Mechanistic inquiry into decrease in probability of defibrillation success with increase in complexity of preshock reentrant activity

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Hillebrenner, Matthew G., James C. Eason, and Natalia A. Trayanova. Mechanistic inquiry into decrease in probability of defibrillation success with increase in complexity of preshock reentrant activity. Am J Physiol Heart Circ Physiol 286: H909–H917, 2004. First published November 6, 2003; 10.1152/ajpheart.00492.2003.—Energy requirements for successful antiarrhythmia shocks are arrhythmia specific. However, it remains unclear why the probability of shock success decreases with increasing arrhythmia complexity. The goal of this research was to determine whether a diminished probability of shock success results from an increased number of functional reentrant circuits in the myocardium, and if so, to identify the responsible mechanisms. To achieve this goal, we assessed shock efficacy in a bidomain defibrillation model of a 4-mm-thick slice of canine ventricles. Shocks were applied between a right ventricular cathode and a distant anode to terminate either a single scroll wave (SSW) or multiple scroll waves (MSWs). From the 160 simulations conducted, dose-response curves were constructed for shocks given to SSWs and MSWs. The shock strength that yielded a 50% probability of success (ED50) for SSWs was found to be 13% less than that for MSWs, which indicates that a larger number of functional reentries results in an increased defibrillation threshold. The results also demonstrate that an isoelectric window exists after both failed and successful shocks; however, shocks of strength near the ED50 value that were given to SSWs resulted in 16.3% longer isoelectric window durations than the same shocks delivered to MSWs. Mechanistic inquiry into these findings reveals that the two main factors underlying the observed relationships are 1) smaller virtual electrode polarizations in the tissue depth, and 2) differences in preshock tissue state. As a result of these factors, intramural excitable pathways leading to delayed breakthrough on the surface were formed earlier after shocks given to MSWs compared with SSWs and thus resulted in a lower defibrillation threshold for shocks given to SSWs.

Energy requirements for successful antiarrhythmia shocks are arrhythmia specific. Cardioversion of a monomorphic ventricular tachycardia (VT) typically requires less energy than termination of ventricular fibrillation (VF). The American Heart Association recommends using lower currents and energies for termination of VT (1); these recommendations are supported by clinical studies (16, 28). The study by Kerber et al. (16) demonstrated that the degree of organization of ventricular tachyarrhythmia determines the energy and current requirements for successful transthoracic cardioversion and defibrillation. Similar were the conclusions by Winkle et al. (28), which were derived from their internal defibrillation studies. However, the mechanisms by which the organization of the arrhythmia affects the probability of success for a given shock strength remain unclear. The present study focused on one aspect of arrhythmia organization and its effect on shock outcome. This research aimed to determine whether an increased number of simultaneous functional reentrant circuits results in a diminished probability of shock success, and if so, to identify the responsible mechanisms.

A large body of research in recent years (10, 11) has demonstrated that a shock delivered to the myocardium induces regions of positive and negative change in transmembrane potential; this is termed virtual electrode polarization (VEP). The shock-induced VEP alters the state of the myocardium and results in success or failure of the shock. We hypothesized that the different probabilities of success for terminating a single vs. multiple reentries stem from differences in transmural postshock behavior that remain inaccessible to the present optical mapping techniques. By testing this hypothesis, we expected to be able to provide insight into some of the mechanisms responsible for the differences in antiarrhythmia shock thresholds that are associated with shocks given in VT and VF. To do so, we employed a sophisticated, anatomically accurate, 3-D computer model of ventricular defibrillation.

Methods

The simulation methods have been partially described elsewhere (18, 24). In brief, the Auckland model (19) of canine ventricular anatomy and fiber orientation was used in this study. The ventricles were placed in a box representing the perfusing bath. Two planes 4-mm apart were passed through the ventricles and the bath to isolate a 4-mm-thick slice. The slice, including cardiac tissue and surrounding conductive media (the perfusing bath and a portion of the blood cavities), measured 85 × 75 × 4 mm. The location of the slice in the canine ventricular model is shown in Fig. 1, which also displays a sampling of the fiber orientation.

