# Epidemiology and Mechanism of Atrial Fibrillation and Atrial Flutter

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Atrial fibrillation (AF) has been recognized as a common arrhythmia since it was first described electrocardiographically in 1909.[1] In recent years it has become apparent that it is a cause of considerable morbidity and mortality. It is the most common cause of embolic stroke, accounting for approximately 75,000 strokes per year in the United States,[2] and leads to more hospital admissions than any other arrhythmia (Figure 1).[3] In addition to causing symptoms of dizziness and dyspnea, AF may precipitate heart failure, syncope, angina, and myocardial infarction, and may trigger ventricular arrhythmias in susceptible individuals.

## INCIDENCE AND PREVALENCE

Although the incidence and prevalence of AF have been studied in depth, there are limitations to these estimates. Large, population-based studies have used 12-lead electrocardiograms and therefore have undoubtedly missed episodes of paroxysmal AF. Likewise, patients may have been unaware of episodes of AF, leading to an underreporting of symptoms. In the Framingham Study,[4] approximately 7.2% of men and women aged 30–62 years developed AF when followed biennially for 30 years. These figures are in accordance with the Manitoba Follow-Up Study in which 7.5% of male air crew recruits developed the arrhythmia when followed for 44 years.[5] AF complicates about 25–30% of coronary artery bypass grafts[6] and an even higher proportion of valvular procedures. Paroxysmal AF was found in 9.9% of patients hospitalized for myocardial infarction (MI).[7] AF commonly complicates thyrotoxicosis, pneumonia, and other acute conditions, and was found listed in 5% of discharge diagnoses in a study of 27,000 consecutive hospital admissions.[8] Age is a major determinant of the prevalence of AF. The overall prevalence of 0.5–1% rises to about 10% over the age of 70.[4] In a longitudinal study of elderly subjects, the prevalence was noted to increase from 5% to 9% over a 5-year period.[9] These figures are of concern when one considers the increase in average age of the population, and the increased susceptibility of the elderly to complications of AF and its treatment. Chronic AF is slightly but significantly more frequent in men than in women.[10]

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## ETIOLOGY AND CLINICAL ASSOCIATIONS

**Cardiac conditions associated with atrial fibrillation and flutter:** Atrial fibrillation and flutter often coexist in the same patient at various times, and although there are differences in their respective mechanisms and management, they share similar etiologies. In one series of patients undergoing direct (DC) electrical cardioversion for chronic AF, approximately 30% had valvular heart disease, 20% had ischemic heart disease, 10% had lone AF, and the remainder had hypertensive heart disease, cardiomyopathy, and other miscellaneous conditions (Figure 2).[11] This is in contrast to the reported frequencies of conditions associated with paroxysmal AF in which lone AF accounted for approximately 60% of cases, with the other conditions listed above accounting in approximately equal proportions for the remainder of cases (Figure 3).[12] In developing nations, it might be expected that valvular heart disease and cardiomyopathy would feature more prominently.

In the Framingham Study,[4] the prevalence of cardiovascular conditions before onset of atrial fibrillation was compared with that in controls. Hypertensive heart disease emerged as the most common cardiac precursor, although hypertension unaccompanied by cardiomegaly or electrocardiographic evidence of left ventricular hypertrophy was only weakly related to the occurrence of atrial fibrillation, suggesting that myocardial damage was a prerequisite. The relation between ischemic heart disease and atrial fibrillation is less clear. Atrial fibrillation has consistently been associated with acute MI,[13,14] and MI associated with paroxysmal atrial fibrillation has been shown to carry a worse prognosis,[7,14] especially when the arrhythmia is of late onset.[15] Interventions such as thrombolysis, which reduce mortality, heart failure, and shock in acute MI also decrease the incidence of AF.[16] In the context of acute MI, atrial fibrillation is probably a reflection of a high-risk group rather than a cause of excess mortality. Chronic stable ischemic heart disease is less likely to be associated with AF.[4,5]

Cardiac failure is a consistent, powerful precursor of AF,[4,5] and the relation is complex, since heart disease may cause both AF and cardiac failure, and the atrial dilation produced by increased filling pressures may predispose to initiation and perpetuation of AF. AF may aggravate cardiac failure by causing a loss of diastolic filling and a rapid ventricular rate, and AF may even be the sole cause of some cases of cardiac failure (''tachycardia-mediated cardiomyopathy''),[17] a proportion of which may be reversible with restoration of sinus rhythm. Congenital heart



