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Drawing the curtain on the isoelectric window?

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While cardiac vulnerability to electric shocks and failure of defibrillation has been attributed to the formation of new reentries via critical points1 or virtual electrode-induced phase singularities,[2] an exhaustive study of all mechanisms responsible for shock failure is far from complete, impeding progress in the quest to significantly lower the defibrillation threshold (DFT) and to ultimately achieve low-voltage defibrillation. One of the most sought-after insights is the mechanism by which the first postshock activation originates in failed defibrillation episodes.

Numerous mapping studies, mostly electrical,[3–7] but also some optical,[8,9] predominantly of large hearts (dog and pig), have demonstrated that after failed defibrillation shocks or shocks applied during the vulnerable period, reentrant patterns are not always immediately observed. Although local activations were detected after strong shocks, these activations did not become global and quickly died[10,11]; the activations were followed by an electrically quiescent period termed the "isoelectric window." The duration of the isoelectric window was found to be short for weak shocks but increased with the increase in shock strength, extending for well over 50 ms.[3–8] Timing of shock delivery also influenced isoelectric window duration10: it was found to be near zero at late coupling intervals, that is, near diastole, and to increase linearly as coupling interval decreased. After the isolectric window pause, activation appeared on the epicardium; in most cases, this activation propagated globally in all directions as a focal pattern, often repeated for several cycles before degenerating into ventricular fibrillation.[6–8] An optical mapping study by Chattipakorn et al11 further elucidated the nature of the first postshock activations and concluded that reentry was responsible for the failure of shocks below the DFT, while a focal source, determined to be located in the subepicardial left ventricle (LV) layers of the pig heart,[7] was behind the failure of near-DFT shocks. The findings of isoelectric windows in large hearts are, however, in contrast with the results of optical mapping studies in small hearts (rabbits and guinea pigs), where no isoelectric window was documented on the epicardium for shocks delivered in the vulnerable period[2,12,13] or after defibrillation/cardioversion shocks.[14–16] These studies observed the continuous presence of activation wave fronts on the epicardial surface, and the activity was typically reentrant.

The mechanisms underlying the origin of the first global postshock activations after the isoelectric window have also been the topic of much discussion and debate. Research has suggested that, for strong shocks, the focal pattern after the isoelectric window is a manifestation of transmural reentry; however, endocardial and transmural mapping studies do not support this conjecture.[3,17] Microreentry has also been considered,[18] but it is difficult to establish without closely spaced transmural recordings. Yet another hypothesis claims that slow propagation of depolarizing cellular graded responses preceding the initiation of a regenerative activation underlies the existence of the isoelectric window.[19,20] However, such

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a mechanism appears to pertain to activity in the vicinity of localized bipolar stimuli only[20, 21] rather than to defibrillation shocks where anode and cathode are widely spaced. Simulations of defibrillation[22] have suggested that a transmural breakthrough could underlie the isoelectric window and the focal appearance of the first global postshock activation; this is supported by observations in the isolated pig right ventricle (RV).[23] Triggered activity from delayed afterdepolarizations has also been implicated in the origin of the first global postshock beat, 8 with postshock oscillations in transmembrane potential believed to arise from Ca^{2+} overload, [24] but this theory was shortly thereafter dismissed.[25] Early afterdepolarizations resulting from Na current reactivation have also been considered[26] as well as ionic fluxes through electroporated cell membranes.[27] Furthermore, recent studies in isolated sheep RV preparations[28,29] have proposed a new mechanism termed “negative virtual electrode polarization-induced graded responses” that could also be responsible for initial slow decremental propagation after the shock end and thus for the existence of the isoelectric window. Finally, Hwang et al[30] demonstrated recently that the hetrogenous distribution of intracellular calcium concentration during the isoelectric window could play a key role in the defibrillation outcome for near-DFT shocks.

The article by Dosdall et al[31] in this issue of the journal throws another ingredient into the stew: it proves that the Purkinje system in the heart could be another candidate for the source of the first postshock activations. This is the first direct recording of Purkinje activations in the intact heart after the delivery of a defibrillation shock. The authors recorded postshock activity in the pig using plunge needle electrodes in both ventricles and a basket catheter in the LV to ascertain that the Purkinje system is active during the early postshock activation cycles after shocks of near-DFT strength. According to the article, Purkinje activations were recorded *prior* to local postshock myocardial activation in 9% of the plunge and in 15% of the basket electrograms during the first postshock activation cycle. Purkinje fibers have been previously shown to exhibit increased automaticity after strong shocks[32]; these electrograms could possibly reflect such rapid firing. In the pig, the Purkinje fibers penetrate the ventricular wall and nearly reach the epicardial surface. The possibility that the earliest postshock activation arises in the fibers of the conduction system is thus consistent with the subepicardial location of the first postshock activation in the pig, as determined by previous studies.[7]

Do these findings mean we now understand the mechanisms behind the origin of the first postshock activation, so we can draw the curtain on the isoelectric window and consider the debate closed? Not really. As Dosdall et al conclude, “Whether activation initiates in subepicardial cardiomyocytes, transitional cells, or the Purkinje system, and then spreads to surrounding tissue has yet to be determined.” Furthermore, the stew of mechanisms could have different ingredients for different species. So stay tuned—more to come.

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