Effect of Second-Phase Duration on the Strength-Duration Relation for Human Transvenous Defibrillation

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Background—The mechanism by which biphasic waveforms improve defibrillation efficacy is unclear. In addition, the optimal shape of the biphasic waveforms remains controversial. Animal experiments suggest that prolonging the duration of the second phase longer than the first worsens defibrillation thresholds (DFT). The purpose of this study was to determine the strength-duration relation for the second phase of a biphasic defibrillation waveform in humans.

Methods and Results—This was a prospective, randomized study of biphasic DFT in 36 patients; a uniform dual-coil transvenous lead system was used. In each patient, 3 DFTs were determined with the pulse duration for the second phase of the defibrillation waveform varying between 1 and 18 ms. The duration of the first phase was fixed at 6 ms and the capacitance was 150 μF. There was a significant increase in the leading edge voltage at DFT only when the second-phase pulse duration was decreased to 1 ms. There was no increase in DFT voltage even when the second-phase pulse duration was increased from 2 to 18 ms. Similar relations were observed for stored energy, leading edge current, or phase 2 energy. The normalized average current delivered during phase 2 decreased monotonically with increasing phase 2 duration.

Conclusions—In humans, the biphasic DFT voltage or energy is increased only when the second phase of the waveform is <2 ms. The DFT voltage is insensitive to increasing the second phase of the defibrillator waveform to as long as 18 ms, or 3 times the duration of the first phase of the waveform. (Circulation. 2000;102:2239-2242.)

Key Words: defibrillation ■ death, sudden ■ ventricles ■ tachyarrhythmias

The use of biphasic waveforms is now standard in all implantable defibrillators.1–3 The development of transvenous lead systems, active pectoral pulse generators, and biphasic waveforms has markedly simplified the implantation process and improved defibrillation efficacy. However, despite the ubiquitous use of biphasic waveforms, the mechanism by which they improve defibrillation efficacy is unclear. In addition, the optimal biphasic waveform shape remains controversial.4–6

Previous work from our laboratory has shown that the defibrillation threshold (DFT) in humans decays monoexponentially with increasing pulse durations.7 Contrary to the results from experiments in animals, there was no worsening of DFT even with pulse durations as long as 18 ms, which have terminal voltages of only 25 V. The strength-duration curve for biphasic waveforms is not known. Experiments in animals suggest that prolonging the duration of the second phase of the biphasic waveform longer than the first leads to worsening DFTs,8–10 possibly because of refibrillation of the heart by the low-terminal voltages of long-duration waveforms. These observations have led to the restriction of the duration of the second phase to be equal to or less than the duration of the first phase in all commercially available devices. The present study was designed to test the hypothesis that prolonged second-phase durations are detrimental to defibrillation success and to define the strength-duration relation for the second phase of a biphasic waveform in humans.

Methods

Patient Population

The patient population consisted of 36 patients undergoing cardioverter-defibrillator implantation for standard clinical indications. The study was performed during defibrillation testing that is carried out in the operating room before device implantation. Each patient gave written informed consent, and the University of Maryland Institutional Review Board approved the study.

Defibrillation testing was performed either under conscious sedation with fentanyl and midazolam for new implants or under general anesthesia with fentanyl (2 to 10 mg/kg), vecuronium (0.1 to 0.15 mg/kg), and isoflurane (0.4% to 0.8%) at the time of pulse generator replacement when performed in the operating room. Experimental testing was initiated after demonstration of an acceptable DFT. All patients had a 2-coil transvenous lead (Endotak, CPI Guidant).

During testing, 3 surface ECG leads and intracardiac electrograms were monitored continuously on a multichannel recording system. Ventricular fibrillation was induced with ramp pacing through the rate-sensing lead. Ventricular fibrillation was defined as a chaotic rhythm on the surface leads with irregular intraventricular electrograms with a mean cycle length <200 ms. After 10 seconds of fibrillation, defibrillation was attempted with an asynchronous bi-
phasic shock from an external defibrillator (HVS-02, Ventritex Inc). If the initial defibrillation shock failed, then rescue shocks were immediately delivered. Sufficient time (≥2 minutes) was allowed between trials for full hemodynamic recovery.