The properties of the myocardium were represented by the bidomain model. The potentials in the blood and perfusing bath were governed by Laplace’s equation. The top and bottom surfaces of the slice were insulated as if pressed between glass plates. The equations that govern the potentials as well as the membrane kinetics and electroporation equations were described in detail in a previous study (9). Values for the model parameters used here can be found in a previous article (18).

An S1-S2 stimulation protocol was used to establish a stable single scroll wave (SSW) in the anterior junction of the septum and left ventricular (LV) wall. The S1 stimulus had a strength of 0.015 A and the S2 was 0.028 A; both were 4 ms in duration. The scroll wave (Fig. 2, left) had an average period of 72 ms and rotated in a counterclockwise direction. Furthermore, a weak 0.14-A shock of 5-ms duration was applied to this scroll wave 300 ms after the onset of the S1
stimulus (Fig. 2, right) to induce multiple scroll waves (MSWs). This shock was delivered through the electrode configuration shown in Fig. 1, where the right ventricular (RV) catheter was the cathode and the external electrode was the anode as common in experimental studies of defibrillation (8, 10, 11). Thus both arrhythmias were based on 3-D stable, functional, reentrant circuits, which allowed us to examine the effects of an increased number of organizing centers of reentry (wavebreaks) on shock efficacy. The arrows in Fig. 2 indicate the wavebreaks on the surface of the slice.

Shocks to terminate the arrhythmia were delivered from the same electrode configuration to the slice where the preshock state was either SSW or MSWs. These shocks were monophasic square waves of 5-ms duration that ranged from 0.35 to 0.8 A. The choice of the 5-ms duration was based on the fact that a 5-ms square monophasic wave has energy comparable to the 8-ms truncated exponential form used in clinical practice. The shocks were administered in increments of 0.05 A in a total of 10 strengths. The shocks were delivered over a cycle of 70 ms at 10-ms intervals (8 different shock timings). With shock strength, shock timing, and preshock state changing, a total of 160 3-D bidomain simulations were conducted to construct dose-response curves and determine the 50% probability of success (ED50) for extinguishing SSWs and MSWs. The ED50 strength was defined as the shock strength that resulted in an equal number of successful and failed shocks over the range of eight shock timings. Dose-response curves representing the dependence of the probability of success on shock strength were generated in a manner described previously (9). The numerical aspects of the simulation have been described elsewhere (24).

RESULTS

Dose-response curves. The dose-response curves for shocks delivered to SSWs and MSWs are displayed in Fig. 3, where the curves have been fit to the simulation data shown. The simulation data show that the probability of success increases with shock strength regardless of the preshock state of the tissue. In addition, these data indicate an ED50 strength of 0.5 A for extinguishing SSWs as compared to 0.55 A for MSWs; the dose-response curves estimate ED50 strength values of 0.506 and 0.577 A for preshock states of SSWs and MSWs, respectively. With the use of the values predicted by the fitted curves, the ED50 strength for terminating SSWs was 13% less than that for MSWs.

VEPs and postshock behavior. In all simulations, the shocks induced VEPs on the surfaces of the slice and throughout its volume; the sign of the polarization on the top-cut surface was reversed on the bottom-cut surface. The results of two 0.45-A shocks, both delivered to SSWs but at different times, are compared in Fig. 4. Figure 4A presents the VEP at shock end (time, 5 ms) on the top-cut surface of the slice (Fig. 4A, middle) and on a cross-sectional plane parallel to it and at a depth of 2 mm below the cut surface, e.g., through the middle of the slice (Fig. 4A, bottom). The VEP was clearly much larger on the cut surface of the slice compared with the depth of the myocardium. In addition, although on the top- and bottom-cut surfaces the polarization was reversed in sign, in the plane through the middle of the slice, the polarization pattern was different from the one on either cut surface.

Figure 4B represents the distribution of the transmembrane potential on the top-cut surface of the slice (as if this surface were imaged optically). The formation of top-surface VEP was followed by break excitations that, as seen in the 15-ms panels,
quickly traversed the shock-induced excitable gaps. After the excitable tissue on the surface was depolarized, there was an isoelectric window (IW) during which no activations were present on the top-cut surface in either simulation. However, at 37 ms, a wave front broke through the top surface of the slice (Fig. 4B, left). Similarly, an activation reached the top surface 12 ms later in the other simulation (Fig. 4B, right). The 12-ms difference in the IW was associated with vastly different shock outcomes: success (Fig. 4B, right) and failure (Fig. 4B, left).

