State of the Art

Atrial Fibrillation: A Question of Dominance?

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The mechanisms underlying atrial fibrillation (AF) remain poorly understood. In some patients, AF initiation often occurs from arrhythmogenic foci arising at muscular sleeves in a pulmonary vein (PV). Either direct radiofrequency ablation of these foci or, more recently, their disconnection from the left atrium by ablation at venous ostia is the basis for curative AF ablation procedures. However, it is likely that, in most cases, the mechanism of AF maintenance is different from that which initiates it. Isolated animal heart experiments suggest that some cases of AF may be maintained by the uninterrupted periodic activity of a small number of discrete reentrant sites (rotors) located in the posterior left atrial (LA) wall, near the PV/LA junction. During sustained AF, such sources activate at an exceedingly high rotation frequency. Thus rotors near the PV/LA junction dominate over any other slower sources that may form elsewhere and act as the drivers for the entire fibrillatory process. High resolution spectral analysis of the spatial distribution of activation frequencies reveals a hierarchy with appreciable frequency gradients across the atria. Here we briefly review our current understanding of the mechanisms and manifestations of AF and discuss the applicability of spectral analysis tools to the study of AF in patients, with the idea of helping to improve the efficacy of ablation therapies. We focus in part on recent clinical studies that provide justification for the combined use of spectral analysis and electroanatomical mapping to systematically correlate the spatial distribution of excitation frequency with cardiac anatomy, to provide mechanistic insight into different types of AF and to facilitate ablation procedures.

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans. It afflicts ~2% of the unselected adult population and 5.9% of the population over 65 years of age.[1] It is the most common cardiac cause of stroke.[2] In addition, the rapid heart rate resulting from AF can cause a number of adverse outcomes, including congestive heart failure and tachycardia-related cardiomyopathy.[3] Medications are only marginally effective in treating this arrhythmia, and have the potential for serious side effects, including life-threatening pro-arrhythmia. On the other hand, it has recently been demonstrated that patients with paroxysmal AF can be cured by a catheter-based ablation procedure.[4] This is based on the observation that the mechanism of atrial fibrillation in these patients is initiated by focal triggers localized usually to one of the pulmonary veins.[5] However, in persistent AF, the prevailing theory regarding its mechanism is that multiple random wavelets of activation coexist to create a chaotic cardiac rhythm,[6] and therapy is more challenging.[7-9] Our recent experimental studies of cholinergic AF in the isolated sheep heart[10] demonstrated that high-frequency sources in the pulmonary vein region predominate over and drive the fibrillatory activity throughout both atria. Motivated by those results, and by a growing body of work investigating how measurements of the cycle length of activity in patients dur-

ing AF can contribute to its treatment,[11-13] we have begun to focus our analysis on the organization of spectral properties of the activity during AF in humans. We are also investigating the mechanisms that underlie the organization of such activity. As suggested in recent preliminary studies,[13,14] high-resolution spectral analysis offers the unique opportunity of being able to correlate systematically the spatial distribution of excitation frequency with cardiac anatomy and ablation procedures and to provide mechanistic insight into different types of AF. In this article, we briefly review our current understanding of the mechanisms and manifestations of this complex arrhythmia and discuss possible approaches that may help to directly improve the efficacy of ablation therapies in certain groups of patients.

Mechanisms of atrial fibrillation

The exact mechanisms underlying AF are still poorly understood despite many years of research and speculation. Since the description of the multiple wavelet hypothesis by Moe et al,[6] it became generally accepted that AF is the result of the random propagation of multiple wavelets across the atria, a process that is independent of the initiating event. Experimental support for this hypothesis came from Allessie et al[15] in the 1980s, who estimated that 4 to 6 wavelets were needed for AF perpetuation in dogs. This theory was strengthened by the clinical observation that chronic AF could be cured in some patients by the placement of multiple surgical lesions (MAZE) to compartmentalize the atria into regions presumably unable to sustain the multiple random wavelets.[16] Indeed, this theory is virtually universally accepted by most clinical electrophysiologists.

However, in studies as early as the 1920s by Sir Thomas Lewis,[17] an alternative hypothesis for the mechanism of atrial fibrillation was proposed. Lewis suggested that the mechanism was due to activation by a rapidly firing reentrant circuit that resulted in wavefront fractionation and presented with a fibrillatory pattern on the surface ECG. More recently, Schuessler et al[18] demonstrated, in an isolated canine right atrial preparation, that with increasing concentrations of acetylcholine (ACh), activation patterns characterized by multiple reentrant circuits converted to a single, relatively stable, high-frequency circuit that resulted in fibrillatory conduction. Studies from our laboratory[19,20] that have applied high resolution mapping of wave propagation and analyzed long episodes of AF in both time and frequency domains, have provided evidence that propagation during AF is not random,[10] but has a high degree of spatiotemporal periodicity. This has led to the hypothesis that perpetuation of AF may depend on the uninterrupted periodic activity of a small number of discrete generators (rotors), most often localized in the left atrium and established by the interaction of propagating waves with anatomical heterogeneities in the atria. We have proposed also that, in the sheep heart, the rapid succession of wave fronts that emanate from such rotors propagate through both atria and interact with anatomical and/or functional obstacles, leading to fragmentation and wavelet formation.[10] As discussed in a recent "insight review article" in *Nature* by Nattel[21] there is strong support in the literature for this hypothesis, including observations made during radiofrequency ablation of AF in humans suggesting that, in some patients, impulses generated by a single source of focal activity propagate from an individual pulmonary vein or other atrial regions to the remainder of the atria as fibrillatory waves.[5,22,23]

