On the mechanism of the probabilistic nature of ventricular defibrillation threshold

MASAAKI YASHIMA, YOUNG-HOON KIM, SEAN ARMIN, TSU-JUEY WU, YASUSHI MIYAUCHI, WILLIAM J. MANDEL, PENG-SHENG CHEN, AND HRAYR S. KARAGUEUZIAN
Division of Cardiology, Cedars-Sinai Medical Center, Department of Medicine, School of Medicine, University of California, Los Angeles, California 90048

Submitted 27 August 2002; accepted in final form 17 September 2002

It is known that in a given heart, shocks of threshold defibrillation strength may or may not succeed in terminating (defibrillation) ventricular fibrillation (VF) (6, 24). The lack of a preset, fixed defibrillation threshold (DFT) (i.e., a shock below threshold will never defibrillate and one above it will always defibrillate) led to the proposal of an alternative approach, “the probability of defibrillation” for a particular defibrillation shock (1, 4). The mechanism of the probabilistic nature of the DFT remains poorly understood. It is not known why in the same heart a given electrical shock strength can be successful in some episodes and fail in others.

It was suggested that shock outcome depends on the electrical state of the heart at the instant of the shock (2), VF regularity (8, 11), and VF voltage amplitude (12). Recent optical mapping studies (28) suggest that failed defibrillation does not result from incomplete termination of VF wavefronts (32) or incomplete resynchronization of repolarization (7, 20). The demonstration of the presence of a postshock optical equivalent of an isoelectric window after near-threshold failed shocks argues for complete cessation of all activation wavefronts and subsequent reinitiation of VF after an isoelectric window (28). The optical equivalent of an isoelectric window supports the earlier electrode-based proposal that subthreshold shock terminates VF but fails to achieve successful defibrillation because the same shock reinitiates VF (3). For successful defibrillation, the shock strength must reach the upper limit of vulnerability (ULV) (3).

The ULV hypothesis states that after the complete cessation of all VF wavefronts, the failed near-threshold shock induces VF by the same mechanism that induces VF when the shock is applied during the vulnerable period of a regularly driven beat (31). A shock induces VF when applied during the vulnerable period by initiating a reentrant wavefront (5). Similarly, it is hypothesized that a failed near-threshold defibrillation shock also reinitiates VF by the formation of reentry (9). Because the pattern and the sequence of wavefront activation during VF are irregular and change constantly (21), the amount of fibrillating myocardium in its vulnerable period also changes. Owing to this inherent irregularity of activation wavefronts during VF, it is therefore likely that at the instant of a given shock, the amount of the myocardium in its vulnerable period will be different compared with another instant of shock. The aim of the present study was to test the hypothesis that near-threshold defibrillation shocks fail because the amount of the myocardium in its vulnerable period is higher than the amount of the vulnerable myocardium at the instant of successful defibrillation.