Figure 5 displays transmembrane potential maps following 0.45-A shocks delivered to SSWs and MSWs. Once again, a quiescent period was present on the surface after the initial break excitations subsided in both simulations. At 28 ms, a wave front broke through the surface in the posterior junction of the septum and the LV wall following the shock given to MSWs. Likewise, a surface breakthrough at 48 ms was seen for SSWs (Fig. 5, right) following an IW 20 ms longer than the one associated with the shock delivered to MSW.

**IW duration.** Although an IW existed after all four cases examined above, the outcomes of these defibrillation attempts were different. In Fig. 4 (left), the breakthrough activation at 37 ms encountered a dispersion of refractoriness in the surrounding tissue. This caused a unidirectional conduction block and eventually led to reentry and shock failure. In Fig. 4 (right) at 49 ms, the focal activation in the right ventricle did not encounter a conduction block and did not result in reentry. In Fig. 5, a wave front reached the surface at 28 ms (Fig. 5, left) and 20 ms later (Fig. 5, right). In the latter case, the surrounding tissue was nearly recovered and reentry did not ensue. In each comparison, the simulation with the longer IW resulted in success, whereas the shock followed by the shorter IW failed.

Figure 6 is a graph of IW duration as a function of shock strength for successful and failed shocks and for SSWs and MSWs. Here, the IW duration was measured from the end of the shock, thus it includes the period over which the initial break excitations took place. Only the IWs associated with the first delayed activations are included in the graph, although in several of the simulations there were numerous breakthroughs (as in Fig. 4B at 49 ms). Each point on the graph represents the average duration of the IW for the given shock strength. The average is taken from all episodes that resulted in delayed activations (of 16 maximum, 8 given to SSW and 8 to MSW). The numbers in the graph adjacent to each data point represent the number of such episodes for the corresponding shock strength. The minimum shock strength included in this graph is 0.4 A, since below this strength the IW is zero: activations continuously follow the end of the shock; i.e., despite generating some break excitations, the shock was too weak to erase the preshock activations on the surface of the slice. In Fig. 6A, shocks that succeeded despite the emergence of delayed activations (black tracing) and those that resulted in failure after the onset of delayed activations (gray tracing) are shown. The number of episodes corresponding to each data point on the black tracing increased with increase in shock strength; i.e., more episodes (out of 16) resulted in success. In contrast, the number of episodes for each point on the gray tracing decreased with increase in shock strength; thus fewer failures occurred for stronger shocks. The gray tracing in Fig. 6A does not extend beyond 0.75 A, because there were no failures at these shock strengths. The sum of both numbers corresponding to a given shock strength should be 16 or less, where the deviation from 16 indicates shocks that resulted in success immediately following the initial postshock break activations. For instance, shocks of strength 0.4 A resulted in 14 failures and 2 successes following an IW. As shock strength increased (see 0.45- and 0.5-A data points), the number of failures decreased with the total number remaining at 16. Additional increase in shock strength resulted in the same trend; however, some immediate successes (without emergence of delayed activations) took place: one episode for strength of 0.55 A and two episodes for strengths of 0.6, 0.65, and 0.7 A. The results in Fig. 6A show that regardless of the preshock state, shocks...
that succeeded had a longer IW than failed shocks with averages of 39.1 ± 1.3 and 35.3 ± 3.0 ms, respectively.

Figure 6B depicts the IW duration following shocks delivered to SSWs and to MSWs as a function of shock strength. Each point of data entry represents the average IW duration for all SSW or MSW episodes including both failures and successes for the given shock strength. For each shock strength, the sum of the two numbers equals the sum of the corresponding numbers in Fig. 6A. Clearly, compared with shocks given to SSWs, shocks delivered to MSWs, which had a lower probability of success as demonstrated in Fig. 3, were associated with shorter IWs. The differences in IW duration are statistically significant for shock strengths in the range 0.4–0.6 A (P < 0.01). Note the large disparity in IW durations for shock strengths <0.55 A, which was the ED$_{50}$ strength for extinguishing MSWs. There the IW corresponding to SSWs

