Response of Relatively Refractory Canine Myocardium to Monophasic and Biphasic Shocks

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Background. Certain biphasic waveforms defibrillate at lower energies than monophasic waveforms, although the mechanism is unknown.

Methods and Results. The relative ability of monophasic and biphasic shocks to stimulate partially refractory myocardium was compared because defibrillation is thought to involve stimulating relatively refractory myocardial tissue. Shocks of 25–125 V were given during regularly paced rhythm in 11 open-chest dogs. Computerized recordings of shock potentials, and of activations before and after the shocks, were made at 117 epicardial sites. To quantify the shock field strength, the shock potential gradients were calculated at the electrode sites. Monophasic action potential (MAP) electrode recordings, obtained in five dogs, confirmed direct myocardial excitation by the shock, that is, activations beginning during the shock. Tissue was directly excited up to 4 cm from the shocking electrode, and the area directly excited increased as the shock was made stronger or given less prematurely. In six dogs, strength-interval curves for direct excitation were determined from plots of potential gradient versus refractoriness at each electrode site. The biphasic curves were located to the right of the monophasic curves by 8±4 msec, indicating a lesser ability to excite refractory myocardium. When the gradient at the directly excited border was at least 3.8±1 V/cm, conduction failed to propagate away from the directly excited zone after the shock, and MAP recordings made near the border showed a shock-induced graded response. This graded response, which prolonged repolarization, may have been responsible for the failure of conduction from the directly excited zone. Although better for defibrillating, the biphasic waveform was thus less effective than the monophasic one in exciting relatively refractory myocardium.

Conclusions. These results indicated that waveform selection for defibrillation should not be guided solely by the ability of the waveform to stimulate tissue, as these two properties can be discordant. (Circulation 1991;84:2522–2538)

Defibrillation shocks should be as small as will reliably defibrillate, because excessively strong shocks can have adverse effects,1–3 and because they unnecessarily deplete implantable defibrillator batteries. Recent studies have examined biphasic waveforms, which have a second phase of opposite polarity to the first phase. In certain cases, biphasic waveforms have been empirically observed to defibrillate more efficaciously than monophasic waveforms of the same duration.4–11 The explanation for this increased efficacy is unknown. Understanding why biphasic waveforms defibrillate better could help explain how defibrillation works and could facilitate selection of an optimal biphasic waveform for clinical use.12–14

Defibrillation theories have emphasized stimulation of myocardium to halt the ventricular fibrillation (VF) activation fronts.15,16 Accordingly, the defibrillation efficacy of a waveform should correlate with its ability to excite fibrillating heart muscle. Early in canine VF, activations occur as often as every 100 msec.17 Consequently, action potentials arise from a reduced take-off potential, when cells are still partially refractory, and before full repolarization from the preceding action potential.18 At the time of a
defibrillation shock ventricular tissue is therefore not only made up predominantly by absolutely or relatively refractory tissue but also by some fully recovered tissue. Thus, excitation of nonfibrillating tissue during the relatively refractory period after paced activations should be similar to excitation of fibrillating tissue. However, as opposed to a paced preparation, the interval and sequence of activations vary during VF, and metabolic abnormalities develop during the course of prolonged VF. Effects of shock fields on relatively refractory tissue is probably most relevant to defibrillation because fully recovered tissue is less prevalent during fibrillation, and absolutely refractory tissue is unlikely to be affected except perhaps by extremely high potential gradient fields.

To begin to understand the differing defibrillation abilities of monophasic and biphasic shocks, this study used multiple extracellular electrodes and a computerized mapping system to evaluate the effects of the two different shocks on relatively refractory myocardium. The amount of relatively refractory myocardium directly excited by monophasic and biphasic shocks was compared. Because defibrillation shocks affect myocardium throughout the ventricles, the effect on tissue relatively distant from (up to 3 cm) as well as tissue nearby the shocking electrodes was examined. Because extracellular electrode recordings cannot definitively prove that a shock has directly excited cardiac tissue, monophasic action potential (MAP) electrode recordings were used to verify that direct excitation did occur. The effect elicited by the two waveforms in tissue not directly excited by the shock was compared as well. A 3-msec waveform duration was selected to minimize recording electrode saturation, thus allowing activation recordings to resume quickly after the shocks. Because biphasic waveforms that have a longer first than second phase are more efficacious for defibrillation, a biphasic waveform with a 2-msec first phase and a 1-msec second phase was chosen and compared with a 3-msec monophasic waveform. Because the duration of the monophasic and biphasic waveforms were equal at a given voltage level, the current for the monophasic and the biphasic would be nearly equal. Energy values for the two waveforms would also by very nearly equal. First, it was determined whether the 3-msec biphasic waveform would defibrillate better than the 3-msec monophasic one. Then, in a separate group of studies using cardiac mapping, the effects of the two different waveforms on refractory tissue were studied.

Methods

Part I: Defibrillation Studies

The defibrillation efficacies of the monophasic and biphasic waveforms were compared using six mongrel dogs (22–32 kg). The dogs were anesthetized with sodium pentobarbital (30 mg/kg), intubated and mechanically ventilated using supplemental oxygen, and given maintenance intravenous fluids. The electrocardiogram and arterial pressure were continuously monitored. Core body temperature, arterial blood gas values, and electrolyte levels were maintained within the normal range throughout the experiment. Succinyl choline chloride was administered to minimize skeletal muscle stimulation by shocks. The chest was opened through a median sternotomy, and a pericardial cradle was created to support the heart. Titanium mesh defibrillation electrodes (10 cm² each) were sutured to the lateral right and left ventricles with the former serving as the anode. The chest was then draped to help retain heat and moisture.

