Mechanisms of superiority of ascending ramp waveforms: new insights into mechanisms of shock-induced vulnerability and defibrillation

Fujian Qu, Li Li, Vladimir P. Nikolski, Vinod Sharma, and Igor R. Efimov

1Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio; and 2Medtronic Incorporated, Minneapolis, Minnesota

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Qu, Fujian, Li Li, Vladimir P. Nikolski, Vinod Sharma, and Igor R. Efimov. Mechanisms of superiority of ascending ramp waveforms: new insights into mechanisms of shock-induced vulnerability and defibrillation. Am J Physiol Heart Circ Physiol 289: H569–H577, 2005. First published March 25, 2005; doi:10.1152/ajpheart.01117.2004.—Monophasic ascending ramp (AR) and descending ramp (DR) waveforms are known to have significantly different defibrillation thresholds. We hypothesized that this difference arises due to differences in mechanisms of arrhythmia induction for the two waveforms. Rabbit hearts (n = 10) were Langendorff perfused, and AR and DR waveforms (7, 20, and 40 ms) were randomly delivered from two line electrodes placed 10 mm apart on the anterior ventricular epicardium. We optically mapped cellular responses to shocks of various strengths (5, 10, and 20 V/cm) and coupling intervals (CIs; 120, 180, and 300 ms). Optical mapping revealed that maximum virtual electrode polarization (VEP) was reached at significantly different times for AR and DR of the same duration (P < 0.05) for all tested CIs. As a result, VEP for AR were stronger than for DR at the end of the shock. Postshock break excitation resulting from AR generated faster propagation and typically could not form reentry. In contrast, partially dissipated VEP resulting from DR generated slower propagation; the wavefront was able to propagate into deexcited tissue and thus formed a shock-induced reentry circuit. Therefore, for the same delivered energy, AR was less proarrhythmic compared with DR. An active bidomain model was used to confirm the electrophysiological results. The VEP hypothesis explains differences in vulnerability associated with monophasic AR and DR waveforms and, by extension, the superior defibrillation efficacy of the AR waveform compared with the DR waveform.

electrophysiology; arrhythmia; mapping

DELIVERY OF A STRONG ELECTRICAL SHOCK to restore the regular rhythm of a fibrillating heart has been commonly used clinically since the first successful demonstration of defibrillation by Beck et al. (3) in 1947. As the field of clinical defibrillation matured, numerous studies were devoted to find the optimal shock waveform that would accomplish defibrillation with minimal delivered energy. It was shown that morphologically distinct waveforms have different defibrillation efficacies in both experimental studies (18, 19, 26, 32, 42) and theoretical studies using lumped models (16, 43). However, the experimental studies that elucidate mechanisms for differences in defibrillation efficacies of the various waveforms are lacking.

Most modern defibrillation waveforms are limited to modified versions of exponential decaying morphologies, which reflect the use of a capacitor as the principal energy delivery element in device circuitry due to the simplicity and reliability of hardware implementation. However, previous experimental studies have already demonstrated that a monophasic ascending ramp (AR) waveform has higher defibrillation efficacy compared with the descending ramp (DR) waveform, with the rectangular waveform having an intermediate efficacy (29, 32, 41). Furthermore, a study using the modified Blair model demonstrated that the monophasic AR waveform has better polarization efficacy than the monophasic exponential decaying waveform (16). The defibrillation efficacies of the AR and DR waveforms are dependent on pulse duration. In a study by Schuder et al. (32), the investigators found that the defibrillation efficacies of AR and DR waveforms were similar when their durations were <10 ms, but diverged for longer durations. Whereas longer DR waveforms were less and less likely to defibrillate, AR waveforms achieved their highest defibrillation efficacy for pulse durations longer than 30 ms. Schuder et al. (32) attributed the superior efficacy of longer AR waveform to a sharp fall in current at the end of the waveform. Furthermore, they argued that it was the leading portion of a DR waveform that accomplishes defibrillation and that the tail portion of the waveforms was unnecessary and may in fact be detrimental because it might reinduce fibrillation. However, lack of advanced experimental techniques, such as optical mapping of transmembrane potentials (V_m), at the time of these experiments prevented these and other investigators from elucidating the exact physiological mechanisms of proposed theory.

