Ascending-Ramp Biphasic Waveform Has a Lower Defibrillation Threshold and Releases Less Troponin I Than a Truncated Exponential Biphasic Waveform

Jian Huang, MD, PhD; Gregory P. Walcott, MD; Richard B. Ruse, BA; Scott J. Bohanan, MSEE; Cheryl R. Killingsworth, DVM, PhD; Raymond E. Ideker, MD, PhD

Background—We tested the hypothesis that the shape of the shock waveform affects not only the defibrillation threshold but also the amount of cardiac damage.

Methods and Results—Defibrillation thresholds were determined for 11 waveforms—3 ascending-ramp waveforms, 3 descending-ramp waveforms, 3 rectilinear first-phase biphasic waveforms, a Gurvich waveform, and a truncated exponential biphasic waveform—in 6 pigs with electrodes in the right ventricular apex and superior vena cava. The ascending, descending, and rectilinear waveforms had 4-, 8-, and 16-millisecond first phases and a 3.5-millisecond rectilinear second phase that was half the voltage of the first phase. The exponential biphasic waveform had a 60% first-phase and a 50% second-phase tilt. In a second study, we attempted to defibrillate after 10 seconds of ventricular fibrillation with a single 30-J shock (6 pigs successfully defibrillated with 8-millisecond ascending, 8-millisecond rectilinear, and truncated exponential biphasic waveforms). Troponin I blood levels were determined before and 2 to 10 hours after the shock. The lowest-energy defibrillation threshold was for the 8-milliseconds ascending ramp (14.6±7.3 J [mean±SD]), which was significantly less than for the truncated exponential (19.6±6.3 J). Six hours after shock, troponin I was significantly less for the ascending-ramp waveform (0.80±0.54 ng/mL) than for the truncated exponential (1.92±0.47 ng/mL) or the rectilinear waveform (1.17±0.45 ng/mL).

Conclusions—The ascending ramp has a significantly lower defibrillation threshold and at 30 J causes 58% less troponin I release than the truncated exponential biphasic shock. Therefore, the shock waveform affects both the defibrillation threshold and the amount of cardiac damage. (Circulation. 2012;126:1328-1333.)

Key Words: cardioversion ■ defibrillation ■ troponin ■ ventricular fibrillation

The implantable cardioverter-defibrillator (ICD) has revolutionized the treatment of patients at risk for sudden cardiac death resulting from ventricular fibrillation (VF).1 However, recent reports indicate that the patients who received defibrillation shocks had higher mortality than those who did not.2 Although it is unclear whether the increased mortality after ICD shocks is just a marker of a more diseased heart or if cardiac damage caused by the shocks also plays a role, it is known that ICD shocks cause direct myocardial injury. This affects electrophysiological and hemodynamic functions and causes biochemical alterations and cellular morphology changes.3-5 Tokano et al.3 demonstrated that ICD shocks of >9 J delivered during sinus rhythm or VF in humans were associated with a 15% reduction in the cardiac index. Biochemical markers of myocardial damage such as a rise in troponin I level have been seen after ICD implantation.6,7 The local injury current after an ICD shock for induced VF has been shown to predict heart failure progression.8 This local injury current is probably caused by transient cell membrane damage resulting from electroporation,9 which in turn is caused by a large potential gradient10 created near the defibrillation electrodes by the shock. The amount of this cardiac dysfunction increases with increasing shock strength.10,11 If shock voltage is sufficiently high, myocardial necrosis can occur.12

Clinical Perspective on p 1333

Although defibrillation shocks cause damage, they are the only effective way to halt VF. It is possible that waveforms exist that cause less damage to the heart than the currently clinically used truncated exponential biphasic waveforms. One way to reduce damage would be to find waveforms with a lower defibrillation threshold (DFT) because damage is related to shock strength.3,10,11 In addition, it is possible that some waveforms cause less damage than others, even when they are the same strength.

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Because postshock arrhythmias are related to myocardial injury\textsuperscript{13} and experimental studies have shown that an ascending-ramp waveform reduces postshock arrhythmias and has a lower DFT than current clinically used truncated exponential biphasic waveforms,\textsuperscript{14} we tested the hypothesis that the ascending-ramp waveform creates less damage and defibrillates with lower shock energy than the truncated exponential biphasic waveform. We generated ascending-ramp waveforms, a rectilinear waveform, and a Gurvich waveform, which has been reported to have a lower DFT energy than a rectilinear waveform,\textsuperscript{15} with a new type of defibrillator circuit that may make it feasible to use such waveforms clinically.