Low tilt, 3-msec monophasic or biphasic defibrillation shocks (Figure 1) were delivered using a 900 µF capacitance device, after 10 seconds of VF that was induced with 60 Hz current. Modified Bourland defibrillation thresholds (DFTs), as described by Dixon et al., were determined in 20-V steps. The smallest successful shock defined the DFT. A larger salvage shock was administered after an unsuccessful defibrillation attempt. Salvage shock results were not analyzed for DFT determinations. Fibrillation was induced at 5-minute intervals. Five pairs of monophasic and biphasic DFTs were determined in each dog. For each pair of DFTs the order for determining the monophasic or biphasic DFT was randomly allocated. A waveform analyzer (Data Precision; Danvers, Mass.), sampling at a frequency of 20 kHz over a bandwidth of DC-5 kHz, measured the voltage, current, resistance, and energy of each shock phase. Monophasic and biphasic defibrillation percent success curves were derived in each dog by pooling the shocks in that dog for each waveform. The 50% and 80% success points were calculated from the curves. After determining the five pairs of DFTs, a lethal dose of KCl was administered.

Part II: Cardiac Mapping Studies

Part A: Monophasic-biphasic comparison. Eleven dogs (22–32 kg) were anesthetized and surgically prepared for the mapping studies as described for the defibrillation studies (part I). Six dogs were used for comparison of the effects of monophasic and biphasic shocks on refractory tissue (part II A), and five dogs were used for MAP studies (part II B). After the median sternotomy and pericardial cradle, the sinus node was crushed to minimize competition with artificial pacing by native beats. A plaque containing 117 epicardial recording electrodes was sutured onto the right ventricle (Figure 1). The 117 recording electrodes (arranged 9×13) consisted of a pair of gold bipolar electrodes, with the bipolar pairs oriented as shown in Figure 1. Eight pacing wires were sutured immediately adjacent to the epicardium along one side of the plaque (Figure 1). The free proximal ends of the wires were joined together and were used for applying a series of small-pacing stimuli, called S1, in parallel to all eight wires. Shocks, called S2, were given from a 45×10 mm
stainless steel electrode that was attached to the epicardium 5–8 mm from the same plaque edge (Figure 1).

The S1 stimuli were 8–11 mA, 3 msec, cathodal pulses with an S1-S1 interval of 325 msec. After 10 S1 stimuli, a monophasic or biphasic S2 shock, which had the same waveform (Figure 1A) as the defibrillation shocks, was given and the activations under the plaque recorded. The S2 magnitude was chosen to achieve potential gradients under the recording plaque ranging from about 1 to 10 V/cm. For each dog one or two different S2 voltages (between 25 and 125 V) were used to create fields that spanned this potential gradient range. At each S2 voltage, shocks were given at five to 10 different S1-S2 intervals. The intervals were chosen to directly excite differing amounts of tissue under the plaque as determined by analyzing results during the study. Monophasic and biphasic shocks were given consecutively at the various combinations of voltage and S1-S2 interval used, with the order in which they were given alternated. When shocks resulted in VF, 5 minutes were allowed to elapse between shocks. Mean current was nearly identical for the two waveforms at a given voltage setting.

The signals from 117 bipolar plaque electrodes were recorded using a 128-channel computer-assisted mapping system,\textsuperscript{29,30} filtered to accept frequencies of 0.1–500 Hz, digitized at 1,000 Hz to 12 bits accuracy, and stored on videocassette tape or computer disk\textsuperscript{31–33} for analysis during and after the experiment. The recording channel gains were set to the highest level that would not result in excessive saturation after the S2 shock. The gain setting most commonly utilized yielded a dynamic range of ±50.0 mV and a least significant bit resolution of 24.4 μV. The recordings were analyzed on a graphics terminal and activation times manually assigned to the fastest slope of biphasic electrograms or to the largest peak of monophasic or triphasic electrograms.\textsuperscript{34,35} Electrodes with signals that were saturated or too noisy to allow the identification of activations were not analyzed. Activations were mapped for the last S1 beat and for the first beat after the S2 shock, with activation times being referenced to the S1 or S2 stimulus, respectively. The S2 activation maps for monophasic and biphasic shocks were compared with regard to the amount of tissue directly excited (vide infra) by the S2 shock. The degree of refractoriness at individual electrode sites at the time of the S2 shock was estimated by the interval between the activation after

![FIGURE 1. Waveforms for defibrillation shocks (part I) and S2 stimuli (part II) and electrode arrangement. Panel A shows that leading edge voltages (V{sub L}) are equal for monophasic and biphasic waveforms. Given from a single capacitor, first phase trailing edge voltage (V{T sub T}) of the biphasic waveform equals second phase leading edge voltage (V{T sub L}). Time between phases of biphasic shock was 250 μsec. Panel B shows 9 x 13 electrode recording plaque and location of S1 and S2 electrodes. The S1 pacing wires (represented by 8 square waves) were sutured to epicardium on right of plaque. The S2 electrode was also sutured to epicardium on right side of plaque as shown. Recording and stimulating electrodes were all epicardial.](image-url)
Statistics

Data are expressed as mean±SD unless otherwise specified. The Wilcoxon paired-sample test was used to compare the mean DFT and the 50% and 80% success points for the monophasic and the biphasic shocks. The \( t \) test for paired samples was used to compare the monophasic and biphasic strength-interval curves and to compare the gradient producing conduction block. A probability value of 0.05 or less was considered significant.42