The external defibrillator delivers truncated exponentially decaying waveforms through a 150-μF capacitor. Waveforms were constructed with the leading-edge voltage of the second phase equal to the trailing-edge voltage of the first phase (0.2-ms delay between phases). Because of limitations in the amount of defibrillation trials that can be performed safely in humans, it was not feasible to define the strength-duration relation for second-phase durations between 1 and 18 ms in each patient. Therefore, 3 DFTs were determined for each patient. The duration of the second phase of the defibrillation waveform was either 1, 6, and 18 ms, or 2, 6, and 12 ms, or 3, 6, and 9 ms. Thus, all patients had a DFT determined with a 6-ms second-phase duration to allow for comparison between groups, as well as a DFT with a shorter and longer second-phase duration. The duration of the first phase of the biphasic waveform was fixed at 6 ms because this was the optimal duration determined for monophasic waveforms.7

The leading-edge voltage at DFT was determined to the nearest 50 V (phase 1 voltage) by means of a step-down to first-miss protocol. The initial voltage tested for all pulse durations in this study was ≥50 V greater than the biphasic DFT previously determined with a standard waveform. This value was chosen to minimize the number of shocks delivered to each patient. The same initial voltage was used to determine the DFT for each waveform tested. If the first shock failed, the defibrillation voltage was increased by 50 V until defibrillation failed. If the first shock failed, the leading-edge voltage was increased by 50 V until defibrillation success. This only occurred in 12% of the trials. The order of testing was randomized to avoid any bias caused by drift with time. Measurements obtained during testing included leading edge voltage (V), pulse duration (d), defibrillation resistance (R), and delivered energy (E) for both phases of the defibrillation waveform. Peak current (I_p) was calculated from Ohm’s law as V/R. Total charge delivered for each phase of the waveform (Q; coulombs×10⁻³) was calculated as I_p × R × 0.15 × (1−exp[−d/R × 0.15]). Average current per phase was calculated as Q/d (amps) and stored energy as (V²/2)×0.000015.

Data were analyzed with an ANOVA with repeated measures. A Newman-Keuls post hoc analysis was used to assess the effect of pulse duration on DFTs. Two-tailed t tests were used to compare differences between groups. Exponential fits were performed with a least-squares algorithm. All results are expressed as mean±SD. A value of P<0.05 was considered significant.

Results

The patient population studied was typical of patients undergoing cardioverter-defibrillator implantation at our institution. They were predominantly men (75%), with a mean age of 61±11 years. Coronary artery disease was present in 20 patients (56%), and the mean left ventricular ejection fraction was 35±13%. Ten patients had a cardiac arrest, 13 had hemodynamically significant ventricular tachycardia, and 13 had syncope, a reduced ejection fraction, and inducible ventricular tachycardia on electrophysiological study. Seventeen patients had congestive heart failure and were in New York Heart Association class II or III. No patient was receiving class I or 3 antiarrhythmic drugs at the time of testing.

Each patient had a DFT determined by means of a symmetric 6/6-ms biphasic waveform. For the 6/6-ms waveform, the mean stored energy at DFT was 9.1±4.4 J, the leading edge voltage of the first phase was 340±85 V, and the mean resistance was 47±7 Ω. The tilt of the first phase of the biphasic waveform averaged 58±5%. There were significant differences between the DFT determined for the 6/6-ms waveform in the 3 groups of patients. Therefore, data from each patient were normalized to that obtained with the 6/6-ms waveform to allow for comparison among groups.

The leading-edge voltage at DFT for each second-phase pulse duration normalized to that obtained with the 6-ms second-phase pulse duration (leading-edge voltage at test duration/leading-edge voltage at 6 ms) is shown in Figure 1. There was a significant increase in the voltage only when the second-phase pulse duration was decreased to 1 ms. There was no increase in phase 1 voltage at DFT when the second-phase pulse duration was increased from 2 to 18 ms. Similarly, normalized stored energy (Figure 2), leading-edge current, and phase 2 stored energy increased only when the second-phase duration was 1 ms. In contrast, the normalized average current delivered during phase 2 of the biphasic waveform decreased monotonically with increasing phase 2 duration (Figure 3).

Discussion

This report is the first demonstration in humans of the strength-duration curve for the second phase of a biphasic
At the short-duration pulses, the improvement in DFT seen involved for the improvement in DFT with biphasic shocks. leading to the conclusion that at least two mechanisms are minima were observed, one at 2 ms and the other at 4 ms, distance and fixed first-phase duration of 3 ms. Two energy phase. As the duration of the second phase is increased is then due to hyperpolarization of cells that were depolarized by the first phase. These results were in contrast with those found in animal experiments. Tang et al first reported a biphasic strength-duration curve for DFT in dogs when the duration of the second phase of a biphasic waveform was increased from 0 to 8.5 ms. In their experiments, there was a dramatic increase in DFT once the second-phase duration exceeded the duration of the first phase of the waveform. These results were extended by Feeser and coworkers, who demonstrated that increasing the duration of the second phase of a biphasic waveform greater than the first phase in dogs worsened DFT whether measured by leading-edge current, leading-edge voltage, or delivered energy. This increase in DFT was observed when the first phase of the waveform was fixed at either 3.5 or 7 ms, which is comparable to the 6-ms, fixed first-phase duration used in our experiments. Similar results were also observed in isolated rabbit hearts.

