Review: Current Perspective

A Tale of Two Fibrillations

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Sudden cardiac death remains a major public health problem in the United States. Ventricular fibrillation (VF) is the most common arrhythmia that directly leads to sudden cardiac death. However, the mechanisms of VF are unclear. Recently, different types ofVF have been demonstrated in isolated, perfused rabbit hearts linked to the electrical restitution properties of the heart (ie, the dynamic dependence of action potential duration [APD] or conduction velocity [CV] on the previous diastolic interval). Type I (fast)VF is associated with a steep APD restitution, flat CV restitution, and multiple wandering wavelets. Type II (slow)VF is associated with flat APD restitution, broad CV restitution, decreased excitability, and spatiotemporal periodicity in activation maps. Our goal in this article is to explain how this new knowledge about the 2 types ofVF can account for seemingly contradictory experimental findings by different investigators, and to speculate on the relevance to patient care.

Four Stages of VF

In normal hearts, physiological triggers such as premature ventricular contractions (PVCs) usually do not have the ability to generate an initial wavebreak causing sustained ventricular reentry. If such an event occurs, however, practically all normal hearts can fibrillate. In contrast, physiological triggers can sometimes induce wavebreak, initiating reentry in diseased hearts, as a result of increased structural and electrophysiological heterogeneity caused by the disease. Wiggers et al² reported that VF occurred in 4 distinct stages visible by cinematography. The first (tachysystolic) stage lasts no more than a few seconds, characterized by either a single spiral wave or a figure-of-eight reentry.³ A second premature stimulus given during the protective zone can terminate this reentry and prevent the induction of VF.⁴ The second (confusional reentry) stage lasts for 15 to 40 seconds. Multiple wavelets and organized reentry coexist.⁵ The third (tremulous incoordination) stage lasts 2 to 3 minutes. The VF activation rate begins to decrease. An endocardial–epicardial gradient in activation rate is present, probably because the endocardial cells and Purkinje fibers are more resistant to ischemia than the myocardial cells elsewhere.⁶ The fourth stage is atonic fibrillation, with complete loss of visible contractility.

Identification of these 4 stages of VF has significant clinical implications. Successful management of VF includes maneuvers both to prevent the onset of VF and to convert VF to sinus rhythm after VF occurs. The PVC suppression hypothesis, although proven to be ineffective, was based on the idea that suppressing the PVC initiating nonsustained ventricular tachycardia (VT) should eliminate stage 1 VF, hence preventing sudden death. The Restitution Hypothesis¹⁰ posits that the steepness of the APD restitution slope is a primary dynamic factor that predisposes cardiac waves to break. Therefore, flattening the APD restitution could both suppress the ability of the PVC to initiate stage 1 VF and prevent the conversion from stage 1 VF (VT) to stage II VF. Once stage II VF develops, electrical defibrillation is the most effective therapy. The implantable cardioverter–defibrillator (ICD) delivers therapies during stage II VF. Automatic external defibrillators, which deliver shocks within approximately 4 minutes after the onset of VF, likely are used during stages III and IV VF. Because the time from dispatch of paramedics to delivery of the first shock in victims of sudden death averages approximately 9 minutes, the majority of these shocks are delivered during stage IV VF.

Controversies in the Mechanisms of VF

Although it is clear that there are 4 stages of VF, there has been no unifying hypothesis to link all these observations together. Instead, with advances in multichannel computerized mapping techniques and optical mapping techniques, data collected from a wide range of animal models have led to apparently conflicting hypotheses on the mechanisms of VF. Most mapping studies show that VF is characterized by the coexistence of multiple wavefronts circulating throughout the ventricular myocardium. Because the individual waves have a finite lifespan, the hallmark of VF is the constant formation of new wavebreaks. The major controversy centers on whether these new wavebreaks are themselves responsible for the continuation of VF (the Multiple Wavelet Hypothe-
sis), or are merely an epiphenomenon caused by a rapidly firing focal source, which the bulk of the cardiac tissue cannot follow with 1:1 conduction (the Focal Source Hypothesis).