Results

Part I: Defibrillation Studies

This part of the study compared defibrillation efficacy of monophasic and biphasic shocks in fibrillating hearts while part II (A and B) studied the effects of premature shocks of both waveforms on paced, nonfibrillating hearts. The 3-msec biphasic shock (Figure 1) defibrillated at lower shock strengths than the 3-msec monophasic shock. In all experiments the mean DFT and the 50% and 80% defibrillation success points were each lower for the biphasic waveform than for the monophasic waveform (\( p=0.05 \)). The biphasic DFT was lower than the monophasic one in 24 of the 30 DFT pairs. The mean DFT voltages and energies were 345±78 V and 4.14±1.7 J for the monophasic shocks, and 299±73 V and 2.90±1.3 J for the biphasic shocks. The mean peak currents at the DFT were 4.66±1.2 A for the monophasic waveform, and 3.96±1.0 A for the biphasic waveform. The mean 50% and 80% defibrillation success voltages were 342±89 and 400±92 V for the monophasic shocks, and 288±71 and 337±90 V for the biphasic shocks.

Part II: Cardiac Mapping Studies

Part A: Monophasic-biphasic comparison. The S1 pacing stimuli produced activations which propagated away from the S1 side of the plaque. Thus, as explained in Figure 2, the recovery interval was longer for electrodes on the right side (e.g., electrode b in Figure 2A, B), than for those on the left side (e.g., electrode a). Figure 2B displays the S1 activation times for the plaque electrodes using isochronal activation lines. The isochronal activation lines are nearly parallel to the S1 side of the plaque.

The electrograms in Figure 2A illustrate S2 shock potential measurement in addition to S1 activation. The S2 potentials measured from the electrograms are shown in Figure 2C, and the gradients calculated from the potentials are shown in Figure 2D. Changing the recording amplifier settings 15 msec before and 3 msec after the S2 shocks produced artifacts or offsets. The S2 shock potentials decreased with distance from the S2 electrode (Figures 2A and 2C). Isopotential lines, connecting points of equal S2 shock voltage, were parallel to the S2 side of the plaque and to each other. Since the isopotential lines are spaced closer near the S2 electrode, the potential gradients are also higher near S2. S2 shock isogradi-
Figure 2. Electrode recordings, S1 activations, and S2 potentials. Panel A shows electrode recordings used to determine S1 activation times and measure S2 shock potentials for a 75 V shock. Locations of electrodes a and b are shown in Panel B. Note that S1 activates tissue under electrode b before tissue at electrode a. Interval (in msec) between S1 stimulus and activation for each electrode defined S1 activation time. Interval between S1 activation and S2 stimulus was defined as recovery interval for that electrode. Activation time is shorter for electrode b (11 msec) than for electrode a (47 msec) and recovery interval is longer for electrode b than electrode a. "On" and "off" refer to status of 1,000:1 voltage divider circuit that is switched on before shock and then switched off after it. Voltage scale is 1,000 times different during period that voltage divider is in use (10 V marker instead of 10 mV marker). "Baseline" is reference voltage level for each recording channel against which S2 potential is measured. S2 potential for each electrode was defined as voltage difference between preceding baseline and voltage 3–4 msec after the S2 leading edge. Potential is −10.7 V at electrode a and −23.2 V at electrode b. Note that by using 7-msec S2 shocks and high gain settings during shock in order to record S2 potentials most accurately, amount of post-S2 recording electrode saturation is great, and activations would not be detected immediately after shock. When 3-msec S2 shocks and optimal settings to permit recording activations soon after shock were used, much less post-S2 saturation was found. (See Figures 3A, 4B, and 4D.) Panel B displays the S1 activation times, as measured from tracings such as panel A. Activation times are shown by isochronal activation lines for simplicity. Locations of electrodes a and b are indicated. Filled circles are electrodes at which activations were not recorded. Electrodes shown as filled circles in two rows closest to the S1 pacing wires probably activated during S1 stimulus, thus obscuring activation signal. Remaining filled circles indicate technically poor recordings. Panel C displays the S2 potentials for shock in panel A. These S2 potentials are displayed with isopotential lines using 2 V steps. Potential gradients were calculated from potentials (using interelectrode distances, Figure 1B). Panel D illustrates isogradient lines drawn every 2 V/cm for shock in panel A. Gradients of outer edge electrodes were not used because of insufficient neighbors for accurate calculations.

ent lines were parallel to the isopotential lines. Thus, from right to left, the S2 field decreased, whereas tissue refractoriness, at the time of S2, increased. Along a column from top to bottom, field strength and refractoriness were very similar.

Plaque electrode and MAP electrode recordings (Figure 3) again illustrate the S1 activation pattern and also show the S2 stimulation results. Electrodes a–h are bipolar plaque electrodes in a column perpendicular to the S1 and S2 side of the plaque as shown. After the last S1 stimulus, activation spread progressively from electrode a toward electrode h. The MAP electrode was located between the halves of the plaque, approximately the same distance
from the S2 electrode as electrode c. The tissue at electrode a is most recovered at the time of S2 and is exposed to the strongest S2 field, whereas electrode h is least recovered and is exposed to a much weaker S2 field. The electrode recordings suggest, however, that electrodes a–e did not activate until more than 90 msec after S2, whereas the electrodes in the less recovered tissue (f–h) recorded activations just after S2. The MAP electrogram resolves the apparent paradox by showing that the tissue close to S2 activated during S2, which is defined as being directly excited. The MAP electrode could detect direct excitation while the plaque electrodes could not, because the MAP records the entire action potential rather than the brief (2–5 msec) activation event. Plaque electrodes did not detect direct excitations during S2 because any activation complexes would be buried in the approximately 1,000-fold larger signal from the S2 shock. Tissue bordering the directly excited zone, indicated by the dashed line in Figure 3B, gave rise to an activation front which spread past electrodes f–h. Activation times are shown for the electrodes, such as electrodes f–h, which were not directly activated by S2 on the activation map (Figure 3B) and electrodes at directly excited sites are shown as open circles since their activations occurred during S2.

