

Mechanisms of Atrial Fibrillation

Rotors, Ionic Determinants, and Excitation Frequency



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KEYWORDS

• Atrial fibrillation • Dominant frequency • Rotors • Remodeling

KEY POINTS

- When a stable, self-sustained rotor forms in the left or right atrium, its high-frequency spinning results in the complex patterns of fibrillatory conduction that characterize atrial fibrillation (AF).
- Although 2 or more rotors can coexist in the atria, the rotor with the highest dominant frequency (DF) predominates and maintains the overall activity.
- In a sheep model of tachypacing-induced AF, the rate of weekly DF increase predicts the time for the transition from paroxysmal to persistent AF.
- The increase in DF during the paroxysmal-to-persistent AF transition is explained by a reduction in the L-type Ca^{2+} current density, which together with an increase in the density of the inward rectifier potassium current, shortens the refractory period to accelerate and stabilize rotors.
- The distribution of DF gradients in patients with paroxysmal AF is different from patients in persistent AF; abolishing DF gradients by radiofrequency ablation of high DF sites predicts freedom of AF.

INTRODUCTION

Atrial fibrillation (AF) is associated with increased morbidity and mortality in patients with cardiovascular disease and its prevalence in the general population continues to increase.¹ However, despite more than 100 years of basic and clinical research, the fundamental mechanisms of AF initiation and maintenance are poorly understood, which has likely contributed to our inability to treat it effectively. A commonly accepted mechanism, the multiple wavelet hypothesis,^{2,3} assumes that cardiac fibrillation results from randomly propagating waves with intermittent blockades, annihilation, and re-generation of discrete waves. A more recent variant posits that AF depends on longitudinal/transmural dissociation,⁴ with the fibrillatory

waves lacking any kind of hierarchical organization. However, multiple theoretic,^{5,6} experimental,⁷ and clinical^{8,9} studies have repeatedly demonstrated that wave propagation during AF is not totally random, but contains deterministic components that depend on self-organized drivers (rotors) that spin at an exceedingly high frequency. The spiraling waves emerging from such rotors give rise to the characteristically complex patterns of fibrillatory conduction as they propagate through the atria. Remarkably, the heterogeneous distribution of ion channels in the atria enables rotors to dwell at specific areas whose structure, electrical properties, and relatively short refractory periods promote rotor attachment.¹⁰ One emergent property of such complex spatiotemporal dynamics was the hierarchical distribution of local

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cycle lengths (CLs) that was first reported in early experimental studies by Morillo and colleagues¹¹ and Harada and colleagues.¹² This was followed by the combined use of phase mapping¹³ and dominant frequency (DF) mapping to quantitate the dynamics and the spatial organization of AF activation rates in both atria and by the demonstration that the highest DF corresponded with the location of the rotor that was driving the arrhythmia.^{14–17} This article has three major objectives: First, to discuss the electrophysiologic significance of spectral analysis in AF; second, to discuss data that strongly support the hypothesis that remodeling in atrial ionic properties contributes to the transition from paroxysmal to persistent AF (PeAF); and third, to review and discuss clinical data showing a distribution of DFs across the atria during AF and how that distribution may be used to guide ablation procedures.

FREQUENCY-DEPENDENT BREAKDOWN OF WAVE PROPAGATION

To gain insight into the distinct spatial distribution of CLs in the study of Morillo and colleagues,¹¹ we used spectral analysis of each of the time series recorded at specific locations in both atria to determine their DFs. Most notably, the activation frequencies in certain areas of the left atrium (LA) were always faster than any other region.^{15,16} In subsequent studies, we confirmed the hierarchical organization of the DFs.¹⁴ In addition, we

demonstrated that such an organization was the result of the exceedingly high frequency at which the spiraling waves emerging from the spinning rotor propagated haphazardly through the heterogeneous atria, undergoing spatially distributed intermittent Wenckebach-like patterns that are typical of fibrillatory conduction.^{18,19} In retrospect, this is not too surprising; it is well known that the atria are very heterogeneous in both their anatomic structure and electrophysiologic properties, and waves that propagate at an high frequency in such an environment are likely to encounter obstacles in their path. To illustrate how we investigate the mechanism of fibrillatory conduction, we used a simplified mathematical model of a heterogeneous substrate consisting of a large pectinate muscle connected to a small sheet representing the thin atrial wall (Fig. 1).⁶ Periodic stimulation was applied to the top free edge of the pectinate bundle (25 mm²) and the impulse was allowed to propagate downstream to invade the 2-dimensional sheet.⁶ The traces on the right show the action potentials (APs) and corresponding power spectra of sites in the bundle and in the sheet. As shown by the top and bottom time series, stimulation at a constant period of 0.119 seconds resulted in a 3:2 propagation pattern across the boundary between the thin bundle and the sheet. This is reflected in the corresponding power spectra as well: Although the source region (the pectinate bundle) displayed a DF of 8.4 Hz, the geometric expansion into the sheet imposed a

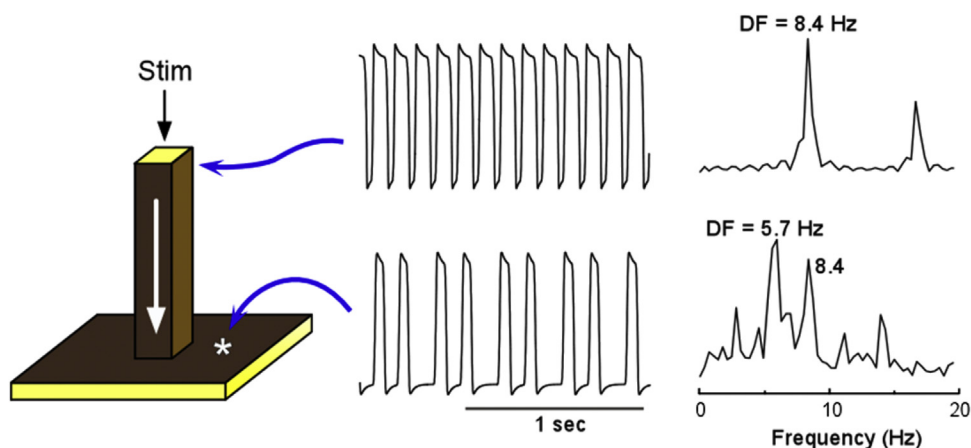


Fig. 1. Computer model of action potential propagation from a pectinate muscle to the atrial wall. A 3-dimensional ($60 \times 60 \times 60$ elements) model includes a 1-dimensional bundle attached to a 2-dimensional sheet (*left panel*). Periodic stimulation (*Stim*) was applied at the top edge of the bundle and the impulse was allowed to propagate downward with conduction velocity of ~ 0.29 m/s and to invade the 2-dimensional sheet. The voltage time series and corresponding power spectra are shown for a site near the stimulation point and a site at the sheet. Comparison between the points indicates a 3:2 pattern of propagation into the sheet with a concomitant spectral transformation and a dominant frequency (DF) shift from 8.4 to 5.7 Hz. (From Jalife J, Berenfeld O, Skanes A, et al. Mechanisms of atrial fibrillation: mother rotors or multiple daughter wavelets, or both? *J Cardiovasc Electrophysiol* 1998;9:S2–12; with permission.)

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