# Electrophysiology of atrial fibrillation: evolving insights

Leonardo Cal , Claudio Pandozi, Filippo Lamberti, Riccardo Riccardi*, Maria Luisa Loricchio, Antonio Castro, Fiorenzo Gaita*, Massimo Santini

*Department of Cardiac Diseases, San Filippo Neri Hospital, Rome, *Division of Cardiology, Hospital of Asti, Asti, Italy*

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**In the last few years many studies have been performed to better understand the pathophysiological nature of atrial fibrillation (AF). These recent observations provide new insights into the initiation and perpetuation of AF, underlying the importance of the pulmonary veins as major sources of atrial triggers and introducing new concepts such as atrial electrical remodeling and spatial heterogeneity of the electrophysiologic characteristics of this arrhythmia. The purpose of this review was to provide current knowledge about AF electrophysiology in an effort to unite old models and new concepts.**

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*Address:*

Dr. Leonardo Cal

*Via della Pedica, 348*
*00046 Grottaferrata (RM)*
*E-mail:*
*leonardo.calo@tin.it*

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia and it has recently become clear that it is not a completely benign arrhythmia as thought for a long time, but actually is associated with increased risk for cardiovascular morbidity and mortality. Even in the case of lone AF, when thromboembolic complications are relatively rare, the frequent patient discomfort and the necessity to assume drugs not tolerated or with proarrhythmic side effects, may significantly worsen the patient s quality of life. However, despite the magnitude of the problem, the main goal of pharmacological therapy, i.e. the maintenance of sinus rhythm, is still unsatisfactory. Therefore, there has been extensive effort to develop new nonpharmacological treatments to cure AF, including surgical operation, radiofrequency catheter ablation, atrial pacing, and the automatic implantable defibrillator.

However, to date, a clearly effective treatment for AF has not been yet defined. This may be explained considering both the heterogeneity of the term atrial fibrillation and the lack of knowledge of the underlying electrophysiologic mechanisms of this arrhythmia. In fact, AF may be present in very different clinical situations and, as a consequence, its electrophysiologic substrate and clinical meaning are also different. In the last few years a growing number of studies have been performed to better understand the pathophysiological nature of this arrhythmia, and new concepts and models have been proposed. These recent observations provide new insights into the initiation and perpetuation of AF, underlying the importance of the pulmonary veins as a major source of atrial triggers and introducing new concepts such as atrial electrical remodeling and spatial heterogeneity of the electrophysiologic characteristics of this arrhythmia.

The purpose of this review was to provide current knowledge about AF electrophysiology, in an effort to unite old models and new concepts. We have attempted to present basic information in a way that can be understood by the clinical cardiologist. To this aim we schematically divided this topic, according to the classic Coumel s triangle, into three different parts: the substrate, the triggers, and the role of the autonomic nervous system.

## Electrophysiological substrate

**The multiple wavelet theory.** In 1959 Moe and Abildskov[1] found that in dogs AF induced by vagal stimulation and atrial pacing continued after the cessation of pacing, but that AF induced by aconitine stopped after isolation of the site of aconitine application. Based on these results, they proposed that the perpetuation of AF depends on the continuous and random propagation of various individual wavelets through the atria. They presented their theory as follows: ... the grossly irregular wavefront becomes frac-

tionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery. It may become extinguished as it encounters refractory tissue; it may divide again or combine with a neighbor; it may be expected to fluctuate in size and change in direction. Its course, though determined by excitability or refractoriness of surrounding tissue, would appear to be as random as Brownian motion. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist [1]. A few years later, Moe et al.[2] confirmed this hypothesis using a computer model, and noted the importance of a critical atrial mass and a short refractory period in the sustainability of this arrhythmia.

Later, an experimental study in dogs by Allessie et al.[3] provided evidence of the reentrant nature of AF, with the estimation that a critical number of three-six simultaneous wavelets was required to maintain this arrhythmia. In 1991 Cox et al.[4], using high-density epicardial mapping of the free wall of the right atrium in patients with Wolff-Parkinson-White syndrome, confirmed the presence during AF of multiple wavelets fleeting in appearance and location . Microreentry or focal automaticity was not observed. The importance of multiple wandering wavelets in perpetuation of AF was confirmed by the successful development of a surgical treatment of AF[5]. In fact, multiple atrial incisions, dividing the atria into smaller segments, interrupt all possible reentrant wavelets.