Recently, we have formulated a new theory that explains defibrillation and shock vulnerability to arrhythmia (6, 9, 11) with virtual electrode polarization (VEP) as the centerpiece. VEP arises because of the bidomain nature of cardiac muscle and describes a phenomenon in which regions far from the electrode are oppositely polarized than those near the electrode. VEP has been confirmed both theoretically (30, 33, 34, 36, 38, 47) and experimentally (21–23, 28, 45, 46). During defibrillation, the VEP theory successfully describes the global polarization pattern induced by a shock in which regions of positive and negative polarization coexist in the heart. The key role played by VEP during defibrillation and shock-induced redefibrillation has been substantiated by many experimental and theoretical studies (1, 2, 7–10, 12, 39). We hypothesized that waveform-dependent differences in VEPs could provide a framework to explain differences in defibrillation efficacies and vulnerability between monophasic AR and DR waveforms. We studied the generation and evolution of VEPs and their role in arrhythmia induction in the rabbit heart for a combination of pulse duration, defibrillation shock strength, and timing of...
shock application with respect to a pacing stimulus [coupling interval (CI)]. To complement and substantiate our experimental findings, we replicated our experiments in a thin three-dimensional myocardial slab model with Luo-Rudy (LR1) ion channel kinetics (25) and bidomain architecture (20, 40).

MATERIALS AND METHODS

The protocol was approved by the Institutional Animal Care and Use Committee at Case Western Reserve University. New Zealand White rabbits (n = 10, Harlan; Indianapolis, IN) of either gender weighing 2–2.5 kg were injected intravenously with pentobarbital sodium (50 mg/kg) and 2,000 units heparin. The hearts were quickly removed, placed on a Langendorff apparatus, and perfused with oxygenated modified Tyrode solution as previously described (10).

The hearts were stained with a gradual injection of 500 μl of stock solution (1.25 mg/ml) of the voltage-sensitive dye di-4-ANEPPS (Molecular Probes; Eugene, OR) in DMSO (Fisher Scientific; Fair Lawn, NJ) delivered by a micropump over 5 min. The excitation-contraction uncoupler 2,3-butanedione monoxime (BDM; 15 mM, Fisher Scientific) was added to the perfusate to suppress motion artifacts in the optical recordings.

Experimental setup. The experimental setup is shown in Fig. 1A. The light from a 250-W quartz tungsten halogen light source (Oriel; Stratford, CT) was filtered by a 520 ± 45-nm excitation filter, reflected by a 585-nm dichroic mirror, and directed to illuminate a 10 × 10-mm region on the anterior ventricular epicardium. The fluorescence emitted from the heart was filtered using the dichroic mirror and an emission filter (>610 nm) and collected by a 16 × 16-element photodiode array (PDA; model C4675-103, Hamamatsu; Bridgewater, NJ) with built-in first-stage preamplifiers. The outputs of the PDA were fed into a 256-channel second-stage amplifier (Innovative Technology; Brooksville, FL) and then recorded by a data-acquisition system (National Instruments; Austin, TX) at a sampling rate of 5,000 frames/s. Each frame included 256 optical channels and 6 instrumentation channels for off-line data analyses. Instrumentation channels recorded electrical field strength, electrocardiogram, shock voltage, shock current, pacing stimuli, and defibrillation triggers.

