Déjà vu in the theories of atrial fibrillation dynamics

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Abstract

This brief review looks back to the major theoretical, experimental, and clinical work on the dynamics and mechanisms of atrial fibrillation (AF). Its goal is to highlight the most important issues, controversies, and advances that have driven the field of investigation into AF mechanisms at any given time during the last ~100 years. It emphasizes that while the history of AF research has been full of controversies from the start, such controversies have led to new information, and individual scientists have learned from those that have preceded them. However, in the face of the most common sustained cardiac arrhythmia seen in clinical practice, we are yet to fully understand its fundamental mechanisms and learn how to treat it effectively. Future research into AF dynamics and mechanisms should focus on the development and validation of new numerical and animal models. Such models should be relevant to and accurately reproduce the important substrates associated with ageing and with diseases such as hypertension, heart failure, and ischaemic heart disease which cause AF in the vast majority of patients. Knowledge derived from such models may help to greatly advance the field and hopefully lead to more effective prevention and therapy.

Keywords

Atrial fibrillation mechanisms • Circus movement reentry • Rotors • Spiral waves • Dynamics of wave propagation

1. Introduction

The history of the recognition of fibrillation of the auricles will impress you with the dimness of our eyes and the opacity of the obstacles which embarrass our vision.

Sir Thomas Lewis

Sir Thomas Lewis made the above statement in a lecture he delivered in 1912 at University College Hospital in London, UK. It is quoted here because it remains so relevant in the twenty-first century. It seems that today we remain as blind to the facts about atrial fibrillation (AF), as investigators in Lewis’ time were 100 years ago. We carry on conspicuously in the dark about the nature of persistent AF. Despite so many years of research and speculation, and in the face of the most common sustained cardiac arrhythmia seen in clinical practice and the major cause of embolic stroke, we are yet to fully understand its fundamental mechanisms and learn how to treat it effectively. Since the times of Lewis, multiple pharmacological approaches have been tried to convert AF to sinus rhythm (SR), as well as to prevent recurrences. However, many of such drugs, while effective, are associated with substantial side effects and pro-arrhythmia, and therefore, their use is frequently in need of being interrupted well before their favourable actions become apparent. Variants of older drugs are being tried with the goal of decreasing the incidence of side effects, but concurrently new and often severe adverse effects arise. New, more atrial-selective ion channel-blocking drugs are currently under development with the hope that atrial-selective prolongation of the effective refractory period could terminate AF without increasing the risk of ventricular arrhythmias, but it is still too early to tell whether such new drugs will be beneficial in the AF population at large.

In a landmark article published in 1998, Haïssaguerre et al. presented the first results of using a highly successful catheter-based procedure in which ablation of ectopic triggers at the pulmonary veins effectively terminated up to 90% of cases of paroxysmal AF. Pulmonary vein isolation has been a vital milestone in the clinical treatment of paroxysmal AF, particularly in those patients without underlying structural heart disease. Unfortunately, over the years, the increasing extension of ablative therapy to the highly heterogeneous persistent AF population has been significantly less successful; very frequently, it requires multiple procedures and the continuation of antiarrhythmic drug therapy. In addition, limitations related to the long duration of the procedure itself, its lack of specificity, and the presence of important side effects make this approach altogether impractical in the majority of AF patients.

The title of this article may sound irreverent to some readers, but I make no apologies. I believe that it is appropriate, given the fact that history repeats itself even in science. As will become apparent in the following lines, many of the concepts on AF mechanisms we consider ‘modern’ today have been around for more than 100 years, which is...
truly humbling and a lesson to us all. Perhaps, ‘thinking outside the box’ may bring new ideas which might actually help advance the field. Sometimes the ‘obvious’ craziness turns out to be a genuine cutting-edge discovery. Thus, it seems reasonable to speculate that today more than ever it remains true that generating insights into AF mechanisms through novel theory and experimentation, the use of relevant numerical and biological models and the translation of basic science concepts into clinical practice will have crucial bearing in our attempts to improve patient care and develop new, safe, and more successful therapies. The article starts with an historical account of the theory of reentry and fibrillation, as well as some of its déjà vu moments. It then focuses on current knowledge about the biophysics of AF dynamics and some recent attempts to judiciously translate that knowledge to real clinical situations.

