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Upper Limit of Vulnerability and Heterogeneity

Peng-Sheng Chen, MD, FHRS and Shien-Fong Lin, PhD

From the Krannert Institute of Cardiology and the Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Fabiato et al¹ discovered the existence of a shock strength above which a defibrillation shock given during the vulnerable period of the cardiac cycle cannot induce ventricular fibrillation (VF), and that this upper limit of vulnerability (ULV) corresponds to the defibrillation threshold. Subsequent studies confirmed this observation both in animal models and in humans.^{2–5} However, the mechanism of ULV remains unclear. In this issue of the *journal*, Mazeh and Roth⁶ studied the importance of myocardial fiber orientation on the mechanisms of ULV. Using computer simulation in an artificially architected fiber orientation, the authors found that a ULV is present if local heterogeneities are created by a randomly placed fiber angles. If smooth fiber geometry is used in the computer model, the wavefronts induced by break excitation can always propagate and induce reentry regardless of the shock strength. The presence of heterogeneity of fiber angles, therefore, plays an important role in mechanisms underlying ULV and the mechanisms of defibrillation.

Virtual Electrodes and Defibrillation

The discovery and characterization of virtual electrode polarizations (VEPs)^{7,8} significantly advanced the understanding of physiological and pathophysiological effects of electrical stimulation on cardiac tissues. The injection of current into an anisotropic tissue induces a transmembrane potential that has a complicated spatial dependence that includes adjacent regions of depolarized and hyperpolarized tissue. The depolarized tissues (virtual cathode) can lead to “make” excitation by directly depolarizing the cell at that site. The hyperpolarized tissue (virtual anode) can lead to “break” excitation due to the current flow from the adjacent virtual cathode into the site with hyperpolarization, resulting in activation at the break of the stimulus pulse. The differential effects of virtual anode and virtual cathode create significant local heterogeneity at the site of a point-stimulus.⁹ Efimov’s laboratory¹⁰ then applied this virtual electrode concept to the defibrillation type of field stimulation. They found that shocks on T waves produce strong VEPs that result in postshock reentrant arrhythmias via a mechanism of phase singularity.

The Importance of Heterogeneity

Because anisotropy is important in the generation of VEPs, it follows that removing anisotropy should result in significant altered electrophysiological responses to electrical stimulation. In addition, Mazeh and Roth⁶ also removed temporal heterogeneity by raising the membrane potential from –85 mV to 0 mV at time zero as the S₁ stimulus. These conditions allow the S₂ to be applied to a 2 dimensional tissue with minimum temporal and spatial heterogeneity.

For Correspondence: Peng-Sheng Chen, MD, 1801 N. Capitol Ave, E475, Indianapolis, IN 46202. Phone: 317-962-0145, Email: E-mail: chenpp@iupui.edu.

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In this condition, ULV is eliminated. Adding only heterogeneity of fiber angles restored the ULV. While the authors did not perform simulation studies on the effects of temporal heterogeneity, there are reasons to believe that heterogeneity in ventricular repolarization is also important in the mechanisms of defibrillation and vulnerability. A major reason is that the intracellular calcium (Ca_i) dynamics are significantly influenced by the shock timing, and that the shock-induced changes of Ca_i does not always follow the same pattern as shock-induced changes of membrane potential,¹¹ creating additional heterogeneity after shock. Therefore, the temporal heterogeneity of repolarization at the time of shock and the differential responses of Ca_i to the shock could also contribute to the ventricular vulnerability and defibrillation.

VEP and Ca_i Dynamics

VEP created by shocks on T waves can result in immediate postshock phase singularities and VF.¹² In near-threshold failed defibrillation, however, a shock is followed by a quiescent period of 64 ± 22 ms during which no propagated activations are observed.¹³ Because the effects of VEPs should have long dissipated at the end of that isoelectric window, the relationship between VEPs and the first postshock activation remains unclear. One possible explanation is that VEP induced an activation that propagated through a transmural tunnel to reach the rest of the myocardium. When the activation emerged onto the epicardium, it becomes the earliest-propagated postshock activation.¹⁴ An alternative explanation is that the contribution of VEP to postshock activation is through its differential effects on the Ca_i transient.^{15,16} By hyperpolarizing the membrane potential on phase 3 of the action potential, virtual anode increases the driving force of extracellular Ca entry via the already opened L-type Ca channel, causing greater Ca induced Ca release from the sarcoplasmic reticulum (SR). In contrast, the virtual cathode results in the opposite effects on Ca transient. Indeed, differential Ca transient at virtual anode and virtual cathode sites have been demonstrated in both cultured cells and in whole heart.^{15,17} Biphasic wave shocks removes the virtual electrode effects half way through the shock, and hence can reduce Ca_i transients heterogeneity and improve the efficacy of defibrillation.¹⁸

Summary

In summary, the work by Mazeh and Roth⁶ and by other authors indicate that shock induced VEP is a major source of postshock heterogeneity. The heterogeneous responses could lead to the immediate generation of phase singularities and reentry, but can also lead to significant heterogeneities of Ca_i transients that contribute to the triggered activity at the end of the isoelectric window. These new mechanistic insights provide hope for further improvement of the efficacy of ventricular defibrillation.