Experimental protocol. The experimental protocol is shown in Fig. 1B. A bipolar Ag-AgCl pacing electrode with 1-mm interelectrode distance was placed at the apex of the heart. The heart was paced at a 300-ms basic cycle length by 2-ms stimuli. After 20 pacing stimuli, a test shock was delivered to the heart through a pair of platinum line electrodes spaced 10 mm apart and placed onto the anterior epicardium. Shocks were delivered using a custom research defibrillator (model 2960, Medtronic; Minneapolis, MN), which consisted of a stand-alone unit controlled by a dedicated computer running proprietary software. AR and DR waveforms of 7, 20, and 40 ms in duration were delivered at CIs of 120, 180, and 300 ms. Furthermore, each waveform was tested at three field strengths: 5, 10, and 20 V/cm. The
electrical field strength ($E$) was measured by a roving bipolar electrode with 1.8-mm interelectrode distance. The bipolar electrode was moved across the entire field between the line electrodes in 2-mm increments in a direction parallel to the line electrodes and 1-mm increments in a direction perpendicular to the line electrodes. The field strengths in the field of view ($8 \times 8$ mm) were uniform within 10%. The field strength at the edge of the field of view was slightly higher than that in the center. During an experiment, $E$ was measured by a bipolar sensing electrodes located in the middle of the shock delivering line electrodes and slightly above the field of view. The heart was allowed to recover for 30 s after each shock and before the next shock delivery. The model 2960 defibrillator was remotely controlled by a main computer through the LabVIEW virtual instrument server’s TCP/IP protocol. Two $7 \times 2$-cm stainless steel mesh electrodes placed on either side of the heart and spaced 1 cm from the epicardium were used to deliver rescue shocks in case an episode of sustained arrhythmia was induced by test shocks delivered via line electrodes. The shock-induced arrhythmia was considered sustained if the number of shocks needed to terminate the arrhythmia was greater than or equal to 6 ($\geq$6) (15).

**Data analysis.** Custom-developed LabVIEW-based data analysis software was used as previously described (9, 10). Maps of $V_m$ were calculated assuming that a normal resting potential of $-85$ mV and an action potential amplitude (APA) of 100 mV were present at all the recording sites. Postshock activation maps were reconstructed using a $(dV/dt)_{max}$ algorithm (31) and built by Origin 5.0 (Microcal Software; Northampton, MA). Shock-induced changes in $V_m$ ($\Delta V_m$) were calculated by subtracting the preshock action potential from the action potential at the end of the shock. We compared the gradient of VEP ($\nabla_{\text{VEP}}$) at the end of the shock and the postshock conduction velocity ($v_c$) between AR and DR waveforms. On the basis of our previous study (5), the total number of pixels with $\nabla_{\text{VEP}}$ larger than 24 mV/mm was defined as the index of $\nabla_{\text{VEP}}$ ($N_{\nabla_{\text{VEP}}}$), which served as a quantitative measure of $\nabla_{\text{VEP}}$ generated by the shocks. Postshock $v_c$ was calculated from the maps of activation using a previously described algorithm (31). The averaged $v_c$ ($\bar{v}_c$) of all excitations within 50 ms after the shock application was used as a quantitative index of postshock $v_c$.

In each of the 10 preparations, optical recordings from 2 columns in the field of view were selected for the analysis of the shock response. These columns were located close to the edges of field of view and $\sim$2 mm away from the two line electrodes. For all shock strengths, we compared the following parameters for AR and DR pairs of both polarities: 1) the peak positive and negative transmembrane polarizations during the shock application ($\Delta V_{p+}$ and $\Delta V_{p-}$, respectively); 2) the positive and negative polarizations at the end of the shock ($\Delta V_{e+}$ and $\Delta V_{e-}$, respectively); and 3) the normalized time at which the peak polarization was reached ($T_p = t_p/T_m$, where $t_p$ is the time to reach peak positive or negative polarization and $T_m$ is the pulse duration). $T_p$ for positive and negative polarizations are designated as $T_{p+}$ and $T_{p-}$, respectively.