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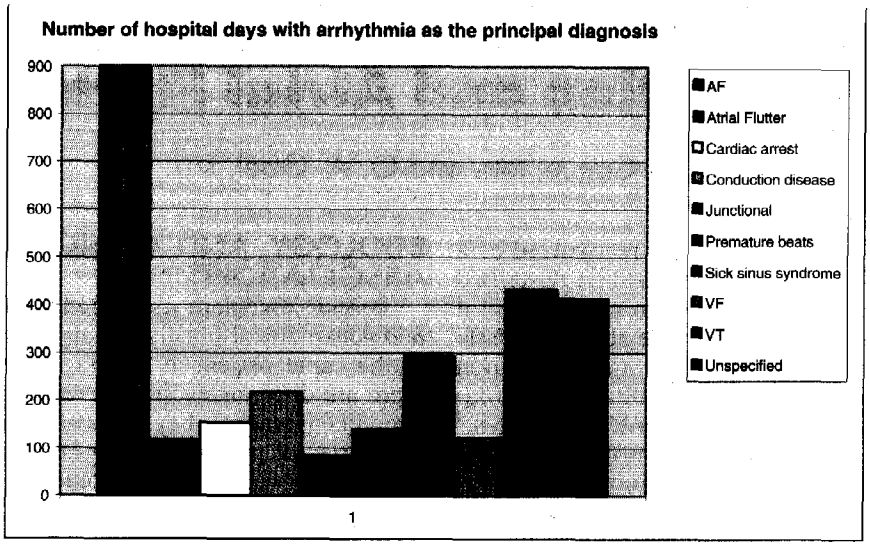


**FIGURE 1. Estimated number of days in hospital with arrhythmia as the primary diagnosis. Vertical axis shows number of days in thousands. (Reprinted with permission from *J Am Coll Cardiol.*[3])**

disease and pericarditis are also known to be associated with AF. AF occurs after coronary artery bypass surgery, with most cases in the early postoperative period.[18] The pathogenesis of AF in this group is likely to be multifactorial. Postoperative pericarditis, surgical trauma to the atria, myocardial ischemia, inadequate atrial protection during cardiopulmonary bypass,[19,20] and high circulating catecholamine levels[21] have been implicated. AF after coronary bypass surgery is strongly related to advanced age[22] and has been found to be more common in those patients who have right coronary artery stenosis compared with those who do not.[23] AF is common after valvular procedures and after surgical repair of tetralogy of Fallot.[24]

**Other conditions associated with atrial fibrillation and flutter:** Metabolic disturbances, especially thyrotoxicosis and pheochromocytoma, as well as alcohol intoxication may present with AF. Hypoxia, electrolyte disturbances, stress, and surgery may precipitate AF in susceptible individuals. Diabetes has also been associated with the occurrence of AF although the relation may not be independent of the effect of ischemic heart disease, hypertension, or heart fail-

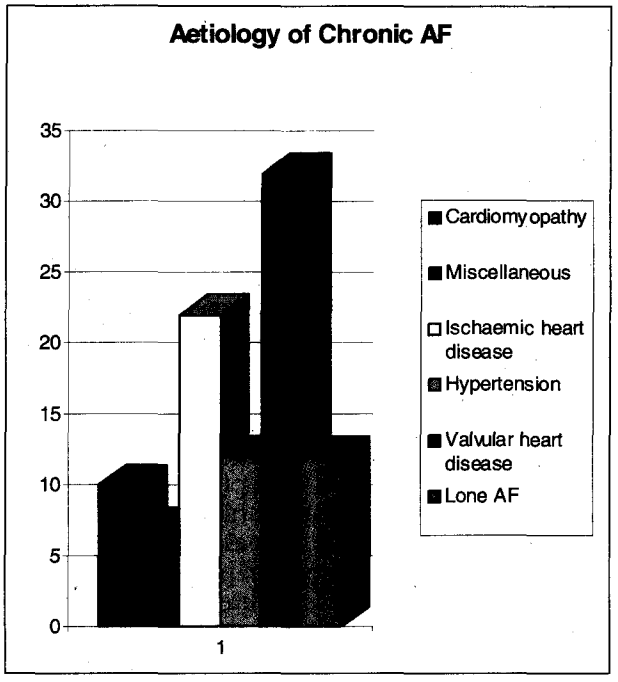


**FIGURE 2. Etiology of chronic atrial fibrillation (AF) in 246 patients undergoing DC cardioversion. y-axis = percentage. (Reprinted with permission from *Am J Cardiol.*[11])**