Reference List

1. Fabiato PA, Coumel P, Gourgon R, et al. Le seuil de réponse synchrone des fibres myocardiques. Application à la comparaison expérimentale de l'efficacité des différentes formes de chocs électriques de défibrillation. *Arch Mal Coeur Vaiss* 1967;60:527–544. [PubMed: 4964651]
2. Lesigne C, Levy B, Saumont R, et al. An energy-time analysis of ventricular fibrillation and defibrillation thresholds with internal electrodes. *Med Biol Eng* 1976;14:617–622. [PubMed: 994572]
3. Chen P-S, Shibata N, Dixon EG, et al. Comparison of the defibrillation threshold and the upper limit of ventricular vulnerability. *Circulation* 1986;73:1022–1028. [PubMed: 3698224]
4. Chen P-S, Feld GK, Kriett JM, et al. Relation between upper limit of vulnerability and defibrillation threshold in humans. *Circulation* 1993;88:186–192. [PubMed: 8319332]
5. Day JD, Doshi RN, Belott P, et al. Inductionless or limited shock testing is possible in most patients with implantable cardioverter- defibrillators/cardiac resynchronization therapy defibrillators: results of the multicenter ASSURE Study (Arrhythmia Single Shock Defibrillation Threshold Testing Versus

- Upper Limit of Vulnerability: Risk Reduction Evaluation With Implantable Cardioverter-Defibrillator Implantations). *Circulation* 2007;115:2382–2389. [PubMed: 17470697]
6. Mazeh N, Roth BJ. A mechanism of the upper limit of vulnerability. *Heart Rhythm*. 2008Ref Type: In Press
 7. Sepulveda NG, Roth BJ, Wikswo JPI. Current injection into a two-dimensional anisotropic bidomain. *Biophys J* 1989;55:987–999. [PubMed: 2720084]
 8. Wikswo JP Jr, Wisialowski TA, Altemeier WA, et al. Virtual cathode effects during stimulation of cardiac muscle. Two-dimensional in vivo experiments. *Circ Res* 1991;68:513–530. [PubMed: 1991354]
 9. Lin S-F, Roth BJ, Wikswo JP Jr. Quatrefoil reentry in myocardium: an optical imaging study of the induction mechanism. *J Cardiovasc Electrophysiol* 1999;10:574–586. [PubMed: 10355700]
 10. Efimov IR, Cheng Y, Van Wagoner DR, et al. Virtual electrode-induced phase singularity: a basic mechanism of defibrillation failure. *Circ Res* 1998;82:918–925. [PubMed: 9576111]
 11. Hwang G-S, Hayashi H, Tang L, et al. Intracellular calcium and vulnerability to fibrillation and defibrillation in Langendorff-perfused rabbit ventricles. *Circulation* 2006;114:2595–2603. [PubMed: 17116770]
 12. Efimov IR, Cheng Y, Yamanouchi Y, et al. Direct evidence of the role of virtual electrode-induced phase singularity in success and failure of defibrillation. *J Cardiovasc Electrophysiol* 2000;11:861–868. [PubMed: 10969748]
 13. Chen P-S, Shibata N, Dixon EG, et al. Activation during ventricular defibrillation in open-chest dogs. Evidence of complete cessation and regeneration of ventricular fibrillation after unsuccessful shocks. *J Clin Invest* 1986;77:810–823. [PubMed: 3949979]
 14. Ashihara T, Constantino J, Trayanova NA. Tunnel propagation of postshock activations as a hypothesis for fibrillation induction and isoelectric window. *Circ Res* 2008;102:737–745. [PubMed: 18218982]
 15. Raman V, Pollard AE, Fast VG. Shock-induced changes of Ca^{2+} and V_m in myocyte cultures and computer model: Dependence on the timing of shock application. *Cardiovasc Res* 2007;73:101–110. [PubMed: 17134687]
 16. Hayashi H, Lin S-F, Joung B, et al. Virtual electrodes and the induction of fibrillation in Langendorff-perfused rabbit ventricles: the role of intracellular calcium. *Am J Physiol*. 2008Ref Type: In Press
 17. Hayashi H, Lin SF, Joung B, et al. Virtual Electrodes and the Induction of Fibrillation in Langendorff-Perfused Rabbit Ventricles: The Role of Intracellular Calcium. *Am J Physiol Heart Circ Physiol*. 2008
 18. Hwang GS, Tang L, Joung B, et al. Superiority of biphasic over monophasic defibrillation shocks is attributable to less intracellular calcium transient heterogeneity in Langendorff-perfused rabbit ventricles. *J Am Coll Cardiol* 2008;52:828–835. [PubMed: 18755345]