**Multiple Wavelet Hypothesis**
Moe et al. hypothesized that the constant formation of new wavelets occurs through the process of wave splitting (wavebreak), resulting in multiple wavelet fibrillation. The wave splitting occurs because of nonuniform dispersion of refractoriness and anatomic heterogeneity. Nonuniform dispersion of refractoriness naturally occurs in the normal myocardium as a result of transmural and base-to-apex heterogeneity of action potential durations and is further exacerbated by disease. The anatomic heterogeneities, which are naturally present, also facilitate conduction blocks and wavebreaks through the source-sink mismatches. For example, epicardial coronary arteries, papillary muscles, transmural sites with abrupt fiber orientation changes, and increased fibrosis resulting from cardiomyopathy can all serve as sites of wavebreaks. With the more recent appreciation that dynamic factors related to electrical restitution also play a key role in facilitating wavebreak, an updated version of the Multiple Wavelet Hypothesis emphasizes that the synergy between dynamic factors and preexisting tissue heterogeneities are the fundamental cause of wavebreaks perpetuating VF.

**Focal Source Hypothesis**
A competing hypothesis of VF is the Focal Source Hypothesis. This hypothesis posits that a single, rapidly firing focal source (reentrant or automatic) is the fundamental driver of VF, and that the multiple wavelets that characterize VF are an epiphenomena caused by "fibrillatory conduction block" because impulses from the rapid focus are unable to conduct 1:1 into the surrounding tissue. Gray et al. first demonstrated that a single meandering spiral wave could underlie polymorphic VT resembling VF. Subsequently, studies from Jalife's group have proposed that a single rapidly firing reentrant scroll wave (rotor) is the mechanism underlying VF. For example, Samie et al. studied Langendorff-perfused guinea pig hearts and showed that the highest frequency region (25 to 32 Hz) was always located on the anterior left ventricular wall and resulted from persistent rotor activity. Fibrillatory conduction blocks at specific locations in the periphery of the rotor were responsible for the organization of discrete dominant-frequency domains over the ventricular surface. Zaitsev et al. performed Fourier analysis of VF in sheep ventricular tissue slabs. They observed that the frequency domain patterns were relatively stable and could persist from several seconds to several minutes. This observation prompted the authors to suggest that the underlying mechanism of VF could be a sustained intramural reentrant source interacting with tissue heterogeneities.

The focal source hypothesis of VF has potentially important clinical implications. If a single mother rotor or mother focus underlies the mechanisms of VF, then catheter ablation of the single focus could cure the arrhythmia. Compatible with this prediction, Haissaguerre et al. successfully performed radiofrequency ablation in 27 patients with idiopathic VF characterized by rapid electrical discharges originating from foci in the distal Purkinje system. In summary, these data strongly support the notion that a rapid-firing focal source can result in fibrillatory conduction and VF in both animal models and in humans. The extent to which these observations apply to the majority of cases of VF causing sudden cardiac death in humans, however, remains unclear.

**New Evidence in Support of Multiple Wavelet Hypothesis**
Although recent evidence for the focal source hypothesis in the experimental models studied by Jalife and coworkers has been compelling, investigators using different experimental VF models have obtained different results. Choi et al. examined VF in guinea pig hearts and found that local velocity vectors during VF showed no preferential directions, and that fast Fourier transform power spectra were broad with multiple peaks, making determination of dominant frequency equivocal. Valderrabano et al. examined VF in arterially perfused porcine ventricle and failed to find evidence of stationary-dominant frequency domains indicative of fibrillatory conduction block. In another study, Choi et al. showed that VF consists of dynamically changing frequency blobs, which have a short lifespan and can be modified by pharmacological interventions, suggesting that VF is maintained by dynamically changing multiple wavelets.

In their letters to the editors of *Circulation Research*, 26,27 2 of these groups suggested that studies published by the opposing group had errors in experimental procedures, data analyses, and data interpretation. The strong convictions of these highly experienced investigators are evident from reading the concluding statements of those letters. However, another possibility is that they were studying different types of VF. If 2 different types of VF can coexist in the same heart, then a resolution to this heated debate on the mechanism of VF could be at hand.