METHODS AND MATERIALS

The right ventricle (RV; 30 ± 2.5 g) of 10 farm pigs was isolated and perfused through the right coronary artery with oxygenated Tyrode solution at 37 ± 0.5°C in a tissue bath...
with the endocardial surface facing up (18). VF was induced by burst pacing [50-ms cycle length (CL) for 3–5 s] with 10 times diastolic current threshold. The 50% successful defibrillation (DFT50) was determined by an up-down method (23) with a pair of 4-cm coil electrodes (model 1228, CPI) mounted in the tissue bath. One of the two electrodes was placed 1 cm away from the left edge of the RV and the second 1 cm away from the right edge of the tissue. In each isolated RV, at least five successes and five failures were obtained with shock strengths equal to the DFT50. After each shock, 3–5 min of recovery time were allowed before another shock was tested. Shocks consisted of biphasic (6 and 6 ms) waves that delivered truncated exponential waveform shocks with fixed pulse duration and a variable tilt (model HVST200, Ventritex. Sunnyvale, CA). The biphasic waveform was generated by a positive-polarity truncated exponential waveform followed by a negative-polarity truncated exponential waveform. Leading edge voltage of the second phase was half the residual value of the first phase (13). The endocardial surface of five isolated RVs was mapped with 477 bipolar electrodes 1.6 mm apart spread over a 3.8 × 3.8-cm plaque that virtually covered the entire isolated, perfused RV endocardium. Less than 10% of the cut edges of the isolated RV remained outside the mapping plaque. The number of sites activated (sampling frequency 1 kHz) at each of the 477 recording electrodes was determined in 1-ms steps during the 100-ms VF interval that preceded the shock. Each activated site first became red, then pink, then yellow, then green, and then blue before fading to black. The persistence of each color was 5 ms (15, 18). This method of data analysis and display allowed us to determine the recovery time of each of the 477 sites at the time of the shock onset. Although we scanned the 100-ms interval preceding the shock with a 1-ms decrement, the sites showing recovery intervals of 5 ms were grouped together. To relate recovery times to the transmembrane action potential phases during VF, in five isolated, perfused swine RVs we continuously recorded with a glass microelectrode (16, 18) endocardial transmembrane action potentials for ~1 min at two different endocardial cells that were spaced 2–3 cm from each other. No activation mapping was performed in these five RV tissues. The total number of responses analyzed in each RV was ~1,500 beats (total of ~7,500 in all 5 RVs). The action potential duration (APD) for 90% repolarization (APD90) of the regenerative action potentials (i.e., amplitude >40 mV) was measured. Lower-amplitude (i.e., <40 mV) responses were considered nonregenerative (i.e., graded responses; Refs. 10, 17) and were excluded. Ten to one hundred milliseconds of recovery time after the upstroke of each regenerative action potential during the VF was related to the phase of the action potential and to the range of transmembrane voltages attained.

Statistical analyses. In each RV tissue, differences between successful and failed defibrillation shocks relative to energy, voltage, and impedance were calculated with paired t-tests. An ANOVA test with Bonferroni correction was used to compare the number of activated sites at multiple pre-shock intervals of 5 ms each. Differences were considered significant if \( P < 0.05 \). Data are presented as means ± SD.

RESULTS

Defibrillation shock parameters. A total of 26 trials of successful and 26 trials of failed defibrillation shocks were analyzed. There was no significant difference in the level of energy (1.52 ± 0.24 vs. 1.56 ± 0.26 J), voltage (192 ± 13 vs. 192 ± 15 V), and impedance (44.5 ± 6 Ω vs. 45.5 ± 6.2 Ω) between successful and failed defibrillation shocks.

VF cycle length. There was no significant difference in the mean VF CL between successful and failed defibrillation shocks (79.7 ± 25.7 vs. 78 ± 24.7 ms; \( P = 0.5 \)).

Amount of tissue recovery at shock onset. At shock onset, the number of sites and the recovery time at each of these sites were computed during successful and failed defibrillation shocks. The number of sites with 45–55 ms of recovery time was significantly (\( P < 0.04 \)) lower for the successful defibrillation shocks than for the failed shocks. The mean number of sites with 45–55 ms of recovery time in five RVs was 23.3 ± 8.8 for the successful episodes versus 28.4 ± 6.7 for the failed episodes (\( P < 0.04 \)). The numbers of sites presented represent the mean numbers of sites within this specific (i.e., 45–55 ms) recovery interval. The numbers of sites during successful and failed shocks correspond to 4.8% and 5.9% of the total recording surface area, respectively. Figure 1 illustrates an example of VF activation snapshots preceding a successful shock. It is apparent that at the instant of the shock there were nine sites in the entire mapped region with 45–55 ms of recovery time. Figure 2 shows an example of VF activation snapshots preceding a failed defibrillation shock in the same tissue as in Fig. 1 with the same shock strength as the successful shock (Fig. 1). In this case of failed defibrillation shock, there were 31 sites in the mapped region that had 45–55 ms of recovery time at the instant of the shock (Fig. 2). Outside this relatively narrow range of recovery time, no statistically significant difference could be detected in the amount of tissue (i.e., number of sites) with recovery intervals lasting <45 ms or >55 ms between successful and failed defibrillation shocks. The number of sites with 0- to 45-ms and 55- to 80-ms recovery times were 27.6 ± 10.1 (successful) versus 27.1 ± 11.3 (failed) and 21.8 ± 9.6 (successful) versus 22.3 ± 11.3 (failed) (\( P = 0.50 \)), respectively.