All variables used in the statistical test are expressed as means ± SD. Fisher’s exact probability test was used for comparing the incidence of shock-induced arrhythmias. Multi-way ANOVA with repeated measures (48) was performed to test the statistical significances of $\Delta V_p$, $\Delta V_e$, $T_p$, $N_{\nabla_{\text{VEP}}}$, and $v_c$ among AR and DR groups, in which the dependent variables were waveform shape, waveform duration, shock strength, CI, and animal. Scheffe’s procedure was applied for multiple-contrasts test (48).

**Bidomain simulation.** We simulated a three-dimensional myocardial slab of $18 \times 12 \times 0.2$ mm with straight fiber geometry using the bidomain approach (20, 40). A thin layer of bath ($18 \times 12 \times 0.4$ mm) was added above the myocardial tissue. The choice of simulation geometry (Fig. 2) was the same as illustrated in the experimental part of the study. Stimulation electrodes (pacing electrode and shock electrodes) were placed in the bath just above the tissue as shown in Fig. 2. For a description of the ion channel dynamics, we used the LR1 model of ventricular action potential (25). The passive parameters (Table 1) were the same as those used by Latimer and Roth (24). At time = 4.5 ms, a 2-ms, 20-mA pacing stimulus was delivered through the pacing electrode, which induced action potential propagation perpendicular to the fiber orientation. Only the boundary opposite to the pacing electrode was grounded. All other boundaries were sealed.

At time = 355 and 395 ms [corresponding to 50% and 75% of the APA (APA$_{50}$ and APA$_{75}$, respectively)], 40-ms AR and DR waveforms were delivered through the shock electrodes. We used percentages of APA rather than action potential duration (APD) for shock CIs in our simulation because the LR1 model generates an action potential with a longer APD and faster repolarization. $E$ in the simulation was

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**Table 1. Bidomain simulation parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
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<tbody>
<tr>
<td>$C_m$</td>
<td>Membrane capacitance</td>
<td>0.01 μF/mm$^2$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Surface-to-volume ratio</td>
<td>300 mm$^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{ix}$</td>
<td>Intracellular conductivity along the fiber</td>
<td>0.1863 mS/mm</td>
</tr>
<tr>
<td>$\sigma_{iv}$</td>
<td>Intracellular conductivity across the fiber</td>
<td>0.0186 mS/mm</td>
</tr>
<tr>
<td>$\sigma_{ix}$</td>
<td>Interstitial conductivity along the fiber</td>
<td>0.1863 mS/mm</td>
</tr>
<tr>
<td>$\sigma_{iz}$</td>
<td>Interstitial conductivity across the fiber</td>
<td>0.0745 mS/mm</td>
</tr>
<tr>
<td>$\sigma_b$</td>
<td>Conductivity of the bath</td>
<td>2 mS/mm</td>
</tr>
<tr>
<td>$V_{rest}$</td>
<td>Transmembrane potential at the resting state</td>
<td>$-84.54$ mV</td>
</tr>
<tr>
<td>$\Delta x$</td>
<td>Space step along the x direction</td>
<td>0.2 mm</td>
</tr>
<tr>
<td>$\Delta y$</td>
<td>Space step along the y direction</td>
<td>0.2 mm</td>
</tr>
<tr>
<td>$\Delta z$</td>
<td>Space step of the tissue along the z direction</td>
<td>0.2 mm</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>Time step</td>
<td>10 μs</td>
</tr>
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calculated according to $E = (\Phi_{\text{cathode}} - \Phi_{\text{anode}})/d$, where $\Phi$ is the extracellular potential at the two stimulating electrodes and $d$ is the distance between them. The peak current was 2.5 mA, which resulted in a maximum of 2.5 V/cm field strength delivered to the tissue. After the shock delivery, all tissue boundaries were sealed. The action potential curves from the two recording sites were plotted and compared with those acquired during the experiments.

RESULTS

Incidence of shock-induced sustained arrhythmia. The incidence of shock-induced sustained arrhythmia was significantly different between AR and DR waveforms for 40-ms duration (Table 2). The difference did not reach statistical significance for 7-ms AR and DR waveforms and was of borderline significance for 20-ms waveforms. None of the tested waveforms induced sustained arrhythmia for 300-ms CI.

