Results are reported as the mean±1 SD. A value of $p≤0.05$ was used to define statistical significance. In part 3, because not all delays were tested in every animal, the data were normalized within each animal to the $ED_{50}$ at 0.2 msec.

Results

Part 1

The mean DFT, whether expressed in terms of leading edge voltage, peak current, or total energy, was not significantly different when the intershock interval was ≤10 msec or ≥75 and ≤125 msec (Figure 2). However, there was a marked rise in the DFT at a delay of 25 msec, which rose to a value at a delay of 50 msec that was approximately 2.5 times the other DFTs noted above. One dog could not be defibrillated at a separation of 50 msec even at 900 V; the results for that animal are reported as one step size higher than the highest value tested for each parameter as an estimate of the DFT. The mean leading edge voltage at DFT for the second shock at a delay of 50 msec was 354±77 V (Figure 2, represented by the open box). For reference, $ED_{50}$ values for the first shock alone (Figure 2, closed arrow) and the second shock by itself (Figure 2, open arrow) from another comparable study by Guse et al were shown. That study used six dogs similar in size to those in the present study and gave single biphasic shocks with the same electrode configurations as the first shock and second shock used in this study. There was no statistical difference between the voltage for the second shock required to defibrillate in this study and the voltage required for a single shock given through the second pathway from the Guse et al study.

![Figure 2. Graph of the mean leading edge voltages at the defibrillation threshold (DFT) versus the time delay in msec between the two shocks (time delay plotted on logarithmic scale). Error bars represent 1 SD. The mean leading edge voltage at defibrillation threshold for the second shock at a delay of 50 msec is given (○). For reference, $ED_{50}$ leading edge voltage values for the first shock alone (----) and the second shock by itself (---) from another study are shown. There is no significant difference in the DFT when the separation between shocks is ≤10 msec or ≥75 msec; however, there is a marked increase in the DFT at 25 msec, which increases sharply at 50 msec and is then followed by a precipitous fall in the DFT back to a value similar to that seen when the delay is ≤10 msec. Peak currents and total energies changed accordingly.](http://circ.ahajournals.org/)

Part 2

The mean leading edge voltages for the $ED_{50}$ points generated from the defibrillation probability-of-success curves for predetermined separations between the two sequential biphasic shocks separated by 0.2, 60, 80, 100, and 120 msec are shown in Figure 3. The results for the peak current and total energy were similar. There was a marked increase in the $ED_{50}$ values when 60-msec separations were compared with 0.2-msec separations. These values decreased as the separations lengthened, however, so that from 80 to 120 msec there were no
significant differences between them and the 0.2-msec delay. One dog in this part could not be defibrillated with the highest shock tested at a separation of 60 msec; one step above the highest parameters obtained was used as an estimate for the ED₉₀. The shapes of the probability-of-success curves were not significantly different for the different shock separations or from the curves for single biphasic shocks alone.⁵

The mean activation interval during VF was 117±25 msec. Figure 4 is a graph of the mean activation interval for each animal versus the time separation between shocks at which the lowest ED₉₀ occurred. It has previously been shown that the mean activation interval during fibrillation in dogs was 86±9 msec.⁵,⁶ Two dogs had mean activation intervals greater than 120 msec. Delays longer than 120 msec were not tested in this part of the study; thus it is not known whether a lower ED₉₀ existed at delays greater than 120 msec for these two dogs. There is a tight linear fit of mean VF activation interval and shock separation with lowest ED₉₀ when these two animals are excluded (Figure 4; y=29+1.2x, r²=0.997). The mean ventricular ERP during sinus rhythm was 163±24 msec. There was no significant relation between the ventricular ERP and the optimal shock separation (y=7+0.6x; r²=0.387).

Part 3

In part 3, we recorded 4 seconds of VF, calculated a fast Fourier transform, and gave the two shocks separated by a delay based on this estimate of the activation interval. The ED₉₀ leading edge voltages are shown for all 12 dogs from part 3 in Figure 5. Figure 6 is a graph of the mean ED₉₀ leading edge voltages after the ED₉₀ leading edge voltage was normalized for the 0.2-msec control for each animal, because not all delays were tested in all animals. There is a marked rise in the leading edge voltage, peak current, and total energy at a shock separation of 70% of the activation interval. This is followed by a minimum value at a separation of 90% of the activation interval, which is not significantly different from almost no shock separation (0.2 msec).

As the delay increased, there again was an increase in all the parameters measured.

The mean activation interval during the initial 4 seconds of VF as estimated from the surface ECG limb lead II peak frequency was 102±11 msec. The mean activation interval during the 4 seconds of VF immediately preceding the defibrillatory shock was 98±11 msec. There was poor correlation between the estimated activation intervals from the first 4 seconds of VF and the 4 seconds immediately before the defibrillation test shock (Figure 7; y=30.8+0.7x; r²=0.44). There was fair correlation between the activation interval as estimated from the plunge electrode versus the surface.
Major Findings

The major findings of this study are that 1) the optimal intershock interval between two sequential biphasic shocks is either short (≤10 msec) or long (≥75 and ≤125 msec); 2) the DFT is greatly elevated with separations between 25 and 75 msec; 3) the delay at which the minimum ED₅₀ occurs is proportional to the activation interval during VF; 4) the optimal separation between shocks based on the activation interval during VF is 90% of the activation interval for the particular waveforms and lead configuration tested; and 5) the ED₅₀ values for a delay of 0.2 msec between shocks and for a shock separation equal to 90% of the VF activation interval are not significantly different.

