Novel Upstream Approaches to Prevent Atrial Fibrillation Perpetuation

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KEYWORDS

• Atrial fibrillation • Myofibroblast • Fibrosis • Myocytes

KEY POINTS

- The mechanisms underlying atrial fibrillation (AF) in humans are poorly understood. In particular, it is unknown how sustained high-frequency excitation leads to electrical remodeling and fibrosis of the atria and results in AF perpetuation.
- Sustained high-frequency atrial excitation results in intracellular accumulation of reactive oxygen species, also known as "oxidative stress", which likely plays important roles in the pathogenesis of AF, triggering both electrical and structural remodeling.
- Inflammation is known to play an important pathogenic role leading to cardiac fibrosis in several cardiovascular diseases, including AF; activated inflammatory cells, such as polymorphonucleated neutrophils, lymphocytes, monocytes, resident macrophages, and activated platelets are all important players in this picture.
- The role of the renin-angiotensin-aldosterone system (RAAS) in AF is a new area of investigation. Both structural and electrical remodeling produced by sustained AF may share common pathways in which the main fibrogenic cell type in the heart, the myofibroblast, plays a central role through its activation by RAAS.
- Through its effects promoting gene transcription via cytokine-mediated signaling pathways, galectin-3 might represent a common upstream link for both structural and electrical remodeling and a mediator in the transition to persistent AF.

THE EPIDEMIC OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common sustained arrhythmia seen by physicians in their practice. It affects about 1.5% of the population in the developed world.[1] In the United States and Europe, overall prevalence of AF is 0.9%. These numbers are projected to grow dramatically and to more than double over the next 2 decades as the elderly proportion of the population increases.[2–4] Thus, in the Western world AF has already reached epidemic proportions.

AF is a major cause of hospitalization and is associated with an increased risk of stroke, heart failure, dementia, and death.[5–7] Yet despite its epidemiologic importance and more than 100 years of basic and clinical research, physicians still do not fully understand its fundamental mechanisms and have not learned how to treat it effectively. When AF lasts continuously for more than 7 days it is designated as persistent AF; shorted episodes are termed paroxysmal.[8] Spontaneous, pharmacologic or ablative resumption of sinus rhythm is infrequent in persistent AF, with prompt recurrences or commonly failed cardioversions. Episodes lasting for more than 1 year are termed "long-term persistent AF". Many drugs have been tried in persistent AF and permanent AF with very limited success. On the other hand, the demonstration of AF triggers in the atrial sleeves

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of the pulmonary veins[9] (PVs) has led to a significant improvement in therapy, and today PV isolation using radiofrequency (RF) ablation is curative in about ~70% to 80% of patients with paroxysmal AF.[10] However, the success rate of RF ablation in the more prevalent and highly heterogeneous persistent and long-term persistent AF population has been inadequate. Arguably only a profound and complete understanding of the mechanisms involved in the maintenance and perpetuation of AF will allow us to generate more specific prevention and/or treatment of this dangerous and debilitating disease.

Persistent AF leads to electrical remodeling and fibrosis of the atria but the mechanism remains poorly understood. The objective of this article is to address the most important factors involved in the mechanism of AF stabilization in the long term, paying particular attention to possible molecular mechanisms leading to both structural remodeling in the form of fibrosis and electrical remodeling secondary to ion channel expression changes, which might contribute to persistent AF. Although excellent reviews have appeared on the subject on AF-related atrial remodeling,[11–13] the tantalizing possibility that both fibrosis and electrical remodeling might in fact be prevented when intervening early enough before the remodeling process reaches a point of no return has seldom been addressed. The idea is based on the repeated demonstration in the literature that during sustained AF the renin-angiotensin-aldosterone (RAAS) system activates common signaling pathways involving galectin-3 (Gal-3), transforming growth factor β1 (TGF-β1), and platelet-derived growth factor (PDGF) that contribute to structural and electrophysiologic remodeling leading to AF stabilization and perpetuation. In this regard, it seems reasonable to postulate that the early use of such agents as mineralocorticoid blockers or Gal-3 inhibitors in hypertensive patients who are at risk of developing AF, or in patients showing the initial symptoms of paroxysmal AF, may be efficacious in preventing sustained AF and adverse cardiac remodeling.

A NEW ANIMAL MODEL OF PERSISTENT AF

Multiple profibrotic conditions, including heart failure, hypertension, a history of myocardial infarction, diabetes mellitus, or obesity, predispose to AF.[14] In addition, AF itself somehow leads to electrical remodeling and fibrosis of the atria but the mechanism remains poorly understood. Atrial electrical remodeling and functional changes in subcellular atrial myocyte function in the short term lead to abbreviation of atrial action potential duration (APD) and refractory period,[15–17] which would help to promote the stabilization of reentry. However, whether and how these changes contribute to AF perpetuation in the long term has not been fully determined. In humans, chronic AF decreases the L-type calcium current in atrial myocytes.[18] In addition, chronic AF increases the inward rectifier potassium current,[19] but decreases the transient outward current and the ultrarapid component of the delayed rectifier current differentially on each atria and increases the slow component of the delayed rectifier current in both.[20] However, the time course of these changes mentioned earlier has not been established. In a recent study in a sheep model of persistent AF induced by intermittent atrial tachypacing, there was a progressive spontaneous increase in the dominant frequency (DF) of AF activation during a 2-week period after the first detected AF episode (**Fig. 1**).[21] The results suggested that, unlike the tachypacing-induced electrical remodeling that can occur over minutes or hours,[15] there existed a protracted, slowly progressing electrical remodeling, which occurred secondary to an AF that sustained for days or weeks.[21] In addition, a consistent left versus right atrial DF difference lasting greater than 22 weeks in most animals (see **Fig. 1**) correlated with the presence of rotors, DF gradients, and outward propagation from the posterior left atrium (PLA) during sustained AF in the explanted, Langendorff-perfused sheep hearts.[21] Similar to other animal models, long-term atrial tachypacing in the sheep resulted in atrial fibrosis,[22] with concomitant release of cytokines that are known to modify atrial electrical function.[23] Also in the sheep model, atrial structural changes leading to PLA enlargement and stretch likely made rotors less likely to drift or to collide with anatomic boundaries, thus contributing to their stabilization and AF persistence.[21,24]

The changes in DF discussed earlier reflect a progressive decrease in the atrial APD, refractory period, and purported stabilization of rotor activity over a 22-day period. They also reflect long-term tachycardia-induced reduction in the gene expression, protein levels, and transmembrane currents of the inward sodium and L-type calcium channels, but increase the expression and transmembrane currents of the inward rectifier potassium current.[25] In addition, there were concomitant increases in serum markers of fibrosis as well as atrial tissue collagen gene transcription and fiber deposition. Moreover, although structural and electrical remodeling are both thought to promote AF persistence, it is unknown whether it is the high-frequency excitation itself that provides the insult that results in the molecular changes