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STATE-OF-THE-ART PAPERS

Atrial Remodeling and Atrial Fibrillation

Recent Advances and Translational Perspectives

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Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. AF and its complications are responsible for important population morbidity and mortality. Presently available therapeutic approaches have limited efficacy and nontrivial potential to cause adverse effects. Thus, new mechanistic knowledge is essential for therapeutic innovation. Atrial arrhythmogenic remodeling, defined as any change in atrial structure or function that promotes atrial arrhythmias, is central to AF. Remodeling can be due to underlying cardiac conditions, systemic processes and conditions such as aging, or AF itself. Recent work has underlined the importance of remodeling in AF, provided new insights into basic mechanisms, and identified new biomarker/imaging approaches to follow remodeling processes. The importance of intracellular Ca^{2+} handling abnormalities has been highlighted, both for the induction of triggered ectopic activity and for the activation of Ca^{2+}-related cell signaling that mediates profibrillatory remodeling. The importance of microRNAs, which are a new class of small noncoding sequences that regulate gene expression, has emerged in both electrical and structural remodeling. Remodeling related to aging, cardiac disease, and AF itself is believed to underlie the progressive nature of the arrhythmia, which contributes to the complexities of long-term management. New tools that are being developed to quantify remodeling processes and monitor their progression include novel biomarkers, imaging modalities to quantify/localize fibrosis, and noninvasive monitoring/mapping to better characterize the burden of AF and identify arrhythmic sources. This report reviews recent advances in the understanding of the basic pathophysiology of atrial remodeling and potential therapeutic implications. (J Am Coll Cardiol 2014;63:2335–45) © 2014 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a major cause of cardiovascular morbidity and mortality (1). AF is a final common endpoint of atrial remodeling caused by a variety of cardiac diseases and conditions (2) and itself causes important remodeling that contributes to the progressive nature of the arrhythmia. A detailed review of the subject was published in 2008 (3). Since then, an enormous amount has been learned about atrial remodeling, its mechanisms, and its role in the AF disease process. Here, we will focus on progress since that report (over the past 6 years), particularly in terms of understanding the basic mechanisms and their clinically relevant applications.

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Overview of AF Pathophysiology and Contribution of Remodeling

There are 4 principal pathophysiological mechanisms contributing to AF (1–4): electrical remodeling, structural remodeling, autonomic nervous system changes, and Ca^{2+} handling abnormalities (red boxes in Fig. 1). Each of these can result from cardiac disease conditions (blue boxes in Fig. 1) and promote the development of AF; AF in turn causes AF-promoting abnormalities in each of these areas (red dashed arrows in Fig. 1). AF-induced atrial remodeling enhances the vulnerability of the heart to AF induction and maintenance; this auto-reinforcing property of AF is often referred to by the term "AF begets AF." Focal ectopic firing (yellow boxes in Fig. 1) can maintain AF or trigger re-entrant AF through a re-entry-maintaining substrate (green boxes in Fig. 1) that has the appropriate conditions to allow re-entry to be induced and then sustained. Induction and maintenance of re-entry require a critical balance between refractory and conduction properties, as discussed in detail by Wakili et al. (2) and Nattel et al. (3). AF is by definition a highly irregular atrial rhythm, yet paradoxically it can be maintained by regularly firing sources (sometimes called "drivers"), whether rapidly firing ectopic foci or single rapidly rotating

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Abbreviations and Acronyms

AF = atrial fibrillation
APD = action potential duration
AT-II = angiotensin II
CaMKII = Ca^{2+}/calmodulin kinase type 2
CREM = cyclic adenosine monophosphate response element modulator
DAD = delayed afterdepolarization
ECM = extracellular matrix
ER = endoplasmic reticulum
ERK = extracellular signal–regulated kinase
HF = heart failure
I_{CaL} = L-type Ca^{2+} current
I_{K1} = inward rectifier background K^+ current
I_{KACh} = acetylcholine-regulated K^+ current
IP3 = inositol triphosphate
LTCC = L-type Ca^{2+} channel
miR or miRNA = microRNA
mRNA = messenger RNA
NCX = Na^+/Ca^{2+} exchanger
NFAT = nuclear factor of activated T cells
PLB = phospholamban
RyR2 = ryanodine receptor type 2
SERCA2a = sarcoplasmic reticulum Ca^{2+}–adenosine triphosphatase
SR = sarcoplasmic reticulum
TG = transgenic
TGF = transforming growth factor
TRPC3 = TRP canonical 3
TRPM7 = TRP melastatin-related 7

re-entry circuits, by virtue of spatially heterogeneous "fibrillatory conduction" (5). The ways in which the 4 principal mechanisms (electrical remodeling, structural remodeling, autonomic nervous system changes, and Ca^{2+} handling abnormalities) occur and promote AF are detailed in the following text.