In 1994 Konings et al.[6] mapped the free wall of the right atrium in a group of patients with Wolff-Parkinson-White syndrome, and confirmed Moe s theory. A wide spectrum of activation patterns of this wall was observed during AF. In attempting to quantify the degree of complexity of activation, three different types of AF were defined. In type I AF the atrial wall was activated by a single wavefront propagating uniformly without significant conduction delay. During type II AF the activation patterns were characterized either by a single wavefront associated with areas of slow conduction or multiple lines of block of conduction, or by the presence of two wavelets. In type III AF the atrial wall was activated by three or more wavelets associated with areas of slow conduction and multiple lines of conduction block.

**The wavelength.** The wavelength concept, first introduced by Lewis[7], was later defined by Wiener and Rosenblueth[8] as the product of refractory period and conduction velocity. Therefore, it expresses the distance traveled by the depolarization wave during the refractory period. Allessie et al.[3] confirmed this concept, by using epicardial electrodes in dogs, demonstrating that the slower the conduction velocity and the shorter the refractory period, the more likely it is that reentry will occur, and very short wavelengths facilitate more complex forms of reentry, such as fibrillation versus flutter. Since for AF a critical number of wandering wavelets are required, the wavelength is important for perpetuation of fibrillation.

If the wavelength is relatively long, a fewer number of waves can circulate through the atria, and AF tends to terminate spontaneously. Conversely, short tissue wavelength tends to favor the onset and perpetuation of AF and may be caused by fibrosis and inflammation (decreasing conduction velocity), increased parasympathetic activity and thyrotoxicosis (shortening the refractory period), ischemia (decreasing both), and stretch that in some experimental studies has been shown to shorten refractoriness[9]. In several studies the intra-atrial conduction disturbances have been observed to characterize patients prone to AF[10]. Also, significant conduction delays may be functional, being due to locations with the longest refractory period that did not maintain rapid 1:1 capture, and thus determining disorganized atrial electrograms[11].

Finally, it might be important to characterize the antifibrillatory action of antiarrhythmic drugs in terms of their effects on the wavelength. Only drugs that lengthen the wavelength can be expected to have antiarrhythmic properties.

**The concept of critical mass.** For maintenance of AF, a critical mass of myocardial tissue is required, since larger tissue masses allow a greater space available for the wavelets to circulate[12]. Direct proof that perpetuation of AF is dependent on a critical mass is provided by the fact that in different animal species larger hearts fibrillate longer than small hearts[13] and that, in a given animal, AF is less stable than ventricular fibrillation. In humans, atrial size has long been known to be critical in the ability to generate AF, and it has been shown to correlate with increased vulnerability. The importance of atrial enlargement may explain the propensity for AF to occur in valvular disease and cardiac failure.

Thus the pathologic substrate of AF should be considered as a balance between the atrial mass and the wavelength. In a given heart of a certain size, smaller circuits (i.e. shorter wavelength) may be easier to sustain. Conversely, larger atria allow the sustainance of more reentrant circuits even in the presence of a relatively longer wavelength.

**The role of dispersion of refractoriness.** In patients with AF an increased dispersion of refractoriness was observed[14-20]. This heterogeneity of refractoriness may provide the setting for unidirectional block when an extrasystole arising in a zone with short refractory periods fails to excite an area with long refractory periods. Probably, as Zipes wrote[21]: A heart that is homogeneous electrophysiologically ... cannot fibrillate . Recently, Ramanna et al.[20] found that patients with idiopathic AF had

an increased dispersion of refractoriness in comparison with a control group and, thus, they concluded that this increased dispersion of refractoriness may be the substrate for the enhanced inducibility and spontaneous occurrence of AF.