Paroxysmal and persistent AF

One reasonable interpretation for the seemingly contradictory results outlined above is that paroxysmal AF is caused by a localized source leading to fibrillatory conduction, and persistent AF is caused by random multiple wavelet reentry. Indeed this is the prevailing accepted interpretation of the data. However, an alternative hypothesis is that most, if not all, patients with AF have a focal or reentrant mechanism as the initiating cause of the arrhythmia and a rotor or a small number of rotors as the drivers that maintain the arrhythmia. Perhaps the only differences between paroxysmal and persistent AF are the rotation frequency, stability and location of such sources: that is, when the driving site(s) is (are) most stable and its (their) frequency is highest, the clinical scenario of persistent AF will be manifest. While this hypothesis has not been tested, there is evidence in the literature that supports it strongly.[24-26] Specifically, one report described the profound antiarrhythmic effect of cryoablation (using a hand-held probe) to areas of shortest cycle lengths in the posterior left atrium (LA) in open chest dogs with chronic AF.[24] While they attributed their success to the fact that the ablated areas were large enough to prevent reentry of multiple wavelets, this could really have represented empiric elimination of potential high-frequency

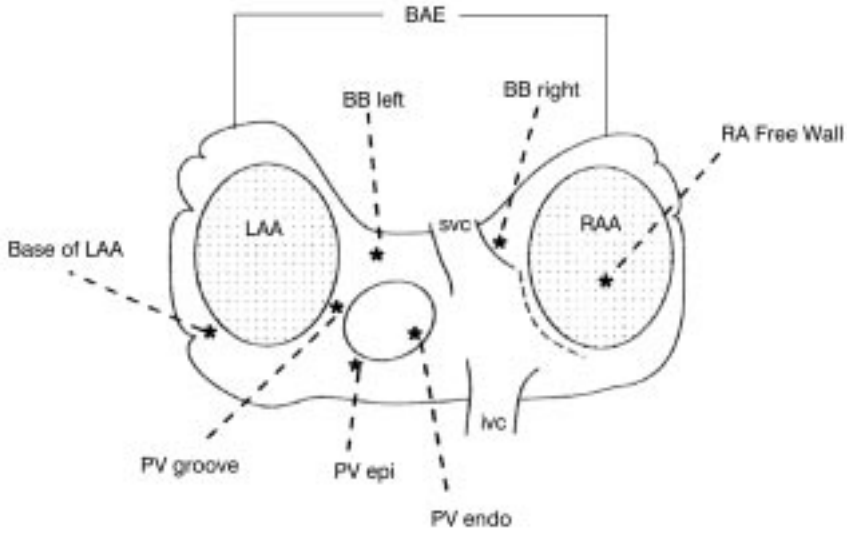

Figure 1. Diagram of the sheep or goat atria showing the location of optical mapping fields and bipolar recording electrodes.
(Adapted from Mansour et al, 2001, by permission of the American Heart Association.)

sources. Roithinger et al[25] used radiofrequency ablation to show that selective linear lesions in the LA significantly reduced AF frequency in a canine model, whereas lesions in the right atrium (RA) did not. Horvath et al[26] reported on human cases of simultaneous LA flutter and RA fibrillation in which the mean LA cycle length of 173 ms (5.8 Hz) was nevertheless shorter than the mean RA cycle length of 236 ms (4.2 Hz). Other studies have shown that refractoriness is shorter in the LA than in the RA.[20,27-29] Recent experiments by Li et al[30] strongly suggest that LA to RA differences in refractoriness at low frequencies correlate strongly with intrinsic differences in the action potential duration recorded from cells obtained from the two atria. A larger density of the rapid delayed rectifier current (I_{Kr}) in the LA seems to explain nicely such chamber specific differences in action potential duration during pacing at relatively low frequencies.[30] A number of studies in patients also support the idea that the left atrium may be the driver for AF in some cases. Harada et al[31] mapped atrial activation in 10 persistent AF patients who were undergoing mitral valve surgery. They demonstrated that the LA underwent regular and repetitive activations with cycle lengths that ranged between 131 and 228 ms. In contrast, the activation sequence in the RA was extremely complex and dysrhythmic. More recently, the same authors[32] demonstrated that resection of the LA appendage and/or cryoablation of the orifice of the left pulmonary vein terminated AF in 10 of 12 additional patients with mitral valve disease. These data support the hypothesis that at least some cases of persistent AF may be due to a single or, at most, a few high frequency periodic sources of activity in some regions of the left atrium.

Acute AF: The sheep heart model

The general working hypothesis that AF results from activity of a small number of high frequency reentrant sources localized in one atrium, with fibrillatory conduction to the other atrium, is based primarily on results obtained in our experimental model of the isolated, Langendorff-perfused sheep heart, where we have studied the mechanism of acute AF induced by burst pacing in the presence of ACh. Our initial work focused on the localization of the high-frequency sources thought to be responsible for maintaining AF in this model.[19,20,33,34] Figure 1 shows a diagram of our experimental preparation for simultaneous optical and electrophysiologic mapping of both atria. The optical fields are represented by the ovals on the LA and RA appendages. A biatrial electrogram was used to monitor global activation frequency during AF. Electrodes were placed at various locations, including the base of the LA appendage, pulmonary vein groove, epicardium and endocardium of the pulmonary vein, Bachmann's bundle and RA free wall. Those studies demonstrated that there was a high degree of spatial and temporal organization during sustained AF. In addition, as illustrated in Figure 2, it was clear that the activation frequency in the LA was much higher that in the RA. Moreover, in many cases our optical mapping studies demonstrated self-sustaining rotors in the LA giving rise to periodic electrical waves[20] and strongly suggested that such rotors were the underlying mechanism of AF in the sheep heart model.