2. From jellyfish rings to fluorescent spirals

For many centuries, health-care workers have written of a gross irregularity of the atrial and ventricular pulsations, especially, in patients suffering from a failing heart. However, systematic research into fibrillation really started at the turn of the twentieth century when new technology began to emerge allowing effective inference through the analysis of arterial and venous pulsations, and subsequently, the electrical signals emerging from the heart itself. Labelled by Hering the pulsus irregulars perpetuus in 1903, AF was initially thought to be an expression of a deficient coordination of the atria and the ventricles, which Mackenzie attributed to a disturbance in the atrioventricular node. But it was Einthoven’s invention of the string galvanometer, which endowed investigators with the ability to obtain electrocardiograms and to more systematically test truly relevant hypotheses on AF mechanisms. From the start, two such hypotheses emerged which were based on variations of two different themes, circus movement and ectopic foci. Engelmann had already postulated that AF was due to the synchronous activity of ‘multiple heterotopous foci’, while in 1899, Cushny first brought attention to irregular oscillations of the arterial pulse during AF and attributed an atrial origin to the oscillations. Subsequently, Rothberger and Winterberg proposed the idea of ‘tachysystole’, which attributed AF to the extremely rapid discharge rate of an ectopic focus. On the other hand, an elegant and insightful experiment performed by Mayer in 1906 soon changed the minds of many investigators. Mayer used the contractile bell of the rhyzostomous Scyphomedusa (jellyfish) Cassiopea xamachana and also utilized rings of muscle cut from the ventricles of turtles. He showed that by applying appropriate combinations of electrical pulses, a wave could be induced to propagate in one direction in the ring and then continue to circulate indefinitely. His experiments were repeated and

![Figure 1](https://academic.oup.com/cardiovascres/article-abstract/89/4/766/261227/006)

**Figure 1** A.G. Mayer’s circulating movements produced in rings cut from the bells of a jellyfish. (A) Top view of Cassiopea. (B) The bell shown after cutting the marginal sense organs which normally trigger pulsations of the subumbrella. The subumbrella tissue in the periphery is a better conductor than the gelatinous substance in the centre of the bell. (C) if an annulus is insulated by a shallow scratch through the subumbrella and then a small sector, B, is isolated by shallow radial cuts, then on stimulating the large sector A at 1 and 2 with a pair of electrodes, a contraction will travel all the distance around A, but the sector B will not contract. (D) The isolated disc can be stimulated mechanically or electrically to trigger a circular wave of current which may continue doing so for hours or days. Printed from a public domain book digitized by Google.
extended in 1913 by Mines on rings of muscle cut from the atria of teleostean fishes. In 1914, both Mines and Garrey demonstrated similar effects in rings of muscle cut from dog ventricle. Thereafter, Lewis incorporated these concepts into what later became to be known as the ‘circuit movement hypothesis of reentry’ in his highly articulate description of the mechanisms of both atrial flutter and AF. He used it as the basis for his proposal of a single circuit generating fibrillatory activity. Lewis postulated that circuit movement reentry around an anatomical obstacle could explain either flutter or AF depending on the size of the circuit and the refractory period of the tissues involved. Accordingly, as illustrated by Lewis’ own drawings which I have reproduced in Figure 2, the case of atrial flutter may be conceived as a large circuit (right) in which the path length of a circular obstacle (e.g. the orifice of a great vein) in an atrium is appreciable longer than the wave length (i.e. there is a large excitable gap). The circular wave will accurately repeat from cycle to cycle, which would result in the fast yet highly organized activity that characterizes typical flutter. However, activity is totally different in the case of a small circuit (right) in which the excitable gap is also small and the crest of the circulating wave tends to follow close upon its own tail. Here, the circuit is completed in a shorter time; the atrial excitation cycles, therefore, follow each other more quickly. Consequently, in Lewis’ own words, ‘the crest of the advancing wave and its tail are deeply crenated. The wave is advancing through small and irregular channels of responsive tissue, as these open up deviously to receive it’. From this diagram, one may further speculate that if the refractory period in the surrounding atrial muscle is briefer than the period of the circulating wave, the propagation of the waves to the atria would become disorganized leading to AF. The process was likened to the irregular discharge of sparks from a revolving pinwheel. Hence, one prediction that might be derived from this theory is that elimination of the reentry circuit should terminate the AF.