Shock-induced $\Delta V_m$, $v_c$, and VEP. A typical comparison of shock-induced responses by AR and DR waveforms is presented in Fig. 3. Whereas an AR 40-ms waveform of 5 V/cm applied at a CI of 120 ms did not induce reentry (Fig. 3A), a DR 40-ms waveform of identical strength and CI resulted in reentry (Fig. 3B). For both waveforms, the shock generated positive [virtual cathode (VC)] and negative [virtual anode (VA)] regions of polarization (Fig. 3, A, left, and B, left and right), thus producing a gradient of VEP ($\nabla_{\text{VEP}}$). Figure 4, B and C, shows $V_m$ and $\Delta V_m$ from the two columns (Fig. 4A) in VC and VA regions for 5 V/cm, 40-ms AR and DR waveforms delivered at a CI of 120 ms. Maximum VEP and hence the maximum $\nabla_{\text{VEP}}$ for the two waveforms were reached at starkly different times. The end-shock VEP maps (Fig. 4D) for the AR and DR waveforms were significantly different. $\nabla_{\text{VEP}}$ reached its maximum value at the end of the shock for the AR waveform ($\nabla_{\text{VEP}} = 101$) but during the shock for the DR waveform so that by the end of the DR waveform $\nabla_{\text{VEP}}$ had decayed to a much lower value ($\nabla_{\text{VEP}} = 5$; Fig. 4E). As illustrated in Fig. 4F, the postshock break excitation resulting from the AR waveform produced a faster propagating wavefront ($v_c = 0.2 \text{ mm/ms}$) and typically could not reenter the VC regions because the tissue in VC regions was less excitable when the wavefront came due to the end-shock strong positive depolarization and faster postshock $v_c$. In contrast, the partially dissipated VEP resulting from the DR waveform induced slower propagation ($v_c = 0.15 \text{ mm/ms}$), which had more time and more excitable VC regions for completing the reentry circuit.

Figure 5 summarizes the results of all experiments and compares end-shock $N_{\text{VEP}}$ and postshock $v_c$ among AR and DR waveforms. $N_{\text{VEP}}$ was greater for the AR waveform than the DR waveform for 20- and 40-ms durations irrespective of the field strength. However, for 7-ms duration, $N_{\text{VEP}}$ for the AR waveform was greater than that for the DR waveform only for a field strength of 20 V/cm. $v_c$ for the AR waveform was greater than that for the DR waveform for all 40-ms shocks irrespective of the field strength. $v_c$ for the 20-ms AR waveform was greater than that for the DR waveform at 10- and 20-V/cm shock strengths. For 7-ms duration, all fields produced $v_c$s with no statistically measurable difference between the two waveforms.

Figure 6 summarizes $T_p$, $\Delta V_p$, and $\Delta V_c$ for both positive and negative polarizations in response to shocks applied at 120- and 180-ms CIs. We found that $T_{p+}$ and $T_{p-}$ were significantly different between AR and DR waveforms for both CIs (120 and 180 ms) and all field strengths (Fig. 6A; $P < 0.05$ for all pair-wise comparisons). None of the comparisons for $\Delta V_{p+}$ and $\Delta V_{c+}$ reached statistically significant values at both 120- and 180-ms CIs. At 120-ms CI, $\Delta V_{p+}$ and $\Delta V_{c+}$ were significantly different for 20- and 40-ms shocks except for $\Delta V_{p+}$ at the lowest shock strength (Fig. 6, B and C, left). At 180-ms CI, only the 40-ms shocks were significantly different at shock strengths of 10 and 20 V/cm (Fig. 6, B and C, right). Independently of the different $\Delta V_{p+}$ and $\Delta V_{c+}$ pairs, the AR waveforms always yielded larger polarization magnitude than the DR waveforms. For 20- and 40-ms AR and DR waveforms delivered at 180-ms CI, the magnitude of $\Delta V_{c-}$ was smaller than the corresponding $\Delta V_{p-}$ for 180-ms CI and $\Delta V_{c-}$ for 120-ms CI. This occurred as a result of excitation during the waveform at the hyperpolarized side (VA region) of the tissue that diminished the magnitude of negative polarization caused...
by earlier portion of the waveform. Such excitation did not occur for 7-ms AR and DR waveforms.

