Basic mechanisms of atrial fibrillation

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By its electrocardiographic inscription, atrial fibrillation (AF) is an easily recognized arrhythmia, yet it remains one of the most vexing arrhythmias to treat. The challenge stems partly from the fact that the common electrocardiographic features mask significant differences in the mechanisms and etiologies of AF in different patients. Differences in etiology suggest that treatment strategies may need to target the underlying arrhythmic mechanisms. This review briefly discusses the mechanisms and pathophysiology of AF.

TYPES AND PROGRESSION OF ATRIAL FIBRILLATION

In a minority of patients, AF exists in the absence of structural heart disease or other apparent risk factors (lone AF). Inflammatory mechanisms have been proposed as initiators of the arrhythmia in these patients.[1]

In its most common form, AF is a degenerative disease that primarily affects older people, often in association with other conditions, including hypertension, valve disease, diabetes, or lung disease. The clinical course of AF frequently progresses from transient and self-terminating episodes (paroxysmal AF) to episodes of longer duration, sometimes becoming persistent (not converting to sinus rhythm without intervention or cardioversion) or permanent (persistent despite cardioversion). Progression from paroxysmal to permanent AF involves changes in the individual atrial myocytes (eg, myolysis, hypertrophy, changes in ion channel density or distribution) and structural changes to the chamber (eg, dilatation, increased fibrosis, fatty infiltration).

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WHAT HAPPENS DURING ATRIAL FIBRILLATION

In its essence, AF is a manifestation of multiple simultaneous waves of electrical activation in the atria. The normal uniform electrical and contractile activation of the atria from the sinoatrial node to the atrioventricular (AV) node is replaced by an apparently chaotic pattern of simultaneous electrical activation at multiple sites with continuously changing, wandering pathways. Intra-atrial activations can be recorded as irregular, rapid depolarizations at rates that often exceed 300 to 400 beats per minute. The asynchrony may be due to the appearance of secondary (ectopic) pacemaker activity and/or to areas of slow conduction that facilitate the persistence of reentrant activity. Ectopic pacemaker activity may be caused by sinoatrial node dysfunction, increased vagal tone, increased sympathetic tone, or cytosolic Ca^{2+} overload.

Mechanically, this rapid, disordered atrial activation results in a loss of coordinated atrial contraction. Irregular electrical inputs to the AV node and the His-Purkinje system lead to irregular ventricular contractions. Clinically, symptoms related to AF may be due to rapid or irregular conduction to the ventricles, leading to rapid ventricular rates and irregularity of ventricular rhythm.

Loss of atrial contractility and loss of AV synchrony also may be hemodynamically detrimental. In normal subjects, loss of atrial "kick" may reduce cardiac stroke output by 20% to 30%.[2] The atrial contribution to cardiac output may be even higher in patients with heart disease. For example, loss of atrial contraction in patients with significant left ventricular diastolic dysfunction or aortic stenosis

may lead to significant symptoms, including heart failure.

ECTOPIC ACTIVITY AS AN INITIATOR OF ATRIAL FIBRILLATION

Recent studies have highlighted the importance of initiating triggers in the pathogenesis of AF, particularly in patients with lone AF. These studies have shown that ectopic activity that can trigger AF frequently arises in the region of the pulmonary veins entering the left atria.[3] Cellular mechanisms underlying this focal ectopic activation are still poorly understood.

Recognition of these initiating triggers has focused much clinical attention on electrically isolating the pulmonary veins from the remainder of the left atrium. This has been done either noninvasively using endocardial ablation[4] or via open heart surgery using the maze procedure and its variants.[5]

The pulmonary veins are a primary location for entry of vagal nerves into the left atrium.[6,7] Depending on the branches stimulated, vagal activity can cause slowing of the heart rate, slowing of AV nodal conduction, or heterogeneous shortening of atrial action potentials; these effects result from activation of the muscarinic potassium channels that are present at high density in atrial and nodal myocytes.[8] In canine models, vagal stimulation alone is sufficient to sustain AF as long as the stimulation is maintained.[9]

Patients with "vagal AF" are typically young and athletic and have high parasympathetic tone and slow basal heart rates. These patients are quite distinct from the majority of older, sicker AF patients, and require different medical management (eg, beta-blockers are contraindicated).