3. From Rothberger with Winterberg through Sherf and Haïssaguerre

‘History repeats itself’, as the old adage goes. For 100 years, we have gone from facts to hypothesis and now return. The studies of Rothberger and Winterberg in 1909, which preceded by 4 months the initial observations of Lewis on the nature of AF, led the former investigators to postulate that AF was the result of a single electrical focus. However, the idea was soon abandoned thanks to convincing evidence provided first by Mayer and subsequently by the independent work of Mines and of Garrey, as well as by Lewis’ persuasive electrocardiographic evidence that supported the circus movement theory. In fact, the evidence that Lewis gathered with regard to circus movement appeared so complete that his conclusions were accepted as fact in most textbooks of physiology, cardiology, and medicine of the time. But some investigators were unconvinced. In 1949, the application a few crystals of aconitine on the epicardial surface of the right atrial (RA) appendage of the dog allowed Scherf and Terranova to induce atrial tachycardia or fibrillation, which led them to suggest that the mechanism of AF was more compatible with an ectopic focus than with circus movement. This rekindled the controversy and thereafter a number of papers appeared disputing the latter idea. A case in point was a paper by Prinzmetal et al., who rejected Lewis’ concept and in 1950 used a high-speed camera to take colour movies from the atrial surface and then run them at slower motion to analyse the characteristics of the contractile fibrillatory waves. They concluded that in both humans and animals, auricular fibrillation was a chaotic hetero-rhythmic disturbance which depended largely upon the rate of discharge from a single focus. Therefore, according to these authors, there was no circus movement. So, it was that many investigators believed that the focal origin of impulses in atrial flutter and fibrillation induced by aconitine was well documented by Scherf’s experiments. The mechanism of impulse formation within the ectopic focus, however, still remained debatable. Scherf and Terranova and Scherf et al. believed that repetitive discharges develop in the cells affected by aconitine, whereas Yelnosky and Clark concluded that the arrhythmia was due to stimulation of the sinus node by aconitine. However, the circus movement school of thought did not give up. DiPalma and Schults and Dawes suggested that a localized circus movement might develop in the area treated with aconitine. However, no experimental evidence was available in the literature at the time to prove or to disprove any of the above possibilities.

Almost 50 years had to pass before the controversy of the ectopic focus was put to rest. The insightful and ground-breaking demonstration in AF patients by Haïssaguerre et al. provided a definite proof that the pulmonary veins were an important source of ectopic beats, that they were capable of initiating frequent paroxysms of AF, and that they could be eliminated by treatment with radiofrequency ablation. This discovery led to a revolution in the clinical treatment of AF and the procedure of pulmonary vein isolation became the gold standard of management in the clinical EP lab. Today, in 2010, radiofrequency isolation of the pulmonary veins is the recommended treatment in drug refractory AF, which very effectively terminates most cases of paroxysmal AF.

4. Circus movement begets the multiple wavelet hypothesis

In an influential paper published in 1946, Wiener and Rosenblueth conducted numerical experiments on the mechanisms of flutter and fibrillation and postulated that wave rotation around single or multiple obstacles was a necessary condition to initiate and maintain both types of arrhythmia, which they assumed to be the result of a single
reentrant mechanism. They also provided an explanation for how successive stimulation of two overlapping small regions in a two-dimensional (2D) excitable sheet, in the absence of an obstacle, gave rise to a single extra wave propagating in one direction.36 They considered this to be an unstable situation and dismissed the possibility that sustained rotating activity could be initiated in a homogeneous 2D system in this or any other manner in the absence of natural obstacles.36 Interestingly, in 1948, Selfridge37 modified Wiener and Rosenblueth’s model and showed a vortex in a 2D medium in the absence of an anatomical obstacle, which anticipated by 29 years the demonstration of the same phenomenon in the isolated rabbit atrial muscle.38