**Methods**

This study consisted of protocol 1, in which the DFTs of 11 waveforms were evaluated, and protocol 2, in which serum troponin I levels were measured before and after a successful defibrillation shock of 3 different types of waveforms that had a low DFT in protocol 1. The same animal preparation was used in both protocols. The study was performed in accordance with the guidelines established in the *Position of the American Heart Association on Research Animal Use* adopted by the American Heart Association on November 11, 1984.

**Animal Preparation**

Twenty-seven pigs of either sex, 6 for protocol 1 and 21 for protocol 2, were used. Animals were placed in dorsal recumbency and maintained under anesthesia for the course of the study. The methods of anesthesia, muscle relaxation, ventilation, and monitoring have previously been published.\textsuperscript{16}

**Electrodes and DFT Measurements**

Under fluoroscopic guidance, via right external jugular access, a 0094 Endotak lead (CPI Inc, St. Paul, MN) with a 4.7-cm-long right ventricular electrode and a 6.9-cm-long superior vena cava electrode was positioned with the tip at the right ventricular apex.

VF was induced for 10 seconds with 60-Hz, 30-V alternating current delivered through the right ventricular electrode of the Endotak lead. The DFT of a selected waveform was determined with the Dixon\textsuperscript{17} method. The initial test shock was set at 400 V, with subsequent test shocks set at increased or decreased voltages in up-down log\textsuperscript{10} 0.1-V steps. After the first reversal in test shock outcomes (eg, test shock success followed by test shock failure or vice versa), 2 additional fibrillation-defibrillation episodes were performed in up-down log\textsuperscript{10} 0.1-V steps. Rescue shocks were delivered immediately after failed defibrillation attempts. The DFT for each waveform was estimated by Xf+kd, where Xf is the last shock voltage administered, k is the tabular value representing the maximum likelihood solutions,\textsuperscript{10} and d is the interval between each shock voltage. Defibrillation episodes were separated by at least 4 minutes. The peak voltage and delivered energy and impedance were recorded with a digitizing oscilloscope (TDS-744A, Tektronix Inc, Beaverton, OR). At the end of the study, the anesthetized animal was euthanized with an injection of potassium chloride solution.

**Defibrillation Waveforms**

Three descending-ramp (Figure 1A), 3 ascending-ramp (Figure 1B), and 3 rectilinear (Figure 1C) biphasic shocks were delivered by a custom-built internal defibrillator that uses a new type of amplifier circuit (Ruse Technologies, LLC, Atlanta, GA). The first-phase durations of the descending, ascending, and rectilinear waveforms were 4, 8, and 16 milliseconds. The second phase was always 8 milliseconds. A 3.5-millisecond rectilinear waveform half the peak voltage of the first phase of each of the above waveforms (Figure 1). A Gurvich waveform (Figure 1D) generated by the same defibrillator was constructed by 2 half-cycle sinusoid waves with a phase 1 duration of 4.25 milliseconds and phase 2 duration of 4.75 milliseconds.\textsuperscript{18}

The peak voltage of phase 2 was 63% of the peak voltage of phase 1.\textsuperscript{18} A clinically used biphasic truncated exponential waveform (Figure 1E) was generated with a model 2815 Ventak cardioverter defibrillator (CPI Inc, St. Paul, MN). The waveform had a 60% phase 1 and a 50% phase 2 tilt. The total duration of this waveform varied between 14.5 and 16.6 milliseconds.

**Protocol 1**

DFTs were determined for all 11 waveforms in each animal in random order. Randomization was performed by drawing a chit for each waveform. The right ventricular electrode was the anode for phase 1 of all waveforms.