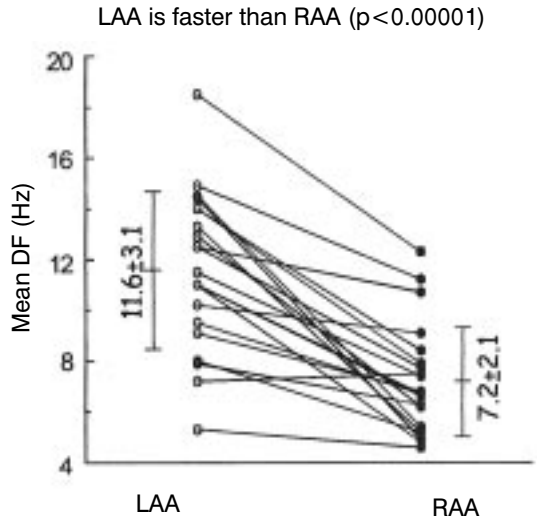

Figure 2. Differences in mean dominant frequency (dominant frequency) measured using spectral analysis of optical signals in left atrial appendage and right atrial appendage in the sheep heart.

Subsequently, we hypothesized that waves emanating from relatively stable rotors in the LA undergo complex, spatially distributed conduction block patterns as they propagate toward the RA, manifesting as fibrillatory conduction and thus resulting in left-to-right frequency gradients. Our objectives here were in part to characterize impulse propagation and LA:RA frequency gradients across Bachmann's bundle and the inferoposterior pathway along the coronary sinus. We induced AF by rapid pacing in the presence of 0.1-0.6 μM ACh; 48 episodes of AF were analyzed. Simultaneous optical mapping of the LA and RA was done in combination with bipolar electrode recordings along Bachmann's bundle (6), the inferoposterior pathway (4), the RA free wall (2), the LA appendage (1) and the pulmonary vein region (1). Power spectral analysis (Fast Fourier Transform) of all signals was performed.[35] A left-to-right decrease in the dominant frequencies occurred in all cases along Bachmann's bundle and inferoposterior pathway, resulting in an LA:RA frequency gradient. This is illustrated in Figure 3, which shows data obtained from a representative experiment.[36] In panels A and D are shown on the left single pixel optical recordings obtained from the LA and RA during a 3-second episode of AF. Panels B and C show electrograms obtained, respectively, on the left and right portions of Bachmann's bundle. On the right are the corresponding power spectra, demonstrating a gradual decrease in dominant frequency from LA through Bachmann's bundle to RA. In Panel E the color dominant frequency map illustrates the distribution of dominant frequency domains, demonstrating a gradient from LA to RA. The mean gradient, calculated as the difference between mean LA and RA dominant frequencies, was 5.7±1.4 Hz. In these experiments left-to-right impulse propagation was present in 81±5% and 80±10% of cases along Bach-

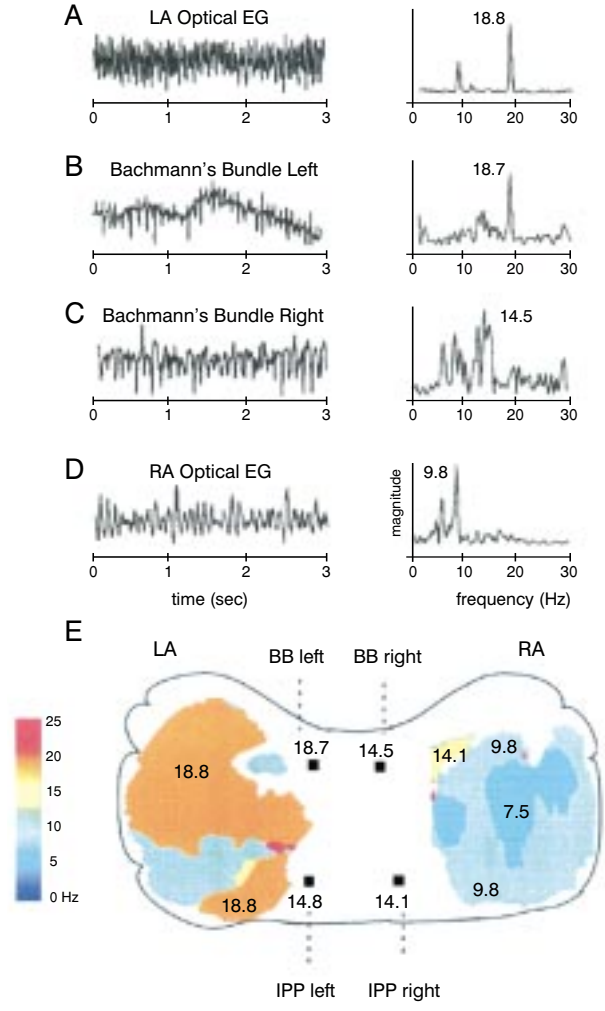

Figure 3. A: optical "electrogram" (EG) and Fast Fourier transform from left atrium.
B, C: true EGs and Fast Fourier transform from Bachmann's bundle left and right.
D: Right atrial optical EG and Fast Fourier transform.
E: Color dominant frequency map of right and left atria including Bachmann's bundle and inferoposterior pathway. Notice LA:RA frequency gradient.
(Reproduced from Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, and Jalife J: Left-to-Right Gradient of Atrial Frequencies During Acute Atrial Fibrillation in the Isolated Sheep Heart. Circulation 2001; 103: 2631-2636, by permission of the American Heart Association.)

mann's bundle and inferoposterior pathway, respectively. Overall, our results strongly supported the hypothesis that AF in the sheep heart is the result of high frequency periodic sources located in the LA, with fibrillatory conduction toward the RA. This work has been published in Circulation.[19,20,36]

