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Atrial remodeling, fibrosis, and atrial fibrillation

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ABSTRACT

The fundamental mechanisms governing the perpetuation of atrial fibrillation (AF), the most common arrhythmia seen in clinical practice, are poorly understood, which explains in part why AF prevention and treatment remain suboptimal. Although some clinical parameters have been identified as predicting a transition from paroxysmal to persistent AF in some patients, the molecular, electrophysiological, and inflammation changes leading to such a progression have not been described in detail. Oxidative stress, atrial dilatation, calcium overload, inflammation, microRNAs, and myofibroblast activation are all thought to be involved in AF-induced atrial remodeling. However, it is unknown to what extent and at which time points such alterations influence the remodeling process that perpetuates AF. Here we postulate a working model that might open new pathways for future investigation into mechanisms of AF perpetuation. We start from the premise that the progression to AF perpetuation is the result of interplay among manifold signaling pathways with differing kinetics. Some such pathways have relatively fast kinetics (e.g., oxidative stress-mediated shortening of refractory period); others likely depend on molecular processes with slower kinetics (e.g., transcriptional changes in myocyte ion channel protein expression mediated through inflammation and fibroblast activation). We stress the need to fully understand the relationships among such pathways should one hope to identify novel, truly effective targets for AF therapy and prevention.

Introduction

Atrial fibrillation (AF) affects over 2.5 million Americans [1] and is the major cause of embolic stroke [2]. In the USA and Europe, overall prevalence of AF is 0.9% and the number of people affected is projected to more than double over the next 2 decades [3–5]. In fact, the projected rise in AF incidence is approaching epidemic proportions [1,6]. Yet despite its importance and more than 100 years of basic and clinical research, we still do not fully understand its fundamental mechanisms and have not learned how to treat it effectively. Some patients suffer relatively short (<7 days) self-terminating episodes (i.e., paroxysmal) of AF indefinitely, but a large proportion progress to long-lasting forms of AF [7]. When AF lasts continuously for more than 7 days it is considered persistent AF [8]. Spontaneous, pharmacological or ablative resumption of sinus rhythm is infrequent in persistent AF, with prompt recurrences or commonly failed cardioversions. AF lasting more than 1 year is termed "long-term persistent AF" [7]. Persistent AF leads to electrical remodeling and fibrosis of the atria but the mechanism(s) remain poorly understood. Experimental and clinical data collected to date point to a very complex pathophysiology involving a large number of significant players, including oxidative stress, calcium overload, atrial dilatation, microRNAs, inflammation, and myofibroblast activation (Fig. 1), all of which are likely to be involved one way or another in AF-induced atrial extracellular matrix (ECM) and electrical remodeling [9,10]. The complexity of disease progression is further amplified by the positive feedback loops that can be established among many of such players. However, it is unknown to what extent and at which time points such

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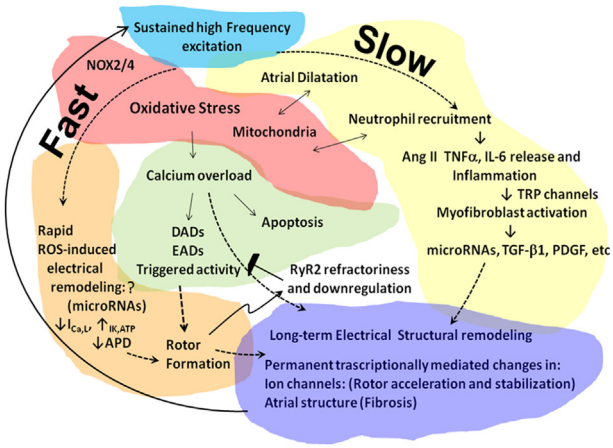

Fig. 1 – Working model for AF-induced remodeling and the substrate for AF perpetuation. Sustained high-frequency excitation of the atria results in a complex series of pathophysiological events involving a large number of significant players. These include oxidative stress, calcium overload, atrial dilatation, inflammation, and myofibroblast activation, all of which are likely to be involved in AF-induced atrial extracellular matrix (ECM) and electrical remodeling through transcriptionally mediated changes in both cardiac myocytes and fibroblasts.

interactions influence the remodeling process that perpetuates AF. This brief review addresses some of the most important factors underlying ECM remodeling, with particular attention paid to the role of oxidative stress and cardiac fibroblast-to-myofibroblast differentiation in the mechanisms of atrial remodeling associated with AF. We also briefly address other potentially important contributors, such as calcium overload, transient receptor potential channels (TRP channels), and microRNAs to the mechanisms of fibrosis and AF maintenance.