**Protocol 2**

Blood samples for cardiac troponin I measurement were obtained before and 2 to 10 hours after the shock with each of 3 selected waveforms from protocol 1. As reported below, protocol 1 found the lowest DFT energy achieved with an 8-millisecond first-phase ascending waveform and the lowest DFT voltage achieved with an 8-millisecond first-phase truncated exponential waveform. In protocol 2, troponin I levels after a single defibrillation shock were determined for both of these waveforms and for the truncated exponential biphasic waveform. If the first shock failed to defibrillate after 10 seconds of VF, the animal was excluded from the study. The protocol was continued until a single successful shock for each waveform was achieved with 6 animals. The shock energy was based on 2 concerns for each waveform: The shock energy should be at least the DFT energy plus a 10-J safety factor, and the shock energy for each waveform should be the same for each waveform. The highest DFT energy among the 3 waveforms was \( \approx 20 \) J for the truncated exponential biphasic waveform. The mean impedance measured from protocol 1 was 55 \( \Omega \). Therefore, we set the single shock energy through the right ventricular electrode of the Endotak lead. The DFT of a selected waveform was determined with the Dixon\textsuperscript{17} method. The initial test shock was set at 400 V, with subsequent test shocks set at increased or decreased voltages in up-down log\textsuperscript{10} 0.1-V steps. After the first reversal in test shock outcomes (eg, test shock success followed by test shock failure or vice versa), 2 additional fibrillation-defibrillation episodes were performed in up-down log\textsuperscript{10} 0.1-V steps. Rescue shocks were delivered immediately after failed defibrillation attempts. The DFT for each waveform was estimated by Xf+kd, where Xf is the last shock voltage administered, k is the tabular value representing the maximum likelihood solutions,\textsuperscript{10} and d is the interval between each shock voltage. Defibrillation episodes were separated by at least 4 minutes. The peak voltage and delivered energy and impedance were recorded with a digitizing oscilloscope (TDS-744A, Tektronix Inc, Beaverton, OR). At the end of the study, the anesthetized animal was euthanized with an injection of potassium chloride solution.

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Blood samples for cardiac troponin I measurement were obtained before and 2 to 10 hours after the shock with each of 3 selected waveforms from protocol 1. As reported below, protocol 1 found the lowest DFT energy achieved with an 8-millisecond first-phase ascending waveform and the lowest DFT voltage achieved with an 8-millisecond first-phase truncated exponential waveform. In protocol 2, troponin I levels after a single defibrillation shock were determined for both of these waveforms and for the truncated exponential biphasic waveform. If the first shock failed to defibrillate after 10 seconds of VF, the animal was excluded from the study. The protocol was continued until a single successful shock for each waveform was achieved with 6 animals. The shock energy was based on 2 concerns for each waveform: The shock energy should be at least the DFT energy plus a 10-J safety factor, and the shock energy for each waveform should be the same for each waveform. The highest DFT energy among the 3 waveforms was \( \approx 20 \) J for the truncated exponential biphasic waveform. The mean impedance measured from protocol 1 was 55 \( \Omega \). Therefore, we set the single shock...
voltages at the level that would deliver about 30 J through a 55-Ω load for each waveform.

Data Acquisition and Statistical Analysis
Results are expressed as mean±SD. The effect of the waveform on DFT leading-edge voltage and delivered energy was analyzed separately with linear mixed-effects modeling (SPSS Inc). When differences were found, individual differences were determined with the Tukey test. The effect of waveform and time on troponin I level was assessed by a 2-factor repeated measures ANOVA with time as the repeated factor and waveform as the between-subjects factor (SPSS Inc). The interaction term indicated whether the waveform effect on troponin I was different at consecutive periods after the 3 different shocks. For all analyses, \( P < 0.05 \) was considered statistically significant.

Results
Six pigs (26±4 kg) were used in protocol 1 and 21 pigs (24±3 kg) were used in protocol 2. No significant differences were found for shock impedances among any of the 11 waveforms in protocol 1, among any of the 3 waveforms in protocol 2, or between protocols 1 and 2.

DFT Energy
The waveform with the lowest DFT was different for different first-phase durations. For the 4-millisecond first-phase duration waveforms, the lowest DFT energy achieved was with the ascending waveform, which was significantly lower than for the ascending and rectilinear waveforms \( (P < 0.05); \) Figure 2A). For the 8- and 16-millisecond first-phase duration waveforms, the lowest DFT energy was achieved with the descending waveform, which was significantly lower than for the same-duration ascending waveform \( (P < 0.05, P < 0.01); \) Figure 2A). Among all waveforms tested, the 4-millisecond descending and 8-millisecond ascending waveforms had the lowest DFT energy. The clinically used truncated exponential biphasic waveform had significantly higher DFT energy than the 4-millisecond descending or the 4- or 8-millisecond ascending waveforms.