Several mechanisms may cause unequal shortening of the refractory period in the atria and thus create electrophysiologic heterogeneity. Between these factors it is important to underline the role of an increased vagal activity; in fact, the distribution of vagus nerve fibers to the atria may not be very homogeneous, and consequently the shortening of action potential may not be uniform in the different atrial regions[16]. Also, it has been observed that the atrial effective refractory period in the thin right atrial free wall is longer than the refractory period of the thick crista terminalis at baseline, and an increase in atrial pressure exaggerated this difference by stretching the thin segments of the atrial myocardium more than the thick segments[21]. Moreover, fibrosis may result not only in slow conduction but, leading to progressive electrical uncoupling, may determine an increase in the dispersion of refractoriness. In fact, in well-coupled cells the current flow during repolarization will tend to decrease dispersion by prolonging action potentials with a short duration and by shortening action potentials with a long duration[22].

**Different kinds of reentry involved in atrial fibrillation.** Different kinds of reentry have been suggested to be present during AF. We can schematically distinguish anatomical and functional reentry.

The dissection of the human atria highlights the complex atrial geometry, which is characterized by: 1) holes (orifices of superior and inferior cava vein, coronary sinus, pulmonary veins and fossa ovalis); 2) thick axial pathways that intervene with thin atrial myocardium (e.g. crista terminalis, pectinate muscles); 3) presence of natural blockades (e.g. mitral and tricuspid annulus, Eustachian ridge, veins) and passages (Cosio s isthmus). This complexity of atrial geometry may provide the anatomic basis for a reentry circuit. The anatomically determined reentry is characterized by a fixed circuit, relatively stable, susceptible to entrainment and thus with a fully excitable gap.

During AF functionally determined reentry has an important role. The first description of reentrant excitation in the heart in the absence of anatomic obstacles was described by Garrey[23] in 1914. Sixty years later in a classic series of experiments, Allessie et al.[24] provided the first direct experimental demonstration that the presence of an anatomic obstacle is not essential for the initiation or maintenance of reentry. These authors on the basis of their observations formulated the leading circle concept, where the dynamics of reentry is determined by the smallest possible pathway in which the impulse can continue to circulate in which the stimulating efficacy of the circulating wavefront is just enough to excite the tissue ahead which still is in its relative refractory phase [24]. Thus, the head of the leading circle bites into its own relative refractory tail. The maintenance of the leading circle is due to repetitive centripetal wavelets that keep the core in a constant state of refractoriness. Therefore, the leading circle reentry is characterized by an unstable circuit changing size and location, not susceptible to entrainment and thus without a fully excitable gap.

In the high density mapping of human AF[6], besides the leading circle reentry, another kind of reentry was observed in the free wall of the right atrium: the random reentry. During this form of reentry a propagating wavelet reexcites an area which shortly before was activated by another wavelet . The random reentry is unstable, susceptible to entrainment and with an excitable gap.

Recently, Jalife[25] proposed a different kind of functional reentry: the spiral wave reentry. It has been defined as a vortex-like reentry determined by a wavefront that curls at its broken end and begins to rotate. An obstacle, such as a scar or a bundle of connective tissue, may break the wavefront in its path. However, the wave breaks may also occur at the intersection of a wavefront with the tail of another propagating wave even in the absence of anatomic or functional discontinuities. A recent study by Athill et al.[26] highlights the difference between the leading circle and spiral wave reentry: in the former the core is kept permanently refractory, and in the latter the core is excitable but not excited. The complicated atrial structure, particularly the highly heterogeneous network of pectinate muscles, may be responsible for the genesis of this kind of reentry[27,28]. More importantly, using high resolution video imaging, it has been observed that stable localized sources are responsible for AF maintenance in the isolated sheep heart[28]. These sources correspond to vortex-like reentry around minuscule cores: in fact, the spiral waves rotate around microreentrant circuits of $\approx$ 1 cm.

**Regional entrainment of atrial fibrillation: evidence of an excitable gap.** It has been observed that both in induced AF in animals and in humans the capture of the atrium by rapid pacing is possible[29-33]. Moreover, Pandozi et al.[34] during spontaneous chronic AF in humans achieved a local capture particularly in the right atrial wall where the electrical activity was more organized.

These observations imply that an excitable gap may be present during AF. Probably, the beat-to-beat variation in local fibrillation intervals can at least in part be explained by a variable excitable gap. Thus, an interval of excitability could be present between the wandering wavelets, excluding the hypothesis that the multiple waves should reenter soon after they have recovered from the previous activation. Although the relative contribution of the different kinds of reentry to the AF perpetuation could be very different, both anatomical and functional reentry (with the exception of leading circle reentry) may explain the presence of an excitable gap during AF.

