Improved Safety Factor for Triphasic Defibrillator Waveforms

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Newly developed biphasic waveforms improve defibrillation efficacy both by reduction of defibrillation threshold and by amelioration of shock-induced dysfunction depending on the relative shape of the first and second pulses. Each of these independent effects improves the waveform's safety factor, the ratio between the shock intensity that produces a specific degree of postshock dysfunction and the shock intensity that produces defibrillation (or cellular excitation). Symmetrical waveforms reduce defibrillation threshold to about 60% that of the corresponding monophasic waveform, probably by reduction of excitation threshold for ischemic cells, but increase postshock arrhythmias. Biphasic waveforms with 10% "tails" reduce postshock arrhythmias. This study tests the hypothesis that these independent mechanisms for improvement of defibrillation efficacy can be combined into a single triphasic waveform that will have a higher safety factor than either of the two biphasic waveforms of which it is composed. Cultured myocardial cells were subjected to high-intensity electric-field stimulation with a control monophasic rectangular waveform, a symmetrical biphasic waveform, and a triphasic waveform consisting of the biphasic waveform with an added 10% "tail." Each waveform portion was 5 msec in duration. Photocell mechanograms monitored contractile activity. We found that the duration of postshock arrest of spontaneous contractile activity increased with stimulus intensity for all waveforms. The voltage gradient producing a 4-second arrest after the biphasic waveform shock was 80.6±1.3% that of the control waveform (100%), while the voltage gradient for the triphasic waveform was 87.1±0.73% of control. The difference between biphasic and triphasic waveforms was significant (p<0.001). Relative excitation thresholds for the biphasic and triphasic waveforms were each 67% that of the monophasic waveform and did not differ significantly. Relative safety factor for the biphasic waveform was 120.3 and that for the triphasic waveform was 130.0 compared with a value of 100 for the control monophasic waveform. These results suggest that triphasic waveforms decrease postshock arrhythmias and increase the safety factor for defibrillation. (Circulation Research 1989;64:1172-1177)
the 1-msec rectangular waveform with a relative safety factor of 70 produces only a 40% success in the calf model, whereas the 4- to 5-msec rectangular waveform with a relative safety factor of 100 produces 93% success in the same model.

Newly developed biphasic waveforms for internal defibrillators, with a second portion that is opposite in polarity to the first and ranges from 50% to 200% of the first portion in amplitude, substantially reduce defibrillation threshold in animal models. The reduced defibrillation threshold appears to be related to the biphasic waveform's improved ability to excite myocardial cells that have become depolarized during fibrillation and must be excited in their relative refractory period to terminate fibrillation.

A differently shaped biphasic waveform having a second negative portion 5 msec in duration and 10% of the first portion in amplitude does not substantially reduce excitation threshold in the cultured cell model, but it does reduce shock-induced dysfunction produced at a specific shock intensity. Similarly shaped biphasic waveforms also decrease the duration of postshock atrioventricular block in the calf model.

The goal of this study was to determine if the excitation threshold-lowering characteristics of the symmetrical biphasic waveform and the dysfunction-reducing characteristics of the 10% undershoot biphasic waveform could be combined into a single triphasic waveform.

Materials and Methods

Myocardial cell monolayers used for arrhythmia studies were produced from 8- to 9-day chick embryos by use of procedures that have been previously described. Hearts were dispersed with 0.05% trypsin in Ca²⁺-Mg²⁺-free phosphate buffered saline. After washing, cells were plated in the center of 60-mm Falcon culture dishes and incubated at 37°C with L-15 medium (GIBCO Laboratories, Grand Island, New York) and 10% fetal calf serum (growth medium; final extracellular potassium (Kₑ) 6.5 mM). After 24 hours the cells had formed a confluent, synchronously beating sheet. Cells 1–2 days in culture were used for experimentation.

Myocardial cell aggregates 100–250 μm in diameter used for pacing studies were produced with the techniques described above except that embryos were 10–12 days old. After washing, cells were suspended in growth medium in a 25-ml flask and rotated at 70 rpm in a 37°C shaker bath (Lab-Line Instruments, Melrose Park, Illinois) for 24 hours. About 1 hour before an experiment, a drop of aggregate suspension was placed at the center of a 60-mm Falcon culture plate. After the aggregates settled to the bottom of the dish and attached lightly, the plate was flooded with growth medium.