Decreasing the S2 voltage or decrementing the S1-S2 interval caused the directly excited region to become smaller. The directly excited zone was smaller for shorter S1-S2 intervals because the tissue had less time to recover after the preceding S1 activation. Conduction from the directly excited zone, as in Figure 3, was inferred when activation adjacent to the border occurred 40 msec or less after the S2 shock (e.g., electrode f in Figure 3) and activation times increased with distance from the border. Below a critical S1-S2 interval, differing for
different S2 voltages and for different experiments, an activation front did not spread away from the directly excited border (Figure 4). Instead, temporary conduction block was induced by the shock at the directly excited border. The tissue adjacent to the directly excited region did not activate until 40–89 msec after the S2 shock (electrode f in Figure 4A and electrode c in Figure 4C), supporting the conclusion that conduction blocked at the directly excited border. Both monophasic and biphasic waveforms produced conduction block at the directly excited border. Both monophasic and biphasic waveforms produced conduction block at the directly excited border if sufficiently strong shocks were delivered at short enough S1–S2 intervals (vide infra). The tissue just outside the directly excited region did not activate by way of propagated activity from the directly excited zone, as it had in Figure 3, but instead was activated from a region off the plaque (Figure 4C). The activation sequence in the tissue past the directly excited region (electrodes i–f in Figure 4A–B), was often from left to right, opposite that found when conduction did propagate from the directly excited border (electrodes f–h in Figure 3).

An alternative interpretation for the activations in the tissue adjacent to the directly excited region occurring 40–89 msec after S2 might be slow conduction from the directly excited zone. However, if conduction did propagate from electrode c in the directly excited region to electrode f (Figure 4A–B), the mean conduction velocity would have been 0.046 mm/msec, below that accepted for normal myocardium.43 In Figure 4C, the calculated conduction velocity from electrode b to c would have been 0.033 mm/msec. Moreover, the left to right activation sequence makes slow conduction in these cases even less plausible, and favors transient conduction block.

The maps of activations after the S2 shocks shown in Figure 4 demonstrate that, for equal voltage shocks and coupling intervals, the monophasic waveform directly excited an equivalent, or more often, a larger region than the biphasic waveform. The larger region of direct excitation for the monophasic than the biphasic waveform was most evident for larger S2 shocks or for shorter S1–S2 intervals.

The relative abilities of the two waveforms to excite tissue at varying stages of recovery were quantified with strength-interval curves (Figure 5).44 The stimulus strength at each electrode was measured by the potential gradient at the site, and plotted on the y axis. The tissue refractoriness was described by the recovery interval at the site and displayed on the x axis. Points were plotted as either directly excited or not directly excited by the S2.

The strength-interval curves that best separated the directly excited group of points from the not directly excited group were fitted to the hyperbolic equation:

\[
\text{Potential gradient} = \frac{a}{(\text{Recovery interval}) - \text{ARP} + \text{DT}}
\]

At recovery intervals shorter than the absolute refractory period (ARP) the tissue cannot be excited, no matter how high the potential gradient. The potential gradient value for the diastolic threshold (DT) indicates the gradient needed to excite fully recovered tissue. The constant, a, also determines the curve's shape. These curves were determined by varying the three constants, ARP, a, and DT, in small increments. The data points (Figure 5A–B), however, cannot be perfectly separated by a single smooth line (see “Discussion”). The optimal curve misclassified the fewest total points such that an equal number of points from either group was misclassified. The best fitted curve misclassified an average of 8% of the approximately 650 total points for either waveform in each dog.

The monophasic and biphasic strength-interval curves were compared for each dog at three values: 1) the ARP, when the cells are too refractory to be excited, 2) the DT, when the cells are fully recovered, and 3) in the relatively refractory period, at the recovery interval at which the curve’s value for potential gradient equaled 2 V/cm (Figure 5C). The monophasic ARP was shorter than the biphasic one in each dog (Table 1), with means of 151 msec and 159 msec (p=0.004), respectively. For relatively refractory tissue (Table 1), the monophasic waveform strength-interval curves were an average of 5 msec to the left of the biphasic ones (p=0.014). The monophasic shocks could thus directly excite refractory tissue better than the biphasic shocks. The mean monophasic DT, 0.63 V/cm, was not significantly different than the mean biphasic DT, 0.82 V/cm (Table 1).

The reason conduction blocked at the directly excited border for certain combinations of S2 voltage and S1–S2 interval was evaluated by analyzing the 9 electrodes immediately adjacent to the directly excited zone for each S2 activation map in Part IIA. These were grouped into those conducting and those exhibiting block. The monophasic and biphasic maps were analyzed separately. Examples of electrodes from a directly excited border exhibiting block for a monophasic shock include electrode f and the eight others adjacent to the solid line in Figure 4A. The group of electrograms indicating conduction from the directly excited zone (e.g., Figure 3B) had activation times less than 40 msec after S2; the activation direction was also right to left. The group of electrograms which identified the occurrence of conduction block at the directly excited border had activation times 40–89 msec after S2; activation was left to right in most regions. The potential gradient at the directly excited border was higher for the points where conduction blocked, than where conduction successfully spread from the directly excited zone. For either waveform, a potential gradient value was chosen that
best separated the two groups of points and misclassified the fewest from each group (Table II). When the gradient that best separated the two groups was applied about 10% of the total points were nevertheless misclassified. The monophasic and biphasic values differed by 1.5 V/cm or less in each experiment (Table 2). The mean monophasic value was $3.8 \pm 0.8$ V/cm, and the mean biphasic value was $3.8 \pm 1.4$ V/cm ($p=NS$).

