Refractoriness Prolongation by Defibrillation Shocks

Francis X. Witkowski, MD, and Patricia A. Penkoske, MD

Rhythm disturbances leading to ventricular fibrillation (VF) account for the majority of instances of sudden cardiac death occurring outside the hospital. VF is perniciously stable. The ventricles will rarely stop fibrillating on their own in a heart larger than a certain minimal size. The only currently employed successful therapy for VF is electrical defibrillation. With the first proposal of the concept of an automatic implantable defibrillator two decades ago, we have witnessed a dramatic reduction in the expected mortality of sudden cardiac death patients based on historical control groups. The future refinement of such implantable devices will require a clear understanding of their mechanism of action to maintain clinical efficacy while attempting to minimize any damage resulting from the delivered energy to the heart, maximize device longevity while decreasing its size, and make implantation minimally invasive.

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The ability of an external source of current to influence cardiac cellular electrophysiology can only be explained if the external current results in a change in the cell's transmembrane potential. VF most likely represents a reentrant phenomenon. Investigations of fibrillating ventricular tissue at the cellular level have been significantly hampered by the need to use large muscle mass preparations, in which stable impalements are technically challenging. Mechanically stabilized intracellular microelectrode recordings during VF reveal that individual action potentials, though shortened and irregularly activated, maintain a remarkably normal morphology. Accordingly, a single ventricular myocardial cell during VF will progress through a sequence of electrical activity that includes activation and an absolute refractory period, followed by a partially refractory period. It is uncertain whether a fourth state, total recovery, is ever achieved by any of the participating cells during VF. An alteration in transmembrane potential produced by a defibrillating shock can find any single ventricular cell in one of these three or four states. In fibrillating myocardium, the most promising phases of the cardiac cycle in which to intervene via existing transmembrane ionic channels would appear to be the partially refractory state, or the fully recovered state if it exists during VF. Additionally, by the use of very high-intensity shocks in isolated myocytes, direct microlesions have been demonstrated that would be produced independent of the electrical state of the cell. Such dielectric breakdown has not yet been documented in situ using energy levels commonly associated with successful defibrillation. A defibrillation shock could thus, at a cellular level, either initiate activation or modify the repolarization process of fibrillating tissue, and in so doing, alter the dynamics of the previous reentrant mechanism. However, at the macroscopic level, critically timed activations during nonfibrillating conditions have been shown to form stable patterns of global activation which can themselves subsequently develop into sustained ventricular fibrillation, as predicted by the elegant theoretical calculations of Winfree.

These possible outcomes of myocardial tissue subjected to an electrical shock form the basis for the three currently proposed mechanisms of defibrillation. The "total extinction" hypothesis is that all fibrillating activity must be extinguished from the ventricular myocardium for successful defibrillation to occur. The "critical mass" hypothesis is an electrical extension of the anatomical observations made by Garrey and confirmed using electropharmacological means by Zipes et al., namely, that successful defibrillation ensues when a critical amount of ventricular tissue is rendered incapable of sustaining VF. The "upper limit of vulnerability" hypothesis is that a defibrillation shock near defibrillation threshold produces an initial complete cessation of all activation fronts, but that after a short latency period, new activation fronts emerge to reinitiate subsequent VF.

The study by Sweeney et al in this issue of Circulation represents an important step toward developing a better mechanistic understanding of how electrical shocks can modulate the repolariz-
tion process during paced rhythms. As the authors observe, whether such findings apply to actual ventricular defibrillation is speculative, but would appear reasonable because similar ionic gating mechanisms are likely responsible for action potential generation in either paced or fibrillating conditions. The electrical shocks used in this study were timed to scan the cardiac cycle, and induced minimal change when timed to coincide with either the instant of activation, absolutely refractory tissue or fully repolarized myocardium. When the shock was applied to tissue that was in the process of recovering postactivation but between the extremes of absolute refractoriness and full recovery, the refractory period was prolonged. This prolongation was clearly demonstrated to be dependent on both the magnitude of the shock and the timing within the local cardiac cycle examined. The larger the shock energy, the larger the prolongation observed at any fixed timing. Similarly, the later the shock was given, the larger was the prolongation observed. Such an effect on electrophysiological recovery of responsiveness could enhance the probability of conduction block during reentrant tachyarrhythmias and hence may play an important role in both defibrillation and cardioversion of more organized rhythms such as monomorphic ventricular tachycardia. There were no measurements of the local voltage gradient produced by the shock in the region of refractory period determination, which would have allowed some comparison with previous mapping studies of electrical defibrillation. These measurements of local voltage gradients would also have permitted correlations between refractoriness prolongation and local shock intensity to be examined, which potentially could assist in estimating minimal requirements for successful defibrillation.

The findings presented by Sweeney et al. are consistent with the initial observations of Weidmann regarding action potential duration modulation by intracellular current injection. They are also consistent with similar, more recent observations using a variety of measurement techniques and tissue preparations including 1) intracellular recordings in Purkinje fibers in vitro; 2) refractory period determinations in myocardial cell aggregates; 3) optical techniques using intracellular voltage-sensitive dyes in isolated perfused rabbit hearts; and 4) in situ refractory period measurements in dog hearts. All of these studies, including the one by Sweeney et al., used paced preparations, with the exception of one that alludes to a similar finding during VF. The consistency of these findings suggests that the observations likely represent a fundamental cardiac electrophysiological property that is tissue preparation-independent. Similar action potential prolongation can be seen with intracellular current injection in a mathematical model of Purkinje fiber electrical activity using the Oxsoft Heart V3 modeling programs (personal communication, Professor Denis Noble) when the current pulses are applied during the late phase of repolarization, but by contrast, the same pulses applied during the very early plateau phase shorten the action potential duration. This may be a modeling explanation for the observation by Sweeney et al. that shocks given simultaneously with the last S wave were observed to minimally reduce the refractory period. Further studies using realistic ventricular muscle models and arrays of such models should prove instructive in elucidating the ionic basis for the measured changes reported. Confirmation of the findings of the present study after shocks given during actual VF will require either microelectrode action potential recordings or other techniques of visualization of the intracellular voltage time course such as the use of voltage-sensitive dyes. This is because refractory period determinations immediately after a defibrillation attempt are confounded by spontaneous rapid ventricular post-shock responses.

The past 10 years have seen an explosive increase in investigations of cardiac defibrillation. The clinical application of automatic implantable defibrillators has offered a dramatic improvement in mortality (to 1–2% per year) from the expected death rate (10–30%) in selected patient populations. Further understanding of the fundamental mechanisms of defibrillation will have an important influence on the design of these devices and their associated electrode systems as well as on potential drug treatments in patients requiring implanted defibrillators.

References
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