Ventricular Fibrillation
How Do We Stop the Waves From Breaking?

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Abstract—Combined experimental and theoretical developments have demonstrated that in addition to preexisting electrophysiological heterogeneities, cardiac electrical restitution properties contribute to breakup of reentrant wavefronts during cardiac fibrillation. Developing therapies that favorably alter electrical restitution properties have promise as a new paradigm for preventing fibrillation. (Circ Res. 2000;87:1103-1107.)

Key Words: fibrillation ▪ electrical restitution ▪ cardiac action potential ▪ antiarrhythmic drugs ▪ arrhythmias

Ventricular fibrillation (VF) remains the most common cause of sudden death. We briefly review the recent synergism between simulation and experiment, providing new insights into its pathogenesis. For more extensive treatment, see the excellent review by Jalife.1

Figure 1A illustrates an ECG of a person suddenly developing VF, typifying the clinical observation that VF is almost always preceded by ventricular tachycardia (VT), lasting from a few to many beats.2 In his seminal 1930 high-speed cinematographic study of electrically induced canine VF, Carl Wiggers3 divided VF into 4 stages, the first of which (the tachysystolic phase) is rapid VT, shown in later studies4,5 to correspond to figure-eight reentry. The progression from sinus rhythm to VF can be logically considered in 3 stages: initiation of VT, degeneration of VT to VF, and maintenance of VF.

Cardiac Excitation as a Wave
What is responsible for the sequence in Figure 1A? Cardiac excitation can be viewed as an electrical wave, with a wavefront corresponding to the action potential upstroke (phase 0) and a waveback corresponding to rapid repolarization (phase 3). The wavelength is the distance between the wavefront and waveback and is equivalent to the product of action potential duration (APD) and conduction velocity (CV) (Figure 1B). The 3 stages of VF all depend on electrical waves in the ventricle breaking up.

In sinus rhythm, cardiac waves emerge focally and spread throughout the ventricle. If the wave breaks at one point, the 2 broken ends become the tips of potential reentrant (spiral or scroll) waves. If successful at propagating, the tips circulate around either a functional core or an anatomic obstacle to create monomorphic VT, polymorphic VT, or, in hearts from small mammals, even VF.6 If additional wavebreaks develop, multiple reentrant waves are created, and VT degenerates to the classic VF of large mammal hearts characterized by multiple wavelets (Figure 2D). The message is that if we understand how to prevent wavebreak, we may have the key to curing VF.

Wavebreak leading to spiral wave reentry and other complex pattern formation is a generic property of excitable media (also called reaction-diffusion or activator-inhibitor systems), of which cardiac tissue is a classic example. Other examples include chemical reactions in the Belousov-Zhabotinski category,7 growth patterns of the slime mold Dictyostelium,8 and Ca2+-induced Ca2+ release in oocytes9 and cardiac myocytes.10 That spiral wave reentry might be relevant to cardiac arrhythmias was first suggested by Kinsky11 and later by Winfree.12 In the 1970s, Allessie et al13–15 provided key experimental documentation by showing that cardiac reentry could occur in the absence of an anatomical obstacle, a phenomenon they termed functional or leading circle reentry. However, the connection between functional reentry and spiral wave reentry was not made explicit until 1992, when Davidenko et al16 published their seminal study documenting spiral wave reentry in ventricle and subsequently proposed this as a mechanism of VF.6

Wavebreak and Preexisting Tissue Heterogeneity
The first quantitative theory of fibrillation, the multiple wavelet hypothesis, predated the recognition that spiral waves might be relevant to cardiac arrhythmias. Moe et al16a used a minimal 2-dimensional cardiac tissue model composed of automata with resting, excited, and refractory states, ie, the bare essentials of a cardiac cell. They discovered that by introducing sufficient electrophysiological heterogeneity into the tissue by randomly assigning different refractory periods to different cells, cardiac waves spontaneously broke up into
patterns of random reentry. This process was self-sustaining, provided the tissue was large enough. Direct experimental evidence for the multiple wavelet hypothesis was subsequently provided by Allessie et al. who mapped the surface of the fibrillating atrium with multielectrode plaques and observed the predicted multiple wavelets meandering in complex random-appearing patterns. Similar findings were subsequently reported in ventricle.

