Dynamics and Molecular Mechanisms of Ventricular Fibrillation in Structurally Normal Hearts

José Jalife, MD

KEYWORDS

• Rotors • Dominant frequency • Fibrillatory conduction ionic mechanisms
• $Na_V1.5$-Kir2.1 interactions

KEY POINTS

- Ventricular fibrillation (VF) is an important immediate cause of sudden cardiac death.
- VF is driven by a small number (1 or 2) of high-frequency rotors that generate spiral waves whose fragmentation in the periphery of the rotor give rise to the complex patterns of activation that are known as fibrillatory conduction.
- The interbeat interval of VF scales as body mass$^{1/4}$ indicating that there is a strong similarity in the underlying mechanisms of VF in all mammalian species, including humans.
- At the molecular level, the frequency and complexity of the rotors that maintain VF depend on the expression, spatial distribution, and intermolecular interactions of the inward rectifier potassium channel, Kir2.1, and the alpha subunit of the main cardiac sodium channel, $Na_V1.5$.

INTRODUCTION

Ventricular fibrillation (VF) is an important immediate cause of sudden cardiac death, which is a major global public health problem accounting for an estimated 15% to 20% of all deaths.[1] Epidemiologic studies from the 1970s through the 1990s suggested that 88% to 91% of deaths that occur within 1 hour of symptom onset were arrhythmic in nature, presumably VF.[2] During VF, the sequence of ventricular activation is extremely abnormal and electrical impulses do not follow the usual paths.[3] The heart rate accelerates to the extreme, and the electrical waves assume a complex vortexlike behavior that brings to mind eddy formation and turbulence in water.[4] Turbulent excitation produces uncoordinated contraction, which renders the heart unable to pump blood. Thus, the blood pressure decreases, immediate loss of consciousness follows, and death is near unless a defibrillating shock is applied. This article reviews the current understanding of the dynamics of wave propagation and the molecular mechanisms underlying VF in the structurally normal mammalian heart. Particular attention is given to the dynamics of self-organization of cardiac electrical waves into the high-frequency rotors that result in fibrillatory conduction and the role of 2 major cardiac ion channels responsible for cardiac excitability in the underlying mechanism of rotor formation and VF maintenance.

Disclosure: The author has nothing to disclose.
This work was supported in part by the National Heart, Lung, and Blood Institute R01 (HL122352) NIH/NHLBI, and the Leducq Foundation: Transatlantic Network of Excellence Program on Structural Alterations in the Myocardium and the Substrate for Cardiac Fibrillation.
Center for Arrhythmia Research, North Campus Research Complex, University of Michigan, 2800 Plymouth Road, Ann Arbor, MI 48109, USA
E-mail address: jjalife@umich.edu

Card Electrophysiol Clin 8 (2016) 601–612
http://dx.doi.org/10.1016/j.ccep.2016.04.009
1877-9182/16/$ – see front matter

MODERN CONCEPTS ON VENTRICULAR FIBRILLATION MECHANISMS

On electrocardiogram (ECG), VF is characterized by the presence of highly irregular QRS complexes of varying morphology, amplitude, and frequency. Traditionally, such an apparently aperiodic and irregular activation of the ventricles was interpreted as being totally disorganized,[5,6] which led to the idea that VF was the result of a continuous self-sustaining activation by multiple wavelets that propagated randomly throughout the ventricles.[6] In the 1970s and 1980s, a new idea began to emerge based on theoretic[7,8] and experimental[9] findings, which showed that the heart could sustain electrical activity that rotated about a functional obstacle. Such "rotors" were thought to be the major organizing centers of fibrillation. Since then, several studies have focused on rotors as the underlying mechanism for ventricular tachycardia (VT) and VF in the heart. However, 2 schools of thought emerged. Many of the proposed mechanisms for fibrillation focused on fleetingness and instability of rotors,[10,11] and for some time substantial experimental[12–14] and theoretic work[15] accumulated suggesting that turbulence in VF is associated with breakup of a single spiral wave or a pair of counter-rotating spiral waves into a multispiral disordered state.[11]

However, alternative explanations for the breakup of the rotor in the three-dimensional myocardium have been proposed. One such mechanism, referred to as the restitution hypothesis, suggests that the breakup of the rotor into a multispiral state ensues when the oscillations of the action potential duration (APD) are of sufficiently large amplitude to cause block of conduction along the wave front.[16] The idea built on previous work showing that the slope of the electrical restitution relation determines certain dynamical behavior that may be conducive to the development of VF.[17] In particular, if the slope of the action potential restitution curve, in which duration of the action potential is plotted against the preceding diastolic interval, is greater than 1, then APD alternans is possible.[17] The initiation of APD alternans was proposed to be the first step in period-doubling sequences that culminate in complex behavior.[18–20] Subsequently, this process resulted in the destabilization of the wave fronts and the formation of a multispiral state.[12] Another mechanism for breakup focused on the highly anisotropic, rotational, and layered nature of the fibers of the three-dimensional ventricular myocardium, which produces twisting and instability of the organizing center (filament), and results in its multiplication following repeated collisions with boundaries in the heart.[21]

Over the past 25 years, work from my laboratory has focused on rotors as the primary engines of fibrillation.[22–25] However, in contrast with the breakup mechanism of VF, we proposed that VF was a problem of self-organization of nonlinear electrical waves with both deterministic and stochastic components.[4,24] Our studies strongly supported and continue to support the hypothesis that, in the structurally normal heart, there is both spatial and temporal organization during VF, although there is a wide spectrum of behavior.[26] On one end, we showed that a single drifting rotor could give rise to a complex pattern of excitation that was reminiscent of VF.[24] On the other end, we showed that VF could also be driven by a highly stable high-frequency source and that the complex patterns of activation were the result of the fragmentation of spiral electrical waves emanating from that source (ie, fibrillatory conduction).[27,28]

FIBRILLATORY CONDUCTION

Gray and colleagues[24] showed unequivocally that, in the rabbit heart, even a single drifting rotor can produce an ECG that is indistinguishable from VF. However, it has also been shown that in other mammalian hearts a more complex spatiotemporal organization may prevail. This finding led us to suggest that some forms of fibrillation depend on the uninterrupted periodic activity of discrete reentrant circuits.[27,29] As shown in the computer simulation of VF presented in **Fig. 1**, the faster rotors act as the dominant frequency (DF) sources, which maintain the overall activity. The rapidly succeeding wave fronts emanating from such sources propagate throughout the ventricles and interact with tissue heterogeneities, functional and anatomic, leading to fragmentation and wavelet formation.[3,23] The newly formed wavelets may undergo decremental conduction or they may be annihilated by collision with another wavelet or a boundary, and still others may form new sustained rotors. Thus, the result would be fibrillatory conduction or the frequency-dependent fragmentation of wave fronts, emanating from high-frequency reentrant circuits, into multiple independent wavelets.[27,30]

Using spectral analysis of optical epicardial and endocardial signals for sheep ventricular slabs, Zaitsev and colleagues[31] provided additional evidence suggesting that rotors and fibrillatory conduction may be the underlying mechanism of VF. The data showed that the DFs of excitation (ie, peak with maximal power) do not change continuously on the ventricular surfaces of slabs[31]; the frequencies are constant over regions termed domains. Moreover, there