Role of atrial structure

At the macroscopic level, studies in animals suggest that the intricate three-dimensional structure of the atrium is an essential component that contributes to the complexity of propagation patterns identified by high-resolution mapping during AF.[19,33,34,37,38] However, the information about how heterogeneous electrophysiology and heterogeneous anatomy interact to lead to AF initiation, maintenance or perpetuation is incomplete at best. Advances have occurred in the understanding of geometrical factors, such as wave front curvature,[39] non-uniform anisotropic coupling,[40] sink-source relationships at areas of tissue expansion,[41] and in the application of nonlinear dynamics theory to the spatial and temporal organization underlying complex cardiac arrhythmias,[42] particularly during ventricular fibrillation. Such advances may be relevant to the ultimate understanding of the mechanisms of initiation of AF by the interaction of the propagating wave fronts with anatomic or functional obstacles.[37] Computer modeling may provide useful tools for research aimed at the study of the manner in which electrical "fibrillatory" waves interact with the highly complex three-dimensional structure of the atria.[43,44]

A more recent study from our laboratory provides detailed analysis of the manner in which propagating waves initiated by high frequency pacing in Bachmann's bundle interact with the RA and result in fibrillatory conduction.[38] Our goal was to determine the underlying basis of the complex patterns of propagation that characterize AF. In other words, we wanted to answer the following question: what is the mechanism of fibrillatory conduction in this model, in which activation by a high frequency rotor in the LA is highly periodic? We hypothesized that the left-to-right frequency gradient and fibrillatory conduction observed in our previous studies resulted from breakdown of waves traveling from the LA across interatrial pathways, into the pectinate muscle network of the RA. Thus, we expected to demonstrate that periodic repetitive input to the RA at increasing frequencies should result in an increase in complexity and a decrease in organization of wave propagation, compatible with fibrillatory conduction. To this end, we used simultaneous high-resolution endocardial and epicardial optical mapping (di-4-ANEPPS) in isolated, coronary perfused sheep RA preparations.[38] Rhythmic pacing at Bachmann's bundle allowed well-controlled and realistic conditions for LA-driven RA. Pacing at increasingly higher frequencies (2.0 to 6.7 Hz) led to increasing delays in activation distal to major branching sites of the crista terminalis and pectinate muscles.[38] As shown by the frequency maps presented in panel A of Figure 4, stimulation of Bachmann's bundle at 5.0 Hz resulted in 1:1 activation of the entire preparation at 5.0 Hz. However, at 7.7 Hz, there were spatially distributed intermittent blockades with the establishment of well-demarcated frequency domains (compare dominant frequency maps on left and right), and significant discordance between epi- and endocardium. In fact, as illustrated in panel B, stimulation at frequencies between 2 and 6.7 Hz resulted in rhythmic flutter-like activation of both epi- and endocardium. However, above the 'breakdown frequency' of ~6.7 Hz, RA activity underwent a significant loss of consistency in the direction of propagation, and thus transformed into fibrillatory conduction.[38] Such frequency dependent changes were independent of action potential duration. Rather, the spatial boundaries between proximal and distal frequencies correlated well with branch sites of the pectinate musculature. From these experiments we concluded that there exists a 'breakdown frequency' in the sheep RA below which activity is flutter-like and above which it is fibrillation-like. The data strongly supported the idea that, during AF, high frequency activation initiated in the LA undergoes fibrillatory conduction toward the RA and that branch points at the crista terminalis and pectinate muscles play a major role in increasing the complexity of the arrhythmia. In addition, a loss of consistency in the propagation patterns demonstrates the difficulty of tracing the origin of the activation during fibrillation.

Role of dispersion of action potential duration and refractoriness

Spatial dispersion in action potential duration and refractoriness, measured at relatively slow stimulation rates, are usually invoked to explain complex wave propagation during AF.[45] Wang et al[46] found that, at a cycle length of 250 ms in dogs susceptible to sustained AF, the dispersion of refractoriness in the

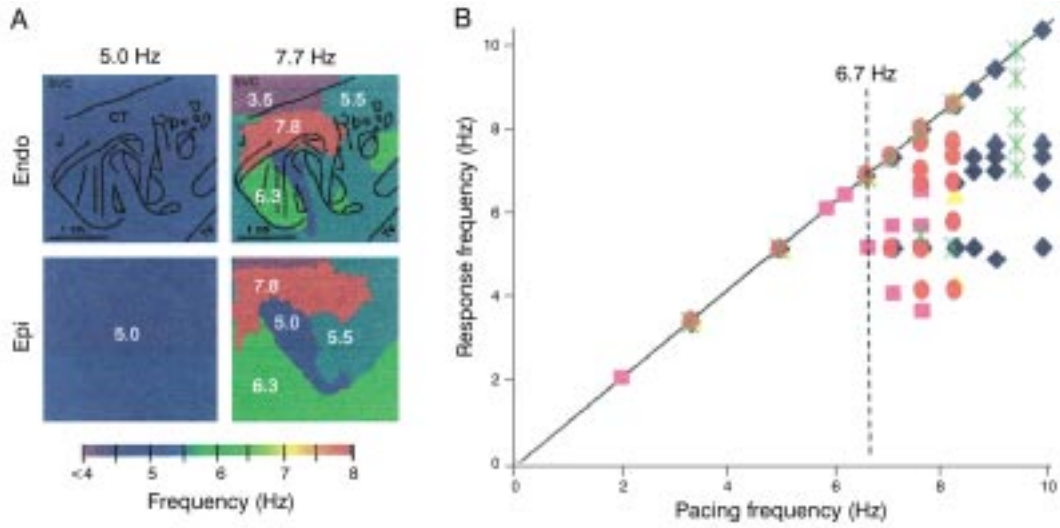

Figure 4. A: color dominant frequency maps of endocardium (top) and epicardium (bottom) of the right atrium obtained during stimulation of Bachmann's bundle at 5 Hz and 7.7 Hz.
B: response frequency as a function of pacing frequency. Note breakdown at 6.7 Hz.
(Reproduced from Berenfeld O, Zaitsev AV, Mironov SF, Pertsov AM, Jalife J: Frequency-Dependent Breakdown of Wave Propagation Into Fibrillatory Conduction Across the Pectinate Muscle Network in the Isolated Sheep Right Atrium. Circ Res 2002; 90: 1173-1180, by permission of the American Heart Association.)