Fig. 5. Transmembrane potential maps on the top surface before and after 0.45-A shocks delivered to MSWs and SSWs. Arrows indicate postshock breakthrough activations. Time is measured from the shock onset. Color scale as in Fig. 4.
was on average 16.3% longer than the IW corresponding to MSWs. As shock strength increased $>0.55$ A, this difference decreased, and at $>0.65$ A, IW duration was nearly identical for SSWs and MSWs. Indeed, for shocks in the range of 0.7–0.8 A, the probability of success neared one for both SSWs and MSWs. Overall, shocks delivered to SSWs and MSWs had mean IW durations of $38.7 \pm 0.9$ and $35.4 \pm 2.0$ ms, respectively. It is noteworthy that for the shock strengths presented, only shocks given to SSWs resulted in immediate success (Fig. 6B, numbers $<$8 on black tracing).

**Preshock state in depth determines IW duration.** To uncover why IW was longer following shocks given to SSWs than for shocks given to MSW, the evolution of the distribution of transmembrane potential within the tissue volume was examined for all pertinent simulations. An example is presented in Fig. 7, which exhibits this distribution before, during, and after the 0.45-A shocks whose results are displayed in Fig. 5. Only the time period before the first breakthrough on the surface is shown in the figure. The brackets under the slices pinpoint the particular region that is being discussed. In the images showing the preshock activity, the tissue undergoing SSW was more refractory in the volume of the bracketed region right before the shock onset as compared with the same region in the case of MSWs (bracketed region is red in SSW vs. green in MSWs). As was seen at 5 ms and is consistent with the data presented in Fig. 4A, the shock-induced VEP was of much smaller magnitude in the depth of the tissue volume as compared with the surface of the slice. Although the surface VEP is the same color in both cases (at 5 ms), there was a distinct difference in the end-shock distribution of transmembrane potential in the volume of the bracketed LV wall portion. For MSWs, the bracketed tissue was recovering right before the shock; the recovering mid-myocardium there was not affected significantly by the shock. For the SSW, the bracketed tissue was just depolarized before the shock, and the mid-myocardium there remained depolarized at the end of the shock. For MSWs, the postshock recovery of the mid-myocardium resulted in the formation of a nonexcitable gap on the bottom surface already activating this gap and the top surface 10 ms later. By 50 ms, the activity was about to become a figure-eight scroll wave. This reentry was sustained and caused shock failure (see Fig. 5). After the shock delivered to the SSW, the tissue in the designated region remained unexcitable until all activity in the region had subsided; the shock succeeded as shown in Fig. 5. Therefore, because the shock-induced VEP was the largest on the surfaces and its magnitude in the mid-myocardium was much smaller, the difference in postshock activity and thus in IW duration was largely determined by the preshock state in the tissue depth.

Examination of all simulation results for failed and successful shocks following an IW for both SSWs and MSWs resulted in two major findings. First, all cases of delayed postshock activation following an IW on the top surface involved wavefronts that propagated transmurally from bottom to top much like the example presented in Fig. 7. These activations originated at the bottom surface as a result of VEP-induced break excitation and subsequent propagation through the shock-induced excitable gaps on that surface. Such activations “dive in” transmurally whenever they encounter recovered or recovering tissue. Depending on the degree of recovery of the mid-myocardium along the pathway, these activations made a breakthrough on the top surface after a shorter or longer period of time.

Second, analysis of the simulation results demonstrates that much like the example in Fig. 7, an intramural excitable pathway that allowed wave front propagation was formed earlier after shocks given to MSWs compared with SSWs. Thus surface breakthrough took place earlier in the case of MSWs. The earlier the breakthrough, the more likely that the resulting focal activation on the top surface would encounter refractory tissue and reenter and thus cause the failure of the defibrillation attempt. Shocks of near-ED$_{50}$ strength erase completely the preshock activity on the surface; therefore, the time of recovery of the surface from shock-induced effects is determined solely by its VEP. Because the surface VEPs for SSWs and MSWs are the same for the same shock strength, the evolution of the spatial pattern of recovery of the surface is the same in both cases. Therefore, the earlier the breakthrough on the surface of the slice, the more likely the tissue on this surface will not recover, and the more likely the activation will encounter unidirectional block and reenter.
DISCUSSION

