Mechanism of Cardiac Defibrillation

A Different Point of View*

Peng-Sheng Chen, MD; Patrick D. Wolf, MS; and Raymond E. Ideker, MD, PhD

Sudden cardiac death resulting from ventricular arrhythmia is one of the leading public health problems of most developed countries. Despite intense research in the areas of ionic channels and pharmacological interventions, a panacea has not been found to control life-threatening arrhythmia and improve survival. In addition, the results of the Cardiac Arrhythmia Suppression Trial demonstrated that some routinely used antiarrhythmic drugs are proarrhythmic and in certain cases can make the cure worse than the disease. An alternative approach, the implantable defibrillator, has been more successful and has been reported to extend life. Such devices could probably be improved if more were known about the mechanisms by which a defibrillation shock fails or succeeds. Many studies have investigated the mechanism of defibrillation by directly recording cardiac activations before and after successful and unsuccessful defibrillation shocks.

These studies have resulted in the proposal of two completely opposite hypotheses. One of the hypotheses is the critical mass hypothesis of defibrillation, which states that a shock can fail to halt activation fronts within a region smaller than a certain critical mass yet still defibrillate. The other is the upper limit of vulnerability hypothesis, which states that unsuccessful shocks slightly weaker than necessary to defibrillate halt all the activation fronts during ventricular fibrillation (VF) but stimulate regions of myocardium during their vulnerable period, giving rise to new activation fronts that reinitiate VF.

The experimental evidence supporting the critical mass hypothesis was obtained before the era of computerized mapping techniques. With only the small number of recording electrodes available, researchers could not determine global patterns of activation or make detailed recordings of small wavefronts that are present during VF. We have partially overcome these difficulties by using computerized mapping techniques to simultaneously record from multiple electrodes over the entire ventricular epicardium and transmurally in a small volume of tissue and obtained experimental evidence that we interpreted to be against the critical mass hypothesis. Using similar techniques, however, Witkowski et al recently reported experimental evidence that they interpreted to support the critical mass hypothesis. Although Witkowski et al performed careful data acquisition and analysis using an advanced new computerized mapping system, we do not agree with their conclusion. We present our point of view about their data interpretation.

Witkowski et al recorded from 120 electrode sites simultaneously on the canine epicardium and determined the mean values and SDs of the time intervals between activations during VF just before a defibrillation shock. Ten consecutive time intervals were measured, the last of which, immediately preceding the shock, is shown in Figure 1 as interval 1. They also determined the time interval between the last activation before the shock and the first activation after the shock (Figure 1, interval 2) for defibrillation episodes that failed and for episodes that succeeded but were followed by at least one rapid activation (pattern 2 or type B2 defibrillation). In the ventricular region in which the electric field created by the shock was weakest, the authors found that at one or more electrodes, this latter time interval was always within 2 SDs of the mean of the 10 time intervals during VF just before the shock. On the basis of this one finding, the authors concluded that the postshock activation recorded at this electrode was the continuation of the VF activation pattern at this site just before the shock. It is intriguing that the Witkowski et al study and our studies that led to the proposal of the upper limit of vulnerability defibrillation hypothesis are similar in purpose, protocol, and instrumentation, except the Witkowski et al study has the advantage of being able to detect

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From the Basic Arrhythmia Laboratory (P.-S.C.), Division of Cardiology, Department of Medicine, UCSD and Veterans Affairs Medical Centers, San Diego, Calif., and the Departments of Medicine and Pathology (P.D.W., R.E.I.), Duke University Medical Center, and NSF Engineering Research Center, Duke University, Durham, N.C.

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Address for correspondence: Peng-Sheng Chen, MD, Department of Medicine, H811A, UCSD Medical Center, 225 Dickinson Street, San Diego, CA 92103.
activations very quickly after the shock and our most recent study has the advantage of recording transmurally with closely spaced electrodes in a region where the shock electric field is weak. It is also intriguing that even though different conclusions are drawn, the experimental results of the two studies are almost identical.