THE MULTIPLE WAVELET HYPOTHESIS

A "multiple wavelet hypothesis" may help to explain how AF is maintained after initiation. Under this hypothesis, AF is sustained by the propagation of multiple reentrant circuits.[10] Continuously changing, wandering pathways are determined by the local refractoriness, excitability, and conduction properties of atrial tissue. This hypothesis has been supported by electrophysiologic mapping studies in animals and humans demonstrating the presence of multiple reentrant wavelets.[11,12] The initiation and perpetuation of AF may depend on increasing atrial size and decreasing reentrant circuit wavelength, the product of conduction velocity and atrial refractory period, conditions that would support more reentrant wavelets.[13] Therefore, structural enlargement of the atria (whether directly by AF-induced hypertrophy, or indirectly as a result of underlying valvular disease) can predispose to AF persistence by allowing more reentrant circuits to sustain in the atria. Also, small reentrant circuits from shortened tissue refractoriness may enhance vulnerability to atrial tachyarrhythmias.

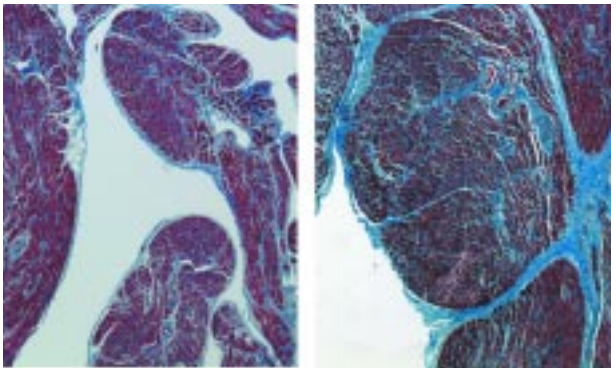

Figure 1. Right atrial appendage specimens from a 72-year-old patient in normal sinus rhythm (left) and from a 73-year-old patient with persistent atrial fibrillation undergoing maze surgery and mitral valve repair (right) (Masson trichrome stain). Fibrosis, shown in blue, is evident in both specimens, but interstitial fibrosis is clearly increased in the atrial appendage of the patient with atrial fibrillation.

THE DUAL SUBSTRATE CONCEPT

Thus, the mechanism of AF may be seen as having two substrates—one for initiation and one for maintenance. The substrate for sources initiating AF and the substrate for maintenance of AF likely underlie the spectrum of disease seen in AF and may explain its varied clinical presentation.[14] Early manifestations may include frequent atrial ectopy, often initiating from a single focal source, which may progress to repetitive bursts of atrial tachycardia and then paroxysms of AF. These paroxysms may become more frequent, longer, or even persistent as electrophysiologic and structural remodeling occur. Factors that may promote remodeling include atrial stretch, calcium overload, left ventricular hypertrophy, ventricular dysfunction, valve disease, autonomic tone, inflammation, and oxidative stress. Whether interventions directed at these factors can prevent or reverse remodeling has not yet been well studied.

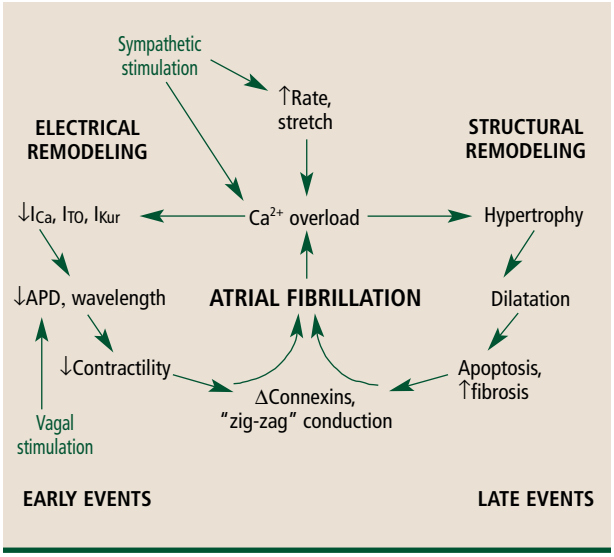

Figure 2. Schematic of the interacting remodeling pathways that underlie the progressive electrophysiologic, contractile, and structural abnormalities associated with atrial fibrillation. APD = action potential duration; I_{Ca} = inward calcium current; I_{TO} and I_{Kur} = repolarizing potassium currents. Adapted from reference 28 with permission from Elsevier.