**Bidomain simulation.** We conducted simulations of defibrillation shocks applied to a bidomain sheet with LR1 membrane dynamics. Figure 7 shows the simulated responses ($V_m$ and $\Delta V_m$) for 40-ms AR and DR waveforms at a shock strength of 2.5 V/cm. For the shock delivered at APA50, $\Delta V_{p+}$ was larger for the AR waveform than for the DR waveform and the $\Delta V_{p+}$ for the AR waveform was reached at its end. Along these lines, $T_p$ was shorter for the DR waveform than for the AR waveform. For the shock delivered at APA75, both the AR and DR waveforms resulted in excitation during the shock at the VA side. The simulation of 7-ms AR and DR waveforms showed a small difference in $\Delta V_p$ and $\Delta V_e$, although the two waveforms reached their respective $\Delta V_p$ at different times (AR: $T_p = 1$; DR: $T_p = 0.85$). Thus our simulations qualitatively reproduced and were consistent with our experimental observations.

**DISCUSSION**

In this study, we used optical mapping to compare and contrast VEP patterns caused by two distinct classes of defibrillation waveforms: AR and DR. Our major finding is that AR is less likely to induce sustained arrhythmias compared with DR of comparable amplitude and duration, albeit the difference between the two waveforms diminishes for shorter duration waveforms (Table 2) and shocks applied at a longer CI (300-ms CI). We show that arrhythmogenicity of the two waveforms is linked to the key metrics of $\nabla V_{\text{VEP}}$ at the end of the shock and $v_c$ of the postshock break excitation wavefront.
ization: the negative polarization region (VA) and the positive polarization region (VC). We have previously shown that postshock $v_c$ during reexcitation depends on the $V_m$ in VA regions at the end of a shock (6); the more negative the polarization, the faster the postshock $v_c$ (6). In our present study as well, the magnitude of the negative response at the end of the shock ($\Delta V_e$) for the AR waveform was greater than that for the DR waveform for all 40-ms shocks irrespective of the field strength. $v_c$ for the 20-ms AR waveform was greater at 10 and 20 V/cm shock strengths than the corresponding DR waveforms. For 7-ms duration, all fields produced $v_c$S with no statistically measurable difference between the two waveforms.

Fig. 5. A: comparison of $N_{VEP}$ between AR and DR waveforms. $N_{VEP}$ was greater for AR waveforms than for DR waveforms for 20- and 40-ms durations and all tested field strengths; for 7-ms duration, the $N_{VEP}$ for the AR waveform was greater than that for the DR waveform only for a field strength of 20 V/cm. B: comparison of postshock average conduction velocity ($v_c$) among AR and DR waveforms. $v_c$ for AR waveforms was greater than for DR waveforms for all 40-ms shocks irrespective of the field strength. $v_c$ for the 20-ms AR waveform was greater at 10 and 20 V/cm shock strengths than the corresponding DR waveforms. For 7-ms duration, all fields produced $v_c$S with no statistically measurable difference between the two waveforms.

Fig. 6. Summary of shock-induced peak $\Delta V_m$ ($\Delta V_p$), the normalized time to reach $\Delta V_p$ relative to the total shock duration ($T_p$), and end-shock $\Delta V_e$ ($\Delta V_e$) for shocks applied at 120- and 180-ms CI. The positive and negative responses were compared separately. A: $T_p$s are all significantly different between the AR and DR shocks for 120- and 180-ms CIs. B: $\Delta V_p$ for 120- and 180-ms CIs. C: $\Delta V_e$ of 120- and 180-ms CIs. *Significant difference ($P < 0.05$).
comparison, \( V_{\text{VEP}} \) and postshock \( v_c \) for the DR waveform were smaller. Two factors are responsible for a smaller VEP and \( V_{\text{VEP}} \) of the DR waveform. First, our previous study (27) implicated that the cardiac tissue cannot follow the very sharp initial rise of an applied shock because of a slower cardiac cell transmembrane time constant. Thus only part of the total energy in a DR waveform is utilized to polarize the membrane. Second, the maximum polarization gradient for a descending waveform is reached during the waveform, and any lengthening of the waveform beyond this time may in fact work to actively dissipate the polarization gradient.