RA epicardium was 19±3 ms, with the longest refractoriness being ~120 ms at the free wall. Satoh and Zipes[47] reported that refractoriness was shortest at the lower portion of the crista terminalis relative to the superior vena cava. Yet none of the above seemingly conflicting studies measured refractoriness in the pectinate muscle region and their data are therefore difficult to compare with our results. We constructed high-resolution action potential duration maps at a cycle length of 300 ms (3.3 Hz; not shown here) to assess indirectly the degree of spatial dispersion of refractoriness.[48] In agreement with the results of Feng et al,[49] our data also indicate that the crista terminalis has the longest action potential duration during pacing at a slow rate (3.3 Hz). Spach et al[50] also reported that, at 1.7 Hz, action potential duration in the crista terminalis is longer than in the pectinate muscles. In single cells, Yamashita et al[51] showed that action potential duration in the rabbit crista terminalis was longer than in the pectinate muscles at 1 Hz. In our experiments, however, the crista terminalis consistently showed the largest dominant frequency when Bachmann's bundle is paced at a rate comparable to the frequency of the LA during AF (> 7 Hz). Thus, the distribution of action potential duration *under normal conditions* seems different from the distribution of dominant frequency domains during AF, which leads us to suggest that dispersion of refractoriness at normal frequencies is a poor predictor of the spatial distribution of intermittent block patterns that characterize AF.

However, both vagal stimulation and administration of ACh have been shown to result in AF.[52-54] In experimental animal models, vagal stimulation results in sustained AF as long as the vagus nerve is continuously stimulated,[53] and in dogs catheter ablation of the cardiac parasympathetic nerves abolishes vagally mediated AF.[55] This has been attributed to the heterogeneous distribution of vagal innervation throughout the atria, which increases spatial dispersion of refractory periods.[56] Notably, any hypothesis put forth to explain an ionic mechanism of maintenance of AF must contend with the fact that local frequencies in some parts of the left atrium sometimes reach values as high as 16-18 Hz.[36] This means that action potential durations at such sites must abbreviate to about 60 ms or less in order to activate repeatedly at such frequencies in a 1:1 manner. The work by Li et al[30] demonstrated significant intrinsic differences in the action potential duration of LA myocytes with respect to RA myocytes of the dog heart. In addition, they showed that LA myocytes

have a larger I_{Kr} density and greater ERG protein expression compared to the RA. At a frequency of 6 Hz, action potential durations in the LA and RA were ~100 ms and 110 ms, respectively. It is possible that such differences contribute somehow to the establishment of LA-to-RA frequency gradients during acute AF in the structurally normal heart through the resultant LA-to-RA differences in effective refractory period. Yet intrinsic action potential duration differences alone are insufficient to explain the mechanism of AF maintenance or the exceedingly high frequency that can be achieved in some parts of the LA. A frequency of 16-18 Hz means that somewhere in the LA the atrial action potential duration during AF is less than 60 ms, which cannot be explained on the basis of a relatively large I_{Kr} whose time constant is about 135 ms at +10 mV.[30] Thus, under acute conditions, continuous vagal stimulation, ACh perfusion or other pro-fibrillatory ministrations that are capable of abbreviating atrial action potential duration to extreme values are necessary for the arrhythmia to be established and maintained. Traditionally, the ability of cholinergic input to promote AF maintenance in the normal heart has been attributed to the heterogeneous distribution of vagal innervation and muscarinic ACh receptors throughout the atria, which increases spatial dispersion of refractory periods and results in complex patterns of activation and wavelet formation.[57] Recently published data from our laboratory in the Langendorff-perfused sheep heart showed that increasing the ACh concentration from 0.2 to 0.5 μM increased the frequency of the dominant source and rotors, as well as the LA-to-RA frequency gradient, suggesting that the LA and RA are indeed different in their response to ACh in this species.[58] Indeed, a very recent work from Pappone et al[59] suggests that in patients with paroxysmal AF isolation of the pulmonary veins together with abolition of all evoked vagal reflexes around all pulmonary vein ostia significantly reduces recurrence of AF at 12 months.

AF in chronically instrumented animal models

In 1995, Wijffels et al[60] in Allessie's laboratory developed a goat model of chronic AF in which the animals were connected to an external automatic fibrillator (see also ref. 24). The device was programmed to deliver a 1-second burst of electrical stimuli (50 Hz) as soon as sinus rhythm was detected. As such, the automatic fibrillator was able to maintain AF for 24 hours a day, 7 days a week. On day one of the experiment, the paroxysms of AF induced by the fibrillator were short-lived. However, in the continuous presence of high frequency excitation for days or weeks, the rate and stability of AF increased, thus demonstrating that "AF begets AF." Importantly, with the persistence of AF, the atrial effective refractory period shortened and the slope of its frequency dependence became flat or inverted, which suggested the occurrence of a process of AF-induced electrical remodeling in the atria of these goats. More recently, the Allessie laboratory showed that electrical remodeling was not significantly affected by changes in autonomic tone or ischemia and concluded that high frequency activation itself was responsible for the AF-induced changes in atrial effective refractory period.[61] On the other hand, it was shown that the remodeling process is reversible and the effective refractory period normalizes completely within one week of resumption of sinus rhythm.[60] The process of remodeling is reproducible in other animal models of chronic AF.[24,62,63] Moreover, recent studies in humans have shown that changes in atrial electrophysiology associated with persistent AF are reversible after cardioversion,[64] which provides convincing evidence for the existence of AF-induced remodeling in humans. However, to date investigators have been unable to rigorously correlate the electrical remodeling process to the molecular and ionic mechanisms underlying the perpetuation of AF.