**Regional differences of atrial electrophysiological properties.** Recent mapping studies in humans[35-38] have clearly demonstrated that during AF different areas of the atria may have a different electrophysiologic behavior. Some regions show a fast, irregular and disorganized atrial activity while, simultaneously, others are activated by relatively organized and almost regular electrical wavefronts. It can be presumed that although the atria as a whole participate in the process of AF not all the parts of the atria contribute equally to the perpetuation of the fibrillatory process[39]. The regions showing the most irregular and disorganized activity may be crucial for the maintenance of the arrhythmia, while other regions with a relatively regular activation may be only bystander. Figure 1 shows an example of extensive atrial mapping demonstrating the simultaneous presence of disorganized electrical activity in some regions and organized activity in other areas.

The electrical activation along the right lateral wall is much more organized[35,36,38] and generally shows a craniocaudal sequence[40]. Thus, when the atrial activity was more regular and organized probably due to the presence of macroreentrant circuits involving the right atrium, the impulse propagation during AF had a behavior similar to common atrial flutter. Conversely, the posterior, posteroseptal and septal regions of both atria are the sites where the most irregular activation is generally present in most cases during AF. The importance of the septum in the perpetuation of AF has recently been highlighted by Kumagai et al.[41] who showed that in dogs a reentrant circuit in the septum may be a major factor in the maintenance of this arrhythmia. Particularly, many studies point to the relevance of the posterior region of the left atrium as a critical area in the maintenance of AF, both in animals[42] and in humans[43-47]. In dogs Morillo et al.[42] observed the presence of the shortest FF interval during AF in the left posterior wall; the cryoablation limited to this zone prevented the reinduction of AF in more than 80% of cases. During intraoperative mapping Harada et al.[44] observed that in 9 of 10 patients with chronic AF and mitral valve disease, the left atrium had a regular and repetitive activation pattern, and thus it could act as an electrical driving chamber for AF. Sueda et al.[46], in the same subgroup of patients, showed that the posterior wall was the area with the shortest FF intervals; the surgical isolation of this area restored the sinus rhythm in most patients. The importance of the left atrium in the maintenance of AF has also been confirmed by the results obtained by percutaneous catheter ablation of AF[43,45,47] showing a significant increase of the success rate when linear lesions were applied within the left atrium.

This nonuniform spatial behavior of electrical activity during AF might be explained by different anatomic and histologic peculiarities of the various parts of the atria, the presence of areas of slow conduction or intraatrial conduction block due to both structural or functional abnormalities, and the role of the local atrial refractory period in the different regions. The spatial dispersion of refractoriness can produce fragmented electrograms by the presence of action potentials in different muscle bundles that are activated out of phase[39]. An interesting hypothesis[11] may be that the locations with disorganized atrial electrograms are those with the longest refractory period that did not maintain rapid 1:1 capture determining low-amplitude action potentials.