Summary of findings. The main objective of this study was to provide insight into some of the mechanisms responsible for the decreased probability of success of shocks delivered to arrhythmias of increased complexity. Specifically, this research aimed to determine whether an increased number of simultaneous functional reentrant circuits contributes to the increased energy requirements for arrhythmia termination, and if so, why. To attain the goal of the study, simulations of the effects of shocks administered to a canine ventricular slice undergoing SSWs or MSWs were conducted. From the 160 simulations run in the study, where shock strength and timing were varied, dose-response curves were constructed for shocks given to SSWs or MSWs. The MSW dose-response curve was shifted to the right from the SSW curve. Compared with SSWs, MSWs were associated with a 13% higher ED50 shock strength, which indicates that a larger number of functional reentries results in increased defibrillation energy requirements. Mechanistic inquiry into this finding revealed that the two main factors underlying the observed relationship are 1) the magnitude of VEP in the tissue depth, and 2) the preshock electrophysiological state in the tissue. Specifically, the smaller magnitude of VEPs in the tissue depth as compared to those on the surface leads to the formation of intramural postshock excitable pathways; these allow wave front propagation that ultimately makes a breakthrough on the surface after an IW. The preshock electrophysiological state in the tissue determines when these intramural pathways are formed, and thus it determines the time of activation breakthrough on the surface (i.e., the IW duration). Our results demonstrate that when given to SSWs, shocks of near-ED50 strength are followed by on average 16.3% longer IW durations compared with shocks given in MSWs. The longer the IW duration, the less likely the breakthrough wave front will encounter significant dispersion of postshock refractoriness on the surface and the more likely the success of the defibrillation attempt.

Role of VEPs. Our findings indicate that the VEP established by the shock is larger on the surface compared with the tissue depth (see Fig. 4A), which was predicted by our passive-tissue theoretical considerations (10), but it is never observed before in either active simulations or experiments. Thus the break excitations that follow the end of the shock take place only on the surface of the preparation: only there does the magnitude of the transmembrane potential gradient between regions of depolarization and deexcitation span the threshold for regenerative depolarization. Therefore, for shocks of near-ED50 strength, the activity on the surfaces is VEP induced and is not a function of the preshock state (as demonstrated in Fig. 5); such behavior has also been reported in experimental studies (8). In contrast, the smaller-magnitude-depth VEP subsides

Fig. 7. Transmembrane potential distribution on the top surface and within the volume of the slice before, during, and after 0.45-A shocks applied to MSWs and SSWs. Time is measured from shock onset. Brackets indicate regions of interest (see text). Color scale as in Fig. 4.
after the shock without giving rise to new activations. The recovery of the tissue in depth determines whether a wave front propagating on the surface will invade the midmyocardium and also determines the timing of this possible invasion. The state of the midmyocardium determines also how quickly an invading activation will traverse the depth and become a breakthrough on the opposite surface, i.e., it determines, at least partially, the duration of the IW. Once a breakthrough occurs following an IW, two possible outcomes were observed in this study: either the wave front encountered conduction block and reentered, or the activity propagated outward in all directions from the origin to result in shock success. The same observation regarding the behavior of the delayed postshock activations was made by Chen et al. (6). Clearly, the fate of these focal activations depends largely on the dispersion of refactoriness of the surrounding tissue at the time of breakthrough and thus on the duration of the IW. The more recovered the tissue (larger IW), the more likely the breakthrough activation will not result in reentry.

**Role of preshock state: SSWs vs. MSWs.** The shorter IW after shocks given in MSWs is due to the fact that an intramural excitable pathway that allows wave front propagation is formed earlier for all shocks given to MSWs compared with SSWs as illustrated by the example presented in Fig. 7. We speculate that this persistent earlier recovery of the midmyocardium following shocks given to MSWs occurs because SSWs are characterized with a larger excitability gap compared with MSWs (12) both on the surfaces and in the tissue depth. When a shock of near-ED50 strength is delivered, the prebreakthrough excitability gaps in the depth are immediately eradicated by shock-induced make excitation. New shock-induced excitability gaps are unlikely to be formed in the tissue depth for such shock strengths, because the threshold for regenerative depolarization is much smaller than for regenerative repolarization (13). Thus on average, the postshock behavior following cardioversion of SSWs is characterized by an overall higher level of refractoriness in depth. Therefore, the time period until an excitable pathway opens through the midmyocardium and thus the IW is longer following shocks given in SSWs. Overall, shocks that achieve 100% probability of success for both SSWs and MSWs must erase the preshock activity both on the surfaces of the preparation and in the depth.