Activation rate in AF

In 1925, Lewis[17] postulated that fibrillation was similar to flutter in that a single circuit did exist in AF, but the path followed by the wave front was uneven. He also proposed that, in contrast to flutter, in fibrillation the circuit is completed in a shorter time. Since then, the differentiation between atrial flutter and fibrillation in patients is usually based on the regularity of the ECG signals, which is typically reduced with increasing rate. Although the upper limit of human atrial flutter rate varies considerably among investigators, its lower value relative to fibrillation is well documented.[26,65,66] For example, according to Wells et al,[65] type I and II atrial flutter have regular rates at less than 338 beats/min (5.6 Hz) and 433 beats/min (7.2 Hz), respectively. On the other hand, Roithinger et al[66] found that frequency increased to a mean of 4.1 Hz during flutter after conversion from various types of AF whose longest cycle

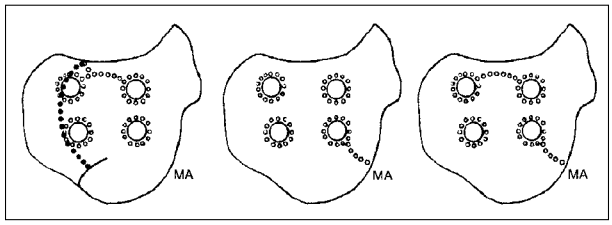

Figure 5. Limited biatrial ablation. Left: pulmonary vein isolation (PVI), roof line and anterior line. Center: PVI and mitral isthmus line. Right: PVI and mitral isthmus line and roof line.
(Reproduced from Haïssaguerre M, Sanders P, Jais P, Hocini M, Shah DC, Clementy J. Catheter Ablation of Atrial Fibrillation: Triggers and Substrate, in Zipes DP, Jalife J (eds): Cardiac Electrophysiology - From Cell to Bedside, Saunders, Philadelphia, 2004 by permission.)

length was 184 ms (5.4 Hz). Horvath et al[26] used an upper limit of 350 beats/min (5.8 Hz) to define atrial flutter. Very relevant to our study is the report these authors made on cases of simultaneous LA flutter and RA fibrillation in which the mean LA cycle length of 173 ms (5.8 Hz) was shorter than the mean RA cycle length of 236 ms (4.2 Hz). Our experimental work in the isolated sheep hearts[36] and RA preparations[38] provides mechanistic support to the idea put forth originally by Lewis[17] and demonstrates for the first time that there is a 'breakdown frequency' below which activity is periodic and above which it is fibrillation-like. In the sheep RA this breakdown frequency is 6.7 Hz but it is important to note that the relevance of our results to the behavior of regions other than the sheep RA (e.g., the LA), or to other species, including man, or even to diseased hearts,[67] remains to be determined. In the case of the LA of the sheep,[19,35,36] dogs[24] and humans[11,22,26] there is substantial evidence that, during AF, activation frequencies are higher than in the RA. Therefore, one might expect that the general 'breakdown frequency' in the LA should be higher than that demonstrated for the RA.

Radiofrequency ablation of AF

Radiofrequency (RF) ablation of atrial tissue by application of energy through intracardiac catheters has become a major therapeutic method for atrial fibrillation in patients,[22,68-77] and there is significant clinical evidence that the pulmonary vein region and the posterior LA are crucial for maintenance of AF in paroxysmal AF patients.[4,22,78] The RF ablation procedure consists of generating electrical barriers in various sites of the atria by altering the tissue properties in the vicinity of the ablating catheter tip. The extent of the altered tissue depends on the power and duration of the application, as well as on the characteristics of the tissue itself. For a typical RF ablation, a power of 20-40 Watts is delivered for several minutes to create an altered substrate in a volume with a radius of about 5 mm around the catheter tip. The recognition that AF often depends on sources localized to the pulmonary veins resulted in the development of techniques designed to isolate those veins from the rest of the LA.[5] Together with cavotricuspid isthmus ablation, the so-called electrical isolation of the pulmonary veins is performed in many patients on a routine basis.[79] Figure 5 shows schematically various configurations for combined limited linear ablation together with pulmonary vein isolation (PVI) performed in the laboratory of one of us.[79] A linear ablation joins the two superior pulmonary veins and connects with a roofline that extends to the mitral annulus to interrupt the entire anterior interatrial band (left). In other patients mitral isthmus ablation is performed to join the left inferior pulmonary vein to the lateral mitral annulus (center); sometimes an anterior line is added (right). However, there is an ongoing debate among electrophysiologists as to what is the most efficient strategy for the ablative treatment of AF. Haïssaguerre and coworkers reported a success rate of 73% in 70 paroxysmal AF patients using limited ablation for segmental pulmonary vein isolation.[80] Pappone and associates use a more extensive circumferential pulmonary vein ablation and reported a success rate of 85% and 80% in 26[22] and 251[81] patients, respectively, with paroxysmal AF and persistent AF. Oral and colleagues[82] reported a 63% success rate in 70 paroxysmal AF and persistent AF patients with segmental pulmonary vein isolation. On the one hand, extensive ablation that is thought to modify the atrial substrate[83] can cure many types of AF, but it exposes the patient to a higher risk of complications[84] and to unacceptable fluoroscopy exposure times; on the other hand, more selective ablations that target localized "triggers" are safer but may be less likely to cure the AF, which may be become prone to recurrences.[73,85] Figure 6 shows surface and intracardiac recordings from a patient undergoing electrical pulmonary vein isolation during AF.[79] In the left panel, bipolar electrograms from the catheter at the circumference of the pulmonary vein show opposite polarity across adjacent bipoles, which in combination with the earliest activation indicate the site of a break-