A working model of AF perpetuation

We start from the premise that the progression to persistent AF is the result of interplay among multiple signaling pathways with differing kinetics [11], some fast and others slow, as illustrated diagrammatically in Fig. 1. The role of many of such signaling pathways remains speculative. Yet fragmented evidence extracted from the literature, together with recent experimental results obtained in a clinically relevant model of persistent AF [12,13], allows us to create a cohesive picture that might open new pathways for future investigation and hopefully the identification of novel targets for AF treatment and prevention. The model put forth in the scheme of Fig. 1 predicts that, once AF is initiated, whether by premature triggered discharges from a pulmonary vein, by rapid electrical pacing of the atria, or by a simple wave break, the first consequence of the sustained high-frequency excitation would be the promotion of oxidative stress. The reactive oxygen species (ROS) released by nicotinamide adenine dinucleotide phosphate oxidases (NOX)2/4 would result in rapid (i.e., within hours or days) L-type Ca^{2+} current ($I_{Ca,L}$) reduction and inward rectifier K^+ current (I_{K1}) increase, leading to shortening of the atrial action potential duration (APD) and refractory period promoting the formation and stabilization of rotors. This would be followed by intracellular Ca^{2+} overload, promoting triggered activity, and apoptosis [14,15]. However, during sustained AF, the exceedingly high frequency of electrical excitation generated by the sustained rotor(s) should lead to refractoriness of the cardiac ryanodine receptor (RyR2) of the sarcoplasmic reticulum (SR) [16] as well as downregulation of Ca^{2+} handling proteins [13,17,18], acting to prevent triggered activity. Nevertheless, Ca^{2+} overload, together with atrial dilatation, mitochondrial ROS, and activation of inflammatory and pro-fibrotic pathways [19] progressively alters gene expression. As demonstrated recently in a clinically relevant sheep model of persistent AF, the consequences of the above changes would be myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling, all of which would occur relatively slowly but reach critical levels when AF becomes persistent at a median time of about 2 months [13]. As time progresses and remodeling continues to occur, enduring transcriptionally mediated changes in ion channel expression and atrial structure persistently work together to preserve sustained high-electrical frequency excitation in a "vicious cycle" that further promotes rotor stabilization, fibrosis, and AF perpetuation (Fig. 1).

Oxidative stress, inflammation, and atrial fibrillation

The role of ROS in mediating changes in atrial ionic remodeling in AF is not well understood [20]. Markers of oxidative stress have been documented in AF, and antioxidants have been shown to partly arrest electrical remodeling in animal models. Studies investigating the sources of ROS in AF have found an important role for NOX2/4 activity, which is increased in the fibrillating atria [21]. Mitochondrial dysfunction and swelling are also known to occur in AF and mitochondrial ROS is potentially another important source of oxidative stress in AF [22]. NOX activity was shown to be increased in the goat after 2 weeks of atrial tachypacing and in human atrial samples obtained after post-operative AF [23]. In contrast, for long-standing persistent AF in humans, and for animals whose atria were tachypaced for 6 months, the major source of ROS was attributed to mitochondrial oxidase and uncoupled nitric oxide synthase (NOS) activity [23]. Previously unpublished experiments from our laboratory (Fig. 2) indicate that NOX-derived ROS might be implicated in the electrical alterations seen in myocytes as early as 1 day after sustained tachypacing. In addition, a yet unpublished proteomic analysis during the transition to persistent AF (i.e., 58 ± 21 days after the onset of atrial tachypacing) suggests that the elevated ROS that is observed in atrial myocytes from persistent AF animals may correlate with NOS reduction, xanthine oxidase elevation, and/or mitochondrial dysfunction. Thus, it is likely that these time-dependent changes in ROS also underlie the temporal changes in atrial remodeling (AF dominant frequency increase, atrial dilatation, and fibrosis) known to occur in AF, as shown by our recent study [13] and also by others [24]. However, whether atrial oxidative stress directly affects atrial APD and refractoriness and thus