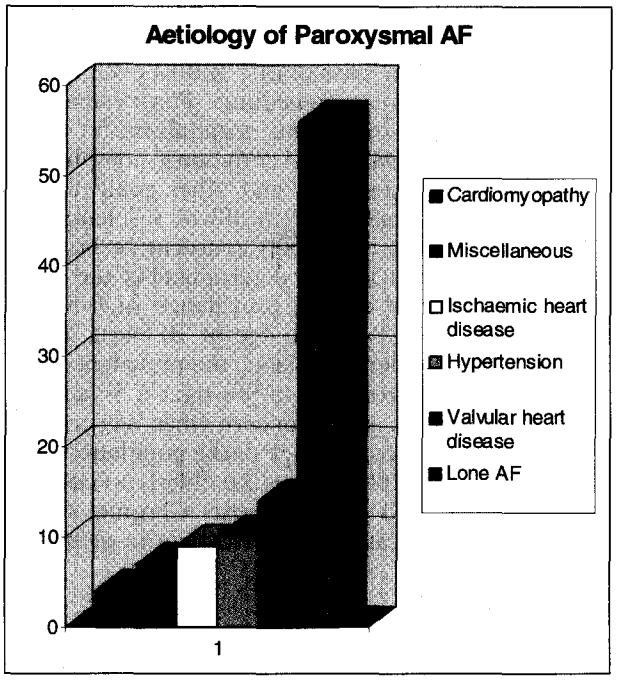


**FIGURE 3. Etiology of paroxysmal atrial fibrillation (AF) in 161 patients. y-axis = percentage. (Reprinted with permission from *J Am Coll Cardiol.*[12])**

ure.[4,5] In one study,[5] obesity was found to be an independent risk factor for AF. Pulmonary embolism and chronic pulmonary disease are known to cause AF. Atrial flutter is mainly a right atrial entity and is therefore often a complication of cor pulmonale, congenital malformations, and other diseases that affect the right side of the heart. However, like AF, atrial flutter may be an isolated finding.[25]

## COMPLICATIONS OF AF

The appearance of AF is associated with an all-cause mortality rate almost double that of controls.[4,5,26,27] This is due in part to increased risk of stroke and other embolic phenomena, but is also a reflection of the association of AF with advanced age, hypertension, heart failure, and coronary artery disease. AF increases cardiovascular mortality and the rate of sudden death.[28] AF can precipitate heart failure, angina, and ventricular arrhythmias. The association of AF with stroke is complex because other risk factors for stroke (e.g., hypertension, cerebrovascular disease, and valvular heart disease) are often present in patients with AF; however, it appears that AF is a major independent risk factor for stroke.[14,29,30] When AF complicates rheumatic heart disease, the risk of stroke is 17 times that of patients in sinus rhythm.[25] However, the risk of stroke is increased even when AF occurs in the absence of structural heart disease or other precipitating conditions ("lone AF").[2] Asymptomatic cerebral infarction detected by computed tomography is also more common in patients with chronic AF.[31] The risk of stroke in AF is greater with increasing age[32] and in patients with heart failure.[25] The risk of stroke appears to be lower in paroxysmal AF than in chronic AF,[33] although this was not confirmed in recent anticoagulation trials of AF.[34] There is a paucity of data on the natural history of atrial flutter, which often coexists with AF.[35] Although the risk of thromboembolism is thought to be lower in atrial flutter than in AF, at least one recent retrospective study suggested that the risk approaches that of AF.[36] This question needs to be addressed by prospective studies.

## MECHANISMS

**Atrial flutter:** Atrial flutter is almost unique among all atrial and ventricular arrhythmias because of the consistency of atrial rate and rhythm as well as the F-wave pattern on the electrocardiogram (ECG). This implies a constant substrate, resulting from a specific pattern of depolarization. Atrial flutter can be classified into type I, which can be divided into a common type and an uncommon type, and type II. In common type I atrial flutter, the F waves on the surface ECG are saw-toothed, with negative deflections in the inferior leads. In uncommon type I atrial flutter, broad flutter waves with an inferior axis (positive F waves in inferior leads) are exhibited on the surface ECG.

EXPERIMENTS ON MECHANISM OF ATRIAL FLUTTER: There is considerable experimental evidence that circus movement around an anatomic obstacle may cause atrial flutter. This concept was first introduced in 1920 by Lewis and coworkers.[37] In studies measuring the spread of excitation in the atria of a dog during a period of electrically induced atrial flutter, a circus movement commencing at the inferior vena cava, traveling up the crista terminalis superiorly, and then turning inferiorly around the orifice of the superior cava was mapped. It was also shown by Rosenbleuth and Garcia Ramos[38] that crushing the atrial tissue between the two caval orifices (and thus effectively creating a single obstacle to conduction) markedly facilitated the induction of flutter by rapid stimulation. By extending the lesion to the atrioventricular groove (so that the obstacle was no longer entirely surrounded by excitable tissue), the flutter suddenly terminated and could no longer be initiated.[38,39] Further studies by Scherf and coworkers,[40] later confirmed by Kimura et al,[39] which involved applying aconitine to the atrial appendage and performing sequential site mapping of the atria, demonstrated that the atrial flutter or fibrillation so produced resulted from rapid firing of the site where the aconitine was placed, thereby suggesting a different mechanism than that suggested by Lewis. We now know that application of aconitine creates an abnormal automatic focus of rapidly firing atrial tissue.[41,42] When the site of aconitine application was excluded from the rest of the atrial tissue, the tachycardia was terminated.