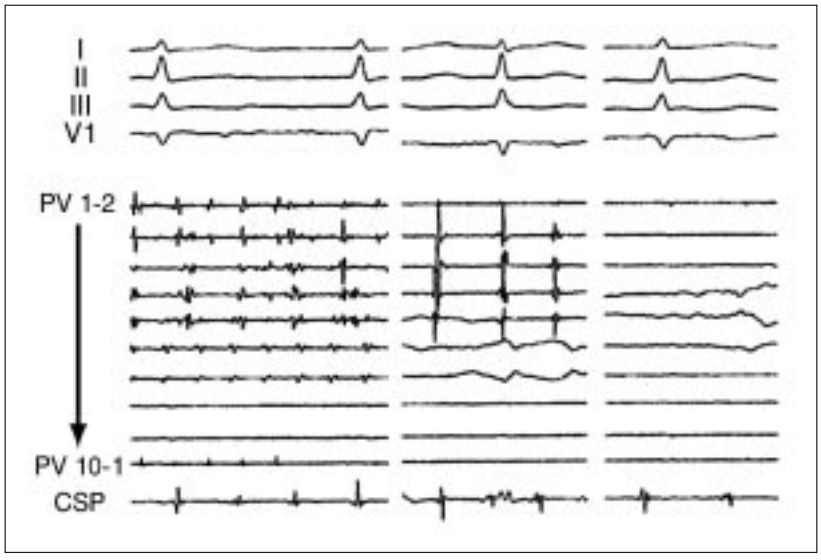

Figure 6. Pulmonary vein isolation and termination of atrial fibrillation. The initial target for this patient was the superior aspect of the pulmonary vein that led to a more organized pulmonary vein activity (panel 2). Ablation at the site of earliest pulmonary vein activity results in electrical isolation (panel 3). CSP - proximal coronary sinus.
(Reproduced from Haïssaguerre M, Sanders P, Jais P, Hocini M, Shah DC, Clementy J: Catheter Ablation of Atrial Fibrillation Triggers and Substrate, in Zipes DP, Jalife J (eds), Cardiac Electrophysiology - From Cell to Bedside, Saunders, Philadelphia, 2004, by permission.)

through.[86] After targeting the superior aspect of the pulmonary vein, the activity became slower with apparently more organized activity (middle panel). Further ablation of the site of earliest activation resulted in the electrical isolation of the pulmonary vein and termination of AF.

Cycle length during atrial fibrillation in humans

Most recent work from Haïssaguerre et al describes the changes in the cycle length measured at the coronary sinus during atrial fibrillation and different, progressive, ablation stages.[12] Prior studies of AF cycle length in animal[45,60,87] and human[26-29,88,89] have emphasized its role as a surrogate measure of local atrial refractoriness. However, already Morillo et al[24] used cryosurgical application to the posterior LA, where cycle length was the shortest, to terminate AF in dogs and demonstrate the link between the rate of local activity and its role in maintaining AF. More recent human studies have also analyzed the AF cycle length.[11,22,90] Pappone et al, while studying the effectiveness of pulmonary vein ablation techniques, found that indeed the shortest local cycle length in all the atria is located in the pulmonary vein region.[11,22] Wu et al mapped human atria during surgery and consistently observed rapid repetitive activity in the posterior wall of the LA at or near the pulmonary veins. They concluded that, during permanent AF associated with organic heart diseases, the AF cycle length was shorter in the posterior wall of the LA than in the RA free wall. Overall, work on AF cycle length supports the finding that concomitantly with the central role of the pulmonary vein region in maintaining AF,[5,24] the posterior LA also shows the fastest activity, as measured by its cycle length.[11,22,24,89] A number of other studies in patients also support the idea that the LA may be the driver for AF in some cases. Harada et al[31] mapped atrial activation in 10 persistent AF patients who were undergoing mitral valve surgery. They demonstrated that the LA underwent regular and repetitive activations with cycle lengths that ranged between 131 and 228 ms. In contrast, the activation sequence in the RA was extremely complex and dysrhythmic. Later, the same authors[32] demonstrated that resection of the LA appendage and/or cryoablation of the orifice of the left pulmonary vein terminated AF in 10 of 12 additional patients with mitral valve disease. The additional studies of Wu[90] and Haïssaguerre[12] give further mechanistic support to our general hypothesis that the pulmonary vein region in some patients hosts the source that maintains the AF. The recent work by Haïssaguerre et al[12] demonstrated that the sequence of vein by vein ablation in the pulmonary vein isolation procedure resulted in a gradual increase in AF cycle length, with only 6 patients out of 56 demonstrating an increase equal to or smaller than 5 ms (see figure 7). This increase was observed with some variability from patient to patient and among pulmonary veins; in other words, while some pulmonary vein ablations did not change the AF cycle length, a jump in the AF cycle length was observed with others. Figure 7 shows the AF cycle length before pulmonary vein isolation, after sequential isolation of 2 and 4 pulmonary veins and after a