In the 1950s, a former brilliant student of Carl Wiggers, named Gordon Moe, undertook the study of the mechanisms of fibrillation from a totally different perspective.25 He found the two prevailing theories, i.e. circumpulsation and ectopic focus, unsatisfactory when attempting to explain chronic AF; it was difficult for him to imagine any condition in which either mechanism could sustain for months or even years. He contended that during fibrillation, the activity was totally disorganized and envisioned the arrhythmia as being the result of ‘randomly wandering wave fronts, ever changing in number and direction’.26 In 1959, Moe and Abildskov39 posited that once established, AF was independent of its initiating agency and that inhomogeneous repolarization was an essential condition for its survival as a highly stable, self-sustaining arrhythmia. In 1962, Moe40 postulated the ‘multiple wavelet’ hypothesis of AF, and subsequently developed a computer model which predicted that randomness in the temporal and spatial distribution of membrane properties played dominant roles.41 Twenty-one years later, Allessie and et al.42 mapped the spread of excitation in the atria during rapid pacing-induced AF in the presence of acetylcholine (ACH). They demonstrated multiple propagating wavelets giving rise to turbulent atrial activity. In those experiments, the number of wavelets required to sustain the arrhythmia was estimated to be between 4 and 6,43 which was somewhat puzzling given the large number of wavelets previously theorized by the computer model of Moe et al.,41 which was >26. Nevertheless, additional support for the theory came from animal and human mapping studies, especially after the observation that some cases of chronic AF could be successfully treated with the surgical MAZE procedure, in which the compartmentalization of the atria would create independent regions unable to sustain the multiple wavelets.43

5. Circulating waves are a common physical phenomenon

Allessie et al.44 made a seminal discovery in 1973, which significantly advanced our understanding of the potential role of reentry in AF. Using microelectrode recordings and an isolated dog atrial appendage preparation, they demonstrated that sustained vortices of reentry could occur in healthy atrial muscle in the absence of an anatomical obstacle (i.e. in the absence of a ring). They proposed that the tissue at the centre of the rotating wave was maintained in a state of refractoriness by bombardment of centripetal wave fronts and that the dynamics of reentry were determined by the smallest possible loop (i.e. the ‘leading circle’) in which the impulse could continue to circulate. This idea of reentry around a functional obstacle, while still based on the Mayer19/Mines21 concept of circus movement around a ring, departed significantly from it in three of its major characteristics.38,44,45 First, in theory, the absence of an anatomical obstacle made it impossible to interrupt the arrhythmia by the application of external pacing stimuli. Secondly, the leading circle forced the crest of the circulating wave to intrude on its own refractory tail, which precluded a fully excitable gap, and in principle made the arrhythmia unstable and prone to spontaneous termination. Thirdly, compared with anatomically determined reentry, the cycle length of functional reentry was expected to be shorter. As such, the leading circle became the most accepted concept to explain functional reentry.38,44,45 It prevailed for about 20 years but it was subsequently demonstrated to be insufficient to explain the dynamics of atrial or ventricular fibrillation (VF).46,47 The major problem was that, by definition, the leading circle implies that refractoriness in the centre of rotation prevents the wave front from invading it. As such it fixes the circulating wave front at a unique location and does not permit the centre of rotation to drift.38 As was demonstrated subsequently using high-resolution recording techniques, drifting and meandering of the circulating wave front are two important characteristics of functional reentry, particularly when the substrate is heterogeneous in terms of ion channel properties as is commonly the case in the mammalian atria and ventricles.48–50