In studies using chronically instrumented dogs, Frame and coworkers[43] created an incision extending from the superior vena cava to the inferior vena cava with an additional lesion extending from this incision toward the right atrial appendage, thus creating a Y shape. This provided a model whereby a rapid, inducible, regular atrial tachycardia resembling atrial flutter was consistently induced by rapid atrial pacing or single atrial premature stimuli. The rhythm was stable until terminated by pacing. Based on the following observations, the mechanism of the tachycardia was found to be reentry due to circus movement: The rhythm was induced by premature impulses or overdrive, the phenomenon of entrainment of the tachycardia was observed (see below), and interruption of the pathway by critically placed ligatures terminated the tachycardia. The authors constructed maps of the activation sequence of the pathway using bipolar electrodes sutured to the atrial epicardium and with a roving probe in two anesthetized dogs. The maps suggested that the path of the reentrant impulse was around the tricuspid ring in both clockwise and counterclockwise directions. It is noteworthy that the tachycardia was much less stable when induced after creation of the intercaval lesion before the connecting incision was made, becoming more persistent and exhibiting a longer cycle length after completion of the Y-shaped incision. This results in a longer excitable gap, and means that the impulse will propagate through more completely repolarized tissue. Greater stability of the tachycardia after the transverse incision may have also resulted from the impulse being protected from block

by ectopic impulses or secondary wave fronts from other parts of the right or left atrium.

Further evidence for reentry as the mechanism for atrial flutter comes from Boineau and coworkers.[44] In a series of experiments in which atrial bipolar electrodes recorded epicardial potentials, atrial repetitive activity was induced in normal dogs by the atrial extrastimulus technique. In those dogs in which repetitive activity was induced, the crista terminalis was ligated and compressed by a loop of suture. Single extrastimuli applied at specific locations and times then produced atrial repetitive activity closely resembling true atrial flutter in 4 dogs. Slow conduction across the compressed crista terminalis (associated with complex or polyphasic waveforms), combined with inhomogeneity in refractory periods in spatially closely related fields, resulted in areas of conduction block, reentry, and subsequent mapping of circus movement tachycardia that compared favorably with their observations in a dog with spontaneous atrial flutter.[45]

Waldo and co-workers[46] first described the phenomenon of entrainment using atrial pacing from high right atrial and mid-sulcus terminalis pacing sites as a method of terminating atrial flutter. These authors subsequently demonstrated, using atrial pacing of patients with Wolff–Parkinson–White syndrome and atrioventricular reentrant tachycardia,[47] that pacing that produced entrainment indicated reentry as the mechanism of the tachycardia. Entrainment refers to capture of the reentrant circuit by the faster pacing rate without interruption of the tachycardia, so that with cessation of pacing, the tachycardia has not been interrupted. Interruption of the tachycardia occurs when, at a pacing rate critically faster than the spontaneous rate of the tachycardia, both the antidromic and orthodromic wave fronts of the same pacing impulse block during the same beat.

The transient entrainment and subsequent interruption of type I atrial flutter during rapid atrial pacing served to establish the presence of a reentrant mechanism and to distinguish it from overdrive suppression of an arrhythmogenic focus (automatic or protected reentrant focus). Certain prerequisites needed to be met before type I atrial flutter could be interrupted. These included a critical atrial pacing rate, a critical duration of atrial pacing at this rate, and often, a critical stimulus strength. They also demonstrated considerable prolongation of conduction time from high right atrial pacing sites to recording sites in the posterior inferior left atrium, which increased with increasing atrial rate, consistent with the presence of an area of functionally slow conduction in the reentry circuit (cf.)

Using a single multipolar catheter electrode to record unipolar electrograms in the right atrial cavity, and esophageal electrograms to record electrodes from the left atrium in patients, Puech[48] concluded that atrial flutter is due to circus activation in the right atrium, with counterclockwise (inferior to superior) activation of the atrial septum. This was confirmed many years later by Olshansky et al,[49] who also demonstrated the presence of an area of slow conduction inferiorly and posteriorly in the right atrium. Cosio et al[50] confirmed and expanded these observations, demonstrating that an area of block was present in the posterolateral right atrial wall, extending the central arc of block superiorly from the inferior vena cava–coronary sinus region. Furthermore, Cosio et al[51] showed that common and uncommon type I atrial flutter used the same reentrant circuit but with counterclockwise and clockwise reentrant activation, respectively.