Schaubert et al also measured a multiphasic second-phase strength-duration response in pigs by using a 70-μF capacitance and fixed first-phase duration of 3 ms. Two energy minima were observed, one at 2 ms and the other at 4 ms, leading to the conclusion that at least two mechanisms are involved for the improvement in DFT with biphasic shocks. At the short-duration pulses, the improvement in DFT seen with phase 2 durations >1 ms is proposed to be due to either unloading or “burping” the residual charge left on the cellular membranes from the first phase of the defibrillation waveform or to depolarization of a portion (<50%) of the cell membranes that were hyperpolarized by the first phase of the defibrillation shock. The subsequent rise in DFT as the duration of the second phase is increased is then due to hyperpolarization of cells that were depolarized by the first phase. As the duration of the second phase is increased further, the latter mechanism predominates and the response is similar to that expected for a monophasic waveform. Interestingly, our data also have two DFT minima, one at 2 ms and one at 6 ms. However, these differences did not reach statistical significance, probably because of the increased variability in determining DFTs in humans with a step down to first-miss protocol when compared with the repetitive up-down protocols used to measure DFT in animal experiments.

The effect of second-phase duration on the charge-burping model of defibrillation should depend on the time constant of the defibrillation waveform (ie, its capacitance). Swedlow et al demonstrated in dogs that DFT energy increases when the second-phase duration is longer than the first-phase duration when a 140-μF capacitor is used but decreased when a 40-μF is used. Although different capacitances were not tested in this study, the lack of increase in DFT in humans when phase 2 duration was increased up to 3 times phase 1 duration indicates a significant difference between animal and human defibrillation.

These results have several important implications for the understanding of human transvenous defibrillation. First, there is no increase in DFT in humans despite increasing the second-phase duration to 18 ms or 3 times the duration of the first phase. At these durations, only 2.5% of the initial voltage remains on the capacitor (≈10 V). Thus, there is no evidence for refibrillation of human hearts at low residual voltages. This result is similar to that seen with monophasic waveforms in humans. Second, the optimal duration for the second phase of the biphasic waveform must be determined for each patient. In fact, one patient had the lowest DFT with a 1-ms second-phase duration. Third, the dogma that the second-phase duration must be equal to or shorter than the first is incorrect. Ten patients (31%) had lower DFTs, with the second-phase duration longer that for the first phase. Last, several models have been proposed to explain defibrillation. In each of these models, the optimal duration for the waveform is determined by a tissue-related parameter called either the membrane time constant or chronaxie. Using monophasic waveforms of various pulse durations, we found that the strength-duration curve could be well fit by a single exponential decay function with a time constant of 1.5 ms (yielding a calculated human membrane time constant of 5.3 ms: see Reference 7). The strength-duration curve for the second phase of the biphasic waveform decays much faster than the first phase, suggesting that the second phase of the biphasic waveform either acts on a smaller “effective” heart area than the first phase of the waveform or that the first phase of the waveform decreases the membrane time constant. In contrast, the rapid decline of DFT with increasing second-phase duration from 1 to 2 ms followed by the relative insensitivity of further increases supports the “charge burping” model for biphasic defibrillation proposed by Kroll.

Our results must be interpreted in the face of certain limitations. First, it was not possible to determine the DFT at each pulse duration for each patient because of concerns about clinical safety. Therefore, data were collected from 3 groups of patients, each of whom had DFTs determined at 3 different second-phase durations. Because each patient had a
DFT determined with a 6/6-ms waveform, data were normalized to this waveform to allow for comparisons among groups. A second limitation is that only 1 transvenous lead system and 1 capacitor were used in this study. This was chosen to allow for direct comparison between groups of patients without the confounding influence of different shock pathways or capacitances. However, it is unknown if these results can be extrapolated to other lead systems including those that use an active pectoral pulse generators or smaller capacitors.

In conclusion, biphasic DFTs in humans are relatively insensitive to alterations in the second-phase duration, increasing only when the second-phase duration is <2 ms. In addition, the strength-duration relation does not increase when the second-phase duration is increased to up to 3 times the first-phase duration, indicating that refibrillation at low residual defibrillation voltages does not occur in humans.

References
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