Circulating waves are not unique to abnormal cardiac rhythms. In fact, the cardiac muscle is an excitable medium and as such it shares many of the features of many other excitable media in regards to wave propagation, including vortex-like waves organized around so-called ‘phase singularities’. Such media include autocatalytic chemical reactions, calcium waves in cardiac cells, the brain, the retina, etc.51–55 About the time Allessie et al.44 were working on the leading circle concept, theorists and computational biologists were conducting chemical and numerical experiments that predicted that the heart could sustain electrical activity that rotated about a functional obstacle.56,57 These ‘rotors’ have been proposed to be the major organizing centres of fibrillation.55,58 Since then, much experimental and numerical work58–63 has focused on rotors as the underlying mechanism for both AF and VF.59,60 In the context of cardiac electrophysiology, we define a rotor as the organizing source (driver) of functional reentrant activity.61 On the other hand, a spiral wave is the 2D wave of excitation emitted by a rotor and whose front is an involute spiral with increasing convex curvature towards the rotation centre.62–64 The 3D equivalent of a spiral wave is a ‘scroll wave’.65

6. Wavelength and the control of rotor dynamics

Although not universally accepted, rotor theory has become an important mechanistic explanation for AF.65,66 I submit that understanding the dynamics of rotors will allow more specific strategies to stop sustained reentry or to prevent its de novo formation and thus avert AF. The initial step in the initiation of a rotor is a wavebreak after the interaction of a wave front with a functional or anatomical obstacle.49,53,67 This process may occur in a totally homogeneous medium with the only condition of a transient heterogeneity in the system, which can be simulated with an S1–S2 protocol.55 The S1 wave is followed by a second wave (S2) perpendicularly to S1. If S2 is initiated before the repolarizing tail of S1 has disappeared, S1 acts as a barrier for S2 propagation at the intersection point, resulting in a rotating spiral wave.48 Under certain conditions of excitability, the
presence of an anatomical or functional obstacle with sharp edges may destabilize the propagation of electrical waves, giving rise to the formation of self-sustained vortices and turbulent cardiac electrical activity. Both situations may initiate high-frequency reentrant sources in the heart and give rise to new reentrant sources and wave fragmentation.

The propagation velocity of a wave front depends on its curvature, in that waves whose fronts are concave propagate faster than planar waves and the latter move faster than convex waves. As illustrated in Figure 3, the wave fronts of the spiral waves emitted by a rotor have an increasingly steeper convex curvature, which results in a progressive decrease of the conduction velocity (CV) towards the centre of rotation (i.e. the core). At the perimeter of the core, the curvature reaches a critical value leading to a mismatch between the depolarizing current supplied by the wave front and the electrotonic current required to depolarize the resting cells inside the core.

Thus, the powerful electrotonic effect exerted by the core shortens the action potential duration (APD) and the wavelength in its vicinity. Consequently, it would be inaccurate to speak of wavelength (WL = CV × APD) as a unique measure when dealing with functional reentry since both CV and APD increase continuously from the centre to the periphery and thus wavelength is shortest near the core.

7. The resurgence of the single AF source hypothesis

Over the last 20 years, computer modelling together with the use of voltage-sensitive probes and high-resolution video imaging to record electrical wave propagation on the surface of isolated hearts has led to a better understanding of the dynamics of AF and of its nature. Ironically, this has led to the resurgence, albeit with important modifications, of Lewis’ original ‘circus movement hypothesis of reentry’ which postulated that a single circuit may be capable of generating and maintaining fibrillatory activity indefinitely. Advanced technology has confirmed that the turbulent electrical activity seen by electrogram recordings of the atria may in some cases be explained by a single or a small number of rapidly spinning sources. However, these sources are really not the waves that Lewis envisioned to circulate around a defined ring, but rather they are rotors, which force the spiral waves that emanate from them to circulate around a tiny pivoting phase singularity. Thus, as articulated by Lewis many years ago, there is more demonstrable order in the disorder than is consistent with other mechanisms.