NONUNIFORMITY AND ANISOTROPY: Any reentrant tachycardia requires the presence of nonuniformities of refractoriness and/or conduction velocity resulting in functionally different conduction pathways. Unidirectional conduction block occurs in the pathway that has a longer refractory period. Propagation is maintained in a second pathway that has a shorter refractory period, and if this wave front encounters tissue that has recovered excitability, retrograde conduction across the area of unidirectional block may occur, producing reentry. The normal atrial myocardium exhibits a certain degree of geometric anisotropy, resulting in complex and delayed conduction.[52] Anisotropic media are those that exhibit nonuniform electrical properties. Resistive discontinuities created by intercellular connections result in electrophysiologic nonuniformity (or anisotropy).[53] When an impulse is propagated, transverse as well as longitudinal conduction occurs. Anisotropy may be either uniform or nonuniform. In uniform anisotropy, smooth transverse conduction in addition to longitudinal conduction occurs. In nonuniform anisotropy, sparseness of electrical connections between cells—as can occur, for example, when fibrous tissue intervenes—can result in uncoupling of side-to-side conduction, complex waveforms, and differences in refractory periods between longitudinally and transversely conducting tissue. Thus, a premature impulse may cause reentry in single cardiac muscle bundles even when no gross macroscopic abnormality exists. Myocardial discontinuities, such as those produced by fibrosis or by dilatation, cause separation of muscle fascicles, enhance anisotropy, and result in slow, disorganized, or fragmented conduction. Changes in the repolarization properties of the atrial myocardium due either to local factors such as occur in acute infarction or by general effects of drugs or the autonomic nervous system, could also increase atrial vulnerability.

THE LEADING CIRCLE MODEL: Although the mechanism outlined above has an area of conduction block around which circus movement takes place, this area need not necessarily be an anatomic obstacle, but may be an area of functional block. In the "leading circle" model developed by Allessie and coworkers,[54] sustained periods of circus movement tachycardia were produced in rabbit atrial myocardium by the induction of a single premature impulse, and the spread of activation was measured. They found that in the absence of an inexcitable central obstacle, the center of the circus movement was in-

vaded by multiple centripetal wavelets. The resulting circuit in which the impulse circulates is defined by the electrophysiologic properties of the fibers composing the circuit, the length of the circular pathway being equal to the wavelength (the product of the conduction velocity and the refractory period) of the circulating impulse. The initiation of reentry is made possible by the different refractory periods of atrial fibers in close proximity to each other. The head of the circulating impulse is continuously encroaching upon its own tail of refractoriness. Impulses spread centripetally from the circumference of the circulating wave toward the center where cells are kept in a refractory state by the circulating impulse, hence creating a functional obstacle to conduction (Figure 4).

ANATOMIC BARRIERS IN ATRIAL FLUTTER: Recent observations in humans with type I atrial flutter using activation and entrainment mapping, guided by intracardiac echocardiography, have confirmed reentry as being the mechanism of type I atrial flutter and have enabled functional electrophysiologic properties to be correlated with specific anatomic landmarks.[55] Catheters were placed along the crista terminalis, the interatrial septum, and into the coronary sinus. A roving catheter was also introduced, and among the sites included for recordings were the anterior and posterior eustachian ridge, the anterior and posterior crista terminalis, and sites between the eustachian ridge and tricuspid annulus. All catheter positions were confirmed by both fluoroscopy and intracardiac ultrasound. Activation maps of the reentrant circuits were then obtained by measuring conduction times from the coronary sinus to each recording site. Entrainment maps were obtained by evaluating surface ECG morphologies of atrial flutter during pacing and by measuring conduction times from the pacing site to the reentrant circuit, through the circuit and back to the pacing site. Sites were thus identified that produced either manifest or concealed entrainment, and were confirmed to be either within or outside the reentrant circuit. In this study, common atrial flutter was confirmed to occur in a counterclockwise rotation. Part of the flutter circuit was mapped, confirming and expanding the work of Olshansky et al[49] and Cosio et al.[50,51] The free wall of the right atrium was activated from superior to inferior in the trabeculated area anterior to the crista terminalis, and the impulse traveled from there to a narrow isthmus of slow-conducting tissue between the eustachian ridge and tricuspid annulus. The authors identified the crista terminalis and eustachian ridge as being anatomic barriers resulting in anisotropic coupling and discontinuous conduction by finding double potentials at these sites and by observing that sites anterior to the crista terminalis and eustachian ridge were activated significantly earlier than sites posterior to these structures.

These findings supported the conclusion of Cosio et al[56] that, for successful radiofrequency ablation of common atrial flutter, a lesion should incorporate the relatively narrow isthmus of atrial tissue bounded posteriorly by the eustachian ridge and anteriorly by the tricuspid annulus. This area is not possible to identify with fluoroscopy alone. Thus, an alternative is to create a lesion between the tricuspid annulus and the orifice of the inferior vena cava, an area that has been shown to be critical in atrial flutter.[49–51,56–58]