A culture plate containing either cell monolayers or aggregates was placed on the 37°C microscope stage, and a Plexiglas shock chamber with a medium depth of 0.6 cm was inserted. This chamber consisted of a disk into which a 1×2.5-cm rectangular hole had been cut. Platinum-platinum-black electrodes were attached to the long sides of the rectangle. The rectangular electrode configuration produced an approximately uniform electric field when the cells were stimulated.

An image of the cells was displayed on a closed-circuit television screen, and contraction was monitored noninvasively with a photocell placed on the screen. The output of the photocell was processed with peak-detector and sample-and-hold circuitry to produce a photocell mechanogram that was then recorded on a strip chart.

Waveforms were generated with an arbitrary waveform-generator module of an LMM computer and amplified with a modified Phase Linear power amplifier module (PhysioControl, Redwood, Washington). Waveforms used in this study are shown in Figure 1. Detailed procedures for cell stimulation and recording have been published previously.

Pacing

Aggregates were placed in growth medium containing 10.5 mM Kₑ and paced at a cycle length of 300 msec to simulate fibrillation conditions. For each of the three waveforms tested, threshold was determined by a gradual increase or decrease in stimulus voltage until consistent capture was obtained. Threshold for each waveform was determined consecutively, and the sequence was repeated three times. Mean threshold for each waveform was determined from the three measurements on the same aggregate. For each aggregate, excitation threshold for the two test waveforms was normalized to that for the 5-msec control waveform by division of the excitation threshold for the test waveform by that for the control waveform.

Arrhythmias

Postshock arrhythmias were determined from photocell mechanograms recorded before, during, and after a single stimulus of specific waveform and intensity given to cells in normal growth medium.
FIGURE 2. Photocell mechanograms showing contractile response to a 55-V/cm shock (S). Arrows indicate first postshock contraction. Panel A: Cells respond to monophasic shock with a 1.7-second cessation of spontaneous contractile activity. Panel B: Biphasic shock increases postshock arrest time to 8.5 seconds. Panel C: Triphasic waveform shortens postshock arrest time to 4.4 seconds.

(Ko, 6.5 mM). The time of the shock was recorded on a second channel. For reduction of possible artifacts due to cumulative effects of several shocks to a single culture, shocks were given in random order, postshock arrest times of over 20 seconds were not allowed to occur, and beat rate was allowed to return to normal for about 1 minute between shocks. With these precautions, data were reproducible throughout the experiment. Curves relating postshock arrest time to shock intensity were constructed and the arrhythmia threshold, or voltage required to produce a 4-second arrest of normal spontaneous activity, was determined from the resulting regression line. For each culture, arrhythmia threshold for each test waveform was normalized to that for the control monophasic 5-msec waveform by division of the arrhythmia threshold for the test waveform by that for the control waveform.

Normalized excitation and arrhythmia thresholds for the two test waveforms were expressed as mean±SEM. Data comparisons were made using the t test for paired samples.

Results

Shock-Induced Arrhythmias

Postshock arrhythmias were determined in nine cultures after high-intensity shocks with a control waveform (5-msec monophasic rectangular wave), a 5-msec symmetrical biphasic waveform (each pulse 5 msec in duration), and a triphasic waveform created by addition of a third positive pulse to the biphasic waveform. The third pulse was 10% of the amplitude of the first two pulses and 5 msec in duration (Figure 1).

For each waveform, the severity of postshock arrhythmia increased with shock amplitude in a pattern that has been described previously. Low-amplitude shocks produced an extrasystole with no subsequent arrhythmias, intermediate-amplitude shocks produced a transient postshock tachyarrhythmia, and high-amplitude shocks produced a transient postshock arrest of spontaneous contractions. The duration of arrest was proportional to shock amplitude. This pattern of shock-induced arrhythmias is produced by a dose-dependent prolonged sarcolemmal depolarization. During the initial phase of membrane potential recovery, small spontaneous action potentials are produced with very gradual upstrokes that are not accompanied by contractions. As membrane potential continues to recover and the quality of action potential improves, weak contractions develop and terminate the period of postshock arrest.