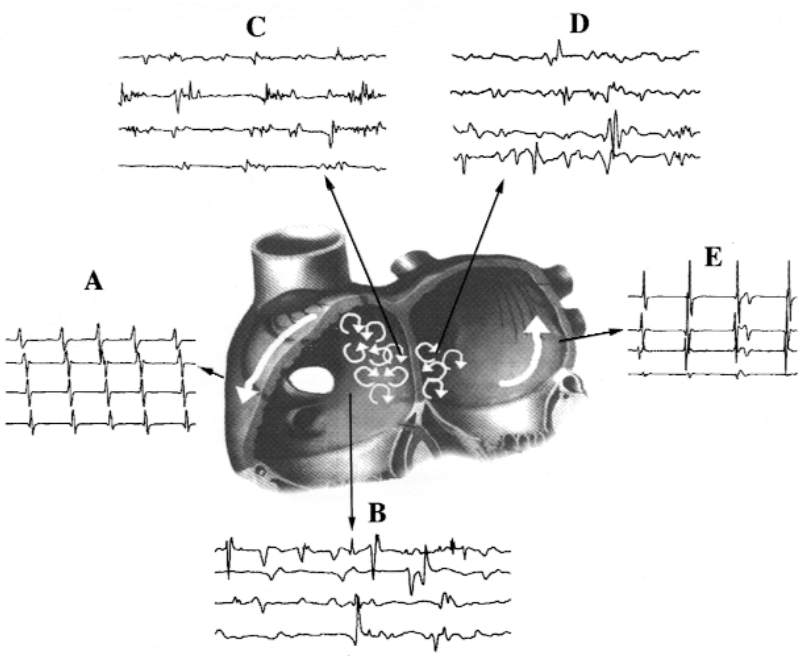


**Figure 1.** *Extensive atrial mapping in a patient during atrial fibrillation. An organized and almost regular atrial activity with a counterclockwise activation (like common atrial flutter) is present along the right lateral wall* (A)*. In the right posterior wall* (B)*, right septum* (C) *and left septum* (D) *is present an irregular and disorganized atrial activity (double potentials and fragmented electrograms). The electrical activity recorded from the coronary sinus is regular and organized* (E)*.*

**The atrial electrical remodeling: atrial fibrillation begets atrial fibrillation .** It is well known that AF episodes have a tendency to become more frequent over time, often evolving in persistent AF. Moreover, the successful restoration and maintenance of the sinus rhythm is more difficult in patients with AF of longer duration[48,49].

Attuel et al.[50] first suggested that a poor or absent adaptation of the atrial refractory period to changes in pacing rate could be a cause of chronic AF in humans.

Recently, several experimental studies in animal models[18,19,42,51,52] observed that prolonged pacing-induced AF favors a progressive decrease in the atrial effective refractory period[18,19,42,51,52] and conduction velocity[19,42,52] and, thus the shortening of the wavelength of the reentrant wavelets. Therefore, AF itself modifies atrial electrical properties in a way that favors the occurrence and maintenance of the arrhythmia, a process that the group of Allessie called AF begets AF [51]. Furthermore, it has been observed that tachycardia-induced effective refractory period remodeling is spatially nonuniform, with an increase in the dispersion of refractoriness among various atrial regions[18,53]. This nonuniform remodeling of refractoriness seems to play an important role in increasing atrial vulnerability to AF induction and the duration of induced AF[18].

In humans, a short duration of AF or rapid atrial pacing[54-56] has also been demonstrated to cause a significant shortening of the atrial effective refractory period, which recovered a few minutes after termination of AF. These short-term changes of atrial electrophysiology are metabolically mediated and probably have nothing to do with the true electrical remodeling. In fact, the group of Allessie[51,57] defined as electrical remodeling the long-term changes of the refractory period (and other electrophysiologic parameters such as conduction velocity) from prolonged changes in atrial rate. Also, they suggested that the term remodeling should be reserved for electrophysiological modifications that are associated with structural alterations in the myocardium. Little is known about the effects of chronic AF on atrial electrophysiology and its recovery course in humans. Franz et al.[58] observed that monophasic action potential of the right atrium after conversion of chronic AF to sinus rhythm was 130 to 150 ms shorter than in the control group. Pandozi et al.[59] found that in a group of 25 patients with chronic AF the effective refractory period was shorter immediately after cardioversion than 4 weeks after sinus rhythm restoration. However, a normal or nearly normal adaptation of the atrial effective refractory period to rate has been reported in the majority of cases. Moreover, Yu et al.[60] showed that chronic AF shortened the refractoriness, but its adaptation to rate was impaired. Hobbs et al.[61] confirmed that the modifications of atrial electrophysiology in chronic AF are reversible after cardioversion and demonstrated that this reversal is dependent on the duration of sinus rhythm after cardioversion. The presence of atrial electrical remodeling may also explain the differences in atrial organization existing between paroxysmal and chronic AF. In fact, in chronic AF both a relevant shortening of the FF interval and an increase in atrial activity disorganization were observed in all atrial regions[38].

Cytosolic calcium overload seems to be the major responsible factor for the shortening of atrial refractoriness promoted by atrial tachycardia (i.e. rapid pacing or induced AF). In fact, some studies have found that verapamil could attenuate this short-term tachycardia-induced shortening of the effective refractory period[55,62,63]. However, recent studies have observed that verapamil does not prevent long-term modifications of atrial electrophysiological properties in animals[64] and determines a shortening of atrial refractoriness in humans[65]. Thus, we can expect that this drug will favor rather than prevent the recurrence of AF, even if it could suppress the firing of the atrial foci triggering AF recurrences by its action on abnormal automaticity, and on early and delayed afterdepolarization[66]. More importantly, three recent studies[67-69] highlighted the relevant role of angiotensin II in atrial electrical remodeling.