The subepicardial fiber orientation was relatively uniform in the mapped area for the six experiments. The mean fiber orientation was $42 \pm 15^\circ$ ($n=6$) with respect to the S1 electrode side of the plaque. Mean fiber orientation did not correlate with either the ARP on the strength-interval curves or with the gradient at which conduction blocked at the directly excited border.

**Part B: Monophasic action potential studies.** Simultaneous recordings from the MAP electrode and the modified split plaque (Figures 3 and 6A) verified the existence of the directly excited zone. Despite the approximately 15 mm separation between the two plaque-halves, the stimulation protocol produced relatively parallel S1 isochronal activation lines and S2 isogradient lines as in part II A. The directly excited region was large for long S1-S2 intervals (e.g., the region to the right of the dashed line in Figure 6A), thus placing the directly excited border in a relatively low ($-1-3$ V/cm) potential gradient region, and an activation front propagated away from the directly excited zone border. When the MAP electrode was positioned in the directly excited region, a monophasic action potential (MAP) beginning during the S2 was recorded (Figures 3 and 6A). Although the

![Activation maps and electrograms comparing monophasic and biphasic shocks and showing conduction block (part IIA). S1 and S2 electrodes were on right. For monophasic shock in Panel A the tissue under the plaque was less recovered from the preceding S1 than in Figure 3, and less myocardium was directly excited. Conduction blocked at directly excited border (solid line) where gradient was ~4 V/cm. An activation front then conducted through mapped region beginning outside mapped area (arrows). A row of electrodes labeled a–i is indicated. Panel B shows recordings for monophasic shock from electrodes indicated in panel A. The last S1 stimulus, S1 activations, S2 shock (with gain switch artifacts on either side) and post-S2 activations are shown. S2 activation times are shown above tracings. Electrodes recording from directly excited zone activate during the S2 shock, and then again ≥90 msec after S2. Due to 1,000:1 voltage divider circuit, the directly excited (DE) activations occurring during S2 cannot be appreciated. Panel C shows biphasic shock with same settings as panels A–B. Less tissue was directly excited than with monophasic; conduction again blocked at the directly excited border. Panel D shows the electrograms labeled in Panel C. Biphasic S2 can be seen between gain switch artifacts. (Figures 4–5 pertain to same part II experiment, number 6, in Tables 1 and 2.)
FIGURE 5. Examples of a monophasic and biphasic strength-interval plot in one dog. Potential gradient (V/cm) is plotted against recovery interval (msec) for tissue at each electrode. Each point represents an individual electrode on activation map following S2 for each monophasic or biphasic S2 shock in this dog. Electrodes recording from directly excited tissue are shown as filled circles, and electrodes in tissue not directly excited as open circles. Curve having best fit for equation 1 (see text) is shown. Panel A illustrates monophasic strength-interval plot. Electrodes labeled a–i in Figure 4A are some of points plotted. They would be found on a diagonal orientation with a in upper right (longer recovery interval and stronger S2 field) and i in lower left (shorter recovery interval and weaker gradient). Electrodes a–e would be in directly excited zone to right and above curve, and electrodes f–i would be below and to left of curve in the nondirectly excited zone. Panel B shows biphasic strength-interval plot and curve. Panel C shows monophasic (M) and biphasic (B) curves superimposed. Biphasic curve is to right of monophasic, indicating that biphasic waveform is less able to directly excite partially refractory myocardium. Absolute refractory period (ARP) is y asymptote of strength-interval curve, whereas diastolic threshold (DT) is x asymptote. ARP values were 155 msec for monophasic curve and 168 msec for biphasic curve. Monophasic DT was 0.7 V/cm and biphasic DT was 0.6 V/cm.

upstroke of this directly excited MAP was obscured by the S2 shock, the remainder of the action potential was visible. This directly excited MAP was reproducibly recorded in each experiment using different S1-S2 intervals and S2 voltages. The MAP tracing substantiates that this region near the S2 electrode, for example the region containing electrode a in Figure 6A, was directly excited. The MAP electrode could detect direct excitation, whereas the bipolar plaque electrodes could not, because the MAP records the entire action potential, rather than just a 2–5-msec local activation event.

The MAP electrode also recorded activations in tissue not directly excited by the shock that were due to an activation front spreading away from the directly excited zone border and propagating past the MAP electrode. The MAP electrogram (Figure 6B) shows an S2 shock occurring during repolarization from the preceding S1 activation; repolarization continues after S2 and is followed by an activation.

When conduction blocked transiently at the directly excited border, the MAP electrode recorded a brief depolarization immediately following the S2 shock. With microelectrode techniques, Kao and Hoffman45 recorded similar signals from critically refractory tissue labeling them “graded responses.” This secondary depolarization delayed the completion of the last S1 repolarization, prolonging the MAPD_{90} from 177 msec for the ninth S1 action potential, to 189 msec for the 10th S1 action potential (Figure 6C). The S2-induced graded response did not propagate, as evidenced by the absence of activation away from the directly excited border (Figure
TABLE 1. Values for Strength-Interval Curve Equation

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Values for best fit to strength-interval curve, determined as described in “Results” for each waveform and experiment. Data represent mean±SD. B, biphasic; M, monophasic; x at 2 V/cm, x-axis value (msec) of strength-interval curve for gradient level of 2 V/cm; a, the value for the constant a from Equation 1; p values comparing M and B by paired t test.