Figure 3 Three-dimensional plots of CV and wavelength in experimental (top) and numerical (bottom) spiral waves. (A and C) CV (red) increases as wave front curvature decreases from the centre of rotation to the periphery. (B and D) Wavelength (yellow) is also a function of distance from the core and follows the changes in APD and CV. (A and B) were obtained from an optical mapping experiment in a 2D monolayer of neonatal rat ventricular myocytes; (C) and (D) were obtained from a simulation using the Luo and Rudy model. Y-axis in (A) and (C) is CV relative to maximal CV. Y-axis in (B) and (D) is wavelength relative to maximal wavelength.
The order lies in the highly periodic nature of the high-frequency rotors that maintain the overall activity.61 The disorder is a consequence of the heterogeneous substrate in which the waves that emanate from such rotors propagate and give rise to fibrillatory conduction.74 Obviously, this idea is incompatible with the ‘multiple wavelets’ theory, which requires as a condition that the wavelets wander randomly throughout the atria in a manner resembling the Brownian motion of particles in water.40 Recall that randomness implies that while at any given point in time, the frequency of activation may differ in different parts of the atria, statistically the frequency should be the same everywhere. This is not what happens in AF, in which frequency of activation is hierarchical in both experimental animals and humans, and in many cases, the activity ceases once the localized source of the arrhythmia is eliminated.49,66,75 – 81

8. The hierarchy of dominant frequencies in AF

What is the evidence that supports the hypothesis that acute AF results from activity of a small number of high-frequency reentrant sources localized in one atrium, with fibrillatory conduction to the other atrium? It derives primarily from results obtained in an experimental model of the isolated, Langendorff-perfused, sheep heart where acute AF is induced by burst pacing in the presence of ACh49,81 and from a similar model in which the arrhythmia is instead induced by stretch.82,83 Initial work focused on the localization of the high-frequency sources thought to be responsible for maintaining AF in this model.49,81 We induced AF by rapid pacing in the presence of 0.1–0.6 µM ACh49 or by elevating the endocavitary pressure in both atria above 10 mmHg.82

In many cases, our optical mapping studies demonstrated self-sustaining, high-frequency rotors in the left atrium (LA) giving rise to periodic electrical waves84 and strongly suggested that such rotors were the underlying mechanism of AF in the sheep heart model.82,84 Simultaneous optical mapping of the LA and RA was done in combination with bipolar electrode recordings along Bachmann’s bundle, along the coronary sinus, the RA free wall, the LA appendage, and the pulmonary vein region.49 Power spectral analysis (fast Fourier transform, FFT) of all signals was performed.49 A left-to-right reduction in the dominant frequencies (DFs) occurred in all cases along Bachmann’s bundle and the coronary sinus, resulting in a substantial left-to-right frequency gradient. Altogether, the results strongly supported the hypothesis that AF in the sheep heart was the result of high-frequency periodic sources located in the LA, with fibrillatory conduction towards the RA.49,80,81,84

9. Left-to-right DF gradients in patients

A significant number of recent studies have characterized the spatial distribution of DFs during AF in patients.75 – 78,85,86 Using the
10. Reentrant sources and persistent AF

It is now feasible to record simultaneously from the endocardium and the epicardium of the isolated heart to infer the nature of the activity inside the atrial wall. However, it is currently not physically possible to directly observe the scroll waves propagating through the 3D atrial muscle during AF due to technical limitations. Fortunately, high-resolution spectral analysis makes it possible to identify the regions of periodic activity. The highest DF (DF\text{max}) sites suggest the presence of organized sources (rotors or focal discharges) and in many cases the domains harboring the highest frequencies are localized in the LA. While tending to hide from view inside the atrial walls, and manifest themselves as focal discharges and/or breakthroughs, some 3-D rotors (scroll waves) that span the atrial wall from epicardium to endocardium are prone to be surprisingly stable. In fact, occasionally it is possible to identify a long-lasting rotor in the highest frequency domain.

As discussed above, in the majority of experimental cases, the posterior wall of the LA harbors the sources with the fastest spatiotemporally organized activity. The waves generated by such sources undergo complex, spatially distributed conduction block patterns as they head towards the RA, and the overall pattern manifests as fibrillatory conduction. The outer limit of the DF\text{max} domain is the area where the most fractionated activity surrounds the most regular activity. Clearly, left to right dominant frequency gradients during AF may not be explained by the presence of many sources or wavelets, completely or transiently independent from each other, and each controlling for a time small sections of the atrial muscle. Support for the idea that AF sources are mostly located in the LA also in patients comes from studies showing that pulmonary vein antral isolation is an effective strategy for the prevention of AF in the majority of patients with paroxysmal AF. However, it is important to note that maintenance of SR in the long-term requires repeat procedure or continuation of antiarrhythmic drugs in a significant proportion of patients. Nevertheless, a recent study has shown that after maintenance of SR 1-year post-pulmonary vein antral isolation, a minority of patients will subsequently develop late recurrence of AF.