In the multiple wavelet hypothesis, wavebreak depends on preexisting electrophysiological heterogeneity, particularly dispersion of refractoriness. For a wave to break, its wavelength must become zero at a discrete point somewhere along the wave. This can happen if the wave encounters a local heterogeneity (refractoriness) that creates block (wavelength=zero) locally, while propagating (ie, nonzero wavelength) elsewhere. In Moe’s simple model, this was achieved by randomly introducing local differences in refractory period (dispersion of refractoriness) to cells throughout the tissue. Subsequently, a large body of experimental work confirmed the importance of preexisting heterogeneity to both atrial and ventricular fibrillation. The clinical observation that diseased hearts fibrillate more easily than normal hearts has been largely attributed to their increased susceptibility to wavebreak because of increased anatomical and electrophysiological heterogeneity from the disease process.

**Wavebreak Attributable to Dynamic Instability**

However, cardiac modeling studies have shown that preexisting heterogeneity is not the only cause of wavebreak. Dynamically induced heterogeneity is another mechanism that requires no preexisting heterogeneity of any kind, just an intervention (eg, very rapid pacing or a large premature stimulus) to create the first wavebreak. After that, wavebreak proceeds spontaneously on its own to create VF. This type of wavebreak is determined primarily by the electrical restitution properties, ie, the dependence of APD and CV on the preceding diastolic interval (DI), defined as the interval between repolarization and the next action potential (Figure 2A through 2C). Intuitively, this makes sense: because wavelength is defined as the product of APD and CV, then either APD or CV must become zero for wavelength to be zero. Because APD and CV are controlled dynamically by DI (ie, restitution), APD and CV restitution are therefore key determinants of wavebreak.

The steepness of APD restitution is a critical parameter for spiral wave stability. When the slope of the APD restitution curve exceeds one, a small change in DI gets magnified into a larger change in APD, which translates into a larger change in wavelength. This creates yet a larger change in DI for the next wave, and so forth. The positive feedback causes small wavelength oscillations to grow progressively until the DI becomes too short for the wave to propagate, resulting in wavebreak (Figure 3B). The analogy is to an amplifier with gain >1. In contrast, an APD restitution slope <1 acts like an attenuator, allowing perturbations in the wave to heal rather than expand (Figure 3A). The role of steep APD restitution in causing APD alternation during pacing and unstable reentry around anatomic obstacles was appreciated from the 1960s.
and long APD, illustrated in Figures 3A and 3B. Electrocardiographically, this is manifested as T wave (repolarization) alternans, a clinically established harbinger of ventricular arrhythmia vulnerability.24 CV restitution plays an equally important role, especially in facilitating initiation of VT/VF. With no CV restitution present (Figures 3A and 3B), each wave by definition propagates at identical velocity. Therefore, once a wavefront emerges, its DI with respect to the wave ahead is set and cannot change over time. Even though different waves have different wavelengths, the APD and wavelength of a given wave will remain fixed as it propagates. When APD restitution slope is >1, wavelengths of successive waves typically alternate between long and short, which is called discordant alternans.

For the case in which CV varies with DI because of CV restitution, a sufficiently short DI causes the wavefront to slow (Figure 3C). As it slows, its distance from the wave ahead increases, resulting in a longer DI. As its DI increases, APD also lengthens, thereby changing the wavelength of the wave. (Whether the wavelength prolongs or shortens depends on the relative degree of APD change versus CV slowing.) Meanwhile, the wave’s changing wavelength also affects the DI of the wave behind it, so that the next wave’s wavelength will also oscillate, and so forth for each successive wave, like a car braking and accelerating on the freeway in response to cars ahead. The important consequence is that the wavelength of the same wave changes while propagating through the tissue, becoming short in some areas and long in others. This discordant alternans markedly enhances dispersion of refractoriness, arising purely from the dynamics of electrical restitution. For the planar waves illustrated in Figure 3, spatial APD dispersion can occur only along the horizontal axis. However, if preexisting heterogeneities are present, asymmetries will develop along the vertical axis as well. The resulting spatial variation in wavelength along the wave amplifies both source-sink mismatches and head-to-tail interactions with adjacent waves to cause localized wavebreak and reentry.25

Although other mechanisms may also be involved, simulations of concordant and discordant APD alternans25 on the basis of electrical restitution properties show close agreement with experimental data,26,27 including reproducing electrocardiographic T and QRS alternans and enhanced arrhythmia susceptibility. The message is that electrical alternans reflects the underlying dynamic instability of cardiac tissue, measuring the likelihood that rapid pacing or extrasystoles will induce wavebreak leading to initiation of VT with subsequent degeneration to VF.