Electrical Remodeling

Atrial electrophysiological properties are governed by ion channels, pumps, and exchangers, any of which can be altered by atrial remodeling. The principal components of electrical remodeling identified to date include decreased L-type Ca^{2+} current (I_{CaL}, carried by L-type Ca^{2+} channels [LTCCs]), rectifier background K^+ current (I_{K1}) and constitutive acetylcholine-regulated K^+ current (I_{KACh}), and abnormal expression/distribution of the gap junction connexin hemichannels that connect cardiomyocytes electrically. Electrical remodeling creates a re-entry-prone substrate.

Down-regulation of I_{CaL}. Ca^{2+} handling in atrial cardiomyocytes is shown schematically in Figure 2. For more details, see reviews by Wakili et al. (2) and Nattel and Dobrev (4). Ca^{2+} enters through LTCCs during AP depolarization, triggering a secondary release of large amounts of Ca^{2+} from the sarcoplasmic reticulum (SR) Ca^{2+} stores via SR Ca^{2+} release channels called ryanodine receptors (RyR2s). This Ca^{2+}-induced Ca^{2+} release induces myofilament movement/cell contraction. SR Ca^{2+} stores are governed by the balance between Ca^{2+} release from the SR into the cytosol via RyR2 channels and Ca^{2+} uptake into the SR via the SR Ca^{2+}–adenosine triphosphatase (SERCA2a). Under basal conditions, SERCA2a function is limited by the inhibitory subunit phospholamban (PLB). Most Ca^{2+} in the SR is bound to the buffer calsequestrin. In situations of adrenergic stimulation or cellular Ca^{2+} loading, Ca^{2+}/calmodulin kinase type 2 (CaMKII) and protein kinase A become activated, phosphorylating RyR2s (increasing their open probability) and PLB (causing it to dissociate from and disinhibit SERCA2a). While this system is adaptive under conditions of acute stress-related increases in demand for cardiac work, sustained Ca^{2+} loading and CaMKII activation cause abnormal diastolic RyR2 Ca^{2+} releases. The released Ca^{2+} is handled via transmembrane extrusion through the Na^+/Ca^{2+} exchanger (NCX), which carries an inward current that causes phase 4 membrane depolarizations known as delayed afterdepolarizations (DADs).

During AF, the high atrial rate causes accumulation of intracellular Ca^{2+}, engaging homeostatic defense mechanisms against chronic Ca^{2+} overload. The Ca^{2+}-dependent calcineurin/nuclear factor of activated T cells (NFAT) system is then activated. NFAT translocates into the nucleus and suppresses transcription of the gene encoding Cav1.2 LTCCs (*CACNA1C*), decreasing I_{CaL} (Fig. 3) (2,6). Reduced I_{CaL} decreases the inward Ca^{2+} current, maintaining the AP plateau, shortening the AP duration (APD), and thereby promoting re-entry.

Up-regulation of I_{K1}. I_{K1}, the principal background cardiac inward rectifier current, determines the resting potential and terminal phase 3 repolarization and is composed primarily of Kir2.1 subunits. Inward rectifier currents such as I_{K1} are a particularly important determinant of AF-maintaining re-entry (7); I_{K1} is up-regulated in AF (2). Another important inward-rectifier current, I_{KACh}, mediates the effects of acetylcholine and underlies the marked ability of vagal activation to promote AF by causing spatially heterogeneous increases in inward rectifier current and reductions in APD (8). AF suppresses agonist-induced I_{KACh} but enhances a constitutive form (I_{KAChc}), promoting maintenance of AF (9,10). Activation of I_{KAChc} is induced by altered protein kinase C regulation of I_{KACh} function resulting from AF-induced atrial tachycardia and Ca^{2+} loading (10).

Up-regulation of the small conductance Ca^{2+}-activated K^+ channel. Small conductance Ca^{2+}-activated K^+ channels, encoded by the genes *KCNN1*/*KCNN2*/*KCNN3*, are activated by increased levels of intracellular Ca^{2+}. Single nucleotide polymorphisms of *KCNN3* are associated with the prevalence of AF (11). Recent work suggests that rapid atrial activation, as seen in AF, may up-regulate small conductance Ca^{2+}-activated K^+ channel expression, which contributes to AF maintenance and susceptibility by abbreviating APD (12). In addition, noncardiomyocyte small conductance Ca^{2+}-activated K^+ channels could play a role in promotion of AF, for example, in fibroblasts (via fibrosis), smooth muscle cells (cardiac vascular changes and/or hypertension), or neurons (altered autonomic regulation).

Gap junction remodeling. Gap junction ion channels such as connexin 40 and connexin 43 mediate cardiomyocyte-to-cardiomyocyte electrical coupling. Connexin 43, which is encoded by *GJA1*, is expressed in all

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