

# Pathophysiology of Atrial Fibrillation

**P**ATHOGENESIS OF ATRIAL FIBRILLATION  
 Atrial fibrillation (AF), the most common chronic arrhythmia, affects 3-5 million Americans;<sup>1-5</sup> causes are unknown and there are no curative therapies. Thus the main goals of treatment are palliative to improve quality of life and relieve symptoms.<sup>1-4</sup> The arrhythmia is characterized by chaotic, electrical conduction in the atria. Although considerable progress in identifying underlying mechanisms has occurred over the last ten years, the underlying cause of AF remains unknown. The main three hypotheses of underlying pathogenesis of AF are discussed below.

## Multiple random propagating wavelets.

The multiple wavelet theory hypothesizes that AF is caused by simultaneously occurring wavelets throughout the left and right atria which propagate randomly across both atria (also referred to as “mother waves” that spawn daughter waves).<sup>5-7</sup> Propagation requires a minimum number of wavelets to sustain AF which require areas of diseased atrial tissue with conduction delays and blocks including: areas of slowed conduction, shortened refractory periods, and increased atrial mass (such as large left atrial size). This hypothesis of the etiology of AF, based on Gordon Moe’s early work,<sup>8</sup> served as the theoretical basis for development of the MAZE surgical procedure and achieved widespread acceptance up until the mid-1980s.<sup>9</sup> Recent findings suggest that although randomly occurring wavelets occur which help to maintain AF, there are not random areas of initiation of these wavelets.<sup>10</sup> There are specific areas in the atria with shorter cycle lengths (left atrium more than the right, specifically the posterior free wall of the left atrium) where the wavelets of AF are more likely to begin.<sup>11</sup>

**Focal electrical discharges.** The landmark breakthrough reported by

Haissaguerre and colleagues<sup>12,13</sup> was the recognition of focal triggers at the base of the pulmonary veins, near the superior vena cava, and the posterior wall of the left atrium that could fire rapidly to initiate episodes of AF. These findings led to the theory of “focal AF” to include triggers as both a source of initiation of AF and a substrate to perpetuate the arrhythmia. Myocardial muscle tissue, a “myocardial sleeve”, has been reported to extend from the left atrium into the pulmonary veins for up to 3 cm inside the veins.<sup>6,14</sup> These triggers, found inside and around the orifices of the pulmonary veins, are now widely accepted to be an important source of initiation of AF, and when firing rapidly, may also serve to drive or maintain the arrhythmia.<sup>2,5,12,13</sup> Techniques were designed in the 1990s to map and ablate specific areas of these pulmonary vein triggers to eliminate AF with mixed results.<sup>2,5,13</sup> These findings offer an explanation as to why AF ablation strategies currently include applying energy to multiple areas of the left atrium thereby increasing the chances of success.<sup>5</sup>

**Localized reentrant activity with fibrillatory conduction.** As discussed earlier, there are areas of the left atrium (especially

around the pulmonary veins and posterior wall) where atrial cells have shorter cycle lengths and variable conduction between cells, which could support reentry as a way to maintain the arrhythmia once initiated.<sup>11</sup> Atrial remodeling, or the hypothesis of ‘AF begetting AF’ was first demonstrated by Allesie et al.<sup>15</sup> Over time with repeated episodes of AF, the atrial cells remodel electrophysiologically, meaning that cell-to-cell conduction changes in a way that actually promotes sustained AF. Remodeling also promotes the activity of triggers which further sustains the arrhythmia.<sup>15</sup> The presence of fibrotic changes seen with heart disease and rapid heart rates during AF over time can cause further cellular remodeling to sustain AF.<sup>16</sup> Although the mechanisms for why this occurs is not completely understood, these findings help explain the trajectory of AF that initially starts with short, infrequent episodes that gradually develop into permanent AF over time.

**Other causative mechanisms.** Other factors potentially involved in the initiation or maintenance of AF include inflammation, atrial ischemia, autonomic nervous system activity, atrial dilation, and structural fibrosis associated with aging.<sup>2,3</sup> Researchers have reported that stretch of atrial myocardial fibers from increased atrial pressure could also lead to cell to cell conduction irregularities predisposing one to rapid reentrant rhythms such as AF.<sup>2,5,17</sup> Increased left atrial pressure, as seen with hypertension and some valvular diseases, have been hypothesized to provide a substrate for AF, but the causal link is not clear. These findings could explain the high incidence of AF seen in hypertension, but does not make clear why all patients with hypertension do not develop AF. There are also strong associations between AF, sleep apnea, and hypertension, although the mechanisms for this currently remain unclear.<sup>18</sup> A specific type of AF has been reported in endurance athletes with low resting heart rates and has been hypothesized to be due to increased vagal tone, changes in electrolytes, or bradycardia; however the exact mechanism is unknown.<sup>2,5</sup>

Genetic forms of AF have been appreci-

ated for many years, but the incidence of this subtype of AF is rare.<sup>2</sup> Over the past decade, population-based studies have suggested that AF is a heritable disease.<sup>19,20</sup> Researchers have uncovered common genetic variants that denote increased susceptibility to the arrhythmia.<sup>20,21</sup> The identification of the genetic substrate underlying familial AF will hopefully lead to the development of new therapies in the future that will help diagnose and treat all types of AF.