6C). These graded response signals were not recorded from the directly excited zone (Figure 6A) or from tissue in which conduction did propagate from the directly excited zone (Figure 6B). Thus, the MAP recorded a graded response due to a sufficiently strong field stimulus in tissue too refractory to be directly excited.

The magnitude of the graded response depended upon the coupling interval. Figure 7B shows that a moderate graded response occurred at an S1-S2 interval of 100 msec, prolonging the MAPD90 and MAPD70 durations by 11 and 7 msec respectively. Reducing the S1-S2 interval to 60 msec (bottom tracing) allowed even less recovery time for the tissue, and a negligible graded response resulted, as evidenced by the absence of prolongation of MAPD90 or MAPD70. On the other hand, at a sufficiently long S1-S2 interval the myocardium would be directly excited instead of having a graded response.

Discussion

Biphasic waveforms can defibrillate at substantially lower voltages than equal duration monophasic ones.4-6,9,10,23,46 We tested the hypothesis that a biphasic shock defibrillates at lower voltages than a monophasic shock because the biphasic can more effectively excite the relatively refractory myocardium present during VF.47 Because some biphasic waveforms defibrillate less effectively than monophasic ones,23 we first demonstrated that the biphasic waveform selected (Figure 1A) did indeed defibrillate better than the monophasic one, whether measured by total energy, peak current or peak voltage. We then compared the stimulating efficacies of the two waveforms in refractory, nonfibrillating myocardium by determining strength-interval curves.44

Strength-Interval Curves for Monophasic and Biphasic Shocks

We found that the monophasic strength-interval curve was situated to the left of the biphasic one in each experiment (Figure 5 and Table 1). The 3-msec monophasic shock therefore excited refractory, nonfibrillating tissue more effectively than the 3-msec biphasic one, yet the biphasic waveform defibrillated better. These surprising results have both theoretical and practical implications and raise the following questions: 1) What are the basic mechanisms of defibrillation? 2) Why do biphasic shocks defibrillate better? 3) How should an optimal waveform for clinical use be selected?

Successful defibrillation has usually been theorized to require the excitation of either all or a critical mass of partially refractory tissue in order to extinguish the activation fronts present during VF.15,16 The hypothesis that we tested is really an extension of this conception of defibrillation: the waveforms that are best able to excite the refractory tissue present during VF should be best able to defibrillate.47 Because the 3-msec biphasic waveform is better for defibrillating, yet less able to excite refractory tissue than the 3-msec monophasic, these results are contrary to the above hypothesis. Whereas excitation of tissue to halt activation fronts may be necessary, it is not sufficient for successful defibrillation. Biphasic

TABLE 2. Potential Gradient for Conduction Block at Directly Excited Border

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Monophasic</th>
<th>Biphasic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>3.7</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>5.7</td>
</tr>
<tr>
<td>6</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>MEAN*</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>SD</td>
<td>0.8</td>
<td>1.4</td>
</tr>
</tbody>
</table>

p = 0.91

NA, no blocking electrodes.

*Excludes experiment 5 for which no blocking electrodes were present for the monophasic waveform.
waveforms appear to defibrillate better than monophasic ones independent of their respective abilities to stimulate refractory tissue.

If the hypothesis that biphasic waveforms defibrillate better because they stimulate refractory tissue better is invalid at least for some waveforms, such as the 3-msec ones tested, what are alternative explanations for the greater efficacy of biphasic waveforms? Several recent cardiac mapping studies help us understand how biphasic shocks could defibrillate better yet stimulate less effectively. Two studies, but not another, suggest that shocks slightly below the DFT, although halting existing activation fronts, give rise to new ones which reinitiate VF. That an interaction of shocks with refractory tissue can cause reentry or VF has long been recognized. A critical determinant of a waveform's capability to defibrillate may be the tendency for recreation of VF by any new activation fronts generated at the border of regions directly excited by the shock, rather than the quantity of tissue directly excited by the shock.

Accordingly, biphasic shocks could defibrillate better than monophasic ones 1) because they initiate fewer such activation fronts, and/or 2) because the shock-generated activation fronts have a lower likelihood of precipitating VF. First, biphasic shocks might fail to give rise to potentially harmful new activation fronts. If the gradient which caused conduction block in refractory tissue at the directly excited border were lower for biphasic than monophasic shocks, fewer activation fronts would derive from equal strength biphasic shocks. However, our data that the gradient leading to conduction block in the directly excited border is similar for monophasic and biphasic shocks argues against this explanation (Table 2). Second, activation fronts deriving from biphasic shocks might lack the propensity to reinitiate VF. Since the biphasic strength-interval curve lay to the right of the monophasic one, the relatively refractory tissue adjoining the directly excited zone should be less refractory for biphasic than for monophasic shocks. Activation fronts propagating from the directly excited border following the biphasic shock would thus travel through more recovered tissue, and might fail to exhibit slow conduction, a requirement for reentry, and therefore be less likely to produce reentry and VF. An alternative explanation not necessarily relating to refractory tissue is that the greater defibrillation efficacy of biphasic waveforms derives from a lesser tendency for conduction block or arrhythmias to be initiated in high gradient zones.

The advent of the implantable defibrillator has prompted identification of an optimal waveform to lower defibrillation thresholds and thereby prolong battery life and minimize damage by large shocks. These provocative results imply that the identification of superior defibrillation waveforms by simply selecting ones which excite refractory tissue best may lead to erroneous choices. Until the exact mechanism(s) can be determined for the greater efficacy of biphasic shocks, waveform selection will remain empirical.