Relation of recovery to transmembrane action potentials. The mean VF CL (measured as the time between 2 consecutive action potential upstrokes) was 79 ± 22 ms, which was not significantly different (\( P = 0.6 \)) from the VF CL measured with the bipolar electrodes of the mapping system. Nonregenerative responses (graded responses) with amplitudes <40 mV (10, 18) were observed with an incidence of 4.2 ± 0.5%. The graded responses were excluded from VF CL calculation (Fig. 3). During VF, the mean action potential amplitude was 67 ± 5 mV and the mean APD90 was 63 ± 26 ms (range 34–88 ms; Fig. 3). The transmembrane voltage range that corresponded to 45- to 55-ms recovery was between −15 and −60 mV in 92% of regenerative action potentials.

DISCUSSION

New findings. The variable (probabilistic) nature of ventricular defibrillation shock outcome with shock strengths equivalent to the DFT50 results from the
variations of the amount of tissue in its vulnerable period at the instant of the shock. The results of the study show that the amount of myocardium in its vulnerable phase was significantly smaller during successful defibrillation shocks than during failed shocks with identical near-threshold shock strengths.

**Vulnerable period, fibrillation, and defibrillation.** The two critical prerequisites for the induction of VF by an electrical stimulus during regular pacing or sinus rhythm are stimulus timing (i.e., during the vulnerable period) and stimulus strength (25). During regular activation, both ventricles normally proceed quasi-synchronously through the vulnerable period. The quasi-synchronous nature of ventricular recovery during regular activation in normal hearts eliminates myocardial mass as a variable, making the shock strength and shock timing the sole determinants of shock outcome.

During VF, however, because of the irregular pattern of activation (21), the amount of myocardium in its vulnerable period changes from moment to moment (Figs. 1 and 2). Our results suggest that variation in the defibrillation shock outcome after the delivery of similar shock strengths might result from the differences in the amount of myocardium in its vulnerable period at the instant of the shock. With this in mind, insight may be gained from comparing the results of ULV measurements with a stable and repeatable amount of myocardium in the vulnerable period to those of DFT measurements with a variable amount of myocardium in its vulnerable period. ULV may be determined either by scanning the vulnerable window (i.e., peak T wave, 20 and 40 ms before the peak of the T wave; Ref. 13) or by using a single shock on the peak of the T wave (26). Malkin et al. (22) performed a detailed analysis of the methods to test ULV. These authors clearly demonstrated that the ULV determined with T wave scanning has a very narrow probability of success curve (steep slope) compared with that of the ULV determined with a single shock (26). Interestingly, Swerdlow et al. (27) showed that in hu-
mans, the ULV is more reproducible than DFT. The implications of Swerdlow et al.’s (27) findings are that the amount of myocardium in its vulnerable period is more stable during ULV testing than during DFT testing both in animals and humans. Therefore, ULV testing results are more reproducible whereas DFT testing results are more dependent on the amount of myocardium in the vulnerable period. These experimental and human findings are compatible with our proposed hypothesis that the amount of the myocardium in its vulnerable period at the instant of the shock is an important determinant of the shock outcome.

Amount of tissue in its vulnerable period versus shock outcome. The mechanism(s) by which myocardial tissue mass in its vulnerable period influences defibrillation shock outcome remains poorly understood. In vitro (10) and in vivo (5) studies of shock-induced VF during regular pacing often develop in the presence of a fixed amount of myocardium in its vulnerable period. Shocks applied during phase 3 prolong the duration of the action potential (19) and cause wave break at the site of the prolonged action potential duration in a repeatable and predictable manner (10) while allowing conduction at sites without prolongation of repolarization. However, this is not the case during VF. Because of the complexity of the activation pattern during VF (14, 21), the amount of myocardium in its vulnerable period changes constantly. Our results suggest that if the mass of myocardium in its vulnerable period at the instant of the shock is relatively high, the shock will fail to defibrillate. It appears that a certain amount of myocardial tissue (critical mass) must be present for the shock to induce and maintain the VF. Because a shock induces VF in normal ventricles by first initiating a reentrant wavefront of excitation, it appears that a critical mass of “vulnerable” myocardium must be present for reentry to be formed (stage I VF) (30). Reentry then evolves to stage II VF (30) by breakup