## Anatomical and anatomo-pathological substrate

**Atrial anatomy: relationship to atrial fibrillation.** The atrial anatomy has a relevant part in determining the behavior of impulse propagation in the different atrial regions. The right atrial free wall generally presents a rather organized atrial activity during AF: probably, the crista terminalis and the tricuspid ring act as functional barriers that favor a forced path of the AF wavelets along the trabeculated right atrium[70]. The preference for a craniocaudal propagation along the right lateral wall may be related to the geometry of the trabeculated right atrium that is more likely to be activated by wavelets coming from the wide roof of the posterior right atrium than via the narrow isthmus between the inferior vena cava and tricuspid annulus. Also, tissue-specific anisotropic conduction properties of this area seem to favor a craniocaudal activation sequence[71]. The prevalent organization of electrical activity more frequently found in the recording by the coronary sinus may be due to the orientation of muscle fibers along this anatomic structure and by its proximity to the mitral annulus barrier. Furthermore, the greater presence of disorganized atrial activity in the posterior walls and septal region could be caused by the wide muscle connections in these areas and by the presence of multiple inputs coming from Bachmann s bundle, the mid-septum and the region adjacent to the coronary sinus[72]. This could favor the creation of pivot points of turning wavelets appearing as fragmented electrograms[39]. This is also supported by the observation[41] that the septal region plays an important role in the re-formation of unstable reentrant circuits with a primary involvement of the region of Bachmann s bun-

dle. The behavior of atrial activity in the atrial septum may be also related to the presence of nonuniform anisotropic characteristics of the posterior triangle of Koch[17]. Moreover, the pulmonary veins might play a critical role in the maintenance of AF both for the location itself of four holes in the posterior region of the left atrium, that can favor an anatomical macroreentry, and for the presence of myocardial sleeves extended over the orifices[73], that might determine microreentry inside these structures. Finally, as underlined by Jalife and Gray[74], it is necessary to review the classic two-dimensional model of propagation of multiple wavelets during AF. In fact, several studies[27,28,75,76] highlight the importance of the three-dimensional atrial structure, characterized by a thin epicardial sheet attached to a complex subendocardial structure in both atria, suggesting its critical role in the behavior of electrical activation during AF and its initiation.

**Anatomo-pathology of atrial fibrillation.** As regards the anatomo-pathology of AF, it should be kept in mind that this arrhythmia has multiple disparate etiologies. It is usually associated with recognizable organic heart diseases, but it may also occur in a considerable number of patients without clinically evident abnormalities (lone AF). The high incidence of AF in hypertensive, dilated, hypertrophic and valvular heart disease could be related to two main factors. First, the presence of a significant atrial enlargement determines an increase in the critical mass. Second, in all these conditions a great degree of atrial fibrosis ranging from scattered foci to diffuse involvement has been found[77,78] that can cause conduction slowing and block. In patients with sick sinus syndrome a high prevalence of prolonged and fractionated electrograms has been reported in the right atrial endocardium, particularly in the region of the sinus node[79,80]. In idiopathic AF, various factors have been suggested to favor this arrhythmia, varying from atrial myocarditis[81] or adipose replacement[82] to an imbalance of the autonomic tone[83].

Also, the importance of the aging modification in the atria should be highlighted. As aging proceeds, there is an elastification of fatty tissue, increased collagen fibers and atrial amyloid infiltration[84]. These changes in the atrial tissue related to age cause delayed and inhomogeneous conduction. Moreover, as observed by Spach et al.[85], with aging there is a loss of lateral connections between small group of cells due to microfibrosis. This determines a nonuniform anisotropy, with a further slowing of conduction during the transverse propagation compared to the longitudinal one. Also, the same authors[85] observed how premature beats did not cause a unidirectional longitudinal block in the young with uniform anisotropic tissues. On the contrary, premature stimuli in older humans with nonuniform anisotropy resulted in a unidirectional longitudinal block that, associated with the very slow conduction during transverse propagation (as above noted), easily induced a reentry.