Recently, data obtained from patients with long persistent AF who underwent a stepwise ablation procedure support the role of high-frequency sources also in long-lasting persistent AF. Ablation was performed in the RA after all LA AF sources had been ablated and an RA-to-LA gradient existed. In 55% of the cases with a persistent right-to-left frequency gradient, the AF terminated upon right atrial ablation. Interestingly, those patients with a right-to-left frequency gradient after LA ablation had a longer AF history and larger right atrial diameter. It is reasonable to speculate that continuous high frequency and heterogeneous bombardment with fibrillatory waves during long-lasting AF produced electrical remodelling substantial enough to spread the likelihood of new sources and rotors to appear in either atrium outside the pulmonary veins. Should this idea be confirmed, it would also explain the lower success rate after ablation of the LA sources, rising up secondary rotors in the RA.

11. Why is the LA faster than the RA during AF?

The reason why the LA harbours the sources with the highest frequencies is not fully understood. It is likely to be multifactorial, which makes the idea of investigating molecular, cellular, and electrophysiological properties that are specific to the LA appealing and clinically relevant. Some of those properties may be summarized as follows. (i) The LA is exposed to higher intracavitary pressures and therefore its walls and muscles are thicker and more heterogeneous than those of the right atrium. (ii) The LA is in direct contact with the four pulmonary veins where the vast majority of AF triggers are located. (iii) The edges of the septopulmonary bundle of the posterior wall form an effective 3D barrier that impairs propagation of premature electrical waves generated in the pulmonary veins. As they move into the atrium, some of those waves may break to initiate reentry. (iv) The richer innervation of the posterior wall of the LA and its greater density of inward rectifier potassium channels likely contribute to shorter refractory periods in that region and to establish the DF gradients that characterize AF. Recently, Voigt et al. conducted a study in patients in which they assessed the contribution of inward rectifier currents (I\text{K1}) to the ionic mechanism of the left-to-right DF gradients seen in AF. Although their results need to be confirmed by greater numbers and by other laboratories, they demonstrated that paroxysmal AF patients had inward rectifier current densities that were about two-fold larger in LA than RA myocytes. However, in chronic AF patients, they observed no significant LA–RA differences, despite greater basal currents. On the other hand, they showed that in SR, the carbachol-activated I\text{K(ACh)} was larger in the RA than the LA for SR patients suggesting a right-to-left gradient in the absence of AF. Because, during sustained AF, the fibrillatory frequency is higher in the LA than in the RA, the ionic remodelling that leads to reduced I\text{Cl} and to increases in I\text{K1} and constitutive I\text{K(ACh)}, would be expected to contribute to greater refractory period shortening and DF increase in the LA than in the RA. However, the idea seems inconsistent with the results of Voigt et al. showing that although the basal I\text{K1} does increase in chronic AF, the left-to-right differences are reduced. The idea also does not seem to be supported by the lack of consistent left-to-right DF gradients that has been reported by some investigators in patients with persistent/permanent AF. Of interest, a recent study utilizing isolated atrial myocytes from patients demonstrated that although in SR there are regionally distributed intra-atrial heterogeneities in the repolarizing currents, in chronic AF, I\text{RTo1} and I\text{Kur} are decreased differentially in the LA and
RA and $I_{Ca}$ is increased in both atria. These changes would be expected to modify the left-to-right gradients and to contribute to the perpetuation of the arrhythmia. Dilatation and stretch establish the conditions for the formation of rotors which are known to locate primarily in the posterior wall of the LA. An excessively high activation frequency in the presence of stretch should favor greater ionic and structural remodelling with fibroblast proliferation, collagen deposition, and patchy fibrosis in the LA than in the RA. As shown recently in acute and chronic AF, these effects appear to be more marked in the LA than in the RA. The above is just a partial list which does not include, for example, familial genetic predisposition, which recently has gained notoriety thanks to genomic-wide association studies. Such studies have identified at least two genetic variants on chromosome 4q25 that are associated with AF. One of such variants is located near the developmental left–right asymmetry homeobox gene, Pitx2, which implicates this gene and its signalling pathways in prevention of atrial arrhythmias. It seems safe to conclude here that investigating in detail the underlying bases of these and other characteristics of the LA, which differentiate it from the RA, may greatly advance therapy by helping to explain the mechanisms of the genesis and perpetration of chronic AF.