Both groups found that VF is sufficiently organized that predictions can be made about activation as long as 100 msec into the future. Since at least 1930 when Wiggers reported that four stages of VF are visible by cinematography, it has been known that activation during the early stages of VF is not completely random. After the first, or "tachysystole," stage lasting only a few seconds, VF enters the "convulsive incoordination" stage for 15–40 seconds, during which distinct contraction waves pass over the ventricular epicardium at a rate of "between 600 and 660 per minute." Both groups recorded activations at approximately this rate with a relatively small SD. The activation rate found by Witkowski et al was sometimes slightly slower than this value (their Figure 4), which may be related to the very large size of the dogs they studied (weight, 28–34 kg). Both groups also found that the activation fronts of VF are halted outside the regions of low-shock electric field strength and that a minimum electric field of approximately 3–9 V/cm is needed for defibrillation. Most interesting of all, like the primary finding of Witkowski et al, we reported that in almost all cases at the electrode first recording activation after the shock, the time interval between the last activation before the shock and the first activation after the shock (Figure 1, interval 2) was within 2 SDs of the mean time interval between activations during VF just before the shock (Figure 1, interval 1). Our method of analyzing the baseline VF cycle length was different from the method used by Witkowski et al. They analyzed one cycle length before the shock at all recording sites, whereas we analyzed 10 consecutive cycle lengths preceding the shock at only the site recording the earliest postshock activation. We found the mean time intervals during VF before the shock (interval 1) to be 96±16 msec, whereas the mean time interval between the last activation before the shock and the first activation after the shock at the electrode recording the earliest postshock activation (interval 2) was 106±11 msec. Thus, despite the difference in methods of analysis, we also found that 2 SDs on either side of the mean of interval 1 (64–128 msec) encompassed 2 SDs on either side of the mean of interval 2 (84–128 msec).

Why, then, are the major conclusions drawn by the two groups so dissimilar? We believe lack of knowledge about the VF activation sequences just before the shock caused Witkowski et al to commit the second of the two types of statistical error that can be made in testing a hypothesis. Suppose we wish to determine if a particular cycle length represents continuous VF activation ("continuation" case) or cessation followed by reinitiation of VF ("reinitiation" case). We could measure the cycle lengths of a large random sample of VF activations and determine the mean and SD of the cycle lengths. If the cycle lengths are normally distributed and we decide to call the cycle length reinitiation only if it differs by more than 2 SDs in length from the mean cycle length of VF, then our probability of committing a type I error (i.e., calling a continuation a reinitiation) is approximately 0.05 and occurs when the cycle length really is for a continuation but differs by more than 2 SDs from the mean cycle length for VF. Another kind of error is also possible, however; a type II error occurs when the cycle length is called an continuation because it is within 2 SDs of the VF cycle length but is really a reinitiation. It is not possible to determine the probability of committing a type II error without also knowing the mean and SD of the cycle lengths associated with reinitiation.

Although Witkowski and coworkers have concluded they have continuation, we believe additional experimental evidence suggests that they may instead have reinitiation. They measured the mean and SD of the activation rate during VF before the shock, but they did not explicitly consider what would be the mean and SD of the time between the last preshock activation and the first postshock activation at the early site of postshock activation (interval 2) if the shock altered the VF activation pattern at the early site. They also did not report the mean and SD they found experimentally for interval 2. Even though, as discussed above, we found that the limit spanning 2 SDs on either side of the mean time between the last preshock activation and the first postshock activation at the electrode registering earliest activation after the shock (interval 2) was encompassed by the limit spanning 2 SDs on either side of the mean cycle lengths during VF just before the shock (interval 1), the two means (106 msec for interval 2 and 96 msec for interval 1) are significantly different (p<0.0015).

If the shock does not influence the electrophysiological state of the region from which activation is first recorded after the shock, then the shock should occur with equal frequency at all portions of the
cardiac cycle in this region. We found, however, that the interval between the last activation before the shock and the time of the shock at the electrode site recording earliest postshock activation (Figure 1, interval 2a) is not uniformly distributed over a range of approximately 96 msec, as would be expected if the shock had no effect on activation in this region (Figure 2A). Instead, this interval clusters within a range of 43–82 msec with a mean of 64±11 msec, suggesting that early sites occur in regions that are in a certain stage of the cardiac cycle (Figure 2B). The refractory period to a 5-V/cm electric field during VF in dogs has recently been reported to be approximately 80% of the VF cycle length.12 The preshock interval 2a is slightly shorter than this (64 msec divided by 96 msec, or 67%), indicating that the sites of earliest recorded postshock activation are in the latter portion of their absolute refractory periods at the time of the shock. As discussed more fully below, this finding raises the possibility that the early sites of recorded postshock activation are near regions that are slightly more recovered so that these nearby regions are directly activated by the shock.