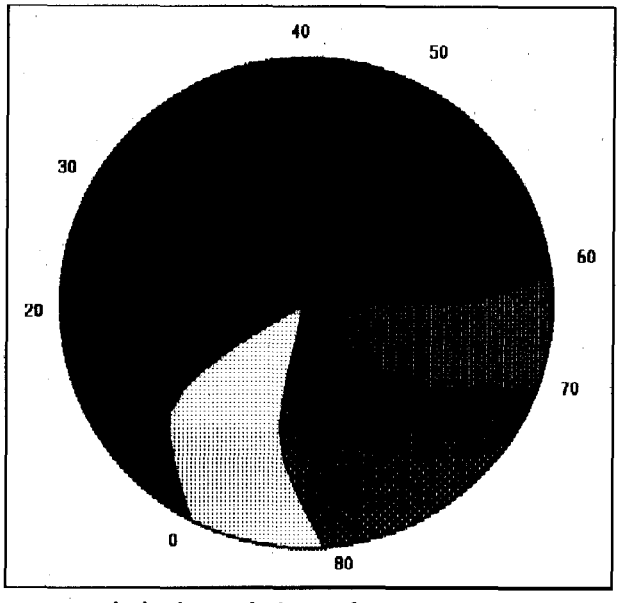


**FIGURE 4. The leading circle theory of circus movement without the involvement of an anatomic obstacle. The map shows the spread of activation in a piece of isolated left atrial muscle during sustained atrial flutter. The activation times are shown in milliseconds. (Modified from *Circ Res.*[54])**

Type I atrial flutter with a clockwise reentrant circuit can often be induced in patients who have type I atrial flutter with a demonstrated counterclockwise reentrant circuit, and the cycle length in both is similar, as are the location of double potentials detected along the length of the crista terminalis and eustachian ridge.[59] The left atrium is activated secondarily in atrial flutter and does not appear to be a necessary component of the reentrant circuit.[49,55,60]

Characteristically, atrial rates in type I atrial flutter are in the range of 240–340 beats/min, while those in type II atrial flutter are faster, in the range of 340–430 beats/min.[61] The ventricular response rate varies with the refractory properties of the atrioventricular conducting system. In contrast to type I atrial flutter, type II atrial flutter cannot be terminated by rapid atrial pacing,[61] so that reentry as a mechanism is in doubt. However, it has been suggested that the mechanism may be leading circle reentry,[62] which is difficult to interrupt with pacing unless the stimulus is introduced in or very near the reentrant circuit.

**Atrial fibrillation:** At least one of the mechanisms already discussed for atrial flutter, namely, a single focus (automatic or localized reentrant), may also apply to atrial fibrillation, and AF is known to occur frequently in patients with atrial flutter. Alternation of fibrillation and flutter during a 24-hour period was documented in 35% of postoperative patients using ambulatory ECG monitoring.[35]

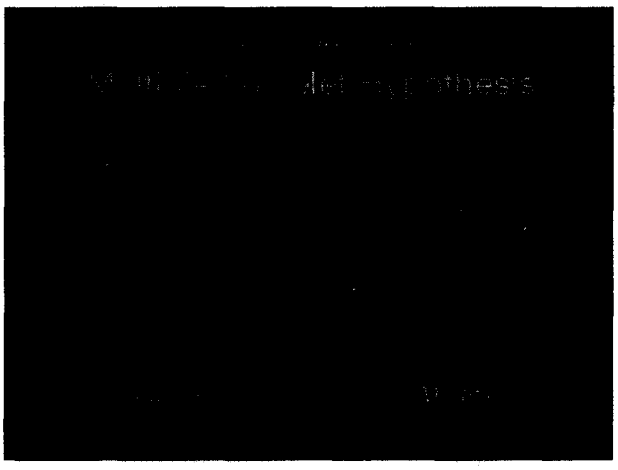

**FIGURE 5. In the multiple wavelet hypothesis, wavelets propagate around the atria in shifting patterns.**

THE MULTIPLE WAVELET HYPOTHESIS: In 1959 Moe and Abildskov[63] conducted experiments on dogs in which they found that AF induced by vagal stimulation and atrial pacing continued after the cessation of pacing, but that AF induced by application of aconitine stopped after isolation of the site of aconitine application. Based on analysis of their data, they proposed a mechanism for AF whereby multiple wavelets wandering through the atrial myocardium around islets or strands of refractory tissue were responsible for the rapid, nonuniform atrial activation seen in the type of AF not due to a single site firing rapidly. In 1963, Moe[64] confirmed the theoretical feasibility of this mechanism with a computer model, and noted the importance of sufficient atrial mass and a short refractory period in the sustainability of the arrhythmia (Figure 5).

Allessie and coworkers[65] tested the multiple wavelet hypothesis by mapping the spread of excitation during rapid pacing–induced AF in isolated, blood-perfused canine atria in which acetylcholine was added to the perfusate. They confirmed the presence of multiple wandering wavelets, which exhibited various properties such as fluctuations in size and changes in direction of propagation. Wavelets were seen to extinguish, divide, and combine with neighboring wavelets. They also encountered new wavelets that appeared to enter one atrium from the neighboring atrium. They confirmed that the more wavelets present, the more likely it was that the arrhythmia would self-perpetuate. Studies in humans that used high-density epicardial mapping of the free wall of the right atrium in patients with Wolff–Parkinson–White syndrome undergoing surgery for interruption of their accessory atrioventricular connection, and in whom AF was induced with rapid atrial pacing, showed patterns of excitation consistent with the presence of multiple wandering wavelets.[66]

