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Beyond the Implantable Cardioverter-Defibrillator: Are We Making Progress?

James N. Weiss, M.D.

UCLA Cardiovascular Research Laboratory, Department of Medicine (Cardiology), David Geffen School of Medicine at UCLA, Los Angeles, CA 90095

Abstract

Sudden cardiac death due to ventricular fibrillation occurs when a dynamic interaction between triggers and substrate leads to the development of reentry, initiation of ventricular tachycardia, and its degeneration to fibrillation. To move beyond the implantable cardioverter defibrillator as the only effective therapy for aborting sudden cardiac death, an improved understanding of the trigger-substrate interaction is essential. This brief review summarizes some of the recent progress in this direction.

Keywords

Ventricular tachycardia; ventricular fibrillation; sudden cardiac death; arrhythmias; alternans

The fortunate aspect in the current state-of-the-art treatment of life-threatening ventricular arrhythmias is that we have an effective therapy for patients at high risk of sudden cardiac death, namely the implantable cardioverter-defibrillator (ICD). The unfortunate aspect is that we only have a crude mechanistic understanding of the how these arrhythmias develop in the clinical setting. As a result, only 20% of the ~300,000 patients dying suddenly each year meet the clinical criteria for implanting an ICD ¹. Among these patients, only 20% will receive a life-saving shock from the ICD ², and overall, approximately 20 ICDs need to be implanted for each life saved ³. The disappointing aspect is that whereas the first beat of ventricular tachycardia (VT) is always a ventricular extrasystole, suppression of ventricular extrasystoles with antiarrhythmic drugs has paradoxically translated into increased, rather than decreased mortality in patients with diseased hearts ^{4, 5}. Ventricular extrasystoles are common even in normal hearts, and in diseased hearts become more frequent. Two ventricular extrasystoles per minute equates to 1 million per year. Yet episodes of sudden cardiac death due to VT and ventricular fibrillation (VF) occur over a time scale measured in months or years. Why is it that only one in a million ventricular extrasystoles is lethal? It cannot be explained by the coupling interval of extrasystoles, since during clinical electrophysiology studies, induction of VT/VF by up to three successive ventricular extrasystoles scanning the full diastolic range has a low yield, especially in patients with nonischemic cardiomyopathy ⁶. The inescapable conclusion is that there is more to it than just a well-timed series of ventricular extrasystoles

Address for correspondence: James N. Weiss, M.D., Division of Cardiology, Rm 3645 MRL Building, UCLA School of Medicine, Los Angeles, CA 90095, *Tel:* 310-825-9029, *Fax:* 310-206-5777, *E-mail:* jweiss@mednet.ucla.edu.

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– the risk of initiating VT/VF also depends on the dynamic state of the tissue substrate that the ventricular extrasystole encounters.

Autonomic tone is the most recognized factor that dynamically alters both triggers and the tissue substrate from one moment to the next, and there is a wealth of information relating arrhythmia risk to autonomic function. Electrolyte fluctuations and drug therapy are also important factors. How these factors convert normal cardiac tissue into a substrate ripe for reentry is not fully understood, but involves modulating the trigger-substrate interaction by both increasing the number of triggers and amplifying electrophysiological dispersion in the tissue.

Triggers can arise from abnormal automaticity or triggered activity due to early (EAD) and delayed afterdepolarizations (DAD). Catecholamines potentiate automaticity, EADs and DADs, as do many common drugs such as digoxin and Type I and III antiarrhythmic drugs. Genetic defects in K, Na, and Ca channels, ryanodine receptors and their various associated proteins also induce afterdepolarizations, and confer a high risk of ventricular arrhythmias in these patients. Although the association between afterdepolarizations and arrhythmias is indisputable, the mechanism by which cellular afterdepolarizations causes extrasystoles at the tissue level is still a major unsolved problem. A myocyte may have all the conditions in place to develop an afterdepolarization. However, if the surrounding myocytes in well-coupled tissue are not similarly inclined, the source sink mismatch will prevent the afterdepolarization from displacing the membrane voltage to a significant extent, as required to induce an extrasystole. For an afterdepolarization to cause a triggered response requires that a critical mass of myocytes all develop an afterdepolarization simultaneously in order to overcome this source-sink mismatch. The mechanism by which this synchronization is achieved is still a mystery. At the next stage, why some of these cellular defects manifest as polymorphic VT, torsades des pointes, or bidirectional VT also remains mysterious.