We also found that the time from the shock to the first postshock activation at this electrode (Figure 1, interval 2b) is not uniformly distributed, as would be expected if the shock had no effect on activation of tissue at the electrode site (Figure 2C). Instead, this interval clusters about a mean of 42±15 msec (Figure 2D). This interval could have been biased by postshock saturation of recordings. Witkowski et al justifiably emphasize the superiority of their recording electrodes and the rapid recovery of these electrodes after the shock. They therefore have the ability to determine how often interval 2b is very short with an activation occurring almost immediately after the shock that we might have failed to detect because of postshock saturation. Although Witkowski and coworkers do not report this information, their examples for unsuccessful defibrillation (their Figure 10) and type B successful defibrillation (their Figure 12) both show early postshock activation times (interval 2b) of approximately 60 msec, suggesting they may have found intervals similar or even longer than ours. Thus, neither interval 2a nor 2b is independent of the time of the shock. This finding raises the possibility that the shock is affecting the electrophysiological state of the tissue at the site of earliest recorded postshock activation, even though defibrillation is not achieved.

Although measuring activation–activation intervals in a single channel during VF can be used to predict when the next activation will be registered in that channel, it is a very limited method by which to
investigate VF activation sequences because the information registered by other channels is not included. A better method of investigating VF is to incorporate the information of multiple channels and directly determine activation patterns. Therefore, there is a more straightforward way to tell whether a shock has altered activation sequences than measuring the length of the preshock-postshock activation interval at the early site of postshock activation, and that is to examine the isochronal maps for activation patterns immediately before and after the shock.

Figure 3 illustrates two idealized examples of ways in which activation patterns can be markedly altered by the shock, yet the time of the preshock-postshock activation interval at the early site of postshock activation (interval 2) be almost the same, as if the shock had no effect on the activation sequence. Figure 3A shows the passage of an activation front part-way through a small ventricular region during VF. The shock occurs when the activation front is approximately one fourth of the way across the region. Figure 3B shows the unaltered continuation of the activation front if the shock has no effect on the activation sequence.

Figure 3C illustrates one possible outcome when the shock directly excites a portion of the tissue (shown by shading). If the shock electric field is relatively constant through the small region shown, the tissue directly excited will be the tissue that is least refractory. The least refractory tissue is probably the tissue that has had the longest time to recover since the last activation, which is usually the tissue that is just in front of the activation front at the time of the shock and that is just about to be excited by propagation from this activation front. By directly activating this tissue, the shock halts the VF activation front in the upper-right-hand corner of Figure 3A because there is no tissue adjacent to this front that is excitable immediately after the shock. A new activation front, however, can originate from portions of the lower-left-hand border of the directly excited region after the shock.

In Figure 3C, the electrode recording earliest activation after the shock (indicated by the large dot) is located in tissue that was in the latter portion of the absolute refractory period at the time of the shock. The time after the shock when the new activation front is first registered at this electrode is difficult to predict. The time could be shorter than if the shock had no effect because the new front has a much smaller distance to travel after the shock—from the border of the directly activated region to the electrode. The tissue between the border of the directly activated region and the electrode is highly refractory, however, so the conduction velocity is probably slower in this region than if no shock had been given. Thus, activation could be registered at the electrode at nearly the same time, as if the shock had not altered the VF activation front as indicated in Figure 3B. If the shock induced a graded response, prolonging refractoriness in the tissue just outside the directly excited region, the time by which the new activation front reached the electrode could be even later than if no shock had been given, which may explain why the site of earliest recorded postshock excitation activated 10 msec later than would be expected if the shock were absent.

Another way in which the shock could greatly alter the activation pattern yet not markedly change the time of earliest recorded activation after the shock is shown in Figure 3D. In this figure, the shock again
halts the VF activation front by a combination of direct excitation and induction of a graded response in the tissue adjacent to the front. After a pause, activation in response to the shock occurs and gives rise to a new front that spreads away radially, forming a focal activation pattern. One possible explanation for this new activation is triggered activity induced by the shock. However, we have no direct evidence that triggered activity occurs. Another possibility is that microcircuitry is initiated by the shock within the region in which the first postshock activation was observed, but the reentrant circuit occupies such a small volume of myocardium that it escapes detection. After unsuccessful shocks, this microreentrant circuit could then regenerate VF from what appears to be a focus.

