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STATE-OF-THE-ART REVIEW

# Structural and Functional Bases of Cardiac Fibrillation

## Differences and Similarities Between Atria and Ventricles

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ABSTRACT

Evidence accumulated over the last 25 years suggests that, whether in atria or ventricles, fibrillation may be explained by the self-organization of the cardiac electrical activity into rapidly spinning rotors that give way to spiral waves that break intermittently and result in fibrillatory conduction. The dynamics and frequency of such rotors depend on ion channel composition, excitability, and refractory properties of the tissues involved, as well as on the thickness and respective 3-dimensional fiber structure of the atrial and ventricular chambers. Therefore, improving understanding of fibrillation has required the use of multidisciplinary research approaches, including optical mapping, patch clamping, and molecular biology, and the application of concepts derived from the theory of wave propagation in excitable media. Moreover, translation of such concepts to the clinic has recently opened new opportunities to apply novel mechanistic approaches to therapy, particularly during atrial fibrillation ablation. Here we review the current understanding of the manner in which the underlying myocardial structure and function influence rotor initiation and maintenance during cardiac fibrillation. We also examine relevant underlying differences and similarities between atrial fibrillation and ventricular fibrillation and evaluate the latest clinical mapping technologies used to identify rotors in either arrhythmia. Altogether, the data being discussed have significantly improved our understanding of the cellular and structural bases of cardiac fibrillation and pointed toward potentially exciting new avenues for more efficient and effective identification and therapy of the most complex cardiac arrhythmias. (J Am Coll Cardiol EP 2016;2:1–13) © 2016 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) and ventricular fibrillation (VF) are the most complex arrhythmias seen by the clinician. Both have important clinical consequences either in the context of cardioembolic events due to AF (1) or more dramatically during VF, leading to sudden death (2). In addition, both are incompletely understood and require combining multiple research approaches to achieve at least a partial understanding of their dynamic behavior and their interaction with their respective myocardial substrates. Atria and ventricles differ from each other in many respects, including myocardial mass, wall thickness, and size, but they also differ functionally in their intracavitary pressures, contractile properties, ionic channel composition, and electrophysiological characteristics (3–5). Structural

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**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**APD** = action potential duration

**ECG** = electrocardiogram

**SP** = singularity point

**VF** = ventricular fibrillation

changes (e.g., fibrosis) and functional parameters (e.g., refractory period) also vary depending on the clinical or experimental scenario (6,7), which increases complexity and precludes extrapolation from one setting to another.

Despite the above-described differences, common theoretical considerations may be applied to help explain the dynamics of wave propagation for either AF or VF occurring within the 3-dimensional (3D) myocardial structure. Experimental and clinical findings strongly support the concept that fibrillation is maintained by a small number of highly localized re-entrant sources (rotors) that activate atria or ventricles at exceedingly high frequencies, which results in spatially distributed intermittent block processes manifested as fibrillatory conduction (8–12). The latter has yielded new mechanistic strategies based on detecting and targeting AF drivers, which are currently emerging as promising alternatives to the classical anatomical approach of pulmonary vein isolation (13–15).

This review focuses on current knowledge of the interactions between the underlying myocardial structure and function that may result in rotor formation and AF/VF maintenance. We examined relevant underlying differences and similarities between atria and ventricles and evaluated the latest clinical mapping technologies used to identify rotors underlying AF or VF. Our main objective is to help clarify for both basic scientists and clinicians the often perplexing information that has appeared in the clinical literature about the current state of knowledge regarding the relative contribution of sustained or transient rotors to the mechanism of cardiac fibrillation (16).

## MECHANISMS UNDERLYING CARDIAC FIBRILLATION

Multiple studies in experimental animal models have contributed to the idea that, whether in atria or ventricles, fibrillation may be explained in terms of highly periodic rotors that activate the atria or ventricles at exceedingly high frequencies and generate turbulent electrical activity (17) (**Central Illustration**). However, although a growing number of prestigious clinical laboratories are finding evidence that rotors may underlie human atrial and ventricular fibrillation, as demonstrated by targeted ablation of rotor sites (13,14,18,19), the idea remains under intense debate, particularly in the field of AF. Of note, recent data from 2 different laboratories have failed to identify rotors in human AF (20,21). Instead, multiple randomly occurring foci (20) or focal non-re-entrant fibrillation waves, due to epicardial breakthrough of waves propagating in deeper layers of the atrial wall (21), have been observed in such studies. However, a clearly defined mechanism of AF maintenance was not put forth by either group particularly in light of knowledge that localized AF ablation is capable of terminating AF in large numbers of patients. As we have argued previously (22), it is possible that interpretation of activation maps based solely on the analysis of electrogram morphology and timing obscures rotation evident in other approaches (e.g., phase mapping), at the resolution used in those studies.

We define a "rotor" as a singularity point (SP) that rotates in cardiac muscle at high speed, organizing the electrical activity around it in the form of spiral waves; its spinning rate determines the degree of turbulence (fractionation) around it: the higher the spinning rate the greater the amount of spiral wave fractionation. Therefore, a rotor can be the organizing center of fibrillation but also of flutter-like activation or re-entrant tachycardia. The difference lies simply in rotor frequency. Rotors may be stationary or drift depending on the electrical (e.g., wavelength) and structural (e.g., fibrosis) properties of the tissue in which they occur (23). A drifting rotor may also become anchored to an anatomical obstacle in its path to begin rotating around it, converting the arrhythmia from one depending on functional re-entry, to one that depends on anatomical re-entry (24,25). Importantly, in 3D atria or ventricles, rotors may span the entire myocardial wall and manifest as scroll waves (see below).

## ROTOR FORMATION AND SUBSTRATE-RELATED STABILITY

Rotor formation requires that a propagating wave front encounters an anatomical or functional obstacle in its path. For example, the interaction of a wave front with an area of transient refractoriness may lead to a wave break and curling of the wavefront (26). This phenomenon enables the wave front to acquire the shape of an involuted spiral with increasing convex curvature toward the wave break (the tip near the spiral center). At the tip the curvature becomes critical, forming a SP that organizes the re-entrant spiral wave activity. This is important because the velocity of a wave depends on its curvature: waves whose front is concave propagate faster than planar waves, and the latter move faster than convex waves (27). In the case of a spiral wave front, its progressively increasing curvature toward the center results in a progressive decrease in the conduction velocity. Near the center (i.e., at the SP) the curvature is so