Electrophysiological Characteristics of Permanent Atrial Fibrillation: Insights from Research Models of Cardiac Remodeling

Journal:	*Expert Review of Cardiovascular Therapy*
Manuscript ID:	Draft
Manuscript Type:	Editorials
Keywords:	Atrial Fibrillation , Tissue Remodeling , Electrophysiological Properties , Persistent AF , Rotors

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Summary

Atrial Fibrillation (AF) results in a remodeling of the electrical and structural characteristics of the cardiac tissue which dramatically reduces the efficacy of pharmacological and catheter-based ablation therapies. Recent experimental and clinical results have demonstrated that the complexity of the fibrillatory process significantly differs in paroxysmal vs. persistent AF. However, the lack of appropriate research models of remodelled atrial tissue precludes the elucidation of the underlying AF mechanisms and the identification of appropriated therapeutic targets. Here, we summarize the different research models used to date, highlighting the lessons learned from them and pointing to the new doors that should be open for the development of innovative treatments for AF.

Keywords

Atrial Fibrillation - Tissue Remodeling - Electrophysiological Properties – Persistent AF – Rotors

Expert commentary

Atrial Fibrillation and Atrial Tissue Remodeling

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The initiation of an episode of AF requires the involvement of a trigger event and a cardiac substrate that allows the perpetuation of the reentrant electrical activity [1]. The elimination of the atrial trigger could be sufficient to successfully treat patients with paroxysmal AF with a healthy atrial tissue [2-4]. However, in persistent AF patients with electrical and structural remodeling, both pharmacological and catheter-based ablation therapies have a limited value. The term remodeling refers to the changes in the atrial tissue properties following periods of sustained AF [5]. These changes include electrical remodeling during the first stages of the fibrillatory process; mainly shortening of the atrial action potential duration and refractoriness. In case of AF episodes lasting for several weeks or months, alterations in the expression of ion channels are followed by an increased fibrosis, chamber dilatation and a reduction of atrial contractility [6]. As a consequence, the atrial substrate is heterogeneous, with regions of short effective refractory period and a decreased conduction velocity, which dramatically increases the susceptibility to maintain AF. However, all the efforts made to date aiming to treat persistent AF by counteracting this tissue remodeling and restoring normal electrophysiological properties have achieved limited success.

Atria Tissue Remodeling and Fibrillatory Process Characteristics

Both experimental [7] and mathematical [8] models have suggested that the main determinants of electrical remodeling are a reduction in the density of the depolarizing inward L-type Ca^{2+} current ($I_{Ca,L}$) and an increased activity of the inward rectifier current, I_{K1}. These two modifications explain both the shortening of the action potential duration and the reduction of the effective refractory period observed in chronically remodeled atrial myocytes. Regarding the structural remodeling of long-term AF, the adaptation to calcium overload and metabolic stress due to a fast activation rate promotes cardiomyocyte dedifferentiation, producing an increment

in cell size which is associated with the modification of main subcellular structures [6]. In addition to atrial cell dilatation, extracellular matrix remodeling produces a profibrotic environment which stimulates fibroblast proliferation and differentiation into myofibroblasts [6]. Moreover, atrial fibrosis disturbs the continuity between cardiomyocytes reducing wavefront homogeneity and conduction velocity, creating the ideal the substrate for FA maintenance.

Extensive evidence suggests that these modifications of the atrial substrate are related with changes in the complexity of the fibrillatory activity. Epicardial atrial recordings from patients suffering persistent AF are characterized by a faster activation rate and a larger number of simultaneous wavefronts [9-10]. The specific mechanisms that produce these changes remain controversial. Whereas some authors suggest that the increase in the complexity of the atrial fibrillatory activity is associated with a more frequent foci activity and electrical dissociation [9-10], other authors relate this increase in the complexity of persistent AF with modifications in the rotation characteristics of reentrant activity [11]. In fact, the use of advanced mapping technologies has suggested that AF is mainly maintained by functional reentries both in animals and humans [4, 12]. These functional reentries, so-called rotors, are characterized by spiraling wavefronts that surround a tip point [11]. The characteristics of rotors (e.g. reentrant rate, tip meandering, curvature, etc.) are governed by the electrophysiological properties of the atrial tissue [11]. It has been shown that a shortening of the action potential duration allows a reduction in the tip meandering and consequently an increase of the reentrant rate which explains the shortening of the atrial cycle length. In addition, an increase of the rotor curvature of a reentry reduces the area needed by a spiral wave to maintain a rotor. The combination of those two effects of the remodeling on the reentrant activity allows the simultaneous existence of several rotors in the atrial tissue and may explain the observed increase in the number of simultaneous wavefronts by Allessie et al. by using epicardial electrodes [9-10].