**The triggers**

Recently, clinical and experimental studies[66,86-95] have shed light on the electrophysiological mechanisms responsible for the onset of AF. To date, on the basis of the results of these studies we can schematically distinguish three different types of AF initiation.

First, AF can occur in patients who have other forms of supraventricular tachycardia. The disappearance of AF in most patients after radiofrequency ablation of these tachycardias confirms their role in AF onset (tachycardia-induced tachycardia). The mechanism involved may be related to the increase in atrial pressure caused by the occurrence of atrial systole during tachycardia when the atrioventricular valves are closed or at least not fully open. The augmentation of atrial pressure causes atrial stretch which prolongs atrial refractoriness[96,97] and, more importantly, increases atrial dispersion of refractoriness[98].

A second interesting mode of AF initiation (focal AF) has recently been identified by the Bordeaux group[87-89]. In this group of patients the initiation and maintenance of AF is due, as confirmed by radiofrequency ablation, to a rapidly discharging focal tachycardia that is underlying and apparently driving the AF. Patients with focal AF are typically younger, without structural heart disease, with frequent runs of atrial tachycardia which may degenerate in episodes of AF. Figure 2 shows the Holter recording in a patient with the typical behavior of a focal AF . The pulmonary veins, particularly the left and right superior veins, are the source of these focal drivers in the majority of cases. The predominant distribution of foci in the superior veins matches the prevalent extension of myocardial sleeves over the orifices of these structures[50]. The mechanism underlying the focal arrhythmia may be abnormal automaticity or triggered activity because this type of arrhythmia could not be induced by programmed electrical stimulation. These clinical observations seem to confirm the original hypothesis by Sherf[99] that AF may result from a single focus firing at such a rapid rate that the remainder of the atria cannot follow synchronously.

The third and, probably, the most frequent mode of onset of AF is caused by single or multiple extrasystoles, more often particularly earlier (P on T) and/or arising in critical areas. Haissaguerre et al.[89] showed that in most patients the pulmonary veins are the source of the premature beats triggering AF. Thus, in the pulmonary veins may be present either a focal driver , continually firing during a paroxysm of AF so that when firing stops, AF ceases, or a focal trigger , with single or multiple extrasystoles favoring reentrant beats and thus the onset of AF. In a minority of patients the ectopic beats initiating AF were found in the right atrium along the crista terminalis and close to the coronary sinus ostium[86,88,89]. Furthermore, a recent study[100] has demonstrated the dominant role of single or multiple ex-

