# Mechanisms Underlying Atrial Fibrillation

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**KEYWORDS**

• Atrial fibrillation • Antiarrhythmic drugs • Reentry
• Rotor dynamics

Atrial fibrillation (AF) is by far the most common sustained arrhythmia seen in clinical practice.[1] AF is associated with a doubling of mortality in both sexes and is a major risk factor for stroke.[1] Specifically, AF is responsible for at least 15% to 20% of all embolic strokes.[2] Overall, AF is thought to be the underlying cause of more than 10,000 deaths per year in the United States. Patients with AF also experience a reduced quality of life compared with controls and the general population.[3] Its prevalence doubles with each advancing decade of age, with a prevalence of 9% in persons 80 years or older.[4] Although it is now clear that AF is already a huge epidemiologic problem, estimates project an increment of 2.5-fold during the next 50 years, and the projected number of persons with AF in the United States may exceed 12 million by 2050.[5] Its importance is also highlighted by the cost of AF management: AF burden has a huge impact on hospitalization costs and on overall health care.[6] It has been suggested that new antiarrhythmic drugs such as dronedarone, which has been shown to decrease hospitalizations,[7] together with implementation of guidelines to reduce the admissions that are not critical for AF care[8] may become essential to support the rapid increase in the prevalence of AF in subsequent years.

However, the authors submit that only a profound and complete understanding of the mechanisms involved in the initiation and maintenance of AF would allow the generation of more specific prevention and/or treatment of new episodes. For many years, various pharmacologic approaches have been tried to convert AF to sinus rhythm, as well as to prevent recurrences. However, many of such drugs, while effective, are associated with substantial side effects and proarrhythmia, and therefore are commonly withdrawn.[9] New, more atrial-selective $I_{Kur}$, $I_{K,ACh}$, or $I_{To}$ blocking drugs are currently under development. Atrial-selective prolongation of the effective refractory period (ERP) could terminate AF without increasing the risk of ventricular arrhythmias. New variants of older drugs are being tried with the goal of decreasing the incidence of side effects, but concurrently new and often severe adverse effects pop up.[10]

The highly successful catheter-based procedure pioneered by Haïssaguerre and colleagues[11] of ablating ectopic triggers that arise from the pulmonary veins in paroxysmal AF has progressively been extended to a much more heterogeneous population, in which unfortunately the success rate is significantly lower and frequently requires the continuation of antiarrhythmic therapy. Limitations related to the long duration of the procedure, its lack of specificity, and the presence of important side effects[12] make this approach impractical for the AF population at large.

From the foregoing it seems reasonable to conclude that generating insights into AF mechanisms from the use of appropriate experimental and numerical models may have crucial relevance in our attempts to improve patient care and to develop new and more specific therapies. This article focuses on current knowledge about such mechanisms and their translation to real clinical situations.

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## CLASSIFICATION OF ATRIAL FIBRILLATION

Several classifications have been proposed for AF, but one based on the temporal pattern of the arrhythmia has been recommended recently. Although such a classification does not account for all aspects of AF, its recommendations are based on its simplicity and clinical relevance.[13]

First, one may distinguish between patients in whom only one AF episode has been detected and patients with 2 or more AF episodes. In such cases with multiple documented episodes, AF is classified as recurrent. In either case, there is no differentiation between symptomatic and asymptomatic episodes, or in terms of the duration or the occurrence of previous, undetected episodes. If the arrhythmia terminates spontaneously it is designated as paroxysmal, but when it is sustained for more than 7 days it is termed persistent. Persistent AF usually requires pharmacologic or electrical cardioversion for termination. The term permanent is used in cases of long-standing AF (>1 year), in which the cardioversion has not been attempted or has failed.

One single patient can be classified into the 3 different categories outlined, depending on the moment.[13] For instance, some patients have episodes of paroxysmal AF for years and never develop persistent AF. Yet others develop persistent or permanent AF. In fact, in a multivariate model, age is the only independent predictor of progression to permanent AF in patients with paroxysmal or persistent AF and no concomitant heart disease or hypertension (lone AF).[14] Furthermore, the presence of premature supraventricular complexes or supraventricular tachycardia on the surface electrocardiogram (ECG) or Holter recording is associated with a decreased risk of progression to permanent AF.[14] The latter highlights the evidence that in some patients rapidly discharging foci, mainly located in the pulmonary veins, initiate the arrhythmia,[11,15] whereas in others a diseased atrial substrate has a dominant role.[16] Therefore, the progression to permanent AF could be explained by the comorbidities associated with the aging process.

In animal models, the stability of AF progressively increases with time in artificially sustained AF by fast atrial pacing.[17,18] After a period of 1 to 2 weeks the AF becomes persistent and the cardioversion success rate decreases until cardioversion is no longer possible in most cases.[19] In humans with paroxysmal and persistent AF it is difficult to know the exact burden and duration of the episodes. Thus, patients with short-lasting episodes and without structural heart disease might not develop permanent AF, because the episodes are usually not long enough to create the remodeling that has been described in animal models.[14]

The clinical relevance of this classification is related to therapeutic implications, specifically related to antithrombotic therapy, because at the present time it is the only therapy that can increase survival in patients with AF.[20] Thus, patients with lone AF who are younger than 60 years would not need antithrombotic therapy to prevent ischemic stroke, because the risk of ischemic stroke is similar to that of the expected risk of the general population.[21] The duration of AF is also important in deciding the cardioversion approach. In those episodes lasting for more than 48 hours or of unknown duration, it is necessary to rule out the possibility of an atrial thrombus by transesophageal echocardiogram or establishing appropriate anticoagulation before the cardioversion. Long-standing AF cases lasting longer than 6 months imply that the likelihood of successful cardioversion is very low, so a strategy focused on rate control and antithrombotic therapy should be pursued.[13]

## MECHANISMS OF ARRHYTHMIAS: IMPLICATIONS IN ATRIAL FIBRILLATION

### *Abnormal Impulse Formation; Abnormal Automaticity*

Automaticity is defined as the ability of some excitable cells to produce spontaneous action potentials (AP) in the absence of an external input. In the heart, under normal conditions, sinoatrial (SA) nodal cells, atrioventricular (AV) nodal cells, and His-Purkinje cells possess the property of automaticity. The APs of all 3 cell types have a characteristic ability to gradually undergo spontaneous depolarization during phase 4, which brings the membrane potential to the threshold for activation. The ionic bases of automaticity are complex and controversial. In the SA and AV nodes, it involves a decrease in $K^+$ conductance and activation of the hyperpolarization-activated current ($I_f$), as well as of inward $Ca^{2+}$ currents and the current carried by the $Na^+/Ca^{2+}$ exchanger.[22] In Purkinje cells, the $I_f$ current seems to predominate. Under pathologic conditions associated with low intracellular pH, elevated extracellular $K^+$, and excess catecholamines, abnormal automaticity may arise from either atrial or ventricular cells.[23]

In some cases of AF, it is possible to identify focal discharges from the pulmonary veins (PVs).[11] Although pacemaker cells in the PVs have not been demonstrated as yet in humans,[24] it is generally assumed that discharges in the myocardial venous sleeves[11,25] generated by cells