DFT Voltage
Rectilinear waveforms had the lowest voltage DFT among the first-phase 4-, 8-, and 16-millisecond waveforms (Figure 2B). The 8- and 16-millisecond ascending waveforms also had significantly lower voltage DFTs than the same-duration descending waveforms, as well as the truncated exponential biphasic and Gurvich waveforms \( (P < 0.01); \) Figure 2B). Increasing the first-phase duration from 4 to 8 or 16 milliseconds significantly decreased the DFT voltage of ascending but not descending waveforms.

Protocol 2
As described, the shock strength used to determine troponin I release was the DFT energy plus a 10-J safety factor. The highest DFT energy for the 3 waveforms selected for protocol 2 was 19.6 J of the truncated exponential biphasic waveform. The actual delivered energies for the 3 waveforms in protocol 2 were as follows: ascending ramp, 29.35±3.4 J; rectilinear, 29.4±3.1 J; and truncated exponential biphasic waveform, 30.4±2.2 J. Although the energies delivered were similar, the ascending waveform had a significantly higher peak voltage \((671±2.1 \text{ V})\) than the rectilinear \((431±3.5 \text{ V})\) and truncated exponential biphasic \((610±3.8 \text{ V})\) waveforms. Twenty-one animals were studied in protocol 2; 18 animals were successfully defibrillated by a single shock (6 for ascending waveform, 6 for rectilinear waveform, and 6 for truncated exponential waveform). Two animals failed to be defibrillated by the single rectilinear waveform shock, and 1 animal failed to be defibrillated with the single truncated exponential biphasic waveform shock. Blood samples were drawn only for the first 6 postshock hours for the first animal defibrillated with the truncated exponential biphasic waveform.

The troponin I levels were similar before the shock for all waveforms (Figure 3). The troponin I levels increased significantly after the shocks compared with before the shocks for all 3 waveforms. The troponin I levels 2 to 10 hours after the truncated exponential shock were significantly higher than those after the ascending and rectilinear waveform shocks (Figure 3). The troponin I levels were significantly lower 4, 6, and 8 hours after the ascending waveform shock compared with the rectilinear waveform shock (Figure 3). The troponin I level 6 hours after the truncated exponential biphasic shock was 1.92±0.47, 1.17±0.45 ng/mL for the rectilinear waveform.
form shock, but only 0.80 ± 0.54 ng/mL for the ascending-ramp biphasic shock.

**Discussion**

The main findings of this study are that an ascending ramp biphasic shock has a significantly lower DFT and causes release of less than half as much troponin I as a truncated exponential biphasic shock at almost the same energy and at a higher peak voltage than the truncated exponential biphasic shock. This result indicates that the shape of the shock waveform, in addition to the peak voltage and energy of the waveform, affects cardiac damage caused by a shock.

**Effect of Defibrillation Waveform Shape on DFT**

Since the first successful defibrillation performed with a shock,19 multiple waveforms have been studied for clinical application. Because of concern mainly about defibrillation efficacy, the external defibrillation waveforms evolved from alternating current, then to monophasic untruncated capacitor discharge, to Edmark and Lown waveforms, and to the currently used biphasic truncated capacitor discharge. Because of size and weight restrictions, the only feasible waveform for the ICD has been a truncated capacitor discharge. Originally, the internal defibrillation waveform was monophasic, but it is now biphasic because the latter markedly reduces the DFT, enabling the implantation of a totally monophasic, but it is now biphasic because the latter mark-

**Defibrillation Shocks and Electric Myocardial Injury**

Electric myocardial injury, ranging from reversible hemodynamic change to irreversible myocardial necrosis, is a well-recognized complication of high-energy defibrillation shocks.12,25 A shock with energy > 9 J delivered during sinus rhythm or VF created detectable hemodynamic depression in patients.1 When cells are exposed to an external electric field, a voltage is induced across the cell membrane. The amplitude of this transmembrane voltage is proportional to the amplitude of the applied electric field and, with a sufficiently strong field, can cause a large increase in membrane permeability called electroporation or electropermeabilization.26 With small duration and amplitude of the field, electroporation is reversible. Reversible electroporation has widespread application in biochemistry, molecular biology, gene therapy, and many fields of medicine. The electric field required to create myocardial electroporation is much lower than that needed to create hemodynamic changes.11,26 For 5- to 10-millisecond monophasic or biphasic waveforms, shocks of 0.4 V for <1 millisecond directly across the cardiac cell membrane in a patch-clamp preparation cause an increase in membrane conductance, presumably as a result of electroporation. The amplitude of the applied electric field and, with a sufficiently strong field, can cause a large increase in membrane permeability called electroporation or electropermeabilization.26 With small duration and amplitude of the field, electroporation is reversible. Reversible electroporation has widespread application in biochemistry, molecular biology, gene therapy, and many fields of medicine. The electric field required to create myocardial electroporation is much lower than that needed to create hemodynamic changes.11,26 For 5- to 10-millisecond monophasic or biphasic waveforms, shocks of 0.4 V for <1 millisecond directly across the cardiac cell membrane in a patch-clamp preparation cause an increase in membrane conductance, presumably as a result of electroporation.11 If electroporation is severe, the cardiac cells may die, leading to a release of troponin I.27