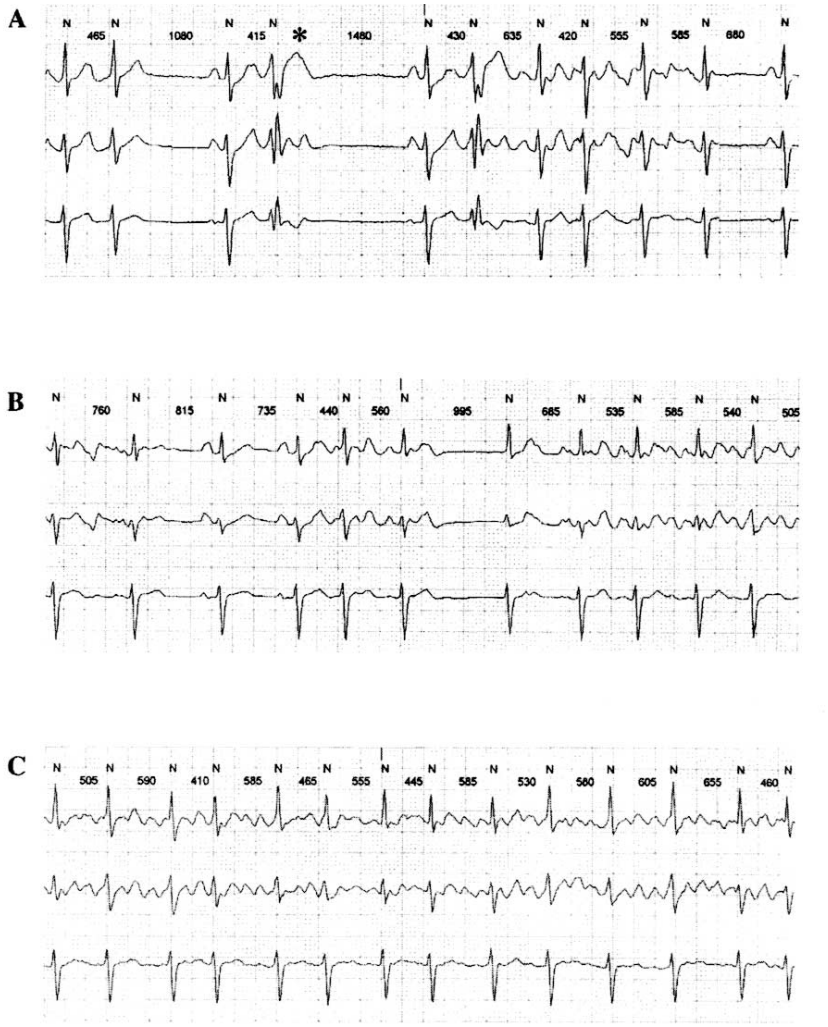


**Figure 2.** *These stripes are taken from a Holter recording obtained in a 38-year-old male with a history of paroxysmal atrial fibrillation.* Panel A *shows very early premature beats and a short run of atrial tachycardia. Some beats exhibit an aberrant intraventricular conduction and one beat (*) is blocked.* Panel B *and* C *(continuous stripes) show the induction of an episode of atrial fibrillation after a short run of atrial tachycardia.*

trasystoles originating in the pulmonary veins in the reinitiation of chronic AF after cardioversion. The ablation of these focal triggers seems to be effective in about 60% of cases.

Some questions need to be answered. How common is the presence of focal drivers as a cause of AF? How important is the role of foci in pulmonary veins in patients with structural heart disease and/or chronic AF? Why do the extrasystoles arising in pulmonary veins seem to be more able to initiate AF than extrasystoles originating in other common areas of ectopy, such as crista terminalis and coronary sinus ostium? What is the relevance of stretch of pulmonary veins in generating ectopic beats and tachycardia?

## The role of the autonomic nervous system

The autonomic nervous system has extensively been studied in relation to the mechanism of AF[15,16,21,101-105]. The vagal activity is very important in the initiation and perpetuation of AF, as shown by animal studies demonstrating that both parasympathetic stimulation and direct application of acetylcholine result in sustained AF[75,106,107]. Moreover, in humans Coumel[83,102,108] proposed the presence of a form of vagally mediated AF, characterized by a predominance in young males with no structural disease, in which the episodes of paroxysmal AF occurring at night and postprandially were generally preceded by a heart rate decrease and/or an increase in high frequency heart rate variability. As long as vagal tone is high, the arrhythmia will be sustained[15], which may explain why the arrhythmia in these patients more frequently occurs during sleep, terminating in the morning[102].

The effects of vagal stimulation on atrial electrophysiology can be summarized in two ways: 1) shortening of the action potential duration, and hence the effective refractory period, of atrial myocytes; 2) increased dispersion of refractoriness[15,16,101]. The latter effect of vagal stimulation seems to be related to a nonuniform action of vagal stimulation on the refrac-

tory period of both atria, probably because the distribution of vagus nerve fibers to the atria is not very homogeneous[15,16] and, thus, the myocardial fibers immediately adjacent to vagal postganglionic endings are exposed to relative high concentrations of cholinergic mediators and are profoundly affected, while fibers more remote from sites of acetylcholine liberation are influenced to a much lesser degree [16]. Both the shortening of the refractory period and the increase in dispersion favor atrial reentry that can initiate and maintain AF.

Adrenergic factors seem to be also involved in the pathogenesis of AF[104,105]. The adrenergically mediated form of AF is less common, occurs more frequently in patients with heart disease during daytime, at stress or with exercise[102]. In some cases this pattern of AF can result from disorders such as hyperthyroidism or pheochromocitoma. The mechanism by which adrenergic influences may determine the occurrence of AF is less well characterized. The principal effect is a reduction in the atrial refractory period[109] that could favor microreentry. The atrial adrenergic modulation is nonuniform and the inhomogeneity is accentuated in diseased tissues[96]. Furthermore, a high sympathetic activity seems to favor automatic and triggered activity and thus increases the atrial extrasystoles triggering AF.

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