**Two Types of VF**
We performed a study in Langendorff-perfused rabbit hearts to test the hypothesis that 2 types of VF resulting from different mechanisms can coexist in the same heart under different conditions. The study used optical mapping to determine VF activation patterns at baseline and during methoxysterapamil (D600) infusion. In additional experiments, we tested the effects of a low concentration of D600 plus a sodium channel blocker, tetrodotoxin (TTX). At baseline, the activation rate was fast, and the dominant frequency of VF was approximately 18 Hz. D600 flattened the APD restitution curve and converted baseline fast (type I) VF to VT at a concentration of 0.5 mg/L. This observation is not surprising because other drugs that flatten APD restitution slope also convert VF to VT in different animal models. However, further increasing the D600 concentration to 2.5 or 5.0 mg/L converted VT to slow (type II) VF with an average dominant frequency of approximately 11 Hz.

Because high concentrations of D600 block Na channels as well as Ca channels, we hypothesized that reduced excitability might underlie type II VF. To test the latter hypothesis, we gave TTX during VT induced by a low concentration of D600. TTX also converted VT to type II VF. Optical maps showed that wavebreaks occurred during both types of VF. However, unlike type I VF with steep APD restitution slope,
during type II VF, the APD restitution slope was flat. Therefore, type II VF was not driven by steep APD restitution, but was the result of another factor related to reduced excitability. The other factor turned out to be the other component of electrical restitution, CV restitution. Although APD restitution slope was flat in type II VF, CV, estimated from the inverse of conduction time, varied widely over a broad range of diastolic intervals as a result of low excitability, ie, the CV restitution curve was broad. It makes sense that broad CV restitution promotes wavebreak, because electrical wavelength is the product of APD × CV. Whereas steep APD restitution drives wave instability by making the wavefront sensitive to small changes in diastolic interval, CV can drive wave instability by making the wavefront sensitive to small changes in diastolic interval, especially if structural and electrophysiological heterogeneities are present. Computer simulations showed that without CV restitution, CV is essentially constant throughout the tissue during rapid pacing. Therefore, the arrival time of an impulse at a given distance from the pacing site has no way to vary between successive beats, assuming no change of the conduction pathway. In situations with flat APD restitution, broad CV restitution is primarily responsible for magnifying spatial variations in cycle length and DI. When the excitability is reduced by D600 or TTX, the low safety factor for propagation can cause local propagation failure when wavefront emanating from a focal source of VF. This VF in general is characterized by large and repeatable patterns of epicardial activations with occasional wavebreaks. These patterns of VF are consistent with those reported by Gray et al and Chen et al, who found significant spatiotemporal organization during fibrillation, suggesting that an ongoing focal and relatively stable source is the engine of VF. Taken together, we propose that VF associated with steep APD restitution but flat CV restitution (normal excitability) has different patterns of activation than VF associated with flat APD restitution with broad CV restitution (low excitability). If different investigators have been studying different types of VF, this could account for their drastically different interpretations.

Other Factors Important in the Maintenance of VF
In addition to electrical restitution, other factors also contribute to the development and evolution of VF. Cell coupling, for example, is also an important determinant of CV and might be important in the generation of conduction block and reentry. On the other hand, good intercellular coupling could facilitate spontaneous defibrillation. It is possible that abnormal cell coupling can reduce excitability and broaden CV restitution sufficiently to produce type II VF. The intracellular Ca cycling also has important effects on wavelength, which could contribute to degeneration of VT to VF.

Two Types of VF in Sudden Cardiac Death
To speculate on how these observations could relate to clinical episodes of sudden cardiac death in patients, Taggart reported that acute ventricular ischemia results in both APD shortening and flattening of APD restitution slope in human patients. In addition, excitability progressively decreases during acute ischemia. The onset of VF immediately leads to global acute ischemia as a result of circulatory arrest. Thus, type I VF normally inexorably leads to type II VF. This is illustrated in Figure 1 by a Holter recording during an episode of sudden cardiac death. The initial fine VF was fast, compatible with type I VF. After a few minutes, the VF cycle length lengthened, reflecting the conversion of type I (fast) VF to type II (slow) VF (arrow) as acute global ischemia flattened APD restitution, reduced excitability, and promoted increased tissue heterogeneity.

