Pathophysiology of Atrial Fibrillation - Current Concepts

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Abstract
Atrial fibrillation (AF) is the most common supraventricular tachycardia and its incidence increases with age. The pathophysiology of AF has been studied extensively and is a subject of continuing research so that better preventive and curative therapies can be developed. The onset and sustenance of AF involves focal atrial ectopic activity and reentry mechanisms through the atrial tissue, a result of various electrical and structural remodeling processes. AF is a progressive disease which in it itself may induce further structural changes and worsening of the underlying disease (ventricular function), thus creating a vicious circle.³

A patient who presents for the first time with symptomatic AF is considered as first diagnosed AF. Clinically, recurrent AF is classified based on presentation and duration of the episodes (Table 1). AF may be asymptomatic and recorded on incidental ECG, Holter study or cardiac implantable...

Introduction
Atrial fibrillation (AF) is a supraventricular tachycardia characterized electrically by a chaotic atrial activation and a resultant mechanically ineffective atrial contraction. Due to a variable number of the total (>300 bpm) atrial impulses conducting through the atrioventricular node, the ventricular (heart) rate tends to be fast and irregular. Epidemiologically, it is the most common arrhythmia encountered in clinical practice, affecting about 2% to 3% of the population. The number of new cases each year increases with age, such that it affects about 8% of the people over the age of 80 years. AF was first documented by ECG in 1909 by Thomas Lewis (Figure 1).¹,²

![Fig. 1: ECG showing Atrial Fibrillation with Fast Ventricular Tachycardia](image)

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Table 1: Classification of atrial fibrillation

<table>
<thead>
<tr>
<th>AF category</th>
<th>Defining characteristics</th>
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<tr>
<td>Paroxysmal</td>
<td>Continuous AF that stop on its own and lasts &lt;48 hours</td>
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<tr>
<td>Persistent</td>
<td>Continuous AF that last more than 7 days and requires cardioversion</td>
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<tr>
<td>Long-standing</td>
<td>Episodic Persistent AF known for &gt;1 year</td>
</tr>
<tr>
<td>Permanent</td>
<td>AF episode more than 1 year duration (accepted or therapy failure)</td>
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electronic device episode log (pacemaker or cardioverter-defibrillator), when it is referred to as silent AF.

In addition to the above AF categories, the American Heart Association (AHA) describes additional AF categories based on underlying related disease.4

Lone AF: AF occurs in absence of clinical or echocardiographic findings of other cardiovascular disease causing left atrial (LA) enlargement or related pulmonary disease.

Nonvalvular AF: AF in absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

Secondary AF: AF occurs in the setting of a primary condition that may be the cause of AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease.

Pathophysiology of AF

Structural remodeling: Structural remodeling, particularly fibrosis, is the mainstay in many forms of AF. The primary pathologic change seen in AF is progressive fibrosis of the atria. This fibrosis is primarily due to atrial dilation. Dilation of the atria can be due to almost any structural abnormality of the heart that can cause a rise in the pressure within the heart. This includes valvular heart disease (such as mitral stenosis, mitral regurgitation, and tricuspid regurgitation), hypertension or congestive heart failure. Also, any inflammatory state that affects the heart can cause fibrosis of the atria. For example, sarcoidosis or an autoimmune disorder that causes autoantibodies against myosin heavy chains can cause atrial inflammation and subsequent atrial fibrosis. Recently, mutation of the lamin AC gene has been found to be associated with fibrosis of the atria that can lead to atrial fibrillation.

Dilated atria leads to the activation of the renin aldosterone angiotensin system (RAAS) and subsequent increase in deposition of matrix metalloproteinases and disintegrin in the atrial walls. RAAS further initiates multiple cell signaling cascades that promote increased intracellular calcium, apoptosis, cytokine release and inflammation, oxidative stress, and production of growth-related factors that also stimulate fibrosis, as well as possible modulation of ion channel and gap-junction dynamics. Angiotensin II, angiotensin-converting enzyme[ACE], and aldosterone which are components of RAAS are synthesized locally in the atrial myocardium and are increased during AF.5 This leads to atrial remodeling and fibrosis, with loss of atrial muscle mass. These changes are not sudden, experimental studies have demonstrated that patchy atrial fibrosis may precede the occurrence of AF and is progressive. Reactive interstitial fibrosis separates muscle bundles, whereas reparative fibrosis replaces dead cardiomyocytes, interfering with electric continuity and slowing conduction. Fibroblasts can couple electrically to cardiomyocytes and when increased in number, promote reentry and/or ectopic activity. Fibrosis causes paroxysmal AF progression to permanent forms.6

Triggers for Atrial Fibrillation:

Electrical remodeling promotes AF by acting on fundamental arrhythmia mechanism: focal ectopic activity and reentry. In this context two principles gained attention: factors triggering the onset and factors perpetuating AF.