Previous studies investigating the ability of monophasic and biphasic shocks to stimulate tissue have used different waveforms and methods making comparisons difficult. Similar to our results, Wharton et al. found biphasic stimuli less effective in exciting refractory tissue but equivalent for stimulating recovered myocardium. Kavanagh et al., however, found biphasic pacing impulses reduced energy requirements for stimulation. Both these studies used local stimuli. Defibrillation, however, requires excitation of tissue distant from the electrode by an electric field.

A study by Jones et al. did compare field stimulation using monophasic and biphasic waveforms to excite cultured chick cells. They found that biphasic shocks could stimulate at a lower field strength than the monophasic stimuli, but the monophasic waveforms were compared with biphasic ones having twice the total duration. Importantly, the biphasic superiority was more apparent for longer duration stimuli. The biphasic waveform was also relatively more effective than the monophasic one in stimulating rapidly paced cells exposed to markedly elevated [K+], conditions felt to simulate VF.
The present study and Jones’ experiment differ in methods and results. First, in this experiment the monophasic and biphasic shocks had equal durations. Second, different experimental preparations were studied, cultured chick embryo cells and the in situ canine heart. Third, Jones’ in vitro experimental protocol used a high [K⁺], to reproduce the elevated transmembrane potential found 5 minutes after the onset of VF, whereas in the present study, premature S2 stimuli were used to make the myocardium partially refractory as is the case especially during early VF.18 The present study did not use an elevated [K⁺], for the stimulation comparison for several reasons: 1) these were in vivo studies, and artificial circulatory support might have been required; and 2) whereas defibrillation comparisons pertaining to implantable defibrillators are conducted after approximately 10–30 sec of VF, such as in part I, the [K⁺], early in VF has apparently not been reported.59–62

The two studies thus reach different conclusions on the relative stimulating efficacies of biphasic waveforms, but Jones’ study suggests that waveform duration may be a reason for the difference. Jones’ group’s data show that longer biphasic shocks stimulate better than equal duration monophasic shocks, whereas shorter duration biphasic shocks stimulate less effectively than monophasic ones.47,63 Thus, the hypothesis concerning defibrillation efficacy of biphasic waveforms which is invalid for the 3-msec waveforms in this study may explain at least some of the greater efficacy of other longer duration biphasic waveforms.

A consideration of the effects of a stimulus on membrane potential may explain our results that short duration biphasic shocks stimulate less effectively than monophasic ones. As the stimulus duration is increased, the transmembrane voltage change initially increases rapidly and then increases more

**Figure 7.** Additional MAP electrograms (part II B). Panel A shows MAP recording from tissue not directly excited by an S2 field of ~2 V/cm; after gain switching and S2 stimulus artifacts MAP quickly resumes tracking of repolarization. Graded response did not occur. This argues against graded response recording in Figure 6C being a shock-induced artifact. Panel B illustrates effect of S1-S2 interval on the MAP-recorded graded response. Graded response, seen at an S1-S2 interval of 100 msec was essentially absent at an S1-S2 interval of 60 msec. Panel C shows an MAP tracing from region directly excited (DE) by a 75 V shock using an S1-S2 interval of 205 msec (top tracing). When S1-S2 was decreased to 200 msec (bottom tracing), tissue under the MAP electrode was no longer directly excited. MAP location and S2 voltage were unchanged from top tracing. After S2 an activation front successfully propagated away from border through tissue under MAP.
slowly until a plateau is reached.64 At pulse durations much less than one time constant in duration the curve relating the resultant voltage change is very steep. Shorter duration biphasic stimuli may excite less effectively than monophasic ones because each component phase may be too short to effect a change in transmembrane potential sufficient to excite. Longer duration biphasic waveforms may stimulate as well (or even better) than equal duration monophasic ones if either phase is long enough to stimulate on its own. A potential limitation of both the Jones’ study and the present one is that the relative ability to stimulate fibrillating tissue may not be the same as for paced preparations.63

Experimental error and true physiologic variability may explain the slight overlapping of data points on the strength-interval plots. The strength-interval curves giving the best fit to the data points misclassified approximately 8% of the points (range 4–12%) for either waveform. Activation time determinations and gradient computations represent sources of experimental error. Autonomic variations resulting from anesthesia, shocks, prior VF episodes, or other factors likely caused small shifts in the strength-interval curves over the course of the experiments. Such shifts were observed in several experiments by giving shocks with identical voltages and coupling intervals several times during the experiment. A second source of biological variability is fiber orientation which might cause tissue in different regions under the plaque to have different stimulation thresholds.39 Whereas the mapped area’s fiber orientation was relatively homogeneous in each experiment, small regions having different orientations were occasionally seen in the histological sections and these may have caused some of the overlap of data points on the strength-interval plots.

Extracellular electrodes cannot identify directly excited tissue with the certainty of intracellular microelectrodes because the identification depends on indirect criteria from the electrograms and the maps. This possible limitation was minimized by using MAP electrode recordings to verify the existence of directly excited tissue. Extracellular electrodes may also overestimate the directly excited region’s size when propagation occurred from the border. Activations occurring after the shock, but during the time required to switch the gains back to levels appropriate for recording activations would be incorrectly labeled direct excitations. Because activations could be recorded as early as 7 msec after the end of the shock, overestimation of the directly excited zone size should be small. Only a difference in the magnitude of this overestimation for the two waveforms would affect the finding that the monophasic waveform directly excited more tissue. In addition, almost half the S2 activation maps had conduction block at the directly excited border (Figure 4); these maps were not subject to this overestimation, and more importantly, to any possible difference in the magnitude of it between the monophasic and biphasic shocks.