In contrast, spontaneous defibrillation occasionally occurs in humans. Figure 2 shows an example. The spontaneous VF episode here is compatible with type I VF with rapid, fractionated electrograms, and terminated spontaneously before there was any substantial slowing in the electrographic appearance as a result of the effects of acute global ischemia. Thus, VF reverted spontaneously in the type I VF stage and sudden death was aborted. By flattening APD restitution, acute global ischemia could initially be antifibrillatory and help to prevent perpetuation of type I VF before the effects of low excitability set in to promote further wavebreak. Note the increased sinus rate after spontaneous defibrillation, suggesting elevated sympathetic activity. Others have suggested that increased myocardial catecholamine content facilitates self-defibrillation. One possibility is that catechol-
amines, which increase excitability, could enhance the probability of self-defibrillation by delaying the conversion from type I VF to type II VF, or delaying the decrease in excitability during type II VF. This latter hypothesis is supported by the observation that during cardiopulmonary resuscitation, the probability of successful defibrillation can be enhanced by epinephrine injection.37 Type II VF can be intrinsically more difficult to defibrillate than type I VF, because in type II VF, wavefronts emerging after the shock are much more likely to break up as a result of low excitability and reinstantiate VF. Another important factor in favor of self-defibrillation in this patient might be the absence of coronary artery diseases. Without preexisting regional ischemia, flattening of APD restitution slope during acute global ischemia could have helped to terminate type I VF spontaneously before reduced excitability converted it into type II VF. Patients with Brugada syndrome are known to have repeated aborted sudden cardiac death as a result of nonsustained VF. The absence of structural heart disease, and specifically coronary artery disease, might also contribute to the self-defibrillation in these patients.

Finally, these observations could help to account for the deleterious effects of class I antiarrhythmic drugs on mortality in patients at increased risk of sudden cardiac death. By blocking Na channels, these drugs reduce excitability and accelerate the conversion of type I to type II VF.

**Two Types of VF and Resuscitation**

The existence of 2 types of VF has significant implications for cardiopulmonary resuscitation. Weisfeldt and Becker38
proposed that cardiac arrest has 3 time-sensitive phases, the electrical phase (0 to 4 minutes), the circulatory phase (4 to 10 minutes), and the metabolic phase (>10 minutes). During the electrical phase, immediate defibrillation has a high success rate, which is characteristic of type I VF. As ischemia progresses, however, electrical defibrillation has a lower success rate unless chest compressions are first applied for several minutes. This is consistent with the transition to type II VF as excitability progressively decreases due to accumulation of ischemic metabolites. Type II VF is more difficult to defibrillate because low excitability promotes new wavebreaks postshock. By restoring some coronary blood flow and washing out ischemic metabolites, chest compressions improve excitability and thereby enhance defibrillation success rate. In the metabolic phase, however, resuscitation efforts should be metabolically focused.

Conclusions

Two types of VF are the result of different mechanisms. Type I VF is associated with steep APD restitution and normal excitability. In the clinical setting, type I VF induces acute global ischemia, which flattens APD restitution and decreases excitability, converting it to type II VF. Acute or chronic regional ischemia preceding the onset of VF can depress excitability sufficiently to produce immediate type II VF in the ischemic zone, whereas type I VF is still present in the nonischemic zone. This is likely to be a particularly lethal situation because type II VF is very unlikely to self-defibrillate and could be more difficult to defibrillate by electrical shocks. It is also possible that a mixed form of type I/type II VF can be induced by drugs that solely depress excitability without flattening APD restitution.

On the opposite end of the spectrum are patients with structurally normal hearts. Their higher rate of spontaneous recovery from VF could in part be facilitated by acute global ischemia on flattening APD restitution, providing a window of opportunity for self-defibrillation before progressive ischemia reduces excitability and converts type I to lethal type II VF. The challenge for the future is to develop effective therapy to prevent both the initiation of type I VF and its conversion to type II VF. Therapeutics designed to modify electrical restitution properties, including both APD and CV restitution, could hold one of the keys.

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References


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