The discovery of defibrillation in 1899 by Prevost and Battelli has left us one of the most exciting clinical and research puzzles of the 20th century despite the obvious success of this treatment for arrhythmias. Initially, the idea of arresting ventricular fibrillation by the application of electric shock had seemed too fantastic even for Wiggers et al, whose research at Western Reserve University had laid the foundation for the first clinical application of defibrillation by Beck et al. During the last 2 decades of the 20th century, we witnessed clinical recognition and widespread application of implantable cardioverter-defibrillators (ICDs), which were stimulated in part by growing concern regarding the potentially harmful effects of antiarrhythmic drugs. Yet compelling evidence has been presented that pharmacological therapy combined with ICD therapy could decrease the frequency of shocks and improve the quality of life. Unfortunately, a lack of understanding of the ionic mechanisms of defibrillation impedes formulation of basic pharmacological strategies of defibrillation and redefinition of the role of antiarrhythmic drugs. The study by Cheek et al in this issue of Circulation Research presents one of the first attempts to build the basic science bridge between pharmacological and nonpharmacological therapies to control arrhythmias.

Many investigators during the 20th century were puzzled by the mechanisms of defibrillation. Unfortunately, the inability of existing techniques to record electrical activity of the heart during electric stimuli has hampered attempts to unravel these phenomena. A major breakthrough in the field occurred recently after the introduction of potentiometric optical probes. Using such probes, Dillon demonstrated the occurrence recently after the introduction of potentiometric optical probes. Using such probes, Dillon demonstrated the occurrence of positive and negative polarizations arranged in a peculiar pattern named virtual electrode polarization (VEP). Optical mapping studies have convincingly confirmed these theoretical predictions.

A few years later, large-scale VEP effects were observed during ICDs and external shocks in intact rabbit hearts in vitro and were generalized theoretically. A recently formulated virtual electrode theory presented a first draft of our understanding of the mechanisms of defibrillation. A concept of a generalized activating function elegantly unified various virtual sources of transmembrane polarization. Spatial asymmetries or nonuniformities of externally applied fields and of the myocardial structure generate depolarizing and hyperpolarizing sources distributed throughout the myocardium. Each such source has a different scale in the spatial, temporal, and transmembrane voltage domains. The spatial scale of VEP ranges from microscopic to macroscopic because of the various scales of nonuniformities of the myocardium, including cell-to-cell junctions, fibrosis, distinct cellular clusters, curvature of myocardial fibers, and tissue-bath interface. It is commonly accepted that all these nonuniformities provide the substrate for VEP in corresponding spatial scales. Uncertainty remains regarding their temporal and voltage scales and, therefore, their significance in defibrillation. One school of thought suggests that microscopic nonuniformities are the major source of the polarizing effects of shocks, whereas the opposite theory favors macroscopic-scale heterogeneities as the source of significantly stronger transmembrane polarization. Imaging of defibrillation in intact hearts supports the macroscopic VEP theory. Yet limitations of experimental methodology in the temporal and spatial domains do not enable rigorous exclusion of the microscopic theory. For example, pathological gap junction remodeling and fibrosis might provide the substrate for clinically relevant microscopic-scale VEP.

Regardless of the exact polarization pattern, VEP has been shown to result in several important effects that may determine the outcome of a defibrillation shock. Positive polarization extends the action potential duration and refractory period, whereas negative polarization shortens it, deexciting the myocardium and creating excitatory gaps. Induction of strong transmembrane polarization gradients present in VEP leads to break excitation and phase singularities, which may underlie defibrillation failure. It has been long known that deexcitation is a phase-dependent phenomenon. Involvement of different ionic channels at different phases of the action potential makes deexcitation an all-or-none phenomenon during the absolute refractory period and a gradual
phenomenon during the relative refractory period.\(^2\) Negative polarization during diastole could trigger entirely different ionic mechanisms, such as cellular break excitation.\(^2\) This difference might explain the vulnerable window phenomenon observed during shock-induced arrhythmia induction,\(^2\) underlining the importance of understanding the participation of ionic current in modulation of both the virtual electrode polarization and the postshock response.

Linear passive bidomain theory has been supported by numerous mapping studies. Yet this theory is incapable of predicting the effect of the VEP on postshock electrical activity without knowledge of the ionic components of stimulus-induced polarization. Such an ionic component of VEP has been evident from the first observations. Both isolated cardiac myocytes\(^2\) and HeLa cells\(^3\) are polarized by an externally applied field. Yet HeLa cells undergo equal positive and negative polarizations at opposite ends, whereas cardiac myocytes show clear asymmetry, with negative polarization being significantly stronger than the positive polarization. In addition to this asymmetry, stimulus-induced polarizations exhibit nonlinearities as functions of time and shock strength. Mechanisms of these nonlinearities have not been fully investigated.

Cheek et al\(^6\) provide the first mechanistic insight into the nature of these asymmetries, demonstrating that both the calcium current and myocardial structure modulate an asymmetric response during the defibrillation shock. This study opens a new chapter in defibrillation research. Improving the spatial and temporal resolution of optical imaging will soon allow more detailed investigation of the ionic mechanisms of defibrillation. Better spatiotemporal resolution is required to address the role of microscopic nonuniformities and electro-poration. Additional studies of the phase dependence of shock-induced polarization might provide new insights into possible pharmacological strategies for reducing defibrillation threshold by selective cancellation of adverse effects of deexcitation related to formation of phase singularities and reducing the risk of degeneration of phase singularities into sustained fibrillation. The study by Cheek et al\(^6\) opens a new frontier of basic research, bridging the rapidly evolving pharmacological and nonpharmacological therapies to control arrhythmia. State-of-the-art experimental and theoretical methodologies, based on fluorescent imaging and on realistic bidomain models of the heart, provide the tools for fulfilling such expectations.

References


Key Words: defibrillation ionic channels optical mapping
A Shocking Experience: Ionic Modulation of Virtual Electrodes in Defibrillation

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Circ Res. 2000;87:429-430
doi: 10.1161/01.RES.87.6.429

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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