Figure 2A shows typical raw data from a culture subjected to a 55-V/cm shock with the control monophasic waveform. The postshock arrest is 1.7 seconds in duration. Figure 2B shows that a shock of the same intensity with the symmetrical biphasic waveform produces a substantially longer arrest time of 8.5 seconds. In Figure 2C, the addition of a small third pulse to the biphasic waveform reduces the arrest time to 4.4 seconds.

The voltage gradient that produced a specific degree of postshock dysfunction (the 4-second arrest of contractile activity) was determined for each waveform in each culture, as shown in Figure 3. The duration of postshock arrest was measured at...
FIGURE 4. Paired data analysis showing relative 4-second arrest voltages for biphasic and triphasic waveforms. In each experiment, triphasic waveform increased relative 4-second arrest voltage as compared with biphasic waveform.

several shock intensities, the data were fitted using linear regression, and the shock intensity that produced the 4-second arrest was determined from the regression line. The measured voltage gradients for the biphasic and triphasic waveforms were normalized to those for the control monophasic waveform as described in “Materials and Methods.” The shock intensity that produced the 4-second postshock arrest (unnormalized arrhythmia threshold) for the monophasic control waveform ranged from 63.5 to 117.0 V/cm with a mean of 87.1 ± 6.3 V/cm. The relative arrhythmia threshold for the biphasic and triphasic waveforms was independent of the unnormalized arrhythmia threshold for the monophasic waveform.

Paired data analysis, as shown in Figure 4, demonstrates that the addition of the third pulse to the symmetrical biphasic waveform reduced postshock dysfunction (duration of postshock asystole) produced at a specific shock intensity so that a higher intensity was required to produce the same degree of dysfunction. The mean normalized voltage gradient for the eight cultures was 80.6 ± 1.3 for the biphasic waveform and 87.1 ± 0.73 for the triphasic waveform. The difference in shock intensity that produced the 4-second arrest for the biphasic and triphasic waveforms was significant at $p<0.001$.

Excitation Threshold for Triphasic Waveforms

Normalized excitation thresholds were determined in six cultures under conditions that simulated fibrillation ($K_C$, 10.5 mM and cycle length 300 msec, as described in “Materials and Methods”). Mean normalized excitation threshold for the monophasic waveform was 3.2 ± 0.24 V/cm. The mean normalized threshold for the symmetrical biphasic waveform was 0.672 ± 0.007 and that for the triphasic waveform was 0.672 ± 0.005. The excitation thresholds for the biphasic and triphasic waveforms were not significantly different.

Safety Factor for Biphasic and Triphasic Waveforms

Safety factors for the biphasic and triphasic waveforms were computed as the ratio of the mean shock amplitude that produced the 4-second arrest to the mean shock amplitude that produced pacing. The safety factor for the biphasic waveform was 120.3. The safety factor for the triphasic waveform was 130.0.

Discussion

Previous studies in the cultured cell model have suggested that biphasic waveforms improve the probability of successful defibrillation by interactions between two separate mechanisms: reduction of defibrillation threshold and amelioration of shock-induced dysfunction. The degree to which each mechanism contributes to the alteration of defibrillation efficacy depends on the relative shape of the first and second portions of the waveform.

Excitation or Defibrillation Threshold

In the cultured cell model, excitation threshold for the monophasic waveform increases under fibrillation-like conditions: high extracellular potassium combined with short cycle length. Under these conditions, symmetrical biphasic waveforms, in which the first and second portions are equal in amplitude, decrease excitation threshold. The degree of threshold reduction with the biphasic waveform (B/M ratio) is inversely proportional to the monophasic threshold. The decreased relative excitation threshold observed with the symmetrical biphasic waveform in the cultured cell model correlates with a decreased defibrillation threshold in the in situ calf model. In the calf model, the curve that relates probability of successful defibrillation with the first shock to the shock intensity for a specific waveform is bell-shaped; that is, it increases with increasing intensity, reaches a maximum, then decreases with increasing intensity. As shown in Figure 5, the symmetrical biphasic waveform produces a 50% success on the ascending limb of the curve at a significantly lower intensity than does the monophasic waveform; that is, it decreases defibrillation threshold. For example, if we define defibrillation threshold as the current that produces 50% success on the first shock, the 8-msec monophasic waveform crosses this point at approximately 39 A while the symmetrical biphasic waveform with 8 msec in each direction reaches the same level at an estimated 27 A. The biphasic threshold-to-monophasic threshold ratio (B/M) is therefore approximately 0.69.