Ectopic focal discharges often initiate AF. Rapidly firing foci initiating paroxysmal AF arise most commonly from the atrial myocardial sleeves that extend into pulmonary veins. Atrial myocardial fibres are oriented in disparate directions, and possess unique anatomical and electrophysiological features for their arrhythmogenic nature. The relatively depolarized resting potentials in pulmonary vein myocyte promote sodium channel inactivation and to the abrupt changes in fiber orientation and thus favors reentry. These myocytes also demonstrate abnormal automaticity and triggered activity that could promote rapid focal firing. Although the pulmonary veins are the most common sites for ectopic focal triggers, they can also arise elsewhere, including the posterior LA, ligament of Marshall, coronary sinus, venae cavea, septum, and appendages.7

The evolution of AF from paroxysmal to persistent to permanent forms through atrial remodeling can be caused by the arrhythmia itself and/or progression of underlying heart disease. Atrial electrical properties are modified by affecting expression and function of ion-channels, pumps, and exchangers, thus a reentry prone substrate is created which promotes arrhythmia. This concept is known as atrial remodeling and was first tested in animal models showing that long-term rapid atrial pacing or maintenance of AF favors the occurrence and maintenance of AF (‘AF Begets AF’).8 The development of functional reentry substrates, which are reversible on AF
Ca\textsuperscript{2+} in response to transmembrane ryanodine receptors (RyRs) release reticulum Ca\textsuperscript{2+} channels (called stores. Specialized sarcoplasmic permanent.9

Structural changes, AF becomes disease progresses to irreversible contribute to persistent AF. As atrial termination (reverse remodeling) becomes permanent.9

**Potential mechanisms for ectopic firing (trigger):** The resting potential of normal atrial cell is maintained by high resting K' permeability through the inward rectifier K' current (IK1). Although normal human atrial cells also manifest pacemaker current (If), it is overwhelmed by much larger IK1, and does not manifest automaticity. *Enhanced automaticity* is caused by changes in this balance resulting from decreased (IK1) and/or enhanced (If).10

Early afterdepolarizations (EAD) (Figure 2) involve abnormal secondary cell membrane depolarizations during repolarization phases. EAD are caused mainly by action potential duration (APD) prolongation. This allows L-type Ca\textsuperscript{2+} current (ICaL) to recover from inactivation, leading to inward movement of Ca\textsuperscript{2+} ions causing EAD. EADs caused by atrial APD prolongation underlies the increased prevalence of AF in congenital long-QT syndrome patients.11

**Delayed afterdepolarizations (DAD) (Figure 2)** are caused by abnormal diastolic release of Ca\textsuperscript{2+} from sarcoplasmic reticulum stores. Specialized sarcoplasmic reticulum Ca\textsuperscript{2+} channels (called ryanodine receptors [RyRs]) release Ca\textsuperscript{2+} in response to transmembrane Ca\textsuperscript{2+} entry. RyRs are normally closed during diastole but can open if they are functionally defective or if the sarcoplasmic reticulum is Ca\textsuperscript{2+} overloaded. When one Ca\textsuperscript{2+} ion is released during diastole, it is exchanged for three extracellular Na' ions by the Na'-Ca\textsuperscript{2+} exchanger, causing a net depolarizing inward positive-ion movement (called transient inward current [I\textsubscript{it}]) that underlies DADs. Congestive heart failure, one of the most common causes of AF, produces atrial cell Ca\textsuperscript{2+} overload and DADs.12

**Reentry-Maintenance of AF:** Reentry requires a suitable vulnerable substrate, as well as a trigger, that acts on the substrate. Such substrates can be caused by altered electrical properties (functional reentry) or by fixed structural changes (anatomical reentry). Numerous cardiac conditions may cause structural substrates for reentry, basically mediated by atrial enlargement and fibrosis. Atrial dimension affects the amount of tissue that can accommodate reentry circuits and makes long pathways available. A shortened refractory period (RP) and/or a slowed conduction velocity (CV) are the main mechanisms contributing to the perpetuation of either one or multiple reentrant circuits. The electrical and structural remodeling process promotes shortening of refractoriness of atrial tissue and thereby decreases the wavelength (WL) of reentry-circuits. The WL is the product of the refractory period (RP) and the conduction velocity (CV) [WL = RP×CV].

AF-related reentry is currently thought to occur through two main concepts: (i) the leading-circle concept and (ii) spiral wave reentry. These mechanisms may underlie AF perpetuation once continuously firing sources or triggers such as the PVs are eliminated.13

**Leading Circle concept:** (Figure 3) The mechanism involves a reentrant activity which is functional and exists without the need of an anatomical obstacle. The shorter the wavelength, the larger the number of simultaneous reentry circuits that the atria can accommodate. Conversely, increasing wavelength reduces the number of possible circuits. This reentry circuit makes smallest possible loop that allows the wave to propagate. Inside the leading circle, multiple impulses propagating centripetally render the core tissue refractory and extinguish. Conversely, centrifugal propagation of impulses at the leading edge of the leading circle depolarizes adjacent tissue as fast as possible.14

**Spiral wave Reentry:** (Figure 4) A spiral wave rotating around a microreentrant circuit adapts a shape of a rotor. Reentry is the result of periodic activity of a stable, meandering self-sustained uninterrupted spiral wave reentry. A premature ectopic activity within the atrium initiates a wavefront, which collides with the previous sinus beat which is in its refractory and
when encountering anatomical obstacles such as orifices or scar tissue.\textsuperscript{15}

**Multiple wavelet hypothesis / multiple circuit reentry:** When a wavefront collides with islets or strands of refractory tissue, it divides and fractionates into independent and eventually unstable daughter wavelets. These daughter wavelets show a very rapid activity with a variable and very short cycle length, may divide again, fuse, block, collide with each other and/or extinguish when encountering refractory tissue (functional block) or sites of slow conduction. As long as number of wavefronts does not decline below a critical level, the multiple wavelets will sustain the tachyarrhythmia, particularly when advanced structural and electrical remodelling processes are present, maintaining its survival. This causes the most frequent common final pathway in sustained AF.\textsuperscript{16}

### Neural / Autonomic Nervous System

**Parasympathetic stimulation** causes vagal discharge which enhances acetylcholine-dependent K\textsuperscript{+} current (IK\textsubscript{ACH}), reducing atrial action potential duration and refractoriness, increasing the susceptibility to reentry mechanism. Sympathetic stimulation causes \( \beta \)-adrenoceptor activation increases diastolic Ca\textsuperscript{2+} leak and promotes DAD by hyperphosphorylating RyR2s, which promotes automaticity and triggered activity. Atrial sympathetic hyperinnervation occurs in persistent AF patients. Autonomic neural remodeling contributes to positive feedback loops that promote AF persistence and recurrence. Plexi of autonomic ganglia that constitute the intrinsic cardiac autonomic nervous system are located in epicardial fat near the pulmonary vein-LA junctions and the ligament of Marshall. Stimulation of the ganglia in animals elicits repetitive bursts of rapid atrial activity. Suppression of autonomic signaling may contribute to the efficacy of Pulmonary Vein-directed ablation procedures for AF.\textsuperscript{17}

**Tachycardiomyopathy:** Atrial contraction contributes \( \sim 20\% \) of left ventricular stroke volume at rest. Loss of atrial contraction may markedly decrease cardiac output, particularly when diastolic ventricular filling is impaired by mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy. The effects of AF on ventricular function and the consequences of LV dysfunction on the atria lead to a vicious circle, with AF promoting ventricular dysfunction, ventricular dysfunction causing atrial remodeling changes that promote AF. Hemodynamic consequences of AF can result from a variable combination of suboptimal ventricular rate control, loss of coordinated atrial contraction, beat-to-beat variability in ventricular filling.\textsuperscript{18}

The pathophysiological mechanism of tachycardiomyopathy is the combination of left ventricle systolic dysfunction inducing a complex neurohumoral response and the cardiomyocyte calcium ion disturbances caused by rapid electrical ventricular activation. Neurohormonal activation due to low cardiac output, results in marked elevations of plasma catecholamines, atrial natriuretic peptide, rennin and aldosterone levels; further worsening the left ventricular function. Prolonged sympathetic activation leads to adrenergic receptor density and function disturbances, ion channel dysfunction, and degenerative changes in cardiomyocytes. These processes end in a loss of structural integrity and in left ventricle enlargement.\textsuperscript{19}

**Thromboembolism:** AF...
also confers an increased risk of stroke and/or peripheral thromboembolism owing to the formation of atrial thrombi, usually in the left atrial appendage (LAA). In AF, the lack of an organized atrial contraction can result in some stagnant blood in the LA or LAA which leads to thrombus formation. If the thrombus becomes mobile and is carried away by the blood circulation, called an embolus which proceeds through smaller arteries until it plugs them resulting in end organ damage. Emboli in the brain may result in an ischemic stroke or a transient ischemic attack (TIA). More than 90% of cases of thrombi associated with AF evolve in the LAA.20

Summary: The pathomechanisms causing and sustaining AF are multifactorial and very complex. The article reviews the basic pathophysiology of AF over a broad range of levels. The tissue mechanisms that maintain the arrhythmia to the relationship between clinical presentation and basic mechanisms. Ion channel and transporter abnormalities that lead to ectopic impulse formation, basic models and tissue determinants of reentry and ion channel determinants of reentry. Also the nature and roles of electric and structural remodeling, autonomic neural components, anatomic factors, interactions between atrial and ventricular functional consequences of AF, and the basic determinants of atrial thromboembolism. Symptoms of AF range from nonexistent to severe. Patients with AF vary clinically from no symptoms to fatigue, palpitations, dyspnea, hypotension, syncope, or HF. Frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events related to AF result in significant morbidity and mortality. Linking the diversity of risk factors and pathomechanisms leading to AF and the understanding of involved pathophysiological concepts may yield an improved performance in AF prevention and treatment.

References