Interactions Between Preexisting Heterogeneity and Dynamic Instability

Simulation and experiment support the existence of 2 main mechanisms of wavebreak: preexisting heterogeneity and dynamic instability. The real heart contains both features, but their relative importance to fibrillation is debated at present. One possibility is that dynamic instability plays only an ancillary role during fibrillation and that most wavebreaks observed during fibrillation are epiphenomena related to fibrillatory conduction block. That is, a wavefront arising

Figure 3. Electrical restitution and wavelength oscillations in 2-dimensional tissue paced at a fixed cycle length (diamonds). A, With APD restitution slope (APDR) <1 and no CV restitution (CVR), APD and wavelength remain constant for each wave (1 through 7) once the DI is set. Concordant APD/wavelength alternans progressively attenuates with APDR <1. B, If APDR >1, however, APD/wavelength alternation can progressively amplify until the DI is too short for the next wave (6) to propagate. (In this example, the whole planar wave would fail, whereas a break in symmetry is required for localized conduction failure to initiate reentry.) C, Effect of adding CVR, showing snapshots of 2 waves (1 and 2) at 3 successive time points. Between t=1 and t=2, the short DI facing wave 2 caused it to slow, increasing its DI and prolonging its APD/wavelength. Between t=2 and t=3, wave 1 approached the preceding wave (0, not shown), shortening its DI and APD/wavelength. This increased the DI of wave 2 additionally, causing additional APD/wavelength prolongation as well. Variation of APD/wavelength of the same wave as it propagates because of CVR is discordant alternans.

However, it was not until 1993 that Karma21 showed that the same mechanism could produce wavebreak in spiral wave reentry. In 2-dimensional and 3-dimensional tissue simulations, dynamic instability arising from steep APD restitution causes spiral waves (VT) to break up into a VF-like state, even in completely homogeneous isotropic tissue (Figure 2D). Furthermore, by reducing APD restitution steepness, spiral or scroll wave breakup can be prevented and spiral and scroll wave behavior can be progressively stabilized (Figure 2E). This concept, termed the restitution hypothesis, has now been validated experimentally in several VF models.22,23 Note that in Figure 2D, spiral wave breakup has caused the multiple wavelets to lose their morphological resemblance to spirals, and rarely does a broken wave make a complete revolution before it is pushed off course by a competing wave. Yet the generic reaction-diffusion processes are identical in Figures 2D and 2E. APD restitution slope should be thought of as a global parameter that controls phenotypical behavior of the tissue.

Electrical Alternans, a Harbinger of Dynamic Instability

A natural consequence of steep APD restitution is APD alternans, in which successive waves alternate between short

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Implications for Developing Effective Antiarrhythmic Drugs

Which of the above mechanisms are most important in clinical VF remains to be determined but is very important with respect to the prospects for developing effective antiarrhythmic drug therapy. Preexisting heterogeneity is difficult as a therapeutic target: it is often made worse by antiarrhythmic drugs, because any differential sensitivity to the drug’s effects on CV or APD is likely to increase dispersion of electrophysiological properties. Reducing dynamical instability by flattening APD restitution slope may be more promising. Figure 4 summarizes schematically the interaction between preexisting heterogeneity and dynamic instability. The hypothetical curve divides stable VT (gray area) from VT that degenerates to VF (white area). In general, increasing either preexisting heterogeneity or dynamic instability increases the probability of VF. The curve is not necessarily monotonic: sometimes preexisting heterogeneities (such as anatomic obstacles) can anchor and stabilize reentry (ie, convert functional reentry to anatomic reentry). The present challenge of researchers in this field is to define the contour of this curve more accurately to determine whether the restitution hypothesis can be translated into the development of effective antidysrhythmic drugs. Standard antiarrhythmic drugs (classes 1 to 4) were developed primarily to prevent initiation of VT by suppressing the triggering events or altering properties of reentrant circuits, with no regard for how they affected electrical restitution. Perhaps this partly explains their failure at preventing sudden cardiac death. It now seems timely to investigate whether a combined antitachycardia (classes 1 to 4) and antidysrhythmic (restitution-based) strategy can produce more successful results.

Conclusions

We have argued that the question “What causes VF?” can be stated more precisely as “What causes wavebreak?” and even more specifically as “How do preexisting heterogeneity and dynamically induced heterogeneity interact to promote VF?” If dynamic instability plays a key role, then developing drugs that favorably alter electrical restitution properties is a promising new approach to a vexing problem.

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References


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