Experimental Models with Persistent Atrial Fibrillation

A potential explanation for the absence of effective treatments for persistent AF is the lack of appropriate research models to elucidate the mechanisms that produce the modifications on the AF process due to remodeling. The main limitation for the development of experimental models of chronic AF is the inherent need for remodeled tissues or whole hearts suffering AF for at least several weeks or months.

Most of our knowledge about the tissue remodeling has been gained by using rapid atrial pacing models both in single cells [7] or the atria of large mammalians [13]. Unfortunately, the mechanisms of AF maintenance in these tachypacing models may differ significantly from clinical persistent AF. Recently, a novel sheep model of long-term persistent AF, in which the tachypacing was stopped once AF was self-maintained [14], was used to indirectly corroborate the essential role of rotors in AF maintenance. This model reproduced the shortening in the dominant atrial cycle length (or an increase in the atrial dominant frequency) observed in persistent AF patients during the remodeling process [15]. Unfortunately, current mapping technology does not allow simultaneous evaluation of the global atrial activity and the tracking of each individual rotor which precludes the identification of the specific mechanisms responsible for AF maintenance. Besides, the generation of these animal research models requires huge economic and time efforts.

Another potential approach to clarify the electrophysiological mechanism that governs persistent AF is the generation of in vitro models in which the fibrillatory process is self-maintained during several days or weeks. By co-culturing neonatal cardiomyocytes and fibroblasts at different fibroblast infiltration ratios, Zlochiver et al. reported that the electrical interaction between myocytes and fibroblasts determines rotor dynamics by altering the conduction velocity and wavefront complexity [16]. In vitro models also allowed the evaluation of the effects of mechanical stretch on the calcium dynamics and the mechanisms of initiation of AF in a model of HL-1 cells (i.e. atrial murine immortalize adult cardiomyocytes) [17].

Interestingly, HL-1 cells have demonstrated their ability to undergo in vitro myocyte remodeling similar to that found in patients with AF (i.e. reduction of the expression of L-type Calcium current proteins, myolisis, nuclear condensation and an increase in calpain actitivity) [18]. However, murine cardiomyocytes present significant differences with human atrial cells and thus extrapolation of these results to the clinical setting is limited. Today, novel advanced cell technologies allow the development of in vitro human cardiac structures from embryonic stem cells or from adult human cells dedifferentiated into induced pluripotent stem cells [19]. In the near future, the investigators will have the possibility to use in vitro models of human atrial cells obtained from specific patients and with different stages of remodeling. Those in vitro models, together with the novel optical mapping techniques that enable simultaneous recording of transmembrane voltage and calcium transients [20], will allow the identification of treatment targets to prevent or even reverse the effects of tissue remodeling.

Five-Year View

Until now, pharmacological treatments trying to counteract specific ionic or molecular modifications produced by the remodeling have shown a limited effect. Potentially, a different therapeutic strategy could aim at modifying of the reentrant process in such a way that prevents the perpetuation of the arrhythmia, even if the structural remodeling cannot be reversed. Specifically, a reduction in the curvature of the reentrant wavefronts and an increase in rotor meandering may increase the probability of termination of the arrhythmia by means collisions, either between rotors or with anatomical obstacles. Novel cell and mapping technologies will be useful for elucidating the mechanisms that govern reentrancy and, more specifically, the excitability at the center of the rotor during persistent AF and may help in defining new therapeutical approaches to terminate AF.

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