12. What next?

It seems that finally after so many years, the controversy of whether AF is the result of circus movement reentry or single or multiple ectopic foci has been put to rest. The demonstration after Haïssaguerre et al. that the isolation of ectopic focal discharges in the pulmonary veins can cure a significant proportion of patients with paroxysmal AF leaves no doubt about their pathophysiological importance. However, it remains to be established whether such discharges are microreentrant, triggered, or abnormally automatic. Similarly, reentry in the form of electrical vortices swirling at high speed and generating fibrillatory conduction from one to the other atrium have been demonstrated to occur, at least experimentally, in both acute and chronic AF. Consistent with such vortices, clinical studies have provided clear evidence for a hierarchical distribution of DFs between the LA and the RA, supporting the idea that localized sources of sustained reentrant activity underlie the mechanism of many cases of paroxysmal AF and even some cases of persistent/permanent AF. Nevertheless, as shown recently in an experimental model of autonomously mediated AF, the complexities of reentrant activity can be substantially compounded by the interaction of the reentrant waves with repetitive or intermittent focal activity. This strongly implicates dysfunctional calcium dynamics in the mechanism of some forms of AF and cannot be ruled out even in those cases in which the clear presence of rotors has been documented. Altogether, full understanding of the underlying mechanisms of the most common forms of AF remains a huge challenge and its treatment is suboptimal at best. In the vast majority of cases, AF is a consequence of underlying heart disease, including hypertension, congestive heart failure, and ischaemic heart disease. It is also a degenerative disease whose perpetuation seems to also result from continuous electrical and structural remodelling secondary to AF itself, as well as to ageing and to progression of the underlying heart disease. So while for the last 100 years much of the insight into electrophysiological mechanisms and complex dynamics of wave propagation in AF have come from detailed investigation in numerical and animal models of AF, translation of the results derived from the use of such models to human persistent AF therapy has been difficult. In general, the models have not included many of the molecular and cellular consequences of structural heart disease, so they are mostly applicable to paroxysmal human AF. Future research into AF dynamics and mechanisms should focus on the development and validation of new numerical and animal models that are relevant to and accurately reproduce the important substrates of the various human AF subtypes. These models will require parallel research into the pathophysiological mechanisms associated with ageing and cardiac disease. In other words, the new models should include not only the complex 3D atrial structure and electrophysiology, but also the consequences of remodelling, including changes in the extracellular matrix and abnormal reciprocal heterocellular interactions, including fibrosis, adiposis, cardiac dilatation, and fatty infiltration. Therefore, complementary integrative research, from the molecule to the patient, should be aimed towards the characterization of the interactions that individual atrial muscle cells have with their neighbouring muscle cells, as well as the extracellular matrix and inflammatory cells, myofibroblasts and adipocytes that are important components of the diseased process. It is highly likely that all such components exert significant paracrine and electrical modulatory effects on cardiac electrical and mechanical function and are important drivers of the pathophysiology of AF.

13. Afterword

In this brief review, I have made an attempt to look back to the mass of intervening theoretical, experimental, and clinical work on the dynamics and mechanisms of AF, with the idea of shining new light into an especially difficult problem. The review is by definition incomplete and of course biased to my own experiences and understanding of the state of the field. I have highlighted what I felt have been the most important issues and controversies that drove the field at any given time during the last ~100 years. I have taken this route because I am a firm believer that, while history can repeat itself even in science, individual scientists learn from those who have preceded them and their work guides those that follow. Hopefully this bird’s eye glance into the past will serve the communities of theoretical, experimental, and clinical scientist in their continuing search for dependable solutions to the problem of persistent/permanent AF, which is one of the most daunting predicaments facing cardiology today.

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