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

Running title: Huang et al.; Waveform Shapes and Troponin I Level

Jian Huang, MD, PhD1; Gregory P. Walcott, MD1; Richard B. Ruse, BA2; Scott J. Bohanan, MSEE2; Cheryl R. Killingsworth, DVM, PhD1; Raymond E. Ideker, MD, PhD1,3,4

1Department of Medicine; 3Biomedical Engineering; and 4Physiology, University of Alabama at Birmingham, Birmingham, AL; 2Ruse Technologies, LLC, Atlanta, GA

Address for Correspondence:
Jian Huang, MD, PhD
University of Alabama-Birmingham
1670 University Blvd, Rm B140 Volker Hall
Birmingham, AL 35294-0019
Tel: 205-975 4710
Fax: 205-975 4720
E-mail: jh@crml.uab.edu

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Abstract:

Background - We tested the hypothesis that the shape of the shock waveform affects not only the defibrillation threshold (DFT), but also the amount of cardiac damage.

Methods and Results - DFTs were determined for 11 waveforms: 3 ascending ramp, 3 descending ramp, and 3 rectilinear first phase biphasic waveforms, a Gurvich waveform, and a truncated exponential biphasic waveform in 6 pigs with electrodes in the RV apex and SVC. The ascending, descending and rectilinear waveforms had 4, 8 and 16 ms 1st phases and a 3.5 ms 2nd rectilinear phase half the voltage of the 1st phase. The exponential biphasic waveform had a 60% 1st phase and a 50% 2nd phase tilt. In a second study, we attempted to defibrillate after 10 s of VF with a single ≈ 30 J shock (6 pigs successfully defibrillated with 8 ms ascending, 8 ms rectilinear wave and truncated exponential biphasic waveforms). Troponin I blood levels were determined before and 2 to 10 hrs after the shock. The lowest energy DFT was for the 8 ms ascending ramp (14.6±7.3 SD J), which was significantly less than for the truncated exponential (19.6±6.3 J). Six hours postshock, troponin I in ng/ml was significantly less for the ascending ramp (0.80±0.54) than for the truncated exponential (1.92±0.47) or the rectilinear waveform (1.17 ±0.45).

Conclusions - The ascending ramp has a significantly lower DFT, and at ≈ 30 J causes 58% less troponin I release than the truncated exponential biphasic shock. Therefore, the shock waveform affects both the DFT and the amount of cardiac damage.

Key words: cardioversion; defibrillation; troponin; ventricular fibrillation
Introduction

The implantable cardioverter-defibrillator (ICD) has revolutionized the treatment of patients at risk for sudden cardiac death due to ventricular fibrillation (VF). However, recent reports indicate that the patients who received defibrillation shocks had higher mortality than those who did not. 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 impacts electrophysiologic and hemodynamic functions, and causes biochemical alterations and cellular morphology changes. Tokano et al 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.

The local injury current after an ICD shock for induced VF has been shown to predict heart failure progression. This local injury current is probably caused by transient cell membrane damage due to electroporation, which in turn is caused by a large potential gradient created near the defibrillation electrodes by the shock. The amount of this cardiac dysfunction increases with increasing shock strength. If shock voltage is sufficiently high, myocardial necrosis can occur.

Even though 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) since damage is related to shock strength. In addition, it is possible that some waveforms cause less damage than others, even when they are the same strength.
Because post-shock arrhythmias are related to myocardial injury, and experimental studies have shown that an ascending ramp waveform reduces post-shock arrhythmias and has a lower DFT than current clinically-used truncated exponential biphasic waveforms, we tested the hypothesis that the ascending ramp waveform creates less damage as well as defibrillates with lower shock energy than the truncated exponential biphasic waveform. We generated ascending ramp waveforms as well as a rectilinear waveform and a Gurvich waveform, which has been reported to have a lower DFT energy than a rectilinear waveform, 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 been previously published.

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 RV electrode and a 6.9-cm-long superior vena cava electrode, was positioned with the tip at the RV apex.