Additional factors other than the activation sequences shown in Figures 3C and 3D are probably also involved in the postshock regeneration of VF; type B defibrillation is an example. Type B defibrillation was characterized by similar location of the early sites as in unsuccessful defibrillation, although the isoelectric window width (interval 2b) was significantly longer. After a few repetitive beats, however, activation ceased before VF was regenerated. This finding implies that factors outside of the mapped tissue or other than activation sequences in the mapped tissue, such as refractoriness, are also important in determining whether a shock will be successful.

Two requirements must be met to determine experimentally if responses of the types illustrated in Figures 3C and 3D actually occur. First, recording electrodes must be placed sufficiently close together to map the VF activation sequences before and after the shock. We accomplished this by placing 120 electrodes transmurally within a 2.5 × 5.5 × 0.6-cm volume of the right ventricular free wall. Second, it must be possible to predict the activation sequences during VF 50–100 msec into the future in the absence of a shock. This is necessary so that the location of activation fronts can be estimated if they are unaffected by the shocks for comparison with the location of the activation fronts actually observed after a shock. As would be expected from the finding by Witkowski et al and by us that intervals between successive activations at each electrode do not vary markedly during VF, we found that although there was some variation from cycle to cycle, VF activation sequences just before the shock were sufficiently repeatable that predictions could be made for 50–100 msec into the future. For example, we found that for 63–77% of the activation fronts, the electrode site that was first recording activation for that front on its first VF cycle was also first to record activation for an activation front in the succeeding cycle.

Having met these two requirements, we found that in at least 90% of unsuccessful defibrillation episodes with shocks approximately 100 V less than that required for successful defibrillation, activation fronts were markedly altered by the shock in a region in which an early site of activation was recorded after the shock. New activation fronts arising after the shock were similar in pattern to Figures 3C and 3D. A recent study found similar results with a plaque of closely spaced recording electrodes confined to the epicardium, performed in case the plunge needles containing the recording electrodes for transmural recording had altered the myocardial response during fibrillation or defibrillation. Regions of direct excitation and graded response, as suggested in Figure 3C, cannot be directly detected by extracellular recordings and will require confirmation by potentiometric dyes, monophasic action potential electrodes, or floating microelectrodes. As discussed previously, however, the fact that the time until the appearance of the earliest recorded activation after the shock averaged 10 msec longer than the time at which the site would have activated if no shock had been given ($p<0.0015$) suggests that the shock is inducing a graded response at that site. Several recent studies support this finding by showing that shock electric fields of a strength appropriate for defibrillation (approximately 5 V/cm) can prolong both action potential duration and refractoriness. This electric field strength is several times greater than the approximate 1 V/cm needed to directly excite fully recovered myocardium not in VF.

Witkowski et al and we both reported the existence of a minimum potential gradient needed for defibrillation over the entire ventricular epicardium. If defibrillation requires halting VF activation fronts in only a critical mass of myocardium and all of the myocardium has a similar minimum electric field requirement for stopping these activation fronts, then this minimum potential gradient should be required just in the critical mass and not in all of the ventricular myocardium. The results of Witkowski et al also suggest that the activation front after the shock is not the unaltered continuation of a VF activation front present just before the shock but rather a new front. Concerning the shape of the unipolar activation complex at the site of earliest recorded activation after the shock, they state that “the morphology of the earliest activation also is of the QS type, consistent with the finding that this site is the origin for this activation front.”