THE CONCEPT OF THE WAVELENGTH: The significance of the wavelength for circus movement in the heart was first discussed by Lewis[67] and later defined by Wiener and Rosenbleuth[68] as the product of conduction velocity times the effective refractory period. Thus, the combination of slow conduction and a short refractory period results in a short wavelength. A short wavelength has been shown in a dog model to be a powerful predictor of inducibility of atrial flutter by premature stimuli.[69] This concept is also of importance when considering the mechanism of atrial fibrillation. The size of the wavelength determines the number of activation wavelets that can circulate through the atrial myocardium, with the smallest wavelengths producing the largest number of wavelets and hence greater sustainability of the arrhythmia. This was verified in experiments using dogs[69] in which it was shown that premature stimuli associated with the smallest wavelengths were the most likely to induce AF, those associated with longer wavelengths induced atrial flutter, and those associated with still longer wavelengths induced atrial repetitive responses only. The authors calculated critical cutoff values for the wavelengths required to induce each of these rhythm disturbances. The wavelength emerged as a far more sensitive predictor of arrhythmia inducibility than either conduction velocity or the refractory period alone. A finding of potentially important clinical relevance was that drugs that prolonged the wavelength were the most likely to terminate AF. Other studies on dogs have shown that the termination of experimental AF by propafenone, procainamide, and sotalol is associated with an increase in the wavelength, especially at rapid atrial rates.[70] Flecainide is thought to act in a similar way.[71]

ATRIAL VULNERABILITY: There have been several studies in humans examining the electrophysiologic substrates that result in atrial vulnerability to AF. In studies during AF, it is not possible to determine effective refractory periods by the extrastimulus technique. Thus, some investigators have used mean intervals between intra-atrial potentials (the ff interval) during AF as an index of the refractory period.[72,73] This concept results from the notion that, during fibrillation, cells can be reexcited as soon as their refractory period ends. The ff interval has been shown to correlate closely with the atrial refractory period.[73]

The other main determinant of wavelength is the conduction velocity, which during AF has been measured by calculating the inverse of the width of intra-atrial potentials, and a "wavelength index," which has been calculated by multiplying this with the ff interval.[72] This wavelength index has been shown to have clinical relevance in that it is longer in patients with AF that terminated spontaneously after induction compared with that in those in whom it did not. It was also shown to increase during AF that terminated after administration of disopyramide. Slow conduction has been shown in several studies to be more common in patients with paroxysmal AF.[74–76] Repetitive atrial firing following a single premature stimulus has been shown to be more common in patients with paroxysmal AF.[77] The same applies to fragmented atrial activity (disorganized atrial activity recorded in atrial electrograms).[76,77]

Tissue mass is an important determinant of the space available for wavelets to circulate. Hence, larger tissue masses can support more wavelets and therefore might be expected to favor the induction and sustainability of AF.[78] Atrial size has long been known to be important, in fact critical, in the ability to generate atrial fibrillation, and it has been shown to correlate with increased vulnerability to AF in humans[79] (Table I).

**TABLE I** Summary of Electrophysiologic and Pathologic Changes Associated With Atrial Fibrillation

| |
|---|
| **Electrophysiologic changes** |
| Short refractory period |
| Areas of slow conduction |
| Small wavelength (combination of above 2 factors) |
| Repetitive atrial firing in response to premature stimulus |
| Fragmented atrial activity |
| Increased dispersion of refractory periods |
| **Pathologic changes** |
| Enlarged left atrium |
| Increased fibrosis of internodal tracts and AV node |
| Damage to SA node |
| Hypertensive heart disease |
| Coronary artery disease |
| Valvular heart disease (especially rheumatic mitral valve disease) |
| Congenital heart disease (especially atrial septal defect) |
| Postoperative heart disease |
| Infiltrative diseases (e.g., amyloidosis and sarcoidosis) |
| Pericarditis |
| Tumors of the heart |
| Alcoholic heart disease |
| Senile amyloidosis |
| Hypertrophic cardiomyopathy |
| Miscellaneous (e.g., myotonia dystrophica and other forms of muscular dystrophy) |

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## AUTONOMIC FACTORS

The autonomic nervous system has been extensively studied in relation to the mechanism of atrial fibrillation and flutter. The heart and blood vessels are supplied by both afferent and efferent autonomic nerve fibers that, through both sympathetic and parasympathetic mechanisms, have profound effects on the genesis, perpetuation, and rate of many arrhythmias. Likewise, arrhythmias themselves influence the autonomic nervous system through effects on blood pressure and atrial and ventricular diastolic pressure. For example, the fall in blood pressure that sometimes accompanies rapid supraventricular tachycardia activates the sympathetic nervous system through reduced afferent activity from the carotid sinus to the vasomotor center and causes the rate to increase further. This may help to explain the transformation of paroxysmal supraventricular tachycardia to AF as occurs in patients with the Wolff–Parkinson–White syndrome. It has been observed in such patients that an increase in the rate of the tachycardia precedes onset of AF and that this transformation may be blocked by propanolol.[80] The rise in atrial and ventricular diastolic pressure during tachycardia can activate mechanoreceptors (C fibers), resulting in a reflex withdrawal of sympathetic tone, an increase in vagal tone, and subsequent slowing of tachycardia. While the sympathetic and parasympathetic systems generally have opposite effects and tend to inhibit each other, their anatomic distribution is not uniform and is incompletely understood. Furthermore, functional responses to cholinergic stimulation occur within milliseconds, whereas those to adrenergic stimulation take seconds for target activation.[81]