VF was induced for 10 s with 60-Hz, 30 V alternating current delivered through the RV electrode of the Endotak lead. The DFT of a selected waveform was determined with the Dixon method. The initial test shock was set at 400 volts, with subsequent test shocks set at increased or decreased voltages in up–down log10 0.1-voltage steps. After the first reversal in test shock outcomes (e.g., test shock success followed by test shock failure, or vice versa), two additional fibrillation–defibrillation episodes were performed in up–down log10 0.1-voltage steps. Rescue shocks were delivered immediately after failed defibrillation attempts. The DFT for each waveform was estimated by the equation Xf + kd, where Xf is the last shock voltage administered, k is the tabular value representing the maximum likelihood solutions10, 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 using a digitizing oscilloscope (TDS-744A, Tektronix Inc., Beaverton, OR, USA). 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 utilizes 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 ms. The second phase was always a 3.5 ms 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 ms and phase 2
duration of 4.75 ms.\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 (\textbf{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 ms.

\textbf{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 RV electrode was the anode for phase 1 of all waveforms.

\textbf{Protocol 2}

Blood samples for cardiac troponin I measurement were obtained before and 2 to 10 hours after the shock with each of three selected waveforms from protocol 1. As reported below, protocol 1 found the lowest DFT energy achieved with an 8 ms first phase ascending waveform and the lowest DFT voltage achieved with an 8 ms first phase rectilinear waveform. In protocol 2, troponin I levels after a single defibrillation shock were determined for both of these waveforms as well as for the truncated exponential biphasic waveform. If the first shock failed to defibrillate after 10 s 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 set based on two concerns for each waveform: (1) the shock energy should be at least the DFT energy plus a 10 J safety factor; (2) the shock energy for each waveform should be the same for each waveform. The highest DFT energy among the 3 waveforms was approximately 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 the 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 ms first phase duration waveforms, the lowest DFT energy achieved was with the descending waveform, which was significantly lower than for the ascending and rectilinear waveforms (\( p < 0.05 \), Figure 2A). For the 8 and 16 ms first phase duration waveforms, the lowest DFT energy was achieved with the ascending waveform, which was significantly lower than for the descending and rectilinear waveforms at the same duration (\( p < 0.05, 0.01 \), Figure 2A). Among all waveforms tested, the 4 ms descending and 8 ms ascending waveforms had the lowest DFT
energy. The clinically-used truncated exponential biphasic waveform had significantly higher DFT energy than the 4 ms descending, or the 4 or 8 ms ascending waveforms.

**DFT voltage**

Rectilinear waveforms had the lowest voltage DFT among the first phase 4, 8, and 16 ms waveforms (Figure 2B). The 8 and 16 ms 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 ms to 8 or 16 ms significantly decreased the DFT voltage of ascending but not descending waveforms.

**Protocol 2**

As described above, 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 ascending ramp 29.35±3.4 J, rectilinear 29.4±3.1 J and truncated exponential biphasic waveform 30.4±2.2 J. While the energies delivered were similar, the ascending waveform had a significantly higher peak voltage (671±2.1 V) than the rectilinear (431±3.5 V) and truncated exponential biphasic (610±3.8 V) waveforms. Twenty-one animals were studied in protocol 2, with 18 animals successfully defibrillated by a single shock (6 for ascending waveform, 6 for rectilinear waveform and 6 for truncated exponential waveform). There were two animals that failed to be defibrillated by the single rectilinear waveform shock and one animal that failed to be defibrillated with the single truncated exponential biphasic waveform shock. Blood samples were only drawn for the first 6 post-shock 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 significantly increased 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 hrs after the truncated exponential biphasic shock was 1.92±0.47 ng/ml and 1.17 ±0.45 ng/ml for the rectilinear waveform 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 less than half as much troponin I release than 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 transvenous lead system. Because the mechanisms underlying defibrillation are still being identified, selection of an optimal waveform for defibrillation has been primarily based on empirical evidence.