Whether the effects depicted in Figures 3C and 3D are better referred to as halting of the original activation front followed by initiation of a new activation front, as we have done, rather than as the perturbation of the original activation fronts is open to debate. We refer to cessation and reinitiation of activation fronts in Figure 3C because most of the tissue between the 20- and 60-msec isochronal lines is directly excited by the shock, so there is no conduction of a propagated activation front between the regions represented by these two lines. Also, at some electrodes near the early site, the activation front is frequently traveling in a direction opposite to the activation front before the shock, as indicated by Figure 3D and by the curved arrows at the top and
right borders of Figure 3C. This major change of the direction of the activation front is too large to be considered simply a perturbation of the existing activation sequence. In addition, Shibata et al. showed that after a strong shock is delivered during the vulnerable period of atrial or ventricular paced rhythm to induce VF, the location of the earliest postshock activation is similar to that after unsuccessful defibrillation with the same shocking electrodes. Furthermore, the latency at the early site (interval 2b of Figure 1) is influenced by the preshock interval in the same way interval 2a influences interval 2b of Figure 1 after an unsuccessful defibrillation shock.7 The longer the interval 2a, the shorter the interval 2b, and vice versa. For example, the latency from the shock to the first postshock activation can be 10 msec or less at one extreme and more than 70 msec at the other extreme, depending on the preshock interval.15 Thus, the responses observed after unsuccessful defibrillation shocks are similar to those observed after the induction of new activation fronts during the vulnerable period that initiate VF. Based on these findings, we propose that the activation fronts observed immediately after the shock are not results of perturbation of the fronts existing before the shock; rather, they are new fronts induced by the shock itself.

In summary, we believe that the major conclusion of Witkowski and coworkers that “... unsuccessful defibrillation is adequately explained by the failure to defibrillate at least one region of myocardium and no additional vulnerability arguments need to be invoked to explain unsuccessful defibrillation” is incorrect. Instead, we believe experimental evidence indicates that in the vast majority of cases, 1) shocks slightly weaker than necessary to defibrillate halt VF activation fronts but give rise to new activation fronts that reinitiate VF, and 2) these new activation fronts arise as a result of a complex interaction of the shock electric field and tissue refractoriness that in different regions can cause either direct activation or prolongation of refractoriness without propagated activation or can have no effect, depending on the strength of the shock field and the degree of refractoriness of the tissue in the region.

If the upper limit of vulnerability defibrillation hypothesis is incorrect, it is not because the shock fails to halt VF activation fronts. Rather, it is because the new activation fronts initiated by the shock sometimes arise by a mechanism that is different than the mechanism by which activation fronts arise when VF is initiated by a shock during the vulnerable period of regular rhythm. With a few exceptions,15 VF initiated by a large premature stimulus in the vulnerable period does not generally appear to arise from a focal (or perhaps microreentrant) pattern as shown in Figure 3D but rather appears to occur by large reentry circuits possibly associated with direct excitation and graded responses as indicated in Figure 3C.27,28

The task undertaken by Witkowski et al. and us is not a simple one; the task is to examine the activation patterns of the heart during the course of an intervention and determine if there has been a change. The problem is even more complicated in these cases because the rhythm is VF. Much analysis of activation sequences has been qualitative, based on simple visual inspection of recordings and isochronal maps. Witkowski et al.8 have made a valuable contribution by attempting to quantify changes in activation. However, we believe their method of quantifying the beat-to-beat variability at a single electrode site is incomplete. Their analysis neglects two important features of the data. First, it fails to consider any information available from nearby recording sites. For example, this omission means the analysis would fail to identify that two activation sequences were similar. Multichannel mapping provides the ability to combine temporal and spatial information. Ignoring the multichannel information eliminates the possibility of detecting repeating spatial patterns of activation in the absence of temporal similarity. Second, their analysis fails to consider the temporal sequence of the VF activation rate at a single site. Clearly, there is some difference between three VF cycles with very similar activation times followed by a VF cycle with a very short interval and four VF cycles with steadily increasing activation intervals even if their mean values and SDs are identical. Using the method of analysis suggested by Witkowski et al. removes all sequential information from the data and treats each interval as an independent measurement.

The primary method of analysis that we use—displaying the activation sequences as isochrones in space—is also incomplete. Although this method incorporates spatial information, much of the beat-to-beat temporal information is lost because beats are mapped as individual events. Also, because there is no quantitative evaluation of the degree of organization of the activation sequences or of the electrode spacing required to accurately portray the activation sequences, it lacks rigor. Clearly, neither method of analysis is completely satisfactory. Quantifying activation patterns in the heart and the differences between them is a critical area of research that requires further efforts if we are to understand the mechanisms of arrhythmias and the effects of electrical interventions to halt them.

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P S Chen, P D Wolf and R E Ideker

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