**Shock-Induced Conduction Block: Graded Responses**

In addition to direct excitation, other effects of the monophasic and biphasic waveforms in partially refractory tissue were assessed, because these could pertain to the difference in defibrillation efficacy. When the potential gradient at the directly excited border was above approximately 4 V/cm, conduction failed to propagate away from the border (Figure 6C). When the border was located in a lower gradient field (Figure 6A–B) conduction successfully spread from the directly excited region. Importantly, these two activation patterns occurred for both monophasic and biphasic waveforms and the gradient values above which they occurred were similar (Table 2).

Shock-induced conduction block has been suggested to occur with monophasic stimuli in several previous studies.53–55 However, the extracellular electrode recordings in those studies and in the present one do not explain how an activation front fails to originate at the directly excited border in a zone of relatively high (≥4 V/cm) potential gradient. One explanation for the shock-induced conduction block could be the interaction of the strong field stimulus with critically refractory tissue to cause a “graded” or “local” response45 which fails to propagate to the surrounding tissue. This small depolarization could delay the recovery of excitability. The MAP electrode recorded graded response-like signals from the tissue in which conduction from the directly excited region blocked (Figure 6C). The simultaneous plaque electrode recordings (Figure 6C) indicate that the post-S2 depolarization recorded by the MAP failed to generate an activation front spreading from the directly excited tissue. Action potential prolongation in relatively refractory tissue by strong shocks has also been reported recently by other investigators.65,66

Misinterpretation of motion artifact as physiologic electrical events can occur with MAP electrodes, as it can with other techniques.67,68 However, the MAP-recorded graded responses occurred immediately after the shocks, before contraction because of the shock would be expected. Also, the graded responses could be recorded reproducibly at the border of the directly excited region when the potential gradient was great enough to cause conduction block (Figure 6C). In less refractory tissue exposed to a large potential gradient, the MAP recorded direct excitations (Figures 6A and 7C). In refractory tissue exposed to a relatively weak field, the MAP electrode recorded the completion of repolarization after the S2 stimulus artifact (Figures 6B, 7A, and 7C). Moreover, when a strong stimulus was applied much earlier than the ARP (Figure 7B), the graded response duration was much reduced, in agreement with prior microelectrode studies.69

In myocardium not directly excited by the stimulus, graded responses occurred if the gradient was above a certain value, as shown on an idealized strength-interval plot55 (upper left region, Figure 8). In a
FIGURE 8. Strength-interval curve showing three responses to a shock. Gradient for dashed line separating graded response zone is mean from Table 2. Figure 7B suggests that graded responses do not occur in extremely refractory tissue.

weaker gradient field the refractory tissue is neither directly excited nor does it develop a graded response (lower left, Figure 8); it can be activated after the shock by an activation front (Figure 6B). In less refractory tissue a strong field will cause direct excitation (right of curve, Figure 8). The existence of the graded response zone on a strength-interval relationship has been verified by the MAP electrode only for monophasic waveforms in these studies. The fact that conduction blocks in the tissue bordering the directly excited region for biphasic shocks, as it does for monophasic shocks, suggests that a similar graded response zone may also exist for biphasic waveforms. The duration, magnitude or other attributes of graded responses for biphasic waveforms may differ, however. The shock-induced graded response, by prolonging refractoriness, can explain transient conduction block at the border of the tissue directly excited by the S2 (Figure 6C). Such graded responses may play a role in other instances where unidirectional block has been implicated, such as in the genesis of reentrant arrhythmias. Moreover, it could explain how subthreshold defibrillation shocks may fail to defibrillate by producing a shock-induced graded response leading to reentry and refibrillation.

Conclusions

Using computer-assisted cardiac mapping techniques, we tested the postulate that the difference in defibrillation efficacy between biphasic and monophasic waveforms is due to different effects on refractory ventricular myocardium. Contrary to a previous hypothesis that biphasic shocks defibrillate better than monophasic ones because they stimulate tissue better, a 3-msec biphasic waveform was less able to stimulate partially refractory tissue than a 3-msec monophasic one. This lesser stimulating ability may be explained by the short durations of the two phases of the 3-msec waveforms. These results argue that the main determinant of success for defibrillation shocks may be the fate of any activation fronts generated by the shock, instead of the amount of tissue directly activated by the shock. Because of the rapid activation rate during VF, it is likely that any activation fronts initiated by the defibrillation shock would encounter relatively refractory tissue. Conduction velocity might be slow, therefore, and unidirectional conduction block could result leading to reentry and resumption of VF. The MAP recordings indicate that shocks may produce temporary conduction block due to the occurrence of graded responses. Since biphasic shocks are less able to stimulate refractory tissue than monophasic ones any activation fronts originating at the border of the directly excited zone would travel through less refractory tissue and might therefore conduct faster, block less readily and be less likely to reactivate VF. Other experiments have shown that longer duration biphasic waveforms may under some situations stimulate better than monophasic ones, yet also defibrillate better than monophasic ones.

Thus, whereas biphasic shocks of different durations may defibrillate better than equal duration monophasic ones, the biphasic waveforms may stimulate tissue either less or more effectively, depending upon waveform duration.

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References


15. Wiggers CJ: The physiologic basis for cardiac resuscitation from ventricular fibrillation—Method for serial defibrillation. Am Heart J 1940;20:413


38. Witkowski FX, Penkoske PA: Relation of defibrillatory potential to the minimia to positive for activation, in Proc 10th Annual Conf of the IEEE Engineering in Medicine and Biology Society, 1988, pp 212–213


43. Scher AM, Young AC, Malmgren AL, Paton RR: Spread of electrical activity through the wall of the ventricle. Circ Res 1953;1:539–547


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