Because of their high degree of sensitivity and specificity for detecting myocardial necrosis, cardiac troponins are the biomarkers of choice in acute coronary syndrome.28 In defibrillation, the elevation of troponin levels may be caused both by the ischemic insult of VF and by a direct effect of the shocks.7 In the present study, troponin levels were measured after a single shock following 10 seconds of VF in healthy pigs. Because of the minimal ischemia produced by 10 seconds of VF, the damage indicated by the troponin I release should be related mainly to the defibrillation shock. In addition, all animals were subjected to 10 seconds of VF, so differences in troponin I levels among the 3 groups of animals should be due to the different shock waveforms and not to different durations of VF.

One factor affecting the severity of cardiac damage and troponin I release is the strength of the shock, with increasing shock strength causing greater damage.10,11,21,27 The results of this study indicate that an ascending-ramp shock caused less troponin I release than a truncated exponential or a rectilinear waveform of the same energy and higher peak voltage. Therefore, the shape of the shock waveform also affects the
severity of cardiac damage. The transmembrane response to the shock as predicted by a resistor-capacitor model\textsuperscript{21} may offer clues as to why the shape of the shock affects damage (Figure 4). In the model, the transmembrane potential in response to the descending ramp rises quickly early during the shock and is near the maximum value for most of the latter portion of the shock. Conversely, the transmembrane potential in response to the ascending ramp rises slowly at a nearly constant level throughout the shock and is near the maximum only briefly near the end of the shock.

Either or both of these effects, ie, the rate of rise of the membrane response and the time near the maximum membrane response, may affect membrane damage. Approximately 40% of the cell membrane by weight consists of proteins that carry electric charges and that would be expected to move in response to the electric field created by a shock.\textsuperscript{29} Perhaps the slower rate of rise of the transmembrane potential change during the ascending-ramp shock allows time for the charged portions of the proteins to move without denaturing the protein or causing electroportation. Perhaps the greater amount of time that the transmembrane potential is near its maximum change during a truncated exponential shock causes more numerous or larger electropores to form and/or causes more ions to flow through the electropores increasing damage.

Study Limitations

The study has the following limitations. First, we tested only 1 measure of cardiac damage, ie, troponin I blood levels after the shock. Second, we tested an ascending ramp instead of an ascending exponential waveform. According to a resistor-capacitor model, the ascending exponential waveform should have a lower-energy DFT than the ascending ramp.\textsuperscript{30} Third, only a single second phase was tested, ie, a 3.5-millisecond rectilinear wave one half the peak voltage of the first phase. This duration was predicted to be optimum by one of the resistor-capacitor models.\textsuperscript{31} Fourth, we tested only healthy hearts. Shock-induced electroporation may be more severe in diseased hearts.\textsuperscript{32}

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Disclosures

None.

References

We demonstrated that an ascending-ramp biphasic shock has a significantly lower defibrillation threshold and causes release of less than half as much troponin I as a truncated exponential biphasic shock at almost the same energy and at a higher peak voltage than the truncated biphasic shock. This result indicates that the shape of the shock waveform, in addition to the peak voltage and energy of the waveform, affects cardiac damage caused by a shock. The results of this study suggest that, in addition to optimizing the shock waveform to decrease the defibrillation threshold, the shock waveform should be optimized to decrease the damage caused by defibrillation. Therefore, it is theoretically possible that the waveform with the lowest defibrillation threshold may not necessarily cause the least damage. Serendipitously, an ascending-ramp first-phase biphasic waveform has both a lower defibrillation threshold energy and a shape that causes less damage than the truncated exponential biphasic waveform. Further investigation is needed to determine whether an ascending ramp biphasic waveform will cause less shock damage to human hearts.
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