**IW following shocks given to SSWs and MSWs.** In the simulations representing shocks delivered to SSWs and MSWs, an IW was observed on the surface of the slice for shocks of near-ED50 strength (as shown in Fig. 6). In both SSWs and MSWs, IW duration varied in a range from 31.9 to 42.5 ms following failed shocks of strength >0.4 A and those that succeed after delayed activations. However, the present results demonstrate that shocks of near-ED50 strength given to SSWs are associated with on average 16% longer IW durations than those given to MSWs. Because longer duration of the IW is correlated with higher probability of success (due to the breakthrough wave front encountering decreased dispersion of postshock refractoriness on the surface as discussed above), the shorter duration of the IW for near-ED50 shocks administered in MSWs is an indicator of the lower probability of success for these shocks.

**IW duration and origin: comparison with previous studies.** Numerous electrical (4–7, 21, 26) and some optical (3, 27) mapping studies have demonstrated an IW following shocks near ED50 in dogs and pigs. Using plunge electrodes to map postshock activity in dogs, Chen et al. (6) determined that the location and pathway of activation fronts are markedly different from those before the shock. Additional mapping studies (3–5, 26) demonstrated that the first delayed postshock activation propagates focally away from the breakthrough site. Our results are consistent with these findings. In the simulations as in the experiment (4), some shocks resulted in immediate success. Finally, Chen et al. (7) concluded that for failed but not successful shocks, there was a correlation between IW duration and shock strength; this correlation ranged between 0.53 and 0.9 for all animals. The results presented in Fig. 6A are consistent with this finding; no correlation was found for successful shocks, whereas a correlation coefficient of 0.765 was determined for failed shocks.

Assuming that IW duration is determined by the recovery rate in the tissue, the arrhythmia cycle length (CL) should represent the absolute limit of IW duration. The average IW duration found here was 35.3 ± 3.0 ms for failed and 39.1 ± 1.3 ms for successful shocks. Given that the scroll wave CL here was 72 ms, the average IW duration was then 49% of CL for failures and 54% of CL for successes. The IW durations determined here are consistent with experimental findings. Chen et al. (6) reported an average IW duration of 42 ± 15 ms for shocks in VF, which represents 44% of CL since 96 ± 16 ms was the CL of the VF. Shibata et al. (21) reported average IW durations for failed shocks ranging from ~20 to ~50 ms as the shock strength increased, no VF CL was reported in the study. A recent article by Ideker’s group (4) documented IW durations of 58 ± 23 ms for failed and 63 ± 16 ms for successful defibrillation shocks. Making the reasonable assumption that VF CL was ~100 ms in this study, then these values are only 9–12% higher than the ones found here. The latter discrepancy is likely due to the fact that a thickness of 4 mm is on the low side of typical cardiac wall thickness in larger animals.

The mechanisms underlying the IW have been a topic of much debate. It has been proposed that the postshock breakthrough pattern following the IW is a manifestation of intramural reentry; however, endocardial and transmural mapping studies do not support this hypothesis (4, 7, 20). Triggered activity has also been implicated in the origin of the delayed postshock activation(s) (3, 4). An alternative hypothesis suggests that slow propagation of graded responses underlies the existence of IW (15). A recent transmural mapping study in pigs (4) also speculated that it could be caused by activity emanating from penetrating Purkinje fibers. Several optical mapping studies of rabbit hearts did not document an IW following shocks (10, 11).

This study posits a novel mechanism to explain the formation of an IW following defibrillation shocks of near-ED50 strength. We suggest that after such shocks, due to the smaller magnitude of the shock-induced VEP in the midmyocardium as compared to the surface, intramural excitable pathways can be created in the tissue depth before the surface recovers from the shock-induced break excitations. An activation would linger along such a pathway until the surface becomes excitable, and then it would break through that surface. The time of this breakthrough would determine the IW duration.