Autonomic factors involved in the mechanisms of paroxysmal AF have been examined in depth by Coumel.[82] They have postulated 2 different patterns, one with a predominantly vagal etiology and another in which adrenergic mechanisms induce AF. Vagal mechanisms appear to predominantly precipitate paroxysmal AF in hearts in which no evidence of structural disease can be found with conventional tests. Episodes of paroxysmal AF occurring at night and postprandially, alternating with periods of atrial flutter and preceded by bradycardia, suggest a predominantly vagal mechanism.[82] Vagal stimulation, by shortening the refractory period, causes wavelength shortening, which favors reentry. This may be a heterogeneous effect, causing an increased dispersion of refractoriness. Increased dispersion of refractoriness, along with shorter refractory periods, has been shown by the extrastimulus technique to be a feature in patients with idiopathic paroxysmal AF in some studies.[83] As long as vagal tone is high, the arrhythmia will be sustained,[84] which may explain why AF in such patients commonly occurs during sleep, terminating in the morning. This form of paroxysmal AF is found more frequently in men and is seen in relatively young patients.[82]

Diseased hearts tend to lose physiologic vagal predominance, and adrenergically induced arrhythmias are more commonly seen.[82] The far less common adrenergically mediated form of paroxysmal AF would be suggested by daytime attacks occurring at times of stress in patients with heart disease. Adrenergic factors involved in the precipitation of AF may include automatic and triggered activity in the atria and a decrease in action potential duration favoring microreentry. They are of importance in AF associated with thyrotoxicosis and pheochromocytoma, and probably are also instrumental in postoperative atrial arrhythmias. Determining which autonomic mechanism predominates in any particular patient can help to guide therapy in paroxysmal AF. For example, $\beta$ blockers are useful in adrenergically mediated paroxysmal AF, but are relatively contraindicated in patients with predominantly vagally mediated paroxysmal AF.

## ALCOHOL AND ATRIAL FIBRILLATION

AF is associated with alcohol, both in the context of brief periods of increased intake in patients without obvious heart disease (the "holiday heart syndrome") and as part of the clinical spectrum of alcoholic cardiomyopathy. Alcohol has also been

shown to decrease action potential duration[85] and can cause a delay in atrial conduction, thus shortening the wavelength. Alcoholic cardiomyopathy is associated with decreased right atrial refractory periods.[86] Alcohol may precipitate AF through adrenergic mechanisms, since it causes release of catecholamines from the adrenal medulla[87] and release of cardiac stores of norepinephrine.[88] Withdrawal from chronic alcohol is associated with a diffuse adrenergic discharge.

## ATRIAL FIBRILLATION AS A SELF-PERPETUATING ARRHYTHMIA

Finally, recent observations strongly suggest mechanisms by which AF itself causes electrical changes in the atria, thereby encouraging the progression of paroxysmal AF to chronic atrial fibrillation ("atrial fibrillation begets atrial fibrillation").[89] In a study using goats with multiple electrodes sutured to the epicardium of both atria, AF was induced by atrial pacing on an automatic repetitive basis (i.e., when sinus rhythm recurred, AF was automatically reinduced by bursts of rapid pacing stimuli). It was found that the duration of paroxysmal AF progressively increased and then became sustained. The "rate" of fibrillation also progressively increased (i.e., the interval decreased). The atrial refractory period progressively shortened and showed a reversal of the normal adaptation to heart rate, in that the refractory period shortened rather than lengthened at longer pacing cycle lengths. These changes were rapidly and fully reversible. Intra-atrial conduction velocity remained largely unchanged, and there was no significant change in dispersion of refractoriness. Recent studies in humans[90] have shown that short episodes of induced AF resulted in shortened refractory periods and hence shortened atrial wavelength. These intriguing observations provide a mechanism whereby AF could perpetuate itself, and they support early and vigorous attempts at reducing the frequency of episodes of paroxysmal AF.

## CONCLUSION

AF is a common arrhythmia that causes distressing symptoms in many patients and is often associated with a poor prognosis. In addition to appropriate anticoagulation in selected patients in whom the arrhythmia cannot be cured, the foregoing newly described details of its electrophysiologic mechanisms should improve clinical management and prognosis.


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