Fig. 2. Snapshots of activation during VF preceding an unsuccessful shock with 477 bipolar recording electrodes (top). This figure is from the tissue shown in Fig. 1 and is organized in the same manner as Fig. 1. There are 31 sites that show 45 ms of recovery at the instant of the shock. The electrical parameters of the shock were the same as in Fig. 1.
(29) and fibrillatory conduction (33). Optical mapping studies have shown that failed defibrillation shocks are associated first with the formation of a postshock reentrant wavefront (phase singularity) that then breaks up into multiple wavelets, signaling the onset of VF (9). However, the role of the tissue mass in its vulnerable period in the formation of postshock reentry was not addressed in that study (9). In the instance of shock-induced VF, it appears that in addition to the shock strength and shock timing, the amount of myocardium in its vulnerable period also plays an important role in the shock outcome.

Limitations of study. Our two-dimensional (2-D) mapping studies were carried out in an essentially three-dimensional tissue. The 2-D maps do not allow the determination of intramural cells in their vulnerable period at the instant of the shock. The number of (endocardial) sites may therefore not represent the true volume of tissue in its vulnerable period. However, the consistent finding of a successful defibrillation outcome with a lower amount of endocardial sites in their vulnerable period suggests that our high-resolution and complete endocardial mapping of the isolated RV provides a reasonably accurate estimate of myocardial tissue mass in its vulnerable period. Although the amount of myocardium in its vulnerable period is higher in failed shocks than in successful shocks, the relation of the earliest site of activity after a failed defibrillation shock to the vulnerable myocardium was not determined in this study.

Fig. 3. Transmembrane action potential recordings in 5 isolated and perfused swine right ventricles (A–E). Each row shows 2 different recordings (cell 1 and cell 2) from 2 different cells 2–3 cm apart in each isolated ventricle during 2 different episodes of induced VF. Arrows indicate nonregenerative, graded responses, and the horizontal lines next to each panel represent zero transmembrane potential.
It may be argued that the 45- to 55-ms recovery time may not coincide with the phase 3 repolarization, which corresponded to the −15- to −60-mV voltage range in our model. This voltage range encompasses part of the vulnerable period for reentry and VF induction by a strong electrical stimulus (10). We do not know whether in different animal models or at other myocardial sites (intramural/epicardial) the 45- to 55-ms recovery interval during VF also corresponds to voltage ranges of −15 to −60 mV. Our study was conducted in normal ventricles; we do not know whether the similar recovery periods versus vulnerability relationship remains applicable in diseased hearts. Finally, it should be noted that our results are not pertinent to episodes of failed shock that are characterized by the formation of postshock reentry. We do not know whether the mass of vulnerable myocardium is important in episodes of failed shocks associated with the formation of nonreentrant focal activity.

Clinical implications. Timing the shock when the mass of the fibrillating ventricles in its vulnerable period is smallest might increase the probability of successful defibrillation without the need to increase shock strength. Such shock timing remains a future challenge.

We thank Avile McCullen and Meiling Yuan for technical assistance, Elaine Lebowitz for secretarial assistance, Nina Wang for reading the manuscript, Dr. Toshihiko Ohara for help in preparing the manuscript, and Drs. P. K. Shah, Terus Takeo, and C. Thomas Peter for support of our effort. This work was supported in part by American Heart Association, Western States Affiliate Grant 0255937Y, Cedars-Sinai Electrocardiographic Heartbeat Organization Foundation and Grand Sweepstakes University of California-Tobacco-Related Disease Research and Prevention Program Grant 11RT-0058, a National Heart, Lung, and Blood Institute Specialized Center of Research Grant on Sudden Death HL-52519, and the Pauline and Harold Price Endowment.

Present address of M. Yashima: First Department of Internal Medicine, Nippon Medical School, Tokyo 113-8603, Japan.

REFERENCES

26. Souza JJ, Malkin RA, and Ideker RE. Comparison of upper limit of vulnerability and defibrillation probability of success...