Clinical Implications

Our results confirm that two sequential shocks applied over two separate electrode configurations can defibrillate with low peak voltage, peak current, and total energy, thus extending the battery life of the cardioverter–defibrillator unit as well as reducing the amount of any myocardial damage. The optimal separation between two biphasic shocks using the described electrode configurations and the particular waveform tested is either ≤10 msec or approximately 90% of the activation interval during VF. In this study, there was only a fair correlation between the activation intervals during the first 4 seconds of VF compared with the 4 seconds of VF immediately before the defibrillation shock. This could be due to either an actual change in the frequency content of the ECG as VF progresses or the instability of the fast Fourier transform as an estimator of the frequency spectrum.

Although the energy required to defibrillate at delays ≤10 msec was not significantly different from the delay between 90% and 120% of the activation interval in VF, in the higher range the risk is greater of actually increasing the amount of energy required for defibrillation as seen at a delay of 50 msec, or approximately 70% of the activation interval. Because there is no difference between the energy requirements at a delay ≤10 msec and the minimum energy requirements at the best delay based on the activation interval during VF, there appears to be no benefit and even an increased risk to incorporating this particular timing sequence into future generations of implantable cardioverter–defibrillators.

Basic Mechanisms

Although separation of the two shocks may not be clinically useful, the marked change in defibrillation efficacy with change in the delay between shocks has implications for the mechanisms of defibrillation. A new finding in this study is the marked increase in the DFT for two sequential shocks over a single shock when the delay between shocks is 25–75 msec. At a delay of 50 msec, energy requirements were consistently and markedly increased, and in fact there was one dog that could not be defibrillated at this delay, even with a 900-V shock. The results between the DFT values for the second shock at a delay of 50 msec are similar to the DFT values found by Guse et al for the second shock by itself. Thus, it appears that the second shock has to be strong enough at a delay of 50 msec to defibrillate independently of the first shock. These results are consistent with the upper limit of vulnerability hypothesis, which states that to defibrillate, a shock must be greater than the range of shock strengths that can reinvoke VF by stimulating myocardium during its vulnerable period. When the interval between shocks is ≤10 msec or 75–125 msec, the two shocks together can defibrillate even though each shock alone is too weak to defibrillate. According to the upper limit of vulnerability hypothesis for defibrillation, the weakest portion of each of the two shock fields at the DFT for these intervals is in the range that could reinvoke VF. The fact that VF is not reinvoked at intervals of ≤10 msec or 75–125 msec suggests that in the region where the second shock is weak, the myocardium is not in its relatively refractory (vulnerable) period at these intervals. At an interval of 50 msec, however, tissue in this region is in its relatively refractory period after its response to the first shock. Thus, the second shock reinvokes VF unless it is increased to a strength great enough to defibrillate by itself.

A relative refractory period of 50 msec after a shock during VF is consistent with intracellular studies. It has been shown through direct intracellular recordings that action potential duration in the early stage of VF is ~50–70 msec. Zhou et al have shown that for a 5-V/cm stimulus lasting 5 msec in dogs during early VF, the refractory period is 62–67 msec, depending on the waveform (monophasic or biphasic). Because action potential duration shortens after a premature stimulus, these data are consistent with a relative refractory period of approximately 50 msec after a shock during VF.

There was close correlation between the optimal separation between shocks and the activation interval during VF. If the activation interval during VF is determined by the refractory period of the tissue, as is true for the types of functional reentry thought to be present during VF, then the VF activation interval should be directly related to the vulnerable period and furnish an estimate of it. The activation interval of 100 msec is an estimate of the time it
takes during VF before a neighboring cell can activate a cell. In contrast, an interval of 50 msec represents the period of time during which a cell can be excited by a defibrillating shock, a stimulus of much greater strength and excitatory effect. The activation interval should furnish an estimate of the vulnerable period; the vulnerable period is not necessarily 100% of the activation interval but may be some percentage of it.

The finding that the optimal separation between two biphasic shocks is 90% of the activation interval is similar to Sweeney et al's finding of 85% for two identical monophasic shocks. One explanation for the slight difference between the two percentages is that Sweeney tested percentages of the activation interval that were odd (i.e., 55%, 65%, 75%, ... to 185%), whereas this study tested even percentages (70%, 80%, 90%, ... to 140%). The activation intervals were also determined using different methods, and both shocks were delivered over a single pathway. However, the optimum separation between shocks as a percentage of the VF activation interval may be different for different waveforms. Zhou et al. demonstrated that the refractory period in dogs during early VF was different for a monophasic waveform versus a biphasic waveform.

The activation intervals immediately preceding the shock may have more bearing on defibrillation efficacy relative to those that are earlier and more temporally remote from the shock. However, we were unable to generate dose–response curves for shocks given at different percentages of the activation interval during the final 4-second interval immediately before the shock to test this idea. The shock voltages and timings were based on the activation intervals for the first 4 seconds of VF and were too poorly distributed to allow calculation of dose–response curves when grouped on the basis of the later activation intervals.

In summary, the optimal intereshock interval between two sequential biphasic shocks is either short (≤10 msec) or long (≥75 and ≤125 msec), with no significant difference between the two; there is a sharp increase in the defibrillation energy requirements between 25 and 75 msec; there is a correlation between the activation interval during VF and the optimal separation between shocks ≥75 msec; and finally, although the clinical implications may be limited, this study gives insight into the basic mechanisms of defibrillation, being consistent with the upper limit of vulnerability hypothesis for defibrillation.

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References


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