As discussed above, VEP can heavily influence the pattern of postshock electrical activity. VA can deexcite regions of refractory tissue through which wavefronts can propagate after shock. These wavefronts of break excitation originating at the border between VA and VC can result in new reentrant circuits and fibrillation, thus causing defibrillation to fail (9). Nevertheless, during defibrillation with a monophasic shock, these wavefronts are unavoidable. We (6) have earlier demonstrated that defibrillation is successful for a monophasic shock only when deexcitation is strong enough that it leads to a rapid postshock propagation, resulting in a conduction block and failure to ensue reentry. Thus an AR waveform creates conditions more amenable to defibrillation success compared with a DR waveform of comparable amplitude and duration.

Nonlinear response of \( \Delta V_{\text{pp}} \). Our previous studies mimicked a “hot can” configuration (10). One drawback of this configuration is that the electrical fields produced by the defibrillation shock are very nonuniform and hence the data are more difficult to quantitate. To address this limitation, we choose the line electrode configuration in this study, which produces a uniform electric field in the field of view. This well-controlled configuration enabled us to make a more direct comparison of the polarization efficacies of the AR and DR waveforms.

Passive resistor-capacitor (RC) models have been demonstrated to be able to predict the relative efficacy of defibrillation waveforms (37, 44). Nevertheless, the active processes of ionic channels play an important role during defibrillation, specifically for a long duration shock delivered at the repolarization phase. Our results showed that \( \Delta V_{p+} \) and \( \Delta V_c \) for longer duration (20 and 40 ms) and higher shock strength (10 and 20 V/cm) were significantly different between AR and DR waveforms, whereas \( \Delta V_{p-} \) was not. This observation, as well as the asymmetric polarization efficacy for positive and negative polarization, cannot be replicated using the simplified lumped models. We therefore conducted simulations of shocks in a bidomain myocardial slab with LRI membrane dynamics. Predictions from this bidomain model confirmed that 1) \( \Delta V_{p+} \) and \( \Delta V_c \) for 7-ms AR and DR waveforms are similar; 2) \( \Delta V_{p+} \) and \( \Delta V_c \) for 20- and 40-ms AR waveforms are larger than those for the DR waveforms; 3) \( \Delta V_{p+} \) and \( \Delta V_c \) for 20- and 40-ms waveforms do not significantly differ; and 4) \( T_p \) are different for all shock strengths and Cs. Thus the bidomain model reproduced our experiment observations, whereas the passive RC model failed. These findings underscore the limitation of lumped element models in studying complex phenomenon of defibrillation by oversimplifying the electrophysiological characteristics of cardiac tissue.

**Design implications.** On the basis of the results of our study and considering that DR waveforms are morphologically close to truncated exponential (TE) waveforms, we surmise that monophasic AR waveforms may be better than monophasic TE waveforms. Nevertheless, caution should be exercised in interpreting this as a firm conclusion because we did not directly compare AR and TE waveforms.