ELECTROPHYSIOLOGIC REMODELING IS RAPID AND REVERSIBLE

Cellular electrophysiologic changes are the earliest adaptation of the atria to fibrillation or high-rate activity that contributes to the maintenance of AF. Using the burst-pacing model of AF in goats, Wijffels et al[15] showed that, in the presence of maintained fibrillation, the atrial effective refractory period (aERP) was reproducibly and rapidly attenuated, with much of the effect being evident within 24 hours of AF. Reversal of the electrophysiologic remodeling followed a time course similar to that of its onset. The effects of 5 days of AF were fully reversed within a 2-day recovery period.[16]

Action potentials in atrial myocytes reflect the integrated activity of all ion channels in the cell membrane. Electrophysiologic studies have shown that several common electrophysiologic changes underlie the abbreviated ERP accompanying both experimental tachycardia models and human AF. These include reductions in the density of repolarizing potassium currents and of the inward calcium current.[17] The net abbreviation of the ERP reflects a greater impact of AF on the inward calcium current than on the repolarizing currents. In experimental studies, the reduction in the inward calcium current is strongly implicated in the loss of contractility that accompanies AF, and both the loss and the recovery of mechanical function are well correlated with ERP recovery.[18]

SLOW CONDUCTION AND FIBROSIS AS A SUBSTRATE FOR ATRIAL FIBRILLATION

The cellular electrophysiologic changes in the atria are too rapid and too reversible to fully explain the increased persistence of AF. In the persistently fibrillating aged or failing heart, the amount of fibrosis between atrial muscle bundles is increased. This fibrosis is associated with broadening of the P wave on the electrocardiogram and impaired ("zig-zag") conduction within the atria.[19] Thus, in the presence of an initiating ectopic beat, it is easy to understand how more fibrotic atria would be more likely to sustain AF. In patients undergoing cardiac surgery, the extent of fibrosis in the right atrial appendage correlates positively with patient age and with the occurrence of AF after surgery[19] **(Figure 1)**.

Fibrosis is a long-term response to injury. In canine models, atrial fibrosis is increased following the induction of heart failure by ventricular pacing but not following rapid atrial pacing.[20] In the heart failure model, fibrosis primarily increases the heterogeneity of conduction, with little change in the cellular electrophysiologic properties of the atrial myocytes. Pretreatment of experimental animals with an ACE inhibitor attenuated, but did not prevent, the increase in atrial fibrosis.[21] It is therefore uncertain whether atrial fibrosis, once developed, can be reversed. This poses a major challenge to the pharmacologic management of AF in older patients.

PATHOLOGIC MECHANISMS IN ATRIAL FIBRILLATION–INDUCED REMODELING

AF is a high-rate rhythm that significantly increases energy utilization. Mechanisms implicated in the long-term structural and electrophysiologic remodeling processes include activation of cellular proteases (eg, calpains[22,23]), activation of Ca^{2+}-dependent kinases or phosphatases, and increased oxidative stress,[24] resulting from altered mitochondrial function and/or inflammatory mechanisms.[25] It is likely that all of these mechanisms and perhaps several more are involved in atrial remodeling. Further studies are needed to identify which, if any, of these mechanisms are effective targets for pharmacologic intervention.

CONCLUSIONS AND IMPLICATIONS

AF is a complex, multifactorial disease **(Figure 2)**. The underlying etiology is likely different in different patient subpopulations. However, electrophysiologic remodeling is commonly observed and is an early contributing factor to the persistence of the arrhythmia. Structural remodeling (at both the subcellular and tissue levels) is also frequently present and contributes to the altered tissue substrate that promotes AF maintenance.[26] Whereas experimental studies suggest that the electrophysiologic changes in AF are quite reversible, the structural changes are much slower and more difficult to reverse.[27] Available drug therapies for AF based on ion channel blockade have had limited efficacy. It will be of great interest to see whether more mechanistically based therapies, device-based therapies, or some combination of the two can improve outcomes for patients with this vexing arrhythmia.

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