The similarity between defibrillation threshold reduction in the calf model and excitation threshold reduction for cells under fibrillation conditions in the cell culture model with symmetrical biphasic
waveforms is consistent with the hypothesis that defibrillation is produced by excitation of cells in a critical mass of the ventricle and suggests that the reduction in defibrillation threshold is caused by the reduction in excitation threshold of cells in the fibrillating heart. Since the symmetrical biphasic waveform is most effective in reduction of excitation threshold when the monophasic threshold is high, these results also suggest that the biphasic waveform will decrease defibrillation threshold most effectively for those hearts that have the highest threshold with monophasic waveforms.

Dysfunction

While symmetrical biphasic waveforms decrease defibrillation threshold, they also decrease the shock intensity at which the probability of success begins to decrease on the high-intensity portion of the bell-shaped curve; that is, they decrease dysfunction threshold (Figure 5). However, since the decrease in defibrillation threshold is greater than the decrease in dysfunction threshold, the maximum probability of success is increased.

In the cell model, symmetrical biphasic waveforms also increase postshock dysfunction produced by a specific shock amplitude (Figure 2) or, alternatively, decrease dysfunction threshold. However, the decrease in excitation threshold (B/M=0.67) is greater than the decrease in arrhythmia threshold (B/M=0.8). Therefore, the symmetrical biphasic waveform has a higher relative safety factor (120) than the corresponding monophasic waveform (100).

The observed increase of the maximum probability for success at the top of the bell-shaped curve with symmetrical biphasic waveforms correlates well with the higher safety factor of similar waveforms in the cultured cell model, as shown in Figure 6.

Asymmetrical biphasic waveforms with 5–20% undershoot reduce shock-induced arrhythmias produced by monophasic shocks of specific amplitude in the cultured cell model. Therefore, the dysfunction threshold or shock amplitude required for production of a specific arrhythmia is increased. Asymmetrical biphasic waveforms appear to reduce shock-induced arrhythmias by reducing the formation of transient shock-induced microlesions in the cell membrane, thereby presumably ameliorating the prolonged sarcolemmal depolarization underlying these arrhythmias. Similar waveforms also reduce postshock time to return of normal sinus rhythm and ST segment alterations in the in situ calf model.

In this study, we showed that the benefits of the symmetrical biphasic waveform and the 10% undershoot asymmetrical biphasic waveform can be combined into a single triphasic waveform for further improvement of safety factor. The initial symmetrical biphasic portion reduces excitation threshold, while the third portion partially ameliorates the increased dysfunction produced by the biphasic waveform. This dysfunction-ameliorating effect is demonstrated in Figure 2, where the postshock arrest of contractile activity is shorter for the triphasic waveform than for the biphasic waveform. If the triphasic waveform produces similar dysfunction amelioration in the in vivo model, it would shift the curve that relates probability of success to shock intensity, as shown by the hypothetical curve (dashed line) in Figure 5, thus producing reliable defibrillation over a wider range of shock intensities.

Since the first pulse of the waveform appears to condition or prepare the cell for the second exciting pulse, we have defined the first pulse as the "conditioning prepulse." The second pulse is then defined as the "exciting" or "defibrillating" pulse, while the third pulse, which ameliorates dysfunction
caused by the first two pulses, is called the "healing postpulse."

We chose the symmetrical biphasic waveform for initial experiments to test the triphasic waveform concept because our previous experience showed a significant correlation between the reduced excitation threshold in the cultured cell model and the reduced defibrillation threshold in the in situ calf model. Similarly, the 10% healing postpulse portion was chosen because previous work showed that this amplitude produced maximum amelioration of dysfunction over a wide range of pulse durations. However, it is important to note that other pulse shapes may produce greater improvements in safety factor because of interactions between the three phases of the waveform.

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References

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