Present day implantable cardioverter defibrillators (ICD) and automatic external defibrillators use biphasic waveforms because of their demonstrated superiority compared with monophasic waveforms. Although VEP plays an important role during defibrillation with both monophasic and biphasic waveforms, some mechanistic differences exist. For the biphasic waveform, the first phase creates VEP, thus halting the ongoing fibrillation, and the second phase then creates a relatively homogeneous postshock \( V_m \) (i.e., lack of VEP regions with VA and VC regions juxtaposed, as are present at the end of a monophasic shock). Homogenization of postshock polarization occurs predominantly via activation of the hyperpolarized regions by the second phase of the biphasic waveform. Alternatively, for monophasic shock, the weakest shocks produce VEP-driven prolongation and shortening of action potentials in areas of positive and negative polarization, respectively (6). This produces a relatively weak \( V_{\text{VEP}} \), which is insufficient to generate new wavefronts necessary to produce reentry. Further increases in shock intensity produce stronger \( V_{\text{VEP}} \). The resulting intermediate-level \( V_{\text{VEP}} \) is conductive to creating new slowly propagating wavefronts, a necessary ingredient for initiating reentry. Further increases in shock intensity result in an even stronger \( V_{\text{VEP}} \) and faster propagation upon shock termination, so that reentry is unable to form and successful defibrillation is achieved. Our results reveal that an AR is more likely to produce the last-described condition, which is less prone to reentry than a DR of comparable strength and energy.
Although this study only compared the shock-induced arrhythmia and polarization efficacy of monophasic AR and DR waveforms, their differences in vulnerability may have important implications for the design of an optimal biphasic waveform as well. Successful defibrillation is based on two effects governed by different mechanisms. First, defibrillation shock must halt all or a critical number of wavefronts supporting fibrillation. Second, defibrillation shock must not reinitiate fibrillation. In general, a larger positive ΔV\text{m} is preferable to halt the ongoing fibrillation because it will eliminate the excitable gap and potential substrate for reentry. The AR waveform resulted in significantly larger positive polarizations (Fig. 6) and hence is superior in context of the first mechanism mentioned above. Reinitiation of fibrillation is mainly determined by the shock-end VEP. The AR waveform produces stronger VEP leading to a rapid postshock propagation and a lower tendency to induce re fibrillation. We suggest that the addition of a second phase to the AR waveform could improve its efficacy even further, because it will provide an additional “kick” after the first phase AR application, which will accelerate reexcitation of deexcited regions, thus erasing the proarrhythmic potential of excitable gap.

Our finding that the 40-ms DR waveform is more arrhythmogenic than the 40-ms AR waveform may have clinical implications for ventricular fibrillation (VF) induction. During ICD implantation, VF is commonly induced using T shock. Sharma et al. (35) compared the efficacy of T shock with a new induction method using a 9-V direct current pulse. The rate of first-attempt VF induction rate using a 9-V pulse (96%) was much higher than the T shock method (68%). Interestingly, the duration of direct current pulse they used was very long (3.8 ± 1.4 s). We suggest that a comparable VF yield may be obtained by using a much shorter DR waveform delivered during the T wave period (e.g., see 40-ms DR in Table 2).

**Study limitations.** During an actual defibrillation, a shock is presumably delivered during a full range of refractory states and not just certain controlled coupling intervals, as was the case in our study. We chose to do experiments under such controlled conditions because it allowed us to isolate the shock response by subtracting a previous baseline action potential from the one during which the shock is applied. The same approach can be applied if the reentrant activity is a stable monomorphic ventricular tachycardia (13). Unfortunately, arrhythmias induced in our rabbit hearts were predominantly polymorphic in nature, thus precluding such type of analyses. However, we believe that because several published studies (4, 14, 17) have established an excellent correlation between the upper limit of vulnerability and defibrillation threshold, our results would be valid for defibrillation as well. We specifically selected 120- and 180-ms CIs because they correspond to the early and late repolarization phases, which are the most interesting phases to investigate because they span the vulnerability window.

Shock-induced VEP is essentially a three-dimensional phenomenon. The results of this study are limited due to the small field of view (0.8 cm², anterior epicardium) and penetration depth that are typical of the optical mapping technique. The possible impacts of the excitation-contraction uncoupler BDM has been previously discussed (10). The effects of BDM on shock-induced responses remain to be investigated.

**REFERENCES**