**Description of model.** This study presents the most sophisticated defibrillation model assembled to date and employs this...
model to further our understanding of defibrillation mechanisms. We use an anatomically accurate 3-D bidomain finite-element model of a slice through the normal canine ventricles to examine the activity following shocks given to SSWs and MSWs. This model enables us to explore the contributions of tissue architecture to VEPs and postshock activity in the myocardium and also represents a significant step forward in our ability to realistically model defibrillation. Although we have previously used slices from the canine heart (18, 24), these slices were only 1-mm thick due to computational constraints. In this case, the surface VEP penetrated throughout the depth and influenced postshock electrical behavior. Here we pushed the computational tractability limit and thereby accepted an enormous increase in computational expense to conduct simulations with a 3-D model that is capable of examining the contribution of the third dimension to shock outcome.

Previous simulation studies (2, 17, 22) have focused on VEPs close to the electrodes or the boundaries of a sheet of tissue vs. a VEP in the middle of the same sheet in an attempt to explore the effects of tissue depth. However, there is not really depth in these models. Because the sheet surface is insulated, the VEP in a sheet corresponds to the VEP on the cut surface in our slice model. From this argument it becomes clear how different our model is from previous attempts to model defibrillation because it offers, for the first time, the possibility of accessing the effects of tissue depth on VEPs. As our results demonstrate, the difference between VEPs on the surfaces and at depth is extremely important in postshock behavior following ED30 shocks and underlies the appearance of breakthrough activations following an IW.

Finally, in contrast with previous defibrillation models that have represented the preshock arrhythmia as a spiral (2, 22) or a SSW (18, 24), here we also implement MSWs. The simulations involved shocks of different strengths delivered at various timings during the reentrant cycle, which allowed us to construct dose-response curves. A similar scope of defibrillation simulations has only been achieved with a simplified model in our previous study (9).

Limitations. The limitations associated with most aspects of the present defibrillation model such as choice of ionic model, lack of representation of tissue discontinuities, etc. have been discussed in previous publications (18, 24) that have utilized the 1-mm-thick canine ventricular slice model. Clearly, the most significant limitation of the present model is that due to computational limitations, it is impossible to represent the canine heart in its entirety. As a result, after the shock, large VEPs are induced on the top and bottom surfaces of the slice. Such effects are, however, not unrealistic: during the shock, large VEPs are formed on the surfaces of the ventricular walls; similar to the effects shown here, the VEPs are of reverse signs on the endo- and epicardial surfaces (10, 25). Thus although the model does not fully and accurately represent reality, it is nonetheless pertinent to defibrillation and can be used in the study of its mechanisms. We expect that the mechanistic insight into the IW and its origin for shocks given to SSWs and MSWs as provided by the present simulation results will contribute to further understanding of defibrillation in the whole heart.

Although we conclude that preshock activity in the mid-myocardium is responsible for the differences in IW duration for SSWs and MSWs, we do not provide an all-encompassing explanation of the mechanisms behind the IW. Other mechanisms such as Purkinje fiber contribution, microreentry, or triggered activity (4) could possibly affect IW duration; the limitations of our tissue representation and ionic model do not allow us to model such conditions. Also, slow propagation of VEP-induced graded responses might play a role in delayed activation (23); these responses could be associated with the smaller-magnitude VEPs in the depth of the slice.

The present study focused on the effects of increased number of functional reentrant circuits on the threshold for arrhythmia termination as an attempt to shed light on what causes the differences in energy requirements for cardioversion vs. defibrillation. Functional reentry underlies both VF and VT predominantly in structurally healthy ventricles (14). In contrast, monomorphic VT in diseased ventricles is typically due to an anatomic reentry that does not rotate around a wavebreak. In addition, CL differences between VT and VF might also contribute to differences in shock thresholds. These factors, which are beyond the scope of the present research, need to be explored to fully elucidate the mechanisms behind the differences in cardioversion and defibrillation thresholds for shocks given in VT and VF.

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DISCLOSURE

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