There has been progress in understanding how dynamic modulation of the substrate increases arrhythmia risk. More than a century ago, the association between electrocardiographic T wave alternans and arrhythmia risk was noted, presaging the development of microvolt T wave alternans in the 1990s as a clinical tool for assessing risk of sudden cardiac death⁷. Subsequently, a seminal study by Pastore et al⁸ showed that T wave (repolarization) alternans, when accompanied by QRS alternans, could create spatial repolarization gradients sufficient to induce unidirectional conduction block and reentry, even in the absence of an extrasystole (Fig. 1). QRS alternans in this highly arrhythmogenic form of spatially discordant repolarization alternans is caused by regional variations in conduction velocity (CV). Subsequent theoretical studies^{9, 10} showed that steep action potential duration (APD) restitution coupled with CV restitution are sufficient to explain the emergence of arrhythmogenic spatially discordant repolarization alternans, providing a mechanistic basis for initiation of VT/VF by rapid pacing, with or without ventricular extrasystoles. In addition, single ventricular extrasystoles can induce transient spatially discordant alternans by a similar mechanism¹⁰, increasing the probability that a second extrasystole will initiate reentry.

APD alternans can also be caused by intracellular Ca transient alternans, due to the effects of the Ca transient on ionic currents regulating APD (primarily, the L-type Ca current and the Na-Ca exchange current)¹¹. Current evidence indicates that this Ca cycling instability is the initial factor driving repolarization alternans as heart rate increases^{12, 13 14}, although the interaction with APD restitution is also influential¹⁵. Furthermore, electrical and excitation-contraction coupling remodeling in heart failure exacerbate Ca transient alternans by suppressing Ca cycling by the sarcoplasmic reticulum (SR)¹⁶. If abnormal SR Ca cycling dynamic is the predominant factor driving the onset of APD alternans in human heart failure, this may explain why the correlation with APD restitution slope is weak in this setting¹⁴.

Complex patterns of cellular and subcellular Ca transient alternans can develop as a result of the bidirectional coupling between APD and Ca transient amplitude^{15, 17}.

In summary, despite the considerable progress made in understanding the molecular basis of cardiac arrhythmias, we still lack the ability to predict why one, among millions, of ventricular extrasystoles initiates VT/VF. It seems likely that the dynamic modulation of the tissue substrate, through development of spatially discordant alternans and other factors, plays as important a role as the triggers (ventricular extrasystoles). Since SR Ca_i cycling abnormalities during heart failure have key influences on both factors, strategies to reverse these deleterious remodeling effects may have therapeutic promise. Until this can be accomplished through advances in pharmacologic, gene and/or cell therapies, however, we are fortunate to have the ICD to protect the highest risk patients. The other 80% at lower risk, however, will just have to wait.

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Abbreviations

APD, action potential duration; CV, conduction velocity; DAD, delayed afterdepolarization; EAD, early afterdepolarization; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, Ventricular tachycardia.

Figure 1. Spatially discordant APD alternans and initiation of reentry by a premature extrasystole
 During spatially discordant alternans, APD alternates out-of-phase at the base (red: long-short at site *a*) relative to the apex (blue: short-long at site *b*), separated by a nodal line with no alternans (white). A premature extrasystole (asterisk) occurring in the region of short APD blocks (black line) as it propagates across the nodal line (region of no alternans) into the region with long APD. Meanwhile, the extrasystole successfully propagates laterally, waiting for the long APD region to repolarize, and then reenters the blocked region to initiate figure-eight reentry. Reproduced from Weiss et al¹⁴ with permission.