The Role of Intrinsic and Induced Vulnerability in Electrically Induced Cardiac Arrhythmias

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Editorial Comment

Although reentrant arrhythmias have been recognized for almost 100 years, the mechanism of initiation is still only partially understood. Such arrhythmias involve a sequence of events including successful impulse formation, an excited region exceeding the liminal region, excitation within a vulnerable region of cardiac tissue, and myocardial mass adequate to support reentry. Historically, reentrant arrhythmias and ventricular fibrillation (VF) were investigated using single electrical pulses applied to the heart during a period of intrinsic vulnerability coinciding with the inscription of the T wave.[1,2] In this issue, Janks and Roth[3] describe numerical studies of pulse train initiation of reentrant arrhythmias. Using a bidomain model of cardiac tissue, they found an 8-fold reduction in the magnitude of current required to initiate reentry as the train of stimulus pulses was extended from 1 to 7. Moreover, varying the interpulse interval, they observed that reentry occurred at the boundaries between different ratios of phase-locking. Their results highlight the proarrhythmic roles of intrinsic vulnerability[4-6] and induced vulnerability caused by external excitation[7,8] and provide a mechanistic framework for understanding the dramatic differences in single pulse and 60-Hz VF thresholds.[9,10]

To provide a context for their studies, let me first review the requirements for initiating a propagating wave: cellular excitation and liminal region of excitation. At the cellular level, the excitation requires that the transmembrane potential be depolarized to a potential more positive than the threshold potential. Exciting a single cell, though, is insufficient to initiate a propagating wave. Instead, a minimal region of adjacent cells (liminal region) must also be excited to initiate propagation in a one-, two-, or three-dimensional medium. For cardiac cells, the cells within the liminal region provide the source of positive charges that flow via gap junction connections into adjacent cells. Propagation results when the availability and transport time of source charges matches or exceeds the sink charge requirements necessary to switch adjoining cells from their rest state to the excited state.

The liminal region requirement for initiating a propagating wave, identified in a uniform cable by Rushton[11] and later in Purkinje fibers by Fozzard and Schoenberg[12] depends on the state of adjacent cells to be excited. Tissue with low excitability requires a larger liminal region (source region) to sustain propagation than tissue with high excitability. To further complicate matters, the liminal region is sensitive to the gradient of Na channel availability.[13,14] For example, an excited region propagating into an area of decreasing excitability may decrementally propagate reflecting the mismatch between charge supplied by the source liminal region and the increased charge required to excite the less excitable adjacent regions.

Interestingly, the liminal requirement for wave propagation is not unique for cardiac cells but is a generic requirement for all excitable media. For example, a tree within a forest is excitable since it can be ignited and will burn. If a single tree is ignited, then unless the temperature of adjacent trees exceeds their ignition threshold, the fire will self extinguish (a collapsing wave). On the other hand, if a small group of trees is ignited thereby raising the temperature of adjacent trees above their ignition threshold, the perimeter of the fire will propagate.

Reentry arises when a wavefront is broken or is incompletely formed subsequent to exciting a vulnerable region of tissue. King[1] recognized the importance of stimulus timing for initiating VF and observed that tissue was vulnerable during inscription of the T wave. Later, Wiener and Rosenblueth[4] used a simple model of a propagating action potential that linked vulnerability with the transition from refractory to excitable cells within the repolarization wave. They postulated that if the repolarization wave traveled with a velocity, v, then the period of vulnerability, VP = L/v where L is the length of the suprathreshold stimulus field. Because many use-dependent antiarrhythmic drugs as well as loss-of-function Na channel mutations slow conduction, they will prolong the VP and are therefore inherently proarrhythmic.[13-15]

Defibrillation failure is thought to be associated with either incomplete defibrillation or initiation of new reentrant waves. Recently, Efimov and colleagues[7] explored defibrillation failure within the context of another type of vulnerability that can be referred to as induced vulnerability. Defibrillation pulses create virtual-electrode polarizations (VEP), adjacent regions of hyperpolarized, and depolarized cells near the physical electrode. The defibrillation waveform and associated VEPs modulate cellular excitability and was observed to alter the likelihood of postdefibrillation arrhythmogenesis. These VEPs were first identified in numerical studies of bidomain models of cardiac tissue by Sepulveda et al.[16] and provide the basis for Janks and Roth's explorations of quatrefoil reentry.

Janks and Roth report here that quatrefoil reentry can be initiated by pulse trains and that the arrhythmogenic threshold associated with pulse train excitation is considerably less than that associated with a single pulse. Why is pulse train initiation of VF interesting? In the early 60s, Zoll[17] warned of the

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potential arrhythmogenic hazards of 60-Hz current applied directly to the heart. Burchell[18] followed the warning with a detailed editorial outlining the hidden hazards associated with cardiac pacing from power-line-operated pacemakers.

The editorials of Zoll and Burchell triggered our (Whalen, Starmer, and McIntosh) systematic investigation of the 60-Hz VF threshold in both dogs and man. Our early measurements indicated that currents as low as 120 microamps were sufficient to initiate ventricular fibrillation in man.[9] One of the puzzles associated with these studies, though, was that our 60-Hz VF thresholds were 10× to 30× less than VF thresholds measured with single DC pulses (2–10 msec duration).

Wallace and colleagues[10] designed several ingenious experiments to resolve the discrepancy. They compared the 60-Hz VF threshold with that associated with trains of one or more DC pulses. By varying the duration of 60-Hz current applied directly to the heart, they found an inverse relationship between VF threshold and duration of 60-Hz current up to 1-second duration (see their Figs. 1–3). While applying 60-Hz current, they observed sequential premature responses and reasoned that the reduction in VF threshold was related to the number of premature responses during the application of 60-Hz current. Because excitation was premature, propagation slowed as a result of incomplete recovery from cellular inactivation. Thus, the intrinsic vulnerable period increased with each subsequent pulse. To verify that the sequence of premature responses was critical, they used pulse trains designed to trigger one, two, or more premature responses. Following each train, they measured the single pulse threshold of VF and found that indeed, as with the application of 60-Hz current, the single pulse VF threshold decreased as the number of sequential premature responses increased (see their Fig. 5).

Can potentially arrhythmogenic pulse train excitation spontaneously arise? Recently Haissaguerre et al.[19] described induction of atrial fibrillation secondary to trains of ectopic beats originating in the pulmonary veins. Although no external stimulation was involved, it is likely that the underlying mechanism was linked to pulse-train-like excitation that fell within the intrinsic VP. Using radiofrequency ablation, the source of these in vivo pulse trains was interrupted thereby reducing the proarrhythmic potential.

In their current paper[3] Janks and Roth provide some new clues for addressing puzzles arising from 100 years of studying arrhythmogenic processes. With bidomain VEPs, they present a link between intrinsic and induced vulnerability. Their observation of arrhythmogenesis at the boundary of phase-locked excitation is consistent with the excitation of vulnerable tissue. They provide a basis for understanding the arrhythmogenic potential of pulse-train stimulation. Finally, their work adds a useful framework for improving arrhythmia management and the design of effective therapeutic strategies.

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