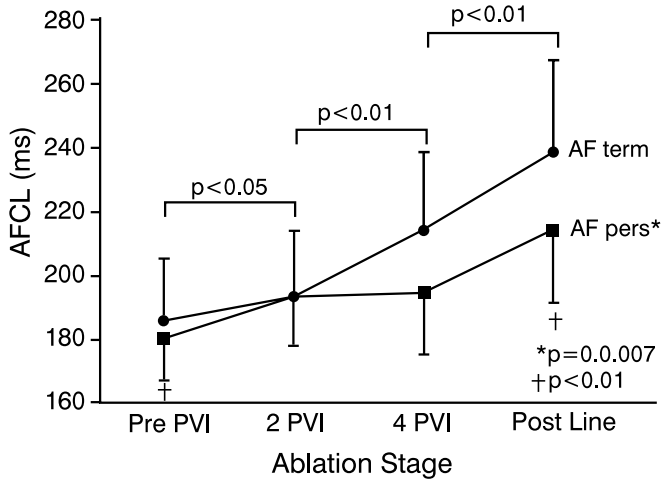

Figure 7. Atrial fibrillation cycle lengths in the coronary sinus as a function of progressive ablation stage.
(Reproduced from Haïssaguerre M, Sanders P, Hocini M, Hsu LF, Shah DC, Scavee C, Takahashi Y, Rotter M, Pasquie JL, Garrigue S, Clementy J, Jais P: Circulation 2004; 109: 3007-3013, by permission of the American Heart Association.)

linear ablation was added. There was a significant increase in the AF cycle length in patients in whom AF terminated during pulmonary vein ablation (186±19 to 214±24 ms, p<0.0001) and to a lesser extent in patients with persistent AF after pulmonary vein ablation (186±20 to 194±19 ms, p=0.002). As shown in Figure 7 the cumulative change in AF cycle length after the procedure was completed in patients in whom AF terminated was greater than that in patients with persistent AF (30±17 vs. 24±11 ms, p<0.005). These results conclusively demonstrate that the cycle length of the coronary sinus, where the AF cycle length was measured, depended on the activity in the remotely ablated sites. Since in this study the pulmonary vein region was the fastest of all the regions in the atria, the findings strongly support the hypothesis that targeting the regions that show the shortest AF cycle length for RF ablation may be a good strategy for AF termination. As may be expected in patients with persistent AF, it would not be surprising to demonstrate that the region with the shortest AF cycle length lies somewhere other than the pulmonary vein or the posterior LA. We surmise that in such cases also, targeting the fastest activating site for ablation may lead to AF termination. Thus, as discussed below, research is currently under way with the objective of determining whether the use of spectral mapping[35,90-92] will make the analysis of the rate of excitation during AF more readily usable and efficient, with greater chances of localizing in real-time the high frequency source(s) that maintain AF.

Mapping dominant frequencies in AF patients

The advance from surface ECG tracings to highly sophisticated intracardiac multisite mapping systems has undoubtedly contributed to the treatment of AF.[93] Various methods for non-fluoroscopic endocardial mapping systems and the localization of cardiac tissue critical for the arrhythmia are the basis for the success of the catheter ablation in terminating AF.[94] Three of the main advanced mapping methods currently used in the clinic are widely known as the multi-electrode basket method,[95,96] the CARTO system[97,98] and the Ensite non-contact mapping system.[99,100] While all three methods provide the clinician with spatial information on the electrical activity, (i.e. electro-anatomic mapping) the ability to obtain such information successfully varies considerably, and there are varying advantages and disadvantages to each technique.[93,94] Recently, we collaborated with the group of Haïssaguerre in a study in which we utilized the CARTO system and a newly developed spectral analysis algorithm to investigate the spatial distribution of dominant excitation frequencies in the endocardium of a small group of patients suffering from AF.[13,14] Based on recent studies of AF progression and ablation we hypothesized that in humans the predominance of dominant frequency values in the pulmonary vein and LA regions over other regions would depend on the duration of the AF. Twelve patients (55±7 yrs; 1 F) undergoing ablation of symptomatic, paroxysmal (n=7) or persistent (n=5) AF were studied. Patients were selected on

the basis of the presence of spontaneous or inducible sustained AF (>10 min). The CARTO mapping system was utilized to acquire local electrogram and surface ECG recordings over 5 seconds during AF while creating a 3D geometry. Points were acquired evenly throughout the atria and coronary sinus. The dominant frequencies and regularity of the electrograms were determined based on the power spectrum highest peak and bandwidth, respectively. The point-by-point dominant frequencies of the electrograms were then color-coded on the geometry map to characterize their spatial distribution. Electrograms showing low regularity were excluded from the analysis. Our results revealed that for both groups of patients regions were organized with the same hierarchy; the highest dominant frequency in the left atrium and pulmonary veins was higher than the highest dominant frequency in the RA and the highest dominant frequency in the coronary sinus. The highest dominant frequencies in the paroxysmal AF patients were located primarily in the pulmonary vein region (4/7) and never in the RA. Interestingly, in the persistent AF patients, the highest dominant frequencies were distributed evenly in the two atria and the coronary sinus and none was found in the pulmonary vein region. We concluded that, in that group of patients, paroxysmal AF was characterized by the hierarchical spatial distribution of dominant frequencies where the LA and pulmonary veins are always the fastest regions. In contrast, in persistent AF, a more uniform distribution of the dominant frequencies was observed, where the highest dominant frequency could not be found in the pulmonary vein region, indicating the loss of this region's predominance. This may have implications for the localization of a target for AF termination in patients.

Although the sequential nature of data acquisition in the CARTO system is a significant limitation, its use presented a relatively low risk for the patient. In addition, it generated accurate maps over a wide range of conditions of geometry and electrical activity and its navigational system allowed for the reconstruction of the LA, RA and coronary sinus in a single global coordinate system, thus allowing repeated catheter visits at specified locations in any atrium.[11] As suggested by the study described above, the combined use of the CARTO system with high-resolution spectral analysis promises to advance the field.

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