According to resistor-capacitor (RC) network models of the cardiac cell membrane, the shape of the monophasic or the first phase of the biphasic waveform affects the DFT. According to these models, a rectilinear wave should have the lowest DFT in terms of peak voltage, while an ascending waveform in which the voltage increases exponentially with time should have the lowest DFT in terms of energy. Ascending waveforms have been demonstrated to be more efficacious for defibrillation than descending ramp, rectilinear or truncated exponential decaying waveforms in animals and humans. Ascending waveforms have been difficult to generate in a way that is both volumetrically and energy efficient with electronic components used in present ICDs. A new type of amplifier circuit has recently become available that makes the production of ascending waveforms feasible. Using this new circuit, we showed that, consistent with model predictions and previous experimental results, a rectilinear wave had the lowest peak voltage DFT (8 ms phase 1 duration) and an ascending ramp had the lowest energy DFT (8 ms phase 1 duration) of all the waveforms tested.

Defibrillation shocks and electrical myocardial injury

Electrical myocardial injury, ranging from reversible hemodynamic change to irreversible myocardial necrosis, is a well-recognized complication of high-energy defibrillation shocks. A shock with energy > 9 J delivered during sinus rhythm or VF created detectable hemodynamic depression in patients. 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 termed electroporation or electroporomeabilization. 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. For 5-10 ms monophasic or biphasic waveforms, shocks of about 0.4 V for less than 1 ms directly across the cardiac cell membrane in a patch clamp preparation cause an increase in membrane conductance presumably caused by electroporation. If electroporation is severe, the cardiac cells may die, leading to a release of troponin I.

Because of their high degree of sensitivity and specificity for detecting myocardial necrosis, cardiac troponins are the biomarkers of choice in acute coronary syndrome. In defibrillation, the elevation of troponin levels may be caused both by the ischemic insult of VF as well as by a direct effect of the shocks. In the present study, troponin levels were measured after a single shock following 10 s of VF in healthy pigs. Because of the minimal ischemia produced by 10 s of VF, the damage indicated by the troponin I release should be mainly related to the defibrillation shock. In addition, all animals were subjected to 10 s 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. 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 an RC 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, i.e., 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 which carry electric charges and which 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 without causing electroporation. Perhaps the greater amount of time 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. (1) We tested only one measure of cardiac damage, i.e., troponin I blood levels after the shock. (2) We tested an ascending ramp instead of an ascending exponential waveform. According to an RC model, the ascending exponential waveform should have a lower energy DFT than the ascending ramp.\textsuperscript{30} (3) Only a single second phase was tested, i.e., a 3.5 ms rectilinear wave one-half the peak voltage of the first phase. This duration was predicted to be optimum by one of the RC models.\textsuperscript{31} (4) We tested only healthy hearts. Shock
induced electroporation may be more severe in diseased hearts.\textsuperscript{32}

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**Conflict of Interest Disclosures:** None.

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Figure Legends:

**Figure 1.** Waveforms tested. Three descending ramp (A), 3 ascending ramp (B) and 3 rectilinear first phase (C) waveforms were tested with durations of 4, 8 and 16 ms. In all 9 waveforms, phase 2 was a 3.5 ms rectilinear wave half the peak voltage of phase 1. Also tested were (D) Gurvich and (E) truncated exponential biphasic waveforms. “a” indicates the peak voltage of the first phase.

**Figure 2.** Mean and SDs of delivered energy DFT (A) and leading edge voltage (B) DFT for each waveform from protocol 1. * denotes *p* < 0.05 compared with truncated exponential biphasic waveform.

**Figure 3.** Time course of changes in cardiac troponin I levels for each waveform. * denotes *p* < 0.05 compared with the troponin I level of truncated exponential biphasic waveform at that time.

**Figure 4.** The transmembrane potential estimated by an RC model with an assumed membrane time constant of 2.8 ms during the 8 ms rectilinear first phase (A), the 8 ms ascending ramp (B), and the truncated exponential waveforms (C) studied in protocol 2. The model transmembrane potential in response to the truncated exponential (C’) and rectilinear waveforms (A’) 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 (B’) rises slowly at a nearly constant level throughout the shock and is near the maximum only briefly near the end of the shock.
Waveform Amplitude

Model Response

Time (ms)

A

A'

B

B'

C

C'
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