## RISK FACTORS

**Impact of Age.** The estimated prevalence of AF in the general population is 0.1% to 1%, increasing with age.<sup>2,22,23</sup> By 2030, it is estimated that the number of Americans 65 years of age and older will double.<sup>24</sup> Because of the aging of the population and the increasing prevalence of obesity and other risk factors for AF, the upcoming decade has been described as an “epidemic of AF”, emphasizing the importance of AF as a present and future healthcare burden. Miyasaka et al. estimated the number of persons with AF to increase three-fold over the next 38 years, from 5.1 million in 2000 to epidemic proportions of 15.9 million in 2050.<sup>1</sup> Those researchers suggest that 65% of the increase is due to the increased proportion of elderly patients as the population ages over the coming years. The reported increase in incidence

with older patients was similar to that reported from the Framingham study.<sup>1,22,23,25</sup> Approximately 12-30% of AF has been reported to occur in athletes and younger individuals as “lone AF”.<sup>2,26</sup> These patients typically have few comorbidities, yet are usually very symptomatic upon presentation.

There is a significantly higher prevalence of AF in men than women in all age categories (1.1% in men, 0.8% in women,  $p < 0.001$ ).<sup>22</sup> Researchers from the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study (N=17,974) reported that African Americans and Latinos were less likely diagnosed with AF when compared with Whites with rates of 3.6%, 2.5%, and 84.7%, respectively; however the mechanisms behind these racial differences is not known.<sup>2,3,22-24</sup> Others have supported the finding of a lower prevalence of AF in African Americans, Hispanics, and Asians compared to Whites.<sup>27</sup>

**Comorbidities.** It is well known that there are numerous risk factors that pre-dispose patients to AF, such as hypertension, increasing age, ischemic heart disease, heart failure, valvular heart disease, obesity, and diabetes.<sup>2,3,25</sup> Huxley et al<sup>28</sup> reported that modifiable cardiovascular risk factors cause more than half of AF cases, implying that not only will the incidence of AF rise with the increasing prevalence of these risk factors; but it may be an opportunity in the future to

prevent AF by focusing on reduction of these modifiable risk factors. The AHA’s strategic plan emphasizes a focus on “Life’s Simple Seven,” stressing modification of lifestyle and health risk factors, including blood pressure, weight, glucose, cholesterol, smoking, diet, and physical activity.<sup>3,29</sup>

## CLASSIFICATION SCHEMES

**New definition of Types of AF.** The recently published HRS/EHRA/ECAS guideline<sup>2,5</sup> attempts to standardize our definitions of AF for reports on future clinical and research comparisons. The new definitions have updated the previous way of classifying AF, known as the 3 ‘P’s of AF’ as described below in the table. Patients’ disease should be classified by the latest pattern of AF during a period of six months prior to presentation to their provider.<sup>2,5</sup> Also recommended is that providers record the patient’s perspective of the average duration and frequency of the episodes, how long patients have experienced symptoms of AF, and any drugs the patient may have previously been prescribed to manage the AF.<sup>2,5</sup> ■

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**TABLE. Types of Atrial Fibrillation**

First diagnosed AF	The new classification developed by the ACC/AHA/ESC 2006 Guideline committee and the 2010 ESC Guidelines committee suggests that each patient who presents with AF for the first time should be labeled as “first diagnosed AF”, regardless of the duration or frequency of the episodes. <sup>2,5</sup>
Paroxysmal	Atrial fibrillation that is recurrent in nature ( $\geq 2$ episodes) and that terminates spontaneously within 7 days is defined as paroxysmal AF. <sup>2,5</sup>
Persistent	Recurrent AF that is sustained for $\geq 7$ days is defined as persistent. <sup>2,5</sup>
Longstanding persistent	Continuous AF of greater than one year’s duration is defined as longstanding persistent. <sup>2,5</sup>
Permanent	Continuous AF where the presence of AF is accepted by the patient and provider as permanent. This definition represents a joint decision by both patient and physician to cease attempts at restoration or maintenance of sinus rhythm. If symptoms or clinical situation changes and the patient wishes to pursue catheter or surgical ablation treatment, the definition of “permanent AF” should be changed to one of the other classifications of AF. <sup>2,5</sup>
Asymptomatic AF	Asymptomatic, or silent, AF is defined as AF without symptoms. Asymptomatic AF is typically diagnosed on routine ECG. <sup>2,5</sup>